

**ANTIMALARIAL DRUG RESISTANCE AND
ARTEMISININ-BASED COMBINATION THERAPY:
A BIO-ECONOMIC MODEL FOR THE ELUCIDATION OF POLICY
ELUCIDATING POLICY CHOICES.**

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ABSTRACT

Antimalarial drug resistance is a major cause of the increasing burden due to *P. falciparum* malaria. Artemisinin-based combination therapies (ACTs) are now recognised to be the ideal choice for the first-line treatment of uncomplicated malaria, in order to achieve two beneficial outcomes: improvement of treatment efficacy and delay in the development of drug resistance. However uncertainties remain about the current and future benefits, risks and costs of ACTs and in particular how these outcomes are affected by differences in malaria epidemiology, health care settings, human behaviour and implementation strategies.

This thesis seeks to address these uncertainties by creating a comprehensive, dynamic, bio-economic model of malaria transmission and the spread of drug resistance, which incorporates vector factors, human immunity, human behaviour, drug characteristics and costs. Central to the model is a biological model, developed in collaboration with a mathematician, which outputs the proportion of drug resistant infections and the incidence of new and recrudescing infections. Parasite biomass is also tracked in order for human “infectiousness” to be measured and fed-back into the model. Sub-models are used to calculate severe malaria, deaths, costs and cost-effectiveness.

Data were obtained to develop and populate the model. This included a community drug usage survey in Cambodia, which was undertaken in order to document the adherence and coverage rates to ACT following the implementation of locally blister-packaged ACT. Coverage was found to be extremely low, and the use of artemisinin derivatives on their own was widespread. However, both of these outcomes were improved by interventions to increase coverage, particularly village malaria volunteers.

Application of the model in a low transmission setting suggests that with a 10-year time-frame, switching from monotherapy to an ACT is very cost-effective and results in overall cost savings in a range of scenarios. High coverage rates with an ACT are required to delay the spread of drug resistance if resistance has already arisen to one of the partner drugs. Running the model with data from Cambodia suggests that even in settings with low coverage, the change will be cost-effective and significant benefits are gained from the implementation of the specific delivery interventions. Strategies for optimising the implementation of ACTs are discussed in light of the findings.

TABLE OF CONTENTS

ABSTRACT	1
TABLE OF CONTENTS	2
LIST OF FIGURES AND TABLE	9
STATEMENT OF WORK	16
ABBREVIATIONS	17
ACKNOWLEDGEMENTS	19
CHAPTER 1 BACKGROUND	21
1.1. Introduction.....	21
1.2. Malaria.....	25
1.2.1. The malaria life-cycle	25
1.2.2. Clinical malaria	26
1.2.2.1. Co-morbidity.....	27
1.2.2.2. Malaria in pregnancy	27
1.2.2.3. Diagnosis	28
1.2.3. Epidemiology.....	28
1.2.4. Antimalarial drug resistance	29
1.2.5. Artemisinin-based combination therapy (ACT).....	32
1.2.6. Combating antimalarial drug resistance.....	32
1.2.7. Antimalarial drug policy – the current situation	34
1.3. Cambodia.....	36
1.3.1. General background	36
1.3.2. The health care system	36
1.3.3. Malaria in Cambodia.....	37
1.3.3.1. Epidemiology.....	37
1.3.3.2. Malaria control.....	38
1.3.3.3. Antimalarial drug policy.....	39
1.4. Summary.....	43
1.5. Outline of thesis.....	43
CHAPTER 2 LITERATURE REVIEW	44
2.1. Economic evaluations	44
2.1.1. Definition and type of evaluation.....	44
2.1.2. The theoretical basis.....	45
2.1.3. The role of models in economic evaluation	46
2.1.4. Types of models	47
2.1.4.1. Decision-analytic models.....	48
2.1.4.2. Markov chain models.....	48
2.1.4.3. Monte Carlo (Stochastic) Simulation.....	48
2.1.4.4. Other modelling approaches based on decision trees and Markov chains.....	48
2.1.4.5. Mathematical models.....	49
2.1.5. General problems with economic models	49
2.1.6. Validation of economic models	49
2.2. Economics and malaria	50
2.2.1. The economic burden of disease	50
2.2.1.1. Macroeconomic studies	50
2.2.1.2. Microeconomic studies	51
2.2.2. Economic evaluations of antimalarial treatment.....	53
2.2.3. Economics of antimicrobial resistance.....	59
2.2.3.1. Interventions to control antimicrobial drug resistance.....	59

2.2.3.2.	Methodological issues.....	60
2.3.	Mathematical models of malaria.....	62
2.3.1.	Mathematical modelling of infectious disease epidemiology.....	62
2.3.2.	Modelling malaria transmission.....	62
2.3.3.	Modelling antimalarial drug resistance.....	65
2.4.	Conclusions.....	69
CHAPTER 3 AIMS, OBJECTIVES AND METHODOLOGY.....		71
3.1.	Aims and objectives.....	71
3.2.	Overall approach and study framework.....	71
3.3.	Economic analysis – Conceptual framework.....	73
3.3.1.	Goals and perspective.....	73
3.3.2.	Time frame and population.....	76
3.3.3.	Costs.....	77
3.3.4.	Outcomes.....	77
3.3.4.1.	Number of clinical cases.....	77
3.3.4.2.	Number of treatment failures.....	78
3.3.4.3.	The consequence of treatment failures.....	78
3.3.4.4.	Total costs.....	78
3.3.4.1.	DALYS.....	78
3.3.5.	Comparators.....	78
3.4.	The development of the bio-economic model.....	79
3.5.	Parameter estimates.....	80
3.6.	Primary data collection in Cambodia.....	81
3.7.	Running the model.....	81
CHAPTER 4 DEVELOPMENT OF A BIO-ECONOMIC MODEL.....		84
4.1.	Introduction.....	84
4.2.	The overall structure of the bio-economic model.....	84
4.3.	The core biological model.....	86
4.3.1.	An outline of the preceding models.....	86
4.3.2.	Computer programming.....	88
4.2.3.	A general description of the core biological model.....	88
4.2.4.	One iteration of the biological model.....	90
4.4.	Parameter estimates.....	94
4.4.1.	Uses of data.....	94
4.4.2.	Sources of data.....	94
4.5.	Details of the biological model.....	95
4.5.1.	Measuring parasites.....	95
4.5.2.	Infections in the human host.....	95
4.5.3.	Period of chemoprophylaxis.....	97
4.5.4.	Symptomatic infections.....	97
4.5.5.	Parasite growth and maximum parasite density.....	97
4.5.6.	Likelihood of treatment.....	99
4.5.7.	“Migrant” or dormant infections.....	100
4.5.8.	Duration of infection.....	101
4.5.9.	Immunity.....	102
4.5.10.	Gametocytes and infectiousness.....	109
4.5.11.	Infectivity to mosquitoes.....	111
4.5.12.	Vectorial dynamics and inoculations from mosquitoes to humans.....	111
4.5.13.	Drug characteristics.....	112
4.5.14.	Drug resistance.....	114
4.5.15.	Failure rates.....	115

4.5.16.	Characteristics of recrudescence infections	116
4.5.17.	Time intervals.....	119
4.6.	Sub-models	119
4.6.1.	Severe outcomes sub-model.....	119
4.6.2.	Behaviour sub-model	121
4.6.2.1.	Coverage.....	121
4.6.2.2.	Adherence	123
4.6.3.	Cost-effectiveness sub-model	125
4.6.3.1.	First-line drug costs	125
4.6.3.2.	Total cost of malaria treatment	126
4.6.3.3.	DALYs.....	127
4.7.	Assumptions.....	128
4.8.	Summary	129

CHAPTER 5 SYSTEMATIC LITERATURE REVIEW:ADHERENCE TO ANTIMALARIAL DRUGS..... 130

5.1.	Materials and methods.....	130
5.1.1.	Blister packaging.....	130
5.1.2.	Criteria for inclusion	130
5.2.	Results.....	131
5.2.1.	Studies identified.....	131
5.2.2.	Types of studies.....	132
5.2.3.	Study populations.....	133
5.2.4.	Definitions.....	133
5.2.5.	Measurement of drug usage of adherence.....	134
5.2.5.1.	Drug assays.....	134
5.2.5.2.	Other measures	135
5.2.6.	Adherence to clinic-prescribed antimalarial drugs.....	135
5.2.6.1.	Chloroquine	135
5.2.6.2.	Chloroquine and primaquine	135
5.2.6.3.	Quinine and tetracycline or doxycycline	136
5.2.6.4.	Artemisinin monotherapies and combination therapies.....	136
5.2.7.	Antimalarial drug usage in the community	136
5.2.8.	Interventions to improve adherence	137
5.2.8.1.	Clinic base interventions.....	137
5.2.8.2.	Community base interventions	140
5.2.8.3.	Cost of interventions.....	141
5.2.9.	How much does adherence affect clinical outcomes.....	144
5.2.9.1.	Chloroquine	144
5.2.9.2.	Chloroquine and primaquine	144
5.2.9.3.	Quinine and tetracycline	145
5.2.9.4.	Artemisinin derivative monotherapy	145
5.2.9.5.	Artesunate and mefloquine	145
5.3.	Discussion.....	148

CHAPTER 6 PRIMARY DATA COLLECTION IN CAMBODIA: COSTING STUDY..... 153

6.1.	Specific aims.....	153
6.2.	Background.....	153
6.2.1.	Blister-packaged artesunate and mefloquine.....	153
6.2.2.	Rapid diagnostic tests (RDTs).....	154
6.2.3.	Interventions to improve access to early diagnosis and appropriate treatment.....	156
6.2.3.1.	Outreach clinics	156

6.2.3.2.	Village Malaria Volunteers (VMVs).....	157
6.3.	Methods	157
6.3.1.	Cost of blister-packaged artesunate and mefloquine.....	158
6.3.2.	Cost of rapid diagnostic tests	159
6.3.3.	Costing interventions to increase access	159
6.3.3.1.	Outreach.....	160
6.3.3.2.	Village malaria volunteers	161
6.4.	Results.....	162
6.4.1.	Blister-packaging and drugs.....	162
6.4.2.	Rapid diagnostic tests	163
6.4.3.	Interventions to improve access.....	164
6.4.4.	Inputs for modelling.....	164
6.5.	Discussion.....	165

**CHAPTER 7 PRIMARY DATA COLLECTION IN CAMBODIA:
COMMUNITY-BASED STUDY OF TREATMENT SEEKING
BEHAVIOUR AND DRUG USAGE..... 167**

7.1.	Specific aims.....	167
7.2.	Methods	168
7.2.1.	Study design.....	168
7.2.2.	Sample size calculation	168
7.2.3.	Site selection	168
7.2.4.	Screening of households	170
7.2.5.	Questionnaire development and piloting.....	170
7.2.6.	The questionnaire	170
7.2.7.	Drug identification board	172
7.2.8.	Blood testing	172
7.2.9.	Ethics and consent.....	172
7.2.10.	Data entry and analysis	172
7.3.	General analytic approach and definitions.....	175
7.3.1.	General approach	175
7.3.2.	Provider type	175
7.3.3.	Drug categories	175
7.3.4.	Adherence	176
7.3.5.	Socio-economic status.....	176
7.4.	Results.....	177
7.4.1.	General characteristics	177
7.4.2.	Results from the household module.....	178
7.4.2.1.	Socio-economic status	178
7.4.2.2.	Poverty indicators	179
7.4.3.	Individual data.....	179
7.4.3.1.	General description of illness	180
7.4.3.2.	Treatment with modern drugs.....	180
7.4.3.3.	Timing of treatment	180
7.4.3.4.	Number of treatments	181
7.4.3.5.	Source of treatment.....	181
7.4.3.6.	Diagnosis	182
7.4.3.7.	Drug treatment.....	183
7.4.3.8.	Adherence	185
7.4.3.9.	Rapid diagnostic test results	186
7.4.4.	Patient costs.....	187
7.4.4.	Inputs for modelling.....	189
7.5.	Discussion.....	191
7.5.1.	Further research.....	196
7.6.	Conclusion	197

CHAPTER 8 MODELLING ANTIMALARIAL DRUG RESISTANCE AND ARTEMISININ-BASED COMBINATION THERAPY: RESULTS199

8.1.	Overview of the chapter.....	199
8.2.	Presentation of results.....	201
8.3.	Base-case scenario – The continued use of monotherapy.....	202
8.3.1.	Results of the biological model.....	202
8.3.1.1.	Drug resistance	204
8.3.1.2.	Recrudescence infections	204
8.3.1.3.	New infections	205
8.3.2.	Results of the sub-models	207
8.3.2.1.	Severe infections, and deaths.....	207
8.3.2.2.	Costs	208
8.4.	Monotherapy versus combination therapy.....	211
8.4.1.	Outcomes	211
8.4.1.1.	Drug resistance and number of infections	211
8.4.1.2.	Severe malaria and deaths.....	213
8.4.2.	Costs.....	213
8.4.3.	Cumulative results and time frames.....	214
8.4.3.	Cost-effectiveness	217
8.5.	Sensitivity analysis	220
8.5.1.	Sensitivity analysis of biological model	
8.5.2.	Sensitivity analysis of inputs for the sub-models.....	220
8.5.2.1.	Severe malaria and mortality rates.....	223
8.5.2.2.	DALYs and discounting	223
8.6.	Scenario analysis.....	226
8.6.1.	Different drug and treatment costs.....	226
8.6.2.	Coverage rates.....	228
8.6.2.1.	Effects	228
8.6.2.2.	Costs	230
8.6.2.3.	Cumulative costs, effects and costs-effectiveness	232
8.6.3.	Choice of drug and timing of switch.....	237
8.6.3.1.	Effects.....	237
8.6.3.2.	Costs and cost-effectiveness	238
8.7.	Application of the model to Cambodian data	244
8.7.1.	Introduction.....	244
8.7.2.	Inputs and parameterization	244
8.7.2.1.	Type of provider	245
8.7.2.2.	Costs	245
8.7.2.3.	Level of drug resistance.....	246
8.7.2.4.	Treatment rate and time to receiving treatment.....	246
8.7.3.	Results	248
8.7.3.1.	Effects.....	248
8.7.3.2.	Costs	252
8.7.3.3.	Cost-effectiveness.....	253
8.8.	Summary.....	257

CHAPTER 9 DISCUSSION I: METHODOLOGICAL STRENGTHS AND WEAKNESSES AND DISCUSSION OF RESULTS260

9.1	Methodological strengths and weaknesses.....	260
9.1.1	Conceptual framework.....	260
9.1.2	Primary data collection in Cambodia.....	262
9.1.3	Secondary data collection.....	266
9.1.3.1.	Review of antimalarial drug usage studies.....	266
9.1.3.2.	Other parameter estimates.....	266

9.1.4	Development of the bio-economic model	267
9.2	Summary of results.....	274
9.2.1	Primary data collection.....	274
9.2.1.1.	Costing	274
9.2.1.2.	Community-based study of treatment seeking behaviour and drug usage	275
9.2.2	Parameter estimates.....	276
9.2.3	Review of antimalarial drug usage studies.....	276
9.2.4	Modelling	277
9.2.4.1.	Factors affecting transmission.....	277
9.2.4.2.	Factors affecting the spread of drug resistance	278
9.2.5	Modelling results.....	278
9.2.5.1.	Drug resistance.....	278
9.2.5.2.	Transmission	282
9.2.5.3.	Importance of migration.....	283
9.2.5.4.	Severe malaria and mortality.....	283
9.2.5.5.	The impact of ACT.....	284
9.2.5.6.	The importance of the coverage rate with ACT	285
9.2.5.7.	Application of the model to the Cambodian data.....	286
9.3	Conclusion.....	286

CHAPTER 10 DISCUSSION II: POLICY IMPLICATIONS AND RESEARCH PRIORITIES288

10.1	Policy implications.....	288
10.1.1	Drug resistance and ACTs.....	288
10.1.2	Coverage.....	289
10.1.3	Artemisinin monotherapy.....	289
10.1.4	An integrated approach	290
10.1.5	Community based interventions.....	291
10.1.6	Adherence.....	292
10.1.7	Biological diagnosis	293
10.1.8	Choice of combination therapy and timing of switch	294
10.2	Research priorities.....	295
10.2.1	Antimalarial drug usage in Cambodia.....	295
10.2.2	Treatment seeking behaviour and antimalarial drug usage	296
10.2.2.1.	Treatment seeking for “malaria”	296
10.2.2.2.	Adherence.....	296
10.2.2.3.	Effectiveness	296
10.2.2.4.	Interventions to improve community drug usage.....	297
10.2.3	Malaria and antimalarial drug resistance.....	297
10.2.4	Further development of the thesis model	299
10.2.4.1.	Checking the model for validity	299
10.2.4.2.	Developing and modifying the model	300
10.2.4.3.	Applying the model	302
10.2.5	Alternative modelling approaches.....	304
10.2.5.1.	“Micro” approaches.....	304
10.2.5.2.	“Macro” approaches.....	305
10.3	Final conclusions.....	306

ANNEXES.....	308
Annex 1 Background information.....	308
A.1.1. Artemisinins	308
Annex 2 Cambodian development and economic indicators	310
Annex 3 Classification for <i>in-vivo</i> antimalarial drug resistance studies	312
A.3.1. WHO 1996 Classification.....	312
A.3.2. Revised WHO Guidelines - 2002 Classification	312
Annex 4 Antimalarial drug policy and incidence of malaria in Cambodia.....	313
Annex 5 Conceptual frameworks for economic analysis.....	315
Annex 6 Parameter estimates	316
A.6.1. Order of presentation.....	316
A.6.2. Rows and Columns.....	316
Annex 7 Immune functions and formula for calculating infectivity of humans to mosquitoes	338
A.7.1. Immunity Function 1 (based on likelihood of symptomatic malaria)	338
A.7.2. Immunity Function 2 (based on parasite density)	339
A.7.3. Immunity Function 3 (based on likelihood of severe malaria).....	340
Annex 8 Original documentation from community-based survey in Cambodia	338
A.8.1. Letter to Head of village.....	342
A.8.2. Consent form	343
A.8.3. Questionnaires	343
Annex 9 Additional results from the household survey in Cambodia.....	363
Annex 10 Modelling results for a high transmission settings	370
A.10.1. Outcomes.....	370
A.10.2. Costs	371
A.10.3. Cumulative cost-effectiveness	371
Annex 11 Sensitivity analysis of biological model.....	375
Annex 12 Additional results from scenario analysis modelling.....	383
REFERENCES.....	385

LIST OF FIGURES AND TABLES

Figures

Figure 1-1: The malaria life-cycle.....	26
Figure 1-2: Estimated incidence of clinical <i>P. falciparum</i> episodes resulting from local transmission, country level averages, 2004.....	31
Figure 1-3: Drug resistance to <i>P. falciparum</i> from studies in sentinel sites, 2004.....	31
Figure 1-4: Official incidence of malaria by geographical distribution (2001).	41
Figure 1-5: Resistance to chloroquine, SP and mefloquine in Cambodia in 1991	41
Figure 2-1: Steps in the development and use of models.....	63
Figure 2-2: Schematic diagram of Koella’s model of malaria transmission adapted to incorporated resistant and sensitive parasites.....	65
Figure 3-1: Study framework	75
Figure 3-2: Schematic diagram of one iteration of the model.....	80
Figure 4-1: Diagram illustrating the relationship between the different components of the bio-economic model	85
Figure 4-2: Schematic diagram of the biological model progression from steady state through to the introduction of resistance and changes in drug policy	89
Figure 4-3: Introduction of patent infections into first iteration of model	90
Figure 4-4: Determination of likelihood of symptoms by age	91
Figure 4-5: Assignment of treatment type.....	92
Figure 4-6: Schematic diagram of where immunity influences age-stratified likelihoods in the model.....	107
Figure 4-7: Course of parasite and gametocyte density in a single infection.....	110
Figure 4-8: Diagram illustrating the calculation of infectiousness of the human population to mosquitoes at each iteration	110
Figure 4-9: Schematic diagram of the course of parasitaemia and gametocytaemia during the course of a recrudescence infection..	118
Figure 4-10: Diagram illustrating severe cases as a consequence of initial infections and recrudescence infections.....	122
Figure 4-11: Diagram showing the sigmoid relationship between resistance and severe malaria or mortality	122
Figure 4-12: Diagram of the decision-tree used to calculate costs of first-line drugs in the economic analysis and the “untreated” and the “CT coverage” rates	124
Figure 5-1: Results of literature search.	138
Figure 5-2: The relationship between dosing and therapeutic response to antimalarial treatment in sensitive and resistant infections	151

Figure 6-1: The blister-packaged A+M4 and Malarine.....	155
Figure 6-2: The Paracheck® RDT	155
Figure 6-3: Breakdown in costs of blister-packaged drugs.....	163
Figure 7-1: Map of study sites in Cambodia.....	169
Figure 7-2: Identifying villages in the health centre catchment area	173
Figure 7-3: Packages of tablet mixtures, as commonly bought for the treatment of malaria.....	173
Figure 7-4: Drug identification board	174
Figure 7-5: Sokhoen, one of the research assistants, interviewing respondent.....	174
Figure 8-1: Sequence of presentation of results in this chapter.....	200
Figure 8-2: Spread of drug resistance to drug A with continued use of drug A monotherapy.....	204
Figure 8-3: Recrudescence infections - a) total number of cases b) by age group	205
Figure 8-4: Annual incidence of patent and treated infections.....	205
Figure 8-5 Annual incidence of a) patent and b) treated infections by age group	206
Figure 8-6: Total number of patent infections showing the proportion due to recrudescence compared to new infections	206
Figure 8-7: Annual incidence by age group of a) severe cases, b) deaths and c) case fatality rate.	208
Figure 8-8: Annual costs in the base-case scenario (continued use of monotherapy).....	210
Figure 8-9: a) Resistance and b) annual EIR with ACT compared to monotherapy.....	211
Figure 8-10: a) Number of new (treated) infections and b) recrudescence infections with combination therapy compared to monotherapy.....	212
Figure 8-11: Number of a) severe cases and b) deaths with combination therapy compared to monotherapy.....	213
Figure 8-12: Annual direct costs of a) first-line drug alone b) all direct treatment costs for malaria	214
Figure 8-13: Cumulative results comparing outcomes with monotherapy compared to combination therapy.....	216
Figure 8-14: Cumulative cost of first line treatment.....	217
Figure 8-15: Cumulative cost-effectiveness of combination therapy (at 100% coverage) compared to monotherapy over time	218
Figure 8-16: Effect of different coverage rates with ACT (drug AB) on resistance (to drug A) and outcomes	229
Figure 8-17: Cost of first-line drugs and of total (direct) cost of malaria including recrudescence and severe infections by level of coverage with combination therapy	231
Figure 8-18: Graphs showing cumulative effects by coverage rate and time frame	233
Figure 8-19: Graphs showing cumulative costs by coverage rate and time	234
Figure 8-20: Cumulative incremental cost-effectiveness in terms of cost per case averted and cost per DALY averted by coverage rate at years 2,5 and 10.....	235

Figure 8-21: Cumulative cost-effectiveness planes showing effect of coverage rate with ACT compared to monotherapy on cumulative incremental cost of drugs compared to cumulative incremental DALYs averted.....	236
Figure 8-22: Drug resistance to drug A comparing the effect of switching to drug AB versus drug BC at different levels of resistance to drug A	237
Figure 8-23: Graphs comparing outcomes between switching from drug A to drug BC and to drug AB at different levels of resistance to drug A.....	240
Figure 8-24: Annual cost of first line drug and annual direct cost of treating malaria comparing monotherapy (drug A) to switching to drug AB or drug BC at different levels of drug resistance to drug A.....	241
Figure 8-25: Annual outcomes predicted by model for Cambodian scenarios	249
Figure 8-26: Annual costs predicted by model for Cambodian scenarios.....	254
Figure 8-27: CE planes comparing the incremental cost of first-line drug and delivery interventions with DALYs averted for the different Cambodian scenarios.	256
Figure 9-1: The rate of spread of resistance to a combination therapy as predicted by Laxminarayan.....	279
Figure 9-2: Age-stratified failure rates predicted by the model in the base-case scenario with monotherapy starting at 1% resistance at year 1	281
Figure 9-3: Cumulative cure rates at day 28 for mefloquine 15mg/kg (M ₁₅), mefloquine 25mg/kg (M ₁₅) and mefloquine plus artesunate (MAS ₃) on the Thai-Burmese border.....	281
Figure 9-4: Drug resistance in KwaZulu-Natal (KZN) and Mpumalanga in South Africa	282

Tables

Table 1-1: Antimalarial drug prices	24
Table 1-2: Summary results by year of results of <i>in-vivo</i> antimalarial drug resistance studies and antimalarial drug policy in Cambodia.....	42
Table 3-1: Relationship between objectives and methodology.....	74
Table 3-2: Chain of events for clinical outcomes.....	83
Table 4-1: Summary of the refinement of the biological models from model 1 to model 3.....	87
Table 4-2: Facets of immunity and data used in model.....	108
Table 4-3: Aspects and manifestations of drug resistance	114
Table 5-1: Descriptive studies of adherence to prescribed regime-health centre (HC) based.....	138
Table 5-2: Community based studies comparing antimalarial drug usage to national drug policy	139
Table 5-3: Studies of interventions to improve community antimalarial drug usage	142
Table 5-4: Studies of interventions to improve patient adherence – health centre based.....	143
Table 5-5: Studies examining the clinical outcomes in unsupervised patients (effectiveness).....	146

Table 6-1: Cost of packaging	158
Table 6-2: Cost of antimalarial drugs.....	159
Table 6-3: Cost of staffing for the outreach intervention	161
Table 6-4: Cost of blister-packaged artesunate and mefloquine	163
Table 6-5: Summary of the annual fixed costs of the outreach and VMV interventions	164
Table 6-6: Estimated activity and fixed cost of interventions per capita, per patient seen and per patient treated	164
Table 7-1: Possible indicators derived from questionnaire	171
Table 7-2: Summary description of sample	178
Table 7-3: Median duration of stay by district.....	178
Table 7-4: Proportion of households who had to borrow money last year	179
Table 7-5: Proportion and likelihood of receiving modern drugs for most recent episode of fever	180
Table 7-6: First source of treatment by intervention.....	181
Table 7-7: Proportion and likelihood of patients seen by a trained or “formal” provider for the most recent episode.....	182
Table 7-8: Proportion and likelihood of having a biological diagnosis for most recent episode of fever.....	182
Table 7-9: Frequency of biological diagnosis by provider type (all contacts).....	183
Table 7-10: Percentage of different antimalarial treatments received in the last 2 months, by intervention area (n)	184
Table 7-11: Proportion and likelihood of treated patients receiving A+M for most recent episode	184
Table 7-12: Adequate duration of treatment (for most recent treatment).....	186
Table 7-13: Proportion “adherent” to artesunate and mefloquine regime by type of provider	186
Table 7-14: Likelihood of positive study RDT	187
Table 7-15: Costs for most recent treatment episode by intervention area	187
Table 7-16: Cost (US\$) of most recent treatment by provider type.....	188
Table 7-17: Cost of different treatments for most recent episode (US\$)	188
Table 7-18: Proportion and likelihood of spending greater than \$1 treatments for malaria	189
Table 7-19: Parameter inputs for “behaviour” sub-model derived from results of the survey	190
Table 8-1: Characteristics of monotherapy (drug A) and ACT (drug AB).....	203
Table 8-2: Values of variable parameters used in base-case scenario.....	203
Table 8-3: Cumulative effects, costs and cost-effectiveness of combination therapy (100%) compared to monotherapy at 1, 5 and 10 years.....	219
Table 8-4: Summary of sensitivity analysis of biological model undertaken by WP for a low transmission setting.....	222
Table 8-5: Sensitivity analysis of input values of likelihood of severe malaria and death with 5 and 10-year time frames.....	224

Table 8-6: Sensitivity of the incremental cost-effectiveness of ACT compared to monotherapy to assumptions about DALYs.....	225
Table 8-7: Sensitivity analysis of total direct costs and cost-effectiveness of ACT to cost assumptions, at 10 years. (The cost used in the incremental CEA is the drug cost alone).....	227
Table 8-8: Cumulative costs, effects and cost-effectiveness of switching to drug AB (artesunate + SP) from SP at 1% resistance to drug A (SP).....	242
Table 8-9: Cumulative costs, effects and cost-effectiveness of switching to drug BC (artemether-lumefantrine) from SP at 1% resistance to drug A (SP).....	243
Table 8-10: Maximum failure rates input into sub-model to calculate overall failure rates	247
Table 8-11: Calculated coverage rate and failure rates to monotherapy mefloquine (drug A) and the ACT, artesunate and mefloquine (drug AB) in non-immune host.....	247
Table 8-12: Cumulative effects, costs and incremental cost-effectiveness of switching policy to ACT with and without interventions to improve coverage, with a 5-year time frame.....	250
Table 8-13: Cumulative effects, costs and incremental cost-effectiveness of switching policy to ACT with and without interventions to improve coverage, with a 10-year time frame.....	251
Table 8-14: Annual cost of first line treatment and total (direct and indirect) costs showing distribution of costs between provider and patient.....	255

Figures and tables in the annex

Figure A4-1: Incidence of malaria in Cambodia.....	314
Figure A6-1: Example of column headings	316
Figure A7-1: Simulated curves of the proportion of symptomatic infections by ages in different transmission intensities by the non-linear immunity function described by Equation A7-1...	338
Figure A7-2: Simulated curves of \log_{10} (parasite biomass) in different age groups and different transmission intensities as described by Equation A7-2	339
Figure A7-3: Simulated curves of the normalised data of treatment failure rate in different age groups and different transmission intensities based on Equation A7-3	340
Figure A10-1: The spread of drug resistance in high and low transmission settings.....	370
Figure A10-2: Annual incidence of new patent and treated infections in low and high transmission settings with monotherapy and combination therapy at 100% coverage	372
Figure A10-3: Annual incidence of new patent and treated infections with monotherapy in a high transmission setting, by age group	372
Figure A10-4: Annual incidence of recrudescence infections and number of DALYs.....	372
Figure A10-5: Annual direct cost of drugs and of treating malaria (including recrudescence and severe infections, in low and high transmission settings with monotherapy and 100% combination therapy	373

Figure A10-6: Cost-effectiveness of combination therapy (100% coverage) over time in a high transmission setting compared to low transmission setting	373
Table A2-1: Cambodian economic indicators.....	310
Table A 2-2: Household expenditure and consumption data from Cambodian socio-economic survey 1999	310
Table A2-3: Poverty indicators	311
Table A2-4: Health related indicators from the Cambodian general population census and the demographic and health survey.....	311
Table A2-5:Other indicators from Cambodian socio-economic survey.....	311
Table A4-1: Dosing of artesunate suppositories for children under 6 years old	313
Table A4-2: Dosing of blister-packaged artesunate and mefloquine	313
Table A5-1: Types of costs and consequences relevant to the economic evaluation of health programmes.....	315
Table A5-2: Conceptual framework of economic analyses of malaria control from “Guidelines for cost-effectiveness analysis of vector control”	315
Table A6-1: Malaria infection in the human host	318
Table A6-2: Age-stratified data used in immune functions	320
Table A6-3: Input parameters for non-immune host for “zeroing” immune function	321
Table A6-4: Characteristics of asymptomatic infections	323
Table A6-5: Characteristics of symptomatic infections	324
Table A6-6: Recrudescence infections	325
Table A6-7: Vector factors.....	326
Table A6-8: Clinical outcomes-Severe malaria and mortality.....	328
Table A6-9: Behaviour – Diagnosis and treatment.....	330
Table A6-10: Implementation - strategies to improve adherence	331
Table A6-11: Direct costs – OPD treatment of uncomplicated malaria.....	332
Table A6-12: Direct cost -IPD treatment of complicated malaria	334
Table A6-13: Indirect costs	336
Table A6-14: Estimated minimum cure rates in the non-immune host dependent on adherence and drug resistance.....	337
Table A 9-1: Summary description of the areas in which the community based treatment seeking and drug usage study took place.....	363
Table A9-2: Size of land owned by households by district.....	364
Table A9-3: Months of food shortage in the last year.....	364
Table A 9-4: Years of schooling	364
Table A9-5: Building material for walls	364
Table A9-6: Building material for roof.....	365


Table A9-7: Number of draft animals	365
Table A9-8: Ownership of means of transport.....	365
Table A9-9: Ownership of means of telecommunications	365
Table A9-10: Source of water	365
Table A9-11: Age distribution of sample.....	366
Table A9-12: Logistic regression analysis of likelihood of being seen by formal provider for recent episode of malaria like illness	366
Table A 9-13: Likelihood of biological diagnosis by district.....	366
Table A 9-14: Logistic regression analysis of likelihood of receiving biological diagnosis for recent episode of malaria like illness	367
Table A9-15: Logistic regression analysis of receiving A+M for recent episode of malaria like illness.....	367
Table A9-16: Average duration of treatment by antimalarial regime	368
Table A9-17: Type of treatment by provider	369
Table A10-1: Cumulative cost-effectiveness of combination therapy (100% coverage) over time in a high transmission setting	374
Table A11-1: Parameters tested in the sensitivity analysis with code.....	375
Table A11-2: The partial rank correlation coefficients of the input parameters and the outcomes in low transmission setting with monotherapy (Scenario A)	376
Table A11-3: The partial rank correlation coefficients of the input parameters and the outcomes in low transmission setting with ACT (Scenario B).....	377
Table A11-4: The partial rank correlation coefficients of the input parameters and the outcomes in high transmission setting with monotherapy (Scenario C).....	378
Table A11-5: The partial rank correlation coefficients of the input parameters and the outcomes in high transmission setting with ACT (Scenario D)	379
Table A11-6: The results of the sensitivity analysis shown as the statistical summaries of the outcomes in the 4 scenarios.....	380
Table 12-1: Cumulative costs, effects and cost-effectiveness of switching to drug AB (artesunate + SP) from SP at 20% resistance to drug A (SP).....	383
Table 12-2: Cumulative costs, effects and cost-effectiveness of switching to drug BC (artemether-lumefantrine) from SP at 20% resistance to drug A (SP).....	384

STATEMENT OF WORK

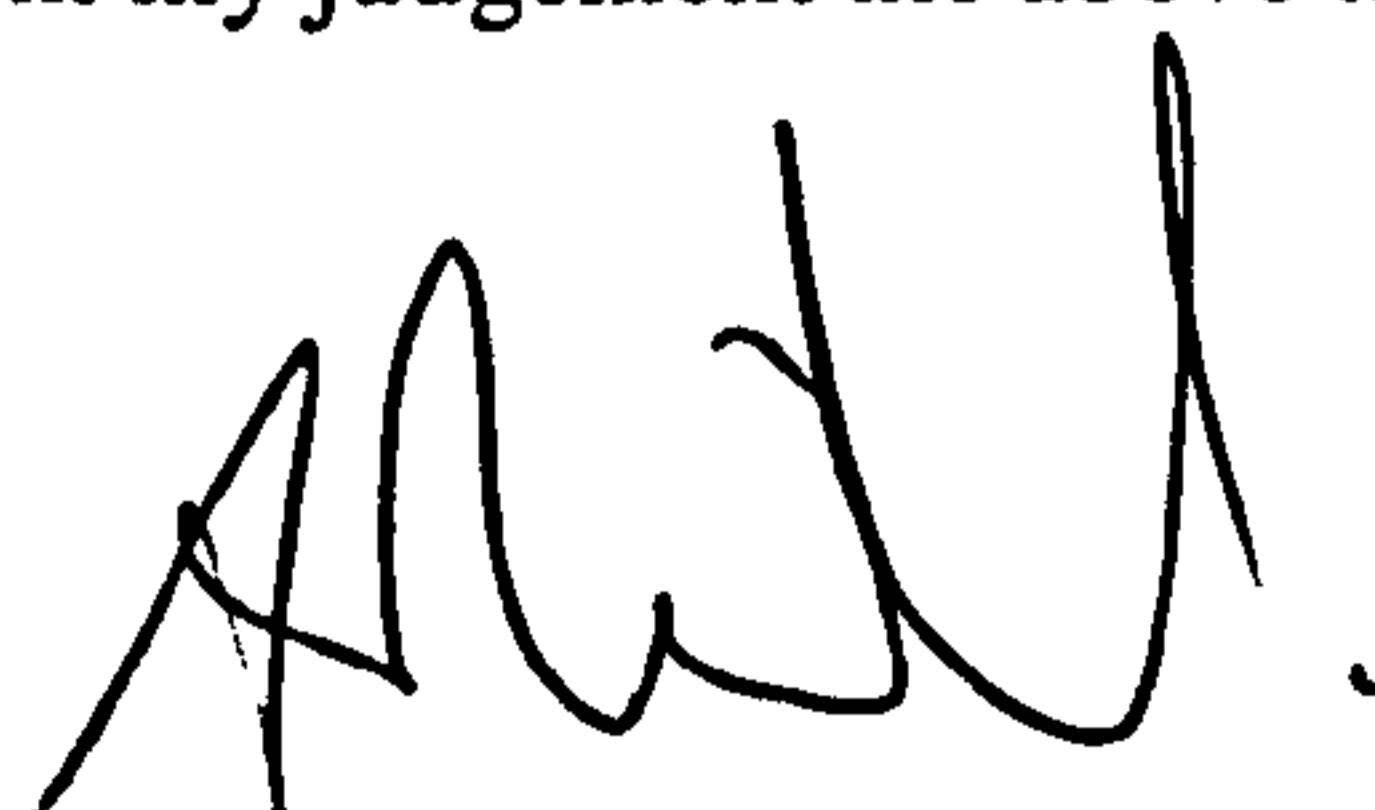
The development of the bio-economic model was a collaborative project between a mathematician, Ms. Wirichada Pongtavornpinyo (WP) and myself. The work presented in Chapter 4 is a result of that collaboration. We were jointly involved in the conceptualisation and designing the structure of the model. WP was mainly responsible for the mathematical programming. My role included ensuring the biological realism and applicability of the model throughout the development of the model. I was also chiefly responsible for the collection, selection, interpretation and some of the transformation of the model parameters. The construction of the clinical and economic sub-models described in Chapter 4 and all of the application of the model presented in Chapter 8 is my own work, except for the sensitivity analysis on the biological model presented in Section 8.5.

The systematic review of studies of adherence to antimalarial drugs presented in Chapter 5 was published as a paper, co-authored by Professor Nick White. I initiated the study and undertook the majority of the work including the initial conceptualisation, searching and selection of the literature, synthesis of the data and writing. Professor White was involved in reviewing and editing the final manuscript.

All of the work presented in Chapters 1,2,3,6 and 7 are solely my work. I was also responsible for the construction of the tables of parameter estimates in Annex 6.


Shunmay Yeung, PhD candidate

I certify that in my judgement the above is a true statement of Shunmay Yeung's contribution to the thesis.


Professor Anne Mills, Supervisor

ABBREVIATIONS

A+M	Artesunate and Mefloquine
ACT	Artemisinin-based Combination Therapy
AIDS	Acquired Immune Deficiency Syndrome
AL	Artemether-Lumefantrine
AMR	Anti-microbial Resistance
AOR	Adjusted Odds Ratio
ARI	Acute Respiratory Infections
AS-AQ	Artesunate and Amodiaquine
AUC _{gam}	Area Under Curve (of time versus gametocyte density)
CBA	Cost-benefit Analysis
CEA	Cost-effectiveness Analysis
CFR	Case Fatality Rate
CHW	Community Health Worker
CI	Confidence Interval
CNM	National Malaria Centre (Cambodia)
DALY	Disability Adjusted Life Years
DDT	Dichloro-diphenyl-trichloroethane
DFID	Department for International Development
DHFR	Dihydrofolate reductase-thymidilate synthase
DHPS	Dihydropteroate synthase
EDAT	Early Diagnosis and Appropriate Treatment
EIR	Entomological Inoculation Rate
FDA	Food and Drug Administration
FU	Follow-up
GDP	Gross Domestic Product
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GSR	Gametocyte Switching Rate
HIV	Human Immunodeficiency Virus
HRP2	Histidine Rich Protein 2
IEC	Information, Education and Communication
ITN	Insecticide Treated Net
KR	Khmer Rouge
KZN	KwaZulu-Natal
MIC	Minimum Inhibitory Concentration
MoH	Ministry of Health

MRSA	Methicillin Resistant <i>Staphylococcus Aureus</i>
MSF	Médecins sans frontières
NA	Not Available
NGO	Non-Governmental Organisation
OR	Odds Ratio
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
PDR	People's Democratic Republic
PF	Plasmodium Falciparum
PfEMP	Plasmodium Falciparum Erythrocytic Membrane Protein
PPAM	Pre-packaged Antimalarial drugs
Q	Quinine
Q7T7	Quinine and Tetracycline for 7 days
R	Resistant
RCT	Randomised Control Trial
RDT	Rapid Diagnostic Test
S	Sensitive
SP	Sulfadoxine/Pyrimethamine
T	Tetracycline
TB	Tuberculosis
UNDP	United Nations Development Programme
US\$	United States Dollars
VC	Vectorial Capacity
VMV	Village Malaria Volunteer
WHO	World Health Organisation
WP	Wirichada Pongtavornpinyo
YLL	Years of Life Lost

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CHAPTER 1

BACKGROUND

This chapter introduces the thesis and gives a brief overview of malaria, antimalarial drug resistance and current antimalarial drug policy. This is followed by background information on Cambodia, where the field work for this thesis was undertaken. The chapter ends with a summary and outline of the remainder of the thesis.

1.1. Introduction

Over three billion people living in 107 countries are at risk of malaria transmission, with an estimated 350–660 million clinical malaria episodes annually. *Plasmodium falciparum* is responsible for many of these cases and for more than one million deaths each year. More than 80% of these deaths occur in sub-Saharan Africa, where it is the cause of about 18% of deaths in children under five years of age (Snow, Guerra et al. 2005; WHO 2005b). In economic terms, the disease is estimated to be responsible for an estimated average annual reduction of 1.3% in economic growth for those countries with the highest burden (Gallup and Sachs 2001).

Antimalarial drug resistance is now generally acknowledged to be the main cause of our inability to “Roll Back Malaria”. Chloroquine, which has been quietly responsible for saving millions of lives since the 1950’s, is now useless for the treatment of *P. falciparum* malaria in Asia, Latin America and much of Africa. Resistance to sulfadoxine-pyrimethamine (SP) spread even faster when it was introduced to replace chloroquine and is now widespread across much of Africa (WHO 2005b). Chloroquine and SP are both affordable drugs at around \$0.10-0.20 per adult course, and their safety and previous efficacy as oral regimens mean they have been easily accessible and widely used. Mefloquine, the next drug to be deployed in Southeast Asia, the historic epicentre for multi-drug resistant *P. falciparum* malaria, fell to drug resistance within six years of its introduction in Thailand in the 1980’s (Nosten, ter Kuile et al. 1991). It is much more costly and has never been deployed on wide scale in Africa. Fortunately, just as the supply of new antimalarials was running dry, artemisinin, a “new” class of drugs used originally in traditional Chinese medicine, were rediscovered and were increasingly being used in China and Vietnam in combination with other drugs. In 2000, Cambodia became the first country in the world to make an artemisinin-based combination therapy (ACT), of artesunate and mefloquine, their nationally recommended first-line drug (CNM 2000b).

Artemisinin-based combination therapies (ACTs) are now recognised to be the ideal choice for the first-line treatment of *P. falciparum* malaria. They are efficacious, rapid acting, well-tolerated, safe, available in all formulations, require only three days of treatment and reduce transmissibility. As for any combination therapy, which involves two effective drugs from different classes, both component drugs are less prone to the development of drug resistance, thus prolonging the useful lifespan of the available antimalarial drugs. However, at more than US\$1 per adult dose, although not expensive by developed world standards, they are too costly to be afforded by communities and governments in poorer countries (Table 1-1).

Although ACTs were officially recommended by the World Health Organisation in 2001 (WHO 2001a), the initial response by policy makers was slow. Chloroquine and SP continued to be recommended and used across sub-Saharan Africa, exacting an enormous and increasing toll in terms of morbidity, mortality and associated economic costs. After several years of controversy apparent inertia (Nantulya and Liden 2004; Watkins, Kokwaro et al. 2004), there is now widespread political and financial support for the switch to ACT and countries are switching to an ACT with increasing momentum (Arrow, K.J., Panosian, C. et al. 2004; WHO 2006b)

Thus in the few years since the inception of this study, the key questions regarding antimalarial drug policy have shifted from whether or not to change from monotherapy to combination therapies, to questions about their implementation and financing. In particular there are concerns about how to maximise coverage of the populations at risk of malaria in order to reduce current morbidity and mortality and to reduce the likelihood of drug resistance developing. Although providing easy access to free ACTs may achieve this aim, it has to be balanced against the costs, the wastage of drugs and the implications of their widespread inappropriate use. When the partner drugs are not co-formulated, the main risk is that artemisinins will be used on their own leaving them exposed to the development of drug resistance (Bloland, Ettling et al. 2000; Whitty, Allan et al. 2004). For the benefit of future generations the life of the currently available drugs must be prolonged for as long as possible. This is one of the main rationales for using ACTs but is also the reason that they must be deployed carefully.

Questions remain about the choice of combination therapy and timing of change, and there is still considerable uncertainty about the implications in terms of future costs, risks and benefits. In order for national governments and donor institutions to make rational decisions regarding drug policy and strategies for implementation, there is a need for a framework in which the current and future risks and costs of antimalarial drug resistance, can be balanced against the cost and benefits of different policies and strategies.

Policy issues such as this, where outcomes are uncertain and decisions complex, are increasingly being explored with the help of models (Rauner and Brandeau 2001; Evans, Edejer et al. 2005). They are ideally suited to exploring both biological and economic influences on outcomes and moreover, they can be used to produce the estimates of the cost-effectiveness of policy options (Weinstein, Toy et al. 2001). However static economic models of malaria do not capture the change in disease transmission or antimalarial drug resistance and ignore the externality benefits and fundamental goals of malaria control: reduction in the number of cases and prolonging the useful life of antimalarial drugs. The development of a sound economic analysis is dependent on the robustness of the underlying epidemiological model of malaria that predicts these changes. Existing mathematical models of malaria have focused on intra-host dynamics, epidemiology, or specific aspects of drug resistance. However the factors affecting the effectiveness of drugs, the development of resistance and disease transmission are complex. Previous models have not incorporated all these important drug, epidemiological, parasitological and human behavioural factors.

The aim of this thesis was to develop a bio-economic model of antimalarial drug resistance, which incorporates all relevant factors and can be used to elucidate different antimalarial drug policy options. In order to maximise the realism of the model, the collection of an extensive amount of data formed an important part of the study. Secondary data including a systematic literature review were used to populate the model and primary data were collected in Cambodia. Cambodia was chosen as the site for the empirical data collection because it was the first country to switch the national antimalarial drug policy to an ACT. In addition the change was accompanied by a number of innovative implementation strategies including the local blister-packaging of an ACT, the social marketing of the ACT through the private sector and the use of village malaria volunteers (VMVs) and outreach to increase coverage with biological diagnosis and ACT. In this thesis the focus of work was on low transmission areas. However, the model can be applied to explore the spread of drug resistance and the impact of combination therapy in high transmission settings.

Table 1-1: Antimalarial drug prices

Drug	Estimated cost estimated for adult course (Source)
Monotherapies	
Chloroquine	US\$ 0.05 – 0.10 (depending on supplier) (2)
Sulfadoxine/Pyrimethamine (SP)	US\$ 0.06 – 2.80 (depending on supplier) (2)
Amodiaquine	US\$ 0.15 (5)
Mefloquine	US\$ 1.05 – 2.95 (depending on supplier) (2) (3)
Artesunate	US\$ 0.50 - 2.68 (depending on supplier) (1)
Quinine	US\$ 0.88 – 3.02 (depending on supplier) (2)
Artemisinin-based combination therapies (ACTs)	
Artesunate + Amodiaquine	US\$ 1.30 (4) (5)
Artesunate + SP (Blister-packaged)	US\$ 1.24 - 2.42 (depending on number of treatments) (1)
Artesunate + Mefloquine (Blister-packaged in Cambodia)	US\$ 2.59 - 3.80 (depending of manufacturing efficiency) (3)
Artemether +Lumefantrine (Co-formulated as Co-artem®)	US\$ 2.40 (for public services in developing countries) (1)
Dihydroartemisinin + Piperaquine (Co-formulated as Artekin®)	US\$ 1.00 (1)

(1) J.M Kindermans in Saving Lives, Buying Time (Arrow, K. J., Panosian, C. et al. 2004)

(2) Based on International Drug Price Index, Management Sciences for Health, 2003 (drug cost only) (Mangement Sciences for Health 2003)

(3) Cost to National Malaria Centre in Cambodia (Tsuyuoka R, personal communication)

(4) From Snow 2003 (Snow, Eckert et al. 2003)

(5) J.M Kindermans in Changing malaria treatment protocols in Africa: What is the cost and who will pay? (Kindermans, Pecoul et al. 2002).

1.2. Malaria

1.2.1. The malaria life-cycle

Plasmodium falciparum malaria, the focus of this thesis, is the most lethal and most prevalent type of malaria out of the four types that cause malaria in humans (*P. vivax*, *P. ovale*, *P. malariae* and *P. falciparum*). It is transmitted by the bite of an infected female anopheles mosquito and has a complex life cycle involving an asexual stage in humans and a sexual stage in the mosquito (Figure 1-1).

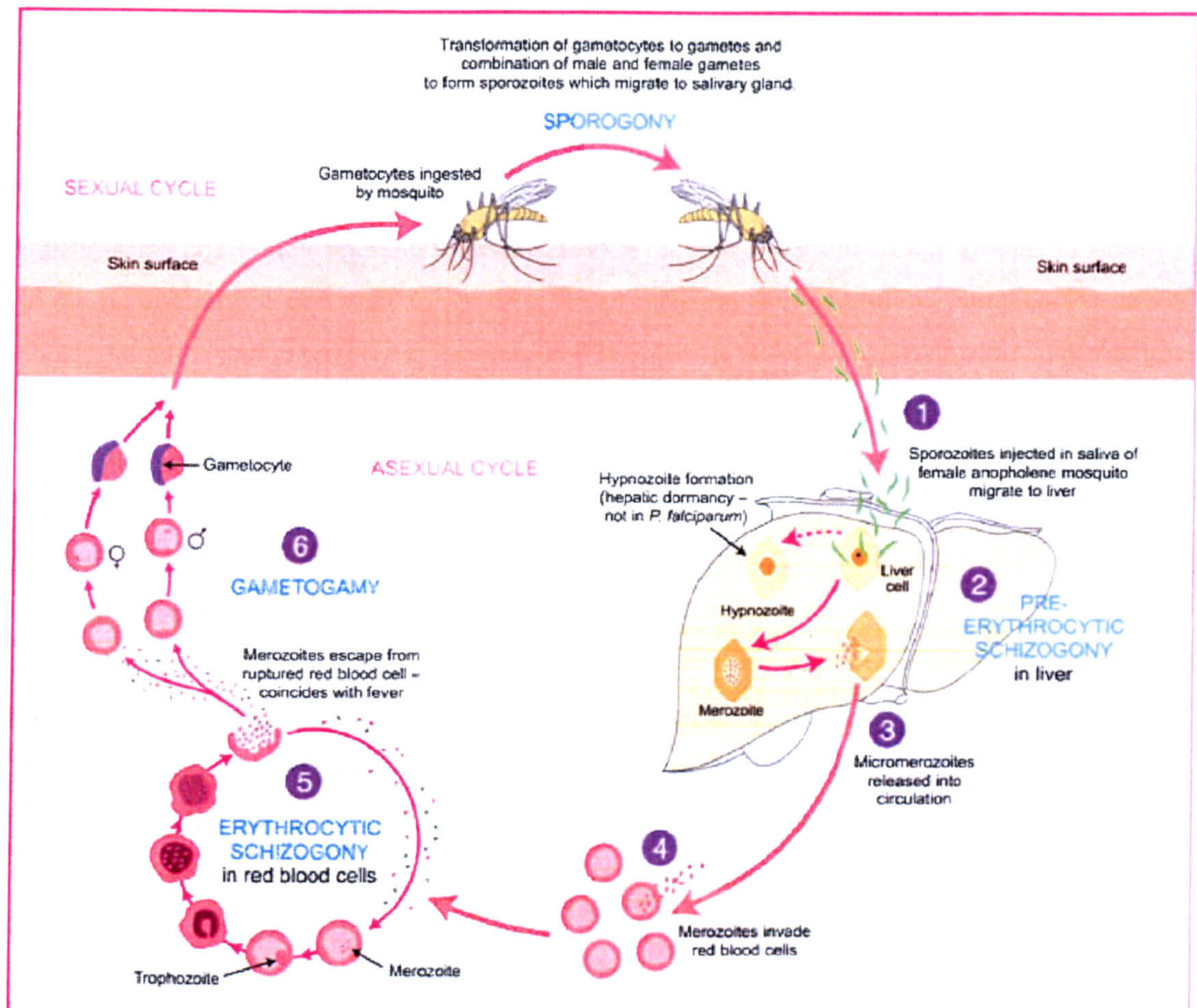
Following inoculation in humans, there is an initial liver stage of reproduction, which is asymptomatic and unaffected by drug treatment. After about 10 days the parasites burst out of the liver cells and into the blood stream.

During this stage in the blood stream, asexual parasites invade red blood cells in which they grow and multiply. Each blood-stage cycle takes 48 hours during which time the parasites transform from small ring-like forms into “schizonts” which contain eight to 24 parasites (“merozoites”). Schizonts adhere to the walls of some small blood vessels in a process called “sequestration”, which results in obstruction of blood flow to certain organs including the brain and placenta, thereby contributing to the pathophysiology of severe malaria¹. The schizonts eventually rupture releasing the merozoites into the blood stream where they invade new blood cells, causing a logarithmic expansion in parasite biomass at a rate of about 10-fold every 48 hours. On average, parasites are detectable in the blood by microscopy on the 11th day after initial inoculation, when the density of parasites is around 20-50 parasites/μl of blood. At this stage the human host may still feel well or only experience vague symptoms, and usually becomes only febrile two days later.

After a series of asexual cycles, a sub-population of parasites differentiates into male and female sexual forms known as “gametocytes”. These do not multiply or cause symptoms but are responsible for transmission of malaria via mosquitoes. Once they are ingested in the blood-feed of a female mosquito, the male and female gametocytes fuse and undergo meiosis (sexual reproduction) and then multiply asexually in the mid-gut of the mosquito in “oocysts”. After about 7-10 days these rupture, releasing parasites that penetrate multiple body sites, including the salivary gland, ready to be inoculated into a human host with the next blood-feed, thereby completing the *Plasmodium* life-cycle.

¹ This process also means that schizonts are rarely visible in the blood on microscopy leading to a systematic underestimation of total body parasite burden.

Figure 1-1: *The malaria life-cycle*



Source: www.hpa.org.uk/infections/toolkit/mosquito.htm

1.2.2. Clinical malaria

The outcomes of infection with *P. falciparum* malaria range from self-limiting asymptomatic infections to rapid death. This depends on a number of factors, the most important being host immunity, age and drug treatment. Symptoms are manifest when a threshold parasite density – “the pyrogenic density” - is reached and is related to the rupturing of red blood cells. Non-immune patients may become febrile before the parasites become visible by microscopy, whereas immune patients can tolerate parasite densities of up to 10,000/μl of blood without symptoms.

Acute uncomplicated malaria is classically associated with episodes of high fever, chills, sweating, headache, malaise, back and abdominal discomfort, anorexia, pallor and in children, often seizures. Other symptoms such as diarrhoea, cough, and fast breathing are also not uncommon.

Severe malaria can affect any organ, with the onset and manifestation of symptoms again largely dependent on age and immunity. In areas of very high transmission, severe malaria is confined to the first few years of life, and is mainly manifest as severe anaemia. As transmission intensity falls, the age distribution of severe malaria moves upwards so that severe malaria is seen in older children as well, in whom it more often manifests as cerebral malaria, lactic acidosis and hypoglycaemia (Snow, Omumbo et al. 1997; WHO 2000b). In areas of low transmission and in non-immune travellers, severe malaria is seen in all age groups. In addition to the manifestations described in children, it can manifest as renal failure, pulmonary oedema, shock, jaundice and macroscopic haematuria (“blackwater fever”). Approximately 3% of adults and 10% of children develop a persistent neurological deficit following cerebral malaria² (Van Hensbroek, Palmer et al. 1997). Although in the majority of cases there is complete recovery within the first month, a proportion of children have more subtle persisting deficits in intellectual and behavioural development (Holding and Snow 2001; Murphy and Breman 2001; Idro, Carter et al. 2006).

CFR

Mortality rates for treated cases of severe malaria are around 15% in children and 20% in non-pregnant adults (Zucker, Lackritz et al. 1996; Bojang, Van Hensbroek et al. 1997; Dondorp, Nosten et al. 2005). However, rates vary widely reflecting differences in case definition, host immunity, access to treatment, type of treatment and settings. Most of the available data are from hospital settings and as untreated severe malaria is rapidly fatal, the actual mortality rate in the community is probably higher (Breman 2001).

1.2.2.1. Co-morbidity

A significant proportion (4 to 9%) of patients presenting with symptoms of *P. falciparum* infection will be bacteraemic (Berkley, Maitland et al. 2005). In addition, there is a complex synergistic interaction between infection with HIV and malaria with recent studies showing that HIV-infected adults are more likely to develop symptomatic and severe malaria, and that acute malaria infections are associated with increased HIV viral load (Francesconi, Fabiani et al. 2001; Grimwade, French et al. 2004; Cohen, Karstaedt et al. 2005; Kublin, Patnaik et al. 2005).

1.2.2.2. Malaria in pregnancy

Pregnant women are at particular risk of malaria as they are relatively immunocompromised and often anaemic. The clinical course is largely dependent on their pre-pregnancy immune status and therefore on transmission intensity. Non-immune pregnant women are three times more likely to develop severe malaria and to die from it if they do (Luxemburger, Ricci et al. 1997).

² This is associated with protracted coma, and specific neurological deficits such as hemiparesis, speech and visual problems.

Their pregnancies are more likely to terminate early and to result in pre-term birth and low birth-weight (Luxemburger, McGready et al. 2001). In high transmission settings, although severe malaria is less likely, malaria during pregnancy (especially first pregnancies), is a significant cause of anaemia, pre-term birth and low-birth weight (Shulman, Marshall et al. 2001; Steketee, Nahlen et al. 2001) and is therefore a significant cause of infant mortality (Guyatt and Snow 2001).

1.2.2.3. Diagnosis

Diagnosis of malaria relies on the presence of symptoms and the presence of parasites in the blood. However, in immune patients the presence of both does not mean that the symptoms are due to malaria, as they may well be due to a concomitant infection. In reality, malaria diagnosis is usually made presumptively based on clinical symptoms, leading to both over- and under-diagnosis.

Microscopy has long been the mainstay of biological diagnosis³. More recently, rapid diagnostic tests (RDTs) based on the detection of parasite antigens, have become popular in some low transmission settings (Mayxay, Newton et al. 2004; Singh, Saxena et al. 2005). They are quick (<20 minutes), sensitive and easy to use and cost less than \$1 per test for a *P. falciparum* specific test. However, these particular tests remain positive for several weeks, due to the persistence of the antigen, histidine rich protein 2 (HRP2)⁴ (Mayxay, Pukrittayakamee et al. 2001). They are therefore less useful in high transmission settings because patients presenting with a fever unrelated to malaria may have a positive test. The use of polymerase chain reaction (PCR) technology is currently limited to clinical and epidemiological studies of drug resistance, where its application has expanded rapidly. Using PCR, parasites can be detected at densities much lower than possible by microscopy and individual parasite clones can be identified, enabling recrudescence infections to be differentiated from initial infections (WHO 2005a).

1.2.3. Epidemiology

An estimated 350–660 million clinical disease episodes occur annually of which about 60% occur in sub-Saharan Africa (Snow, Guerra et al. 2005). Although sub-Saharan Africa carries the greatest burden, malaria remains a significant problem in Southeast Asia and Latin America (Figure 1-2). The former in particular, is estimated to carry 25% of the burden of *P. falciparum*

³ This involves the examination of a drop of blood, usually from a finger prick, on a glass slide. The sample is smeared, stained and fixed and examined in order to identify and quantify parasites. The latter requires counting the number of parasitized red cells in relation to the number of red cells or white cells in a certain number of microscopic fields and then multiplying up the number according to the total red cell or white cell count in order to obtain a quantity in terms of parasites per μ l of blood.

⁴ RDTs based on the detection of plasmodial lactate dehydrogenase are also available for testing for other species.

clinical episodes and 10% of the deaths (WHO 2005b). In addition to acute disease episodes and deaths, malaria also contributes significantly to anaemia in children and pregnant women, adverse birth outcomes such as spontaneous abortion, stillbirth, premature delivery and low birth-weight, and overall child mortality through synergy with other illnesses. The disease is estimated to be responsible for an estimated average annual reduction of 1.3% in economic growth for those countries with the highest burden (Gallup and Sachs 2001; Sachs and Malaney 2002).

Until well into the 20th century, malaria was common in many parts of the world including Europe and North America. Eradication in these areas was due to socio-economic development and malaria control programmes, particularly the Global Malaria Eradication campaign in the 1950s and 1960s (Bradley 1998; WHO 2005b). The latter involved widespread spraying with DDT and treatment with chloroquine. In contrast malaria continued to blight much of sub-Saharan Africa and areas in Latin America and Southeast Asia. Relative success in control in South Asia in the 1970s and 1980s was followed by a re-emergence in areas where it had almost been eradicated and an increase in the severity of infection and mortality elsewhere (WHO 2005b). In sub-Saharan Africa, as childhood mortality fell from other causes, mortality due to malaria doubled (Korenromp, Williams et al. 2003). Although other factors have contributed⁵ to the failure to control malaria, the main reason for this resurgence is the emergence and spread of antimalarial drug resistance. Although difficult to quantify, it has been estimated that chloroquine has been responsible for a two to 11-fold increase in childhood mortality in Africa (Trape, Pison et al. 1998; Trape 2001).

1.2.4. Antimalarial drug resistance

Resistance to chloroquine was first reported in South America (Moore and Lanier 1961) and Southeast Asia (Harinasuta, Suntharasamai et al. 1965). There was then a 17- year time lag before its appearance in East Africa after which dispersal occurred in a 'step by step country to country' fashion (Payne 1987). Chloroquine resistance has been linked to mutations in the *pfcr1* gene that encodes the *P. falciparum* resistance transporter (*PfCRT*) protein and to a lesser extent the *P. falciparum* multi-drug resistance gene (*pfmdr1*). Recent evidence suggests that most of the currently existent *pfcr1* mutants arose from four original mutants, one in Southeast Asia that spread to Africa, two in South America and one in Papua New Guinea (Fidock, Nomura et al. 2000; Wootton, Feng et al. 2002). In addition there may be one or two other origins in Philippines (Chen, Wilson et al. 2005) and Cambodia (Lim, Chy et al. 2003).

⁵ Other factors that have caused local epidemics include population movement, the breakdown in control programs and local primary health services, vector resistance to insecticides and the HIV/AIDS epidemic.

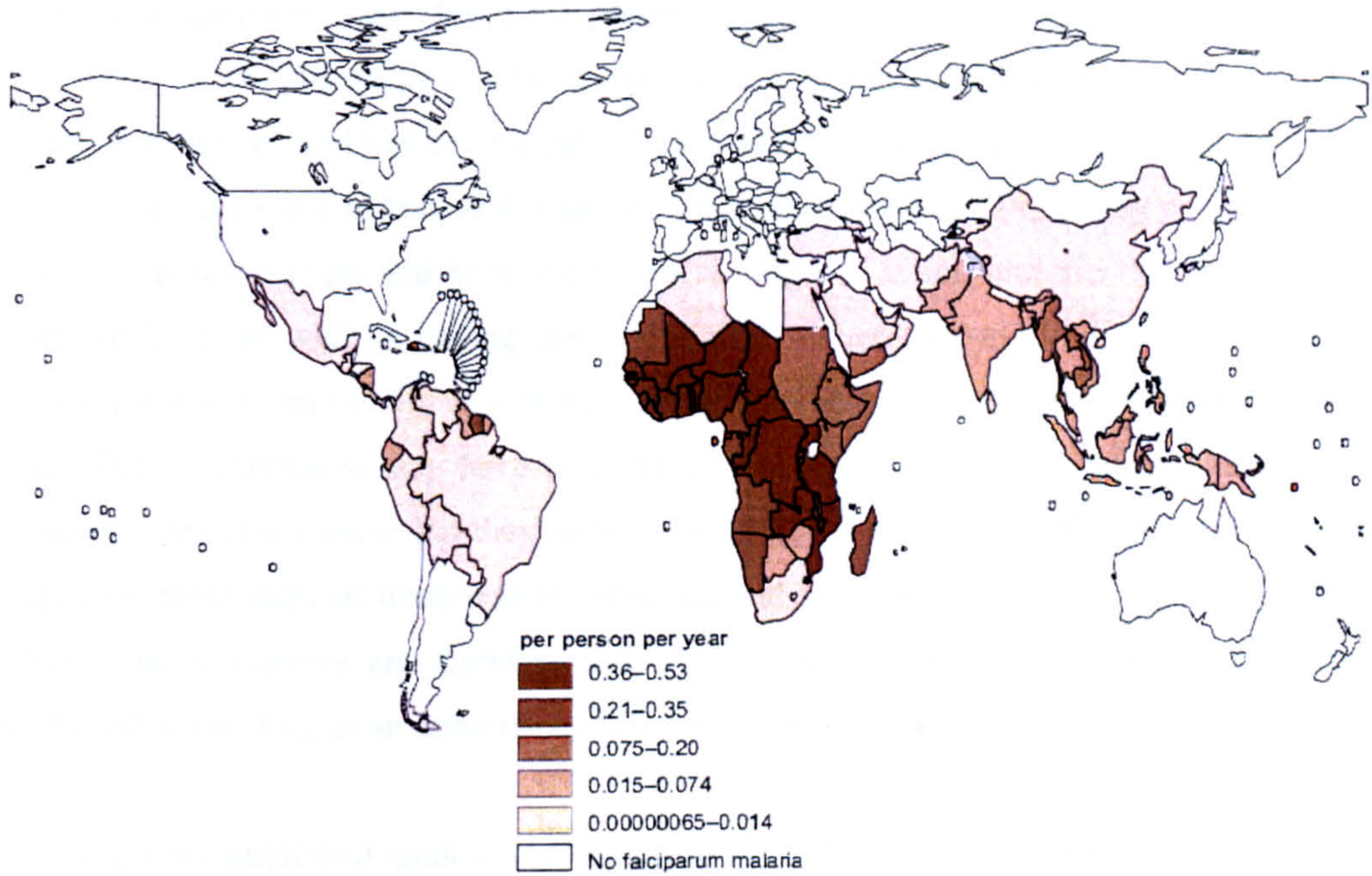
As chloroquine efficacy has fallen, sulfadoxime/pyrimethamine (SP) has taken its place⁶. However resistance developed much more rapidly following its deployment than to chloroquine and is now widespread in Asia, Latin America and increasingly Africa (EANMAT 2006), as shown in Figure 1-3. The rapidity of its spread may in part be due to its long half-life (Watkins and Mosobo 1993) and the fact that it appears to stimulate the production of gametocytes (von Seidlein, Drakeley et al. 2001). Pyrimethamine resistance is acquired in a step-wise fashion and arises from the sequential acquisition of four point-mutations in the gene encoding for dihydrofolate reductase (*dhfr*) (Plowe, Cortese et al. 1997). It is easy to generate in the laboratory (Paget-McNicol and Saul 2001) and it was therefore widely believed that existing drug resistant mutants arose from multiple new mutations. However recent evidence suggests that, like chloroquine resistance, the existing highly-resistant “triple mutant” was transported into Africa from Southeast Asia (Roper, Pearce et al. 2004). Less is known about sulfadoxime resistance, but this too is associated with the sequential acquisition of mutations in a gene, in this case, encoding for dihydropteroate synthase (*dhps*).

Mefloquine, like SP has a long half-life and therefore only needs to be taken in a single dose and is useful for chemoprophylaxis. It is significantly more expensive than chloroquine or SP and is not commonly available in Africa. Resistance developed to mefloquine within six years of its introduction in Thailand (Nosten, ter Kuile et al. 1991) and is associated with gene amplification of the *pfmdr1* gene (Price, Uhlemann et al. 2004).

Quinine is the mainstay of treatment of severe malaria. It has also been used for the treatment of drug-resistant uncomplicated malaria. It is relatively cheap and widely available and safe to use in pregnancy. However its use as a first-line treatment is limited mainly by the frequency and duration of treatment (three times daily for seven days) and its association with frequent minor side effects. Although it remains widely efficacious, its efficacy has waned in areas of multi-drug resistant malaria (WHO 2005a). Amodiaquine is related to chloroquine and is effective against chloroquine-resistant *P. falciparum*. However there is cross-resistance and amodiaquine is not sensitive against highly chloroquine resistant parasites (Olliaro, Nevill et al. 1996) and high levels of resistance have been recorded in East Africa (Mutabingwa, Anthony et al. 2005b). Atovaquone is a new class of antimalarial. It is available only in co-formulation with proguanil as Malarone®. It is highly effective and well tolerated but its use is currently mainly limited to chemoprophylaxis for non-immune travellers, largely because of its cost. Resistance to atovaquone is linked to a single mutation in cytochrome *b* gene codon and is easy to induce in the laboratory and develops rapidly if the drug is used on its own (Looareesuwan, Chulay et al. 1999).

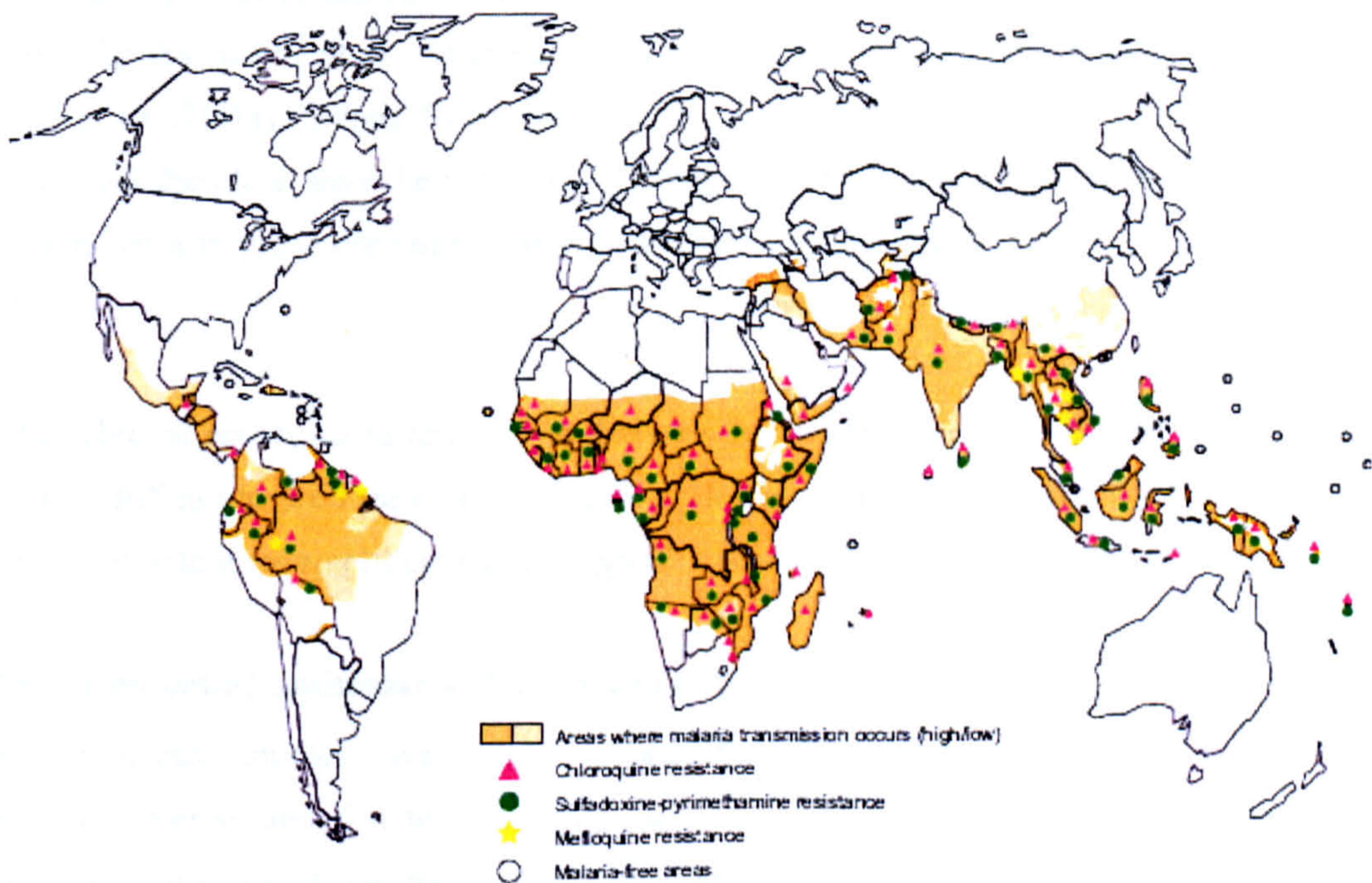
⁶ Sulfadoxime and pyrimethamine are two different drugs that belong to the same group of drugs and are only available as a co-formulation. “SP” is therefore commonly referred to as a single monotherapy drug.

Figure 1-2: Estimated incidence of clinical *P. falciparum* episodes resulting from local transmission, country level averages, 2004



Source: World Malaria Report 2005

Figure 1-3: Drug resistance to *P. falciparum* from studies in sentinel sites, 2004



Source: World Malaria Report 2005

1.2.5. Artemisinin-based combination therapy (ACT)

Artemisinin derivatives are the most powerful class of antimalarial drugs we have to date. Artemisinin or Qinghaosu as it is known in Chinese, is derived from the plant *Artemisia annua* (sweet wormwood) and has been used in China as a traditional remedy for thousands of years (see Annex 1 for more history and detailed information about ACTs). They produce the fastest decline in parasite mass and have the broadest range of action and are therefore effective in severe malaria, as well as having the potential to reduce transmissibility. They are rapidly absorbed, are available orally as well as parenterally and have excellent tolerability (Taylor and White 2004). Although they have an extremely short half-life that protects them from drug resistance, this also means that they need to be taken for seven days. With an effective partner drug, only three days of treatment are required and protects both drugs from drug resistance. Artemisinin derivatives are therefore only recommended for treatment in combination with another effective drug as an artemisinin-based combination therapy (ACT).

There are more published randomised control trials (RCTs) on artemisinins than any other class of drug (Adjuik, Babiker et al. 2004; Myint, Tipmanee et al. 2004). The efficacy of ACTs in the treatment of uncomplicated malaria has been shown in numerous studies in Asia (Price, Nosten et al. 1997; Nosten, van Vugt et al. 2000; Mayxay, Khanthavong et al. 2004; Tran, Dolecek et al. 2004) and Africa (von Seidlein, Milligan et al. 2000; Adjuik, Agnamey et al. 2002). Intravenous artesunate has also recently been shown to be more efficacious than intravenous quinine for the treatment of severe malaria in adults resulting in a 35% reduction in mortality (15% versus 22%) (Dondorp, Nosten et al. 2005). Artesunate and artemether can both be given rectally and therefore have the potential for being life-saving if used for the early treatment of severe malaria in the community (Barnes, Mwenechanya et al. 2004; Aceng, Byarugaba et al. 2005).

So far, clinical resistance to artemisinin derivatives has not been demonstrated and resistance has been difficult to produce in the laboratory. However in-vitro susceptibility has been found to correlate with gene amplification of the *pfmdr1* gene (Price, Uhlemann et al. 2004).

1.2.6. Combating antimalarial drug resistance

Recent molecular studies have clearly indicated that it is extremely rare for a new resistant mutant to emerge, and that the spread of existing mutants is responsible for most cases of antimalarial drug resistance today (Wootton, Feng et al. 2002; Roper, Pearce et al. 2004). However, for years this was uncertain and there has been, and continues to be, much interest in elucidating the factors affecting the emergence and spread of drug resistance. Such an understanding of drug resistance is central to the design of rational antimalarial drug policies

that will not only treat malaria effectively now, but will result in the prolongation of the useful life of drugs.

The factors affecting the initial emergence of a *de novo* mutation include variation between different drugs and parasites (Rathod, McErlean et al. 1997; Paget-McNicol and Saul 2001), host immunity, and whether drugs are used alone or in combination. The latter is one of the key rationales for using combination therapy. Simply put, if each parasite has a one in a million chance of spontaneously mutating to become resistant to drug A and a similar but independent chance of spontaneously mutating to become resistant to an unrelated drug B, then the chance that both mutations occur in a single parasite is one in 10^{12} (1×10^6 multiplied by 1×10^6) (White 1999a). In addition, because two independent mutations are required, it is much more likely that these will be broken down during sexual recombination resulting in a loss of the double mutation (Hastings and D'Alessandro 2000).

Once a drug resistant infection has emerged, the subsequent spread is dependent on the presence of drug pressure, which results in the cure of sensitive infections but the survival of resistant mutants. Therefore the proportion of parasites that are exposed to drugs, especially at sub-therapeutic levels, is particularly important to the rate of spread. This proportion is higher when most infections are symptomatic and therefore treated (i.e. non immune patients), when parasite densities are high (i.e. non-immune patients who remain untreated), when the half-life of the drugs is long, when inadequate amounts of antimalarial drugs are taken (poor adherence) and when antimalarial drugs are taken in the absence of malaria infection. The latter may be because antimalarial drugs are taken presumptively for malaria-like symptoms, for chemoprophylaxis or as part of a mass drug administration programme⁷ (D'Alessandro and Buttiens 2001). Human population movement is also important in transporting drug resistance between areas. Other factors include clone multiplicity, cross-resistance between drugs, the "fitness cost" of drug resistance⁸ (Kublin, Cortese et al. 2003) and the *PfEMP1 var* gene switch rate (Gatton, Hogarth et al. 2001)⁹.

Strategies to delay the development of antimalarial drug resistance can therefore be targeted at any of these factors. Some strategies also succeed in addressing goals other than the control of drug resistance. For example the use of an ACT will result in an increased cure rate in an area where the current monotherapy is failing, as well as hopefully decreasing the likelihood of a

⁷ This occurred with chloroquine in the early 1960s when the WHO added pyrimethamine or chloroquine to cooking salt.

⁸ In the absence of drug treatment resistant parasites may experience a survival disadvantage ("fitness cost") which may lead to a decline in the prevalence of the resistant mutants once drug pressure is removed.

⁹ One of the important difference between malarial parasites and bacteria is the ability of parasites to introduce antigenic variation to the immunogenic protein *PfEMP1*, which enables it to evade host immunity.

new drug resistant mutant emerging and, in a low transmission area, may also decrease the incidence of malaria. This was dramatically demonstrated in the KwaZulu-Natal in South Africa when SP monotherapy was replaced with artemether-lumefantrine (Barnes, Durrheim et al. 2005), and in Thailand with the introduction of artesunate-mefloquine (Nosten, van Vugt et al. 2000). In both places, the cure rates increased and malaria transmission decreased and in Thailand there was an increase in the sensitivity of the parasite to mefloquine (Brockman, Price et al. 2000).

However, there can be conflict between different policy goals. For example the desire to minimise morbidity and mortality now, by maximising access to drugs needs, to be balanced against limiting their current use, in order to decrease the development of drug resistance. Prioritising the former over the latter may result in a lower burden of disease for the current generation at the expense of future generations.

1.2.7. Antimalarial drug policy – the current situation

Malaria experts first publicly warned of the impending disaster due to antimalarial drug resistance in the late 1990s (Marsh 1998; White, Nosten et al. 1999). In April 2000, more than 20 African heads of state met in Abuja, Nigeria and called on the world community to allocate at least US\$1 billion per year towards reaching the Roll Back Malaria (RBM) target of halving malaria deaths by 2010. The following year, the WHO recommended the use of artemisinin-based combination therapies (ACTs) for the first-line treatment of uncomplicated *P. falciparum*. The four recommended treatments were artemether-lumefantrine (Coartem®), artesunate-mefloquine, artesunate-SP and artesunate-amodiaquine (WHO 2001a). However, initial scientific opinion was divided and the response from national governments and international donor organisations was slow. Most countries continued to recommend either chloroquine or SP, despite clear evidence that they were no longer effective (EANMAT 2006) and that their continued use was resulting in a relentless rise in morbidity, mortality and economic cost (Watkins, Kokwaro et al. 2004).

In the last two years, there has been a considerable change in momentum. ACT is now generally acknowledged to be the treatment of first choice and countries are increasingly changing their national antimalarial drug policies to one of the recommended ACTs. In part, this acceleration can be credited to the vocal advocates who challenged the WHO and GFATM into action, in an exchange of letters in the *Lancet* (Nafu-Traore 2004; Nantulya and Liden 2004; Watkins, Kokwaro et al. 2004). Further weight was added to argument for change by the Institute of Medicine report “Saving lives, buying time: Economics of malaria drug in an age of resistance”. The report unequivocally supports of the urgent and wide scale deployment of ACTs. Moreover its central recommendation is for a “sustained global subsidy of artemisinins

co-formulated with other anti-malarial drugs” at an estimated annual cost of \$500 million (Arrow, K. J., Panosian, C. et al. 2004).

Currently, out of 43 countries in Africa, 14 countries have deployed an ACT (four with artemether-lumefantrine and 10 with artesunate-SP or artesunate-amodiaquine). Another 19 countries have committed to but not yet implemented a switch to an ACT. In Asia, ACTs have officially been deployed for several years in Cambodia, Thailand and Vietnam, artesunate-mefloquine in the case of the first two countries and dihydroartemisinin-piperaquine, in the latter. Other countries are planning to switch (Bangladesh, Bhutan, Indonesia and Myanmar), or have deployed ACTs in some areas (India and China). However chloroquine and SP continue to be used either alone or in combination elsewhere. In the Americas, six out of 11 countries with *P. falciparum*, have officially switched to an ACT (WHO 2006b). The Global Fund is responsible for funding much of this change and has committed to help purchase 264 million doses of ACTs (GFATM 2006).

However serious concerns remain around the implementation of ACTs (Bloland, Ettlting et al. 2000; Whitty, Allan et al. 2004; Mutabingwa 2005a). The high cost of the drugs remains a central issue, as they are clearly unaffordable to the vast majority of those at risk and are likely to continue to be so for some time. ACTs will therefore need to be provided for free or very cheaply and this requires a significant and sustained financial commitment from donors. National governments worry about sustainability, and both they and donors have to weigh up the relative cost and benefit of implementing ACTs, compared to other health and non-health related interventions. Many of the doubts centre on the actual effectiveness of ACTs when they are implemented in “real-life”, where infrastructures are poor, access to health care is low and there is widespread inappropriate use of antimalarial drugs. In particular, there are concerns about poor adherence leading to the use of artemisinins on their own and the potentially disastrous consequences in terms of drug resistance arising to the artemisinin derivatives. This has recently led WHO to demand an immediate halt to the use of artemisinins on their own (WHO 2006c). Whether or not the use of ACTs should be limited to biologically confirmed malaria, targeted to specific at-risk groups, such as children, or used for “home-treatment” remains controversial (D'Alessandro, Talisuna et al. 2005). Finally, a considerable source of the benefit of ACTs in low-transmission areas is their ability to reduce malaria transmission and drug resistance. Enthusiasm for their deployment in high transmission settings is therefore tempered by the expectation that these consequences are less likely to occur in these settings.

1.3. Cambodia

1.3.1. General background

Cambodia lies in the Mekong delta region bordered by Thailand, Lao PDR, Vietnam and the Gulf of Thailand, covering an area of 181,040km². The total population is approximately 13.5 million (MoH 2003). The majority of the population are Khmer, with the ethnic minority population concentrated in the two remote Northeast provinces of Rattanakiri and Mondulkiri. Most of the population (84.3%) live in rural areas, mainly concentrated around the capital, Phnom Penh and to a lesser extent the provinces bordering Thailand. The population is very young, with nearly half the population under 15 years. Average household size is 5.2 people per household (NIS 1999). Following the Khmer Rouge's (1975-1979), forced move of city dwellers to the countryside and the years of ensuing conflict, there has been a long history of population movement¹⁰. In recent years, in response to a relative over-population of the central plains area, families have been moving into the sparsely inhabited forested areas that were previously dangerous and inaccessible because of conflicts, poor roads and unexploded landmines.

Cambodia has only recently begun to recover from its turbulent past. The economy is now growing fast, with an annual gross domestic product (GDP) growth rate of around 5-6%. In 2001-2002 the GDP was around \$4 billion or US\$278 per capita (World Bank 2002). However, of this some US\$400 million or US\$30 per capita was from foreign aid, accounting for 12% of the GDP (UNDP 2002) and Cambodia still remains amongst the poorest countries in the world, ranking 130th out of 173 in the Human Development Index (UNDP 2002). Next to the Lao PDR, it is the poorest country in Southeast Asia. Of note is the low life expectancy (average 57.4 years), high child and infant mortality rate (124 and 95 per 1000 live births respectively) and high maternal mortality (440 per 100,000 live births) (UNDP 2002). In 2002 it was estimated that 36% of the population lived below the national poverty line. In rural areas only 11% of the adults were in paid employment and the average monthly household expenditure was \$75, of which 6.6% was on medical care (NIS 1999). Further details of Cambodia's socio-economic status are provided in Annex 2.

1.3.2. The healthcare system

Following the abolition of modern medicine and the murder of most health workers during the rule of the Khmer Rouge, the existing health system was developed by a Vietnamese-led administration and a handful of non-governmental organisations (NGOs). In 1989, as socialist countries withdrew support and political and economic liberalisation evolved, increasing international aid flowed into the country and with it, an attempt to reform the structure of the

¹⁰ 32% of the population report to having being born in a place different from their current residence.

health system (Lanjouw, Macrae et al. 1999; Hill 2000). In the last few years, decentralisation has taken place with financial and management responsibilities devolved to the provincial health departments and operational districts. However, significant problems with delivery and access remain, exacerbated by poor infrastructures and inadequate salaries. Only 4% of the health budget is spent on salaries and the average health worker earns US\$15-20 per month (MoH 2001).

The government health budget (recurrent costs) for 2001 was US\$ \$37.4 million (10% of the total government budget), representing a per capita allocation of \$3.1 per person¹¹. In addition, Cambodia receives \$25-30 million per annum from donors (WHO, World Bank, DFID, USAID, EC) (Grose, Sorya et al. 2002) and has been allocated substantial funding from the GFATM - almost US\$40 million for HIV/AIDS, \$26 million for TB and \$10 million for malaria.

1.3.3. Malaria in Cambodia

Malaria reportedly accounts for 7% of admissions and 3% of outpatient attendances, with rates varying significantly between provinces (Figure 1-4). Based on official statistics, in 2003, there were 71,258 confirmed cases of malaria of which 63,739 were due to *P. falciparum*, and 492 deaths (MoH 2001). Annual incidence has generally been falling since 1997 although the rate in 2003 represented an increase from the previous two years (Figure A4-1). As the vast majority of Cambodians seek treatment in the informal sector, these numbers significantly underestimate the true burden of disease.

1.3.3.1. Epidemiology

Cambodia is generally flat in the centre with forest-covered mountains in the north, west and east. Between 35% to 63 % of the land mass is covered by thick forest and jungle (Hong 2004), the main breeding sites for the main malaria vectors, *Anopheles minimus* and *Anopheles dirus*. The climate is generally warm and humid throughout the year with an annual mean temperature of around 25°C, rising to the low 30s just before the rainy season. This occurs between mid-May to mid-September with a drier season from November to March. The transmission of malaria is largely determined by the proximity of humans to forest and is highly seasonal, peaking at the beginning of the rainy season.

About two million of the population are considered “at-risk” of malaria and fall roughly into three categories¹². The first group comprises the ethnic minority families living in thickly forested villages in Mondulkiri and Rattanakiri (approximately 350,000). The second and largest group comprises approximately 1.7 million temporary forest migrants - a heterogenous group of mainly adults, mainly men, who travel into the forest for work. The group includes

¹¹ Although in 1998 only one third of the then US\$1.53 per inhabitant per year was actually disbursed.

¹² There appears to be some confusion with regards to numbers and percentage of at-risk population.

hunters, gatherers, woodcutters, gem miners and soldiers. The third risk group comprises returning refugees and new migrants from lowland areas, settling in forested ex-Khmer Rouge areas (approximately 150,000) (CNM 2001).

1.3.3.2. Malaria control

Malaria control continues to be a vertically controlled programme run by the National Centre of Entomology, Parasitology and Malaria control (or “the National Malaria Centre”). The programme is responsible for making and implementing antimalarial drug policy and for vector control through the provision of insecticide treated nets (ITNs) and insecticides, the training and supervision of peripheral health staff, public health education and operational research. The malaria control programme has a reputation in Cambodia as being relatively well organised and has been heavily dependent on external agencies for financial and technical support. Key players have included the WHO, the World Bank, the European Commission – Cambodia Malaria Control Project (EC-CMCP), the UK Department for International Development and Médecins sans Frontières (MSF). The malaria control programme successfully applied for US\$10 million worth of funding from the GFATM for the provision of ACTs through village malaria workers, the expansion of the social marketing of ACTs and increasing the coverage of ITNs.

Like elsewhere in the Mekong region, antimalarial drug resistance is one of the major problems for malaria control. *In vivo* studies have been carried out since 1983 and the antimalarial drug policy has been changed a number of times in response to increasing drug resistance, firstly to chloroquine, followed by SP and mefloquine. This is described in Table 1-2. Drug resistance has traditionally been worse on the Cambodia-Thai border and better in the east (Figure 1-5). This is due to a number of factors, the most important being the mobility of the population in the former where the at-risk population is mainly temporary forest migrants and new settlers¹³. This compares to the east, where the at-risk population is mainly isolated ethnic minorities. Because of the difference in level of drug resistance, a differential antimalarial drug policy was in place until 2000.

In addition to antimalarial drug resistance, there are number of other interlinked challenges facing the control programme. Firstly the population affected by malaria is particularly difficult to access: not only are they in the remotest areas, but they are either highly mobile or from ethnic minorities who do not speak or understand Khmer. Secondly, because the formal healthcare infrastructure is weak, the majority (80-90%) of patients seek treatment in the unregulated informal sector (Bury 1999a; NIS 2001; Brown, Montavy et al. 2002). These

¹³ It is likely that another important contributory factor is the addition of chloroquine to salt in Pailin in the Southwest in the 1960s.

informal (or “private”) sector providers range from village vendors, who sell everyday goods such as cigarettes and simple drugs, to trained health workers in larger towns. The latter are a heterogeneous group composed of individuals who received training in the refugee camps or from the Khmer Rouge; as well as pharmacists, nurses and doctors who are also officially employed in the formal (or “public”) sector (WHO 1996). There is little government control of the informal sector, limiting the impact of any change in treatment policy. Fake antimalarial drugs are widely available, with potentially disastrous consequences to patients (Rozendaal 2001). Finally, both in public health facilities and in the informal sector, rates of biological diagnosis are low leading to the widespread misuse of antimalarial drugs.

1.3.3.3. Antimalarial drug policy

In response to the growing problem of antimalarial drug resistance, Cambodia changed its antimalarial drug policy to artesunate and mefloquine in 2000, and in doing so was hailed as the first country to make the switch to an ACT (WHO 2002). The rapidity of this change, to what was seen as the ideal “evidence-based” choice, was facilitated by a number of factors including most importantly, strong advocacy and financial support from WHO. Although a differential policy depending on region was considered, a national policy was chosen because of logistic reasons, because artesunate was already widely available and because international donors were willing to bear the costs of such a strategy. This change was accompanied by a number of highly innovative strategies including:

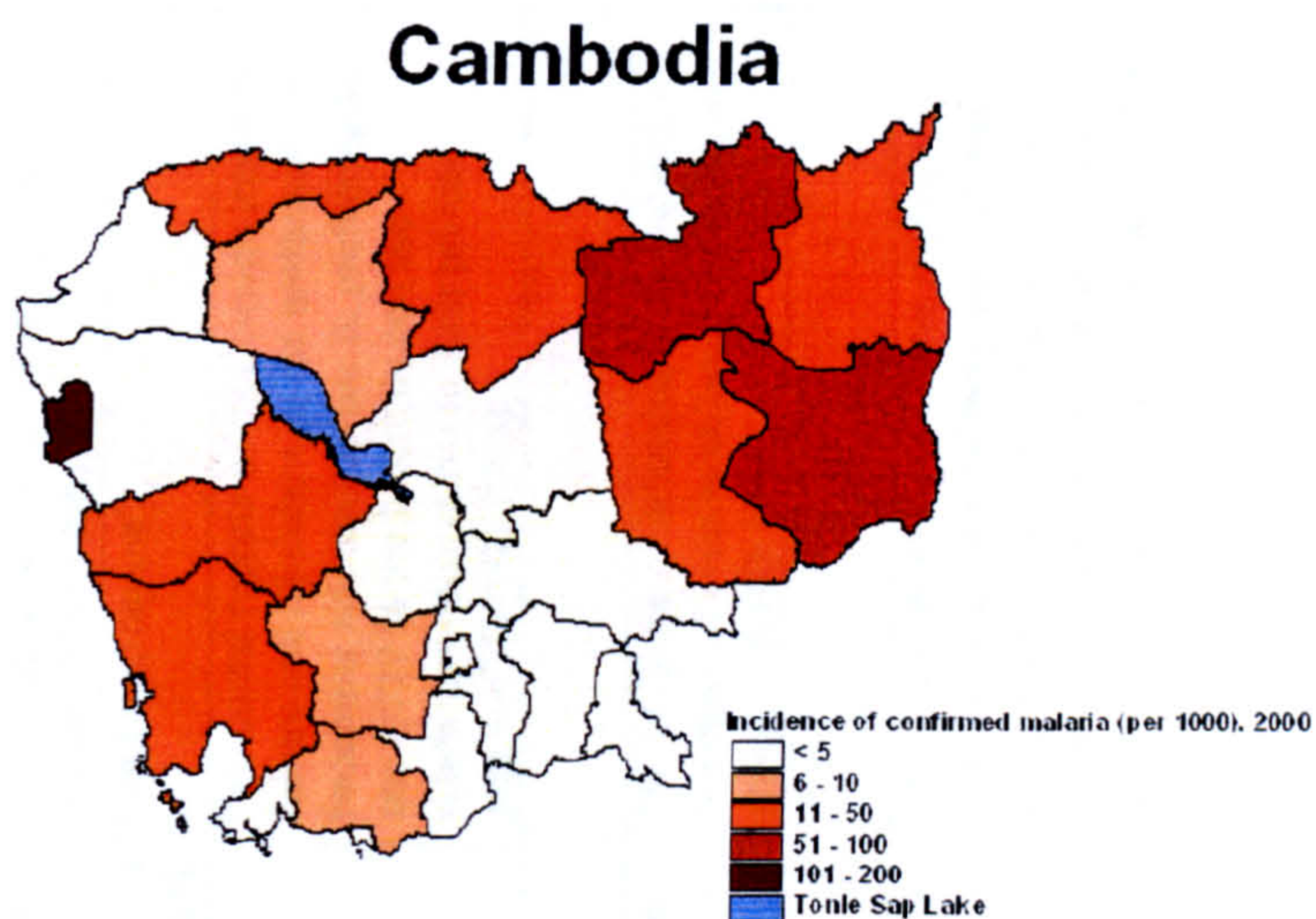
- The local blister-packaging of the combination into three age-group packages, to encourage provider and patient adherence and to aid product recognition and ensure consistent drug quality (See Annex 4 for details of age-weight groupings).
- The social marketing of blister-packaged artesunate and mefloquine as “Malarine®” in the private sector at a subsidised price
- A publicity campaign to raise awareness about fake antimalarial drugs
- The promotion of the use of the rapid diagnostic test, in both the public and private sector.

In addition, there were a number of specific interventions aimed at increasing access to diagnosis and treatment, namely a malaria outreach programme in Anlong Veng district supported by MSF, and the training of village malaria workers (VMVs) in Rattanakiri and Ko Kong.

However, the actual impact of the policy change and individual strategies was uncertain. Although there was a decrease in the number of reported cases in 2001 (Figure A4-1), there had already been a decreasing trend since 1997. However these numbers only reflect the use of public health facilities, and do not accurately reflect actual incidence rates. There were also

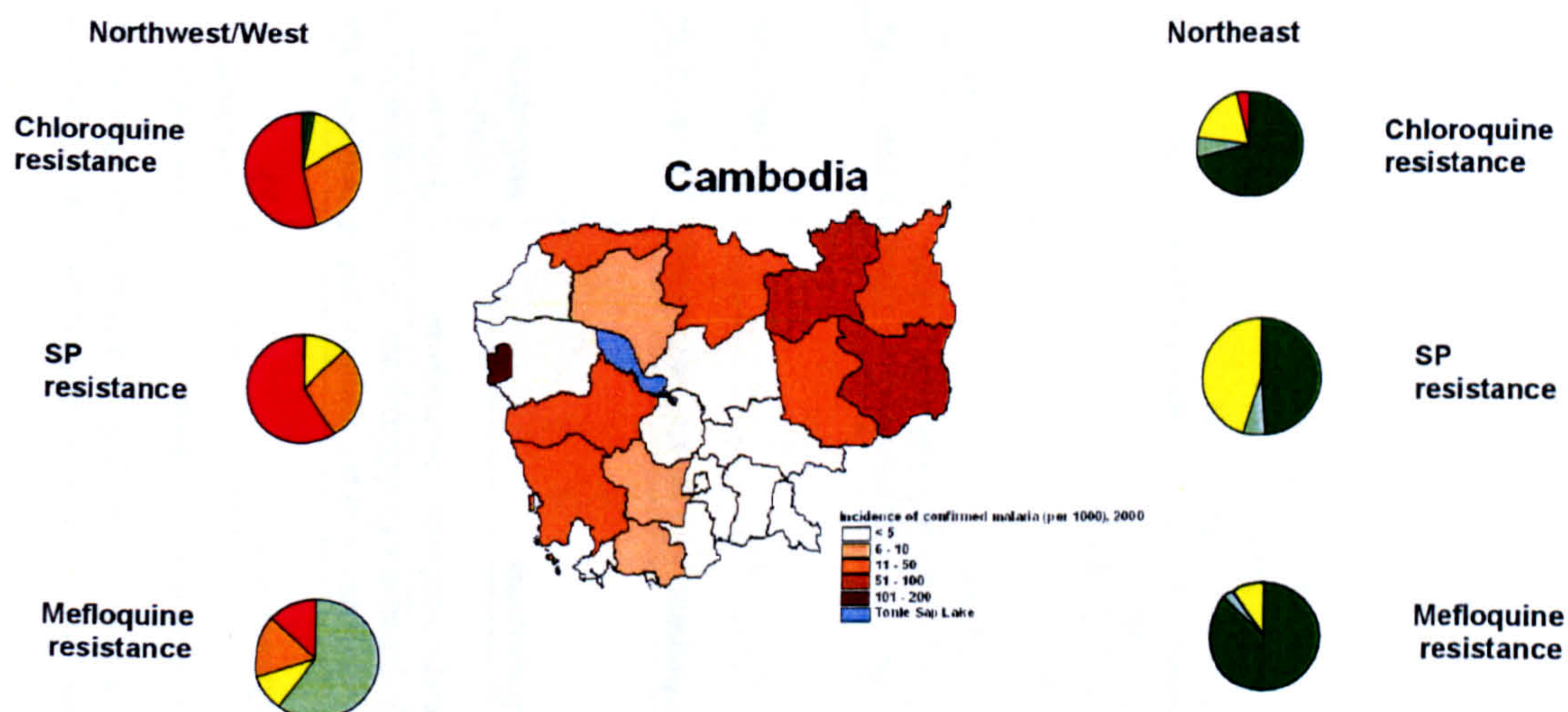
little data available even from the public health sector on whether patients were in fact receiving the first-line therapy and whether treatment had been preceded by biological diagnosis. There was therefore no indication of the success of the programme, either in terms of process indicators or outcome indicators. This was unfortunate as Cambodia was at the forefront of a global change in antimalarial drug policy and such information would have been useful for other countries that were earlier in the process of change.

Figure 1-4: Official incidence of malaria by geographical distribution (2001)



Source: www.wpro.int/themes_focuses

Figure 1-5: Resistance to chloroquine, SP and mefloquine in Cambodia in 1991
(See Annex 3 for description of the WHO criteria for in-vivo studies of antimalarial drug resistance)



Key	Level of resistance
	S
	S/RI
	RI
	RII
	RIII

Table 1-2: Summary results by year, of in-vivo antimalarial drug resistance studies (in grey), and of antimalarial drug policy in Cambodia (in white). Drug doses are given at the bottom of the table and the WHO classification of in-vivo studies (S,RI,RII and RIII) is given in Annex 3

Date (length of FU)	Recommended first-line treatment	Second-line treatment	Third-line treatment	Comment
Pre-1991	All country - Chloroquine	SP	Quinine + Tetracycline	"Mefloquine widely used along Thai border(WHO 1996)
1991-1992	Northwest: S/RI resistance to chloroquine and SP both=0% but "no RII or RIII resistance to Q7T7* and mefloquine"			
28-days	Northwest: S/RI resistance to chloroquine=97%. Sensitivity to SP, Q7T7 and mefloquine= 100%			
1991-1994	All country except Northeast - Mefloquine	Quinine + Tetracycline	-	"anecdotal reports of mefloquine treatment failure and clinicians in the northwest were becoming reluctant to use it, preferring to use Q7T7 in the hospitals and the artemisinin derivative in their private practice" (WHO 1996)
	Northeast - Chloroquine	Mefloquine	-	
1994-1995	Northwest: Mefloquine RIII resistance to 20mg /kg dose =23%			
14 days				
1996	As 1991-1994 (CNM 1996)	As 1991-1994	Artesunate (200mg on day 1 then 100mg for 4 days)	"In 1996 use of artemisinin derivatives is widespread even in chloroquine sensitive areas." (WHO 1996)
1997-1999	Northwest: Mefloquine RIII resistance to 25mg/kg dose= 11% Northeast: Chloroquine S/RI= 76%, RIII= 12%			
1999*	Northwest - Mefloquine As 1996 Central and South Chloroquine OR mefloquine Northeast - Chloroquine	Artesunate + mefloquine	Quinine + Tetracycline	The National Malaria Centre started to provide some referral hospitals and health centres with artemisinin suppositories for treatment of severe cases in adults and also in uncomplicated malaria cases in children.
1999	Northwest: Mefloquine S/RI to 25mg /kg/dose = 77% Northeast: Chloroquine S/RI = 66% Central: Chloroquine S/RI = 60%			
2000*	All country - Artesunate +mefloquine	Quinine + Tetracycline		

Mefloquine 20mg/kg; Chloroquine 25mg/kg/3days; Artesunate + mefloquine according to age-weight (see Annex 4).

*Q7T7= Quinine (30mg/kg/day) and tetracycline (dose not specified) for 7 days.

** Cambodian Malaria Treatment Guidelines (CNM 1999; CNM 2000).

1.4. Summary

Antimalarial drug resistance is contributing to an enormous burden of disease in some of the world's poorest communities and yet there are tools available to help combat it. Foremost amongst these is the use of ACTs. However, these drugs are relatively expensive and there are complex decisions to be made regarding choice of drug, timing of switch, subsidies, targeting and access to treatment. The future costs and benefits are uncertain and not easy to predict. An economic analysis that incorporates the important biological and economic factors could be useful in elucidating these difficult policy choices. In addition documentation of the experience of a country such as Cambodia, which has implemented ACTs in difficult settings, may be helpful for other similar countries and for exploring the value of such an analysis in the "real world".

1.5. Outline of thesis

This thesis has nine further chapters. In Chapter 2 a review of the literature is presented, focusing on the economic evaluation of antimalarial drugs and the modelling of antimalarial drug resistance. Chapter 3 describes the aims, objectives and conceptual framework of the study, and introduces the methodologies used in the thesis. The development of the bio-economic model, which forms the core of the study, is then presented in Chapter 4. The next three chapters describe the collection of data required for application of the model to realistic scenarios. This starts with Chapter 5, a systematic review of the literature of adherence to antimalarial drugs. In Chapter 6 and Chapter 7 the collection and analysis of empirical data in Cambodia are described, starting with the costing of some of the implementation strategies for ACT (Chapter 6) and followed by a presentation of the community based survey of antimalarial drug usage and treatment seeking behaviour (Chapter 7). In Chapter 8 the results are provided from running the bio-economic model for a low transmission setting with input parameters for a number of policy relevant scenarios. The chapter culminates in an application of the model to Cambodia using the results of the primary data collection. In chapter 9, the first of two discussion chapters, the strengths and limitations of the study are discussed followed by a summary of the results from the data collection and a detailed discussion of the results from the modelling. The final chapter discusses the implications for policy and future research arising from the findings of the study.

CHAPTER 2

LITERATURE REVIEW

In this chapter, a review of the relevant literature is presented. The first section focuses on economic analyses and starts with an overview of economic evaluations followed by a review of those focusing on antimalarial drugs and antimicrobial drug resistance. The second section focuses on the literature of the modelling of antimalarial drug resistance. An overview of the epidemiological models of malaria is first provided and is followed by a review of the key papers on the modelling of antimalarial drug resistance.

The literature on economic evaluations of antimalarial drugs and on the modelling of antimalarial drug resistance was searched using PubMed® and the bibliographies of reviews and relevant papers. Terms used in the initial search included combinations of the terms: “malaria” or “antimalarial”; “economic or “cost”; “drug resistance” and “model”.

2.1 Economic evaluations

2.1.1 Definition and type of evaluation

Economic evaluation can be broadly defined as the comparative analyses of alternative courses of action in terms of both their cost and consequences. The types of costs and consequences relevant to the economic evaluation of health programmes are described by Drummond et al. and are shown in Table A-5.1 in the annex (Drummond, Stoddart et al. 1987). There are different types of analysis and some disagreement about the terminology, but the important difference between them lies in the way the outcomes are measured and this in turn is determined by the objective of the analysis, the perspective taken and the audience to whom it is directed. The most commonly used technique in health care is the cost-effectiveness analysis (CEA), where the outcome is measured in units of health, such as cases prevented or disability adjusted life years (DALYs) averted.

The DALYs caused by a disease consist of the sum of years of life lost (YLL) and the “years of life lived with disability” and as a single measure the DALY attempts to capture both mortality and morbidity. The “years of life lived with disability” are calculated based on weights ranging from zero (for full health) to one (death) and are available from the Global Burden of Disease

study (Murray and Lopez 1996). The DALY can be used to compare interventions across the health sector and allows benefits in the future and benefits to people other than the patient (externalities) to be measured. Although there are methodological problems in its use (Anand and Hanson 1997; Arnesen and Nord 2000; Reidpath, Allotey et al. 2003), the DALY is increasingly accepted as a means of comparing the cost-effectiveness of interventions especially in developing countries (Adam, Lim et al. 2005; Baltussen, Floyd et al. 2005; Edejer, Aikins et al. 2005; Hogan, Baltussen et al. 2005; Morel, Lauer et al. 2005).

There is no firm cut-off point to define whether an intervention is cost-effective or not, as this depends on the perspective of the analysis and resources available. As a guide to decision making, in 1996, a WHO Ad Hoc Committee recommended that for low-income countries with a gross domestic product (GDP) per capita of less than \$765 (in 1996 dollars), interventions that cost \$25 or less per DALY averted could be considered “highly attractive”. Interventions costing \$150 or less were considered “attractive” (WHO 1996a). More recently interventions costing less than three times the GDP per capita for each DALY averted have been defined as “good value for money” (WHO 2001b) or “cost-effective” (WHO 2002b), and those costing less than the GDP per capita as “very cost-effective” (WHO 2002b).

Outcomes can also be measured in monetary units in terms of total monetary benefits or cost savings. Such analyses are termed cost-benefit analyses (CBA). Although there are difficulties associated with attaching monetary values to health outcomes, CBAs do allow comparison between health and non-health related spending. Cost utility analyses (CUA), where the outcome is usually measured in quality-adjusted-life-years, and cost minimisation analyses, where the outcome is assumed to be the identical, are less common in the developing country literature.

2.1.2 The theoretical basis

There is no single theoretical framework underlying all economic evaluations. The original justification for cost-benefit analysis was provided by Paretian welfare economics. Welfare economics embodies certain value judgements, specifically that social welfare should comprise individuals' welfare and that individuals should be considered the best source of information for their own welfare. The Pareto principles are based on these foundations. The first principle is of “actual Pareto improvement” where a policy makes everyone better off and no one worse off. The second principle is of “potential Pareto improvement”, where a policy creates winners and losers in welfare but the gainers have the potential to compensate the losers and overall there is a gain in social welfare. Because the compensation does not actually have to be paid, problems

with distributional equity can arise (Drummond, Stoddart et al. 1987). Cost-benefit analysis can be justified as the application of this principle. However, because of both practical and theoretical constraints - including difficulties in measuring peoples' health in monetary terms and the lack of a universally acceptable human welfare measure - a pragmatic approach using non-monetary outcomes, i.e. a cost-effectiveness analysis, is more often used. The theoretical basis for CEAs and CUAs tends to be more rooted in a 'decision-making' philosophy (Drummond, Stoddart et al. 1987). Because CEAs do not necessarily adhere to the Paretian principles, the technique has been criticised for not being able to handle questions of allocative efficiency (Donaldson, Currie et al. 2002).

The approach used in undertaking an economic evaluation depends on the aim and theoretical basis of the analysis and the data available. Traditionally, approaches have been divided into predictive modelling approaches or evaluations performed alongside clinical trials, retrospectively or prospectively. However, this division is argued to be redundant as in reality most economic evaluations are a synthesis of both trial evidence and modelling with few evaluations drawing solely from one approach (Brennan and Akehurst 2000).

Modelling plays an integral role in most economic evaluations but particularly when there is significant uncertainty and where events in the future are being predicted. Models are a way of representing the complexity of the real world in a more simple and comprehensible form to better understand the way a system works or to predict effects. Typically such models are mathematical representations of quantitative relationship between the variables and may be deterministic or stochastic.

2.1.3 The role of models in economic evaluation

Broadly the roles and applications of modelling in health economics can be identified through a number of overlapping perspectives. These applications and their associated problems are summarised below (Brennan and Akehurst 2000).

Extending results from a single trial

Often clinical trials are not designed to capture the appropriate policy relevant costs and outcomes. Therefore models are used to extrapolate outcomes and to convert disease-specific outcome into general health outcome measures (e.g. quality-adjusted-life-years). Whilst this is a well-established means of bridging the gap between data from randomised control trials (RCTs) and policy needs, there is a danger of trying to compensate for inadequate data collection with extrapolation models (Sheldon 1996).

Combining multiple sources of evidence to answer policy questions

As one study on its own is unlikely to have all the information needed to inform policy, results from other studies often need to be incorporated. This includes the linking of intermediate clinical endpoints from clinical trials to final outcomes from databases as well as the synthesis of head-to-head comparisons where relevant trials do not exist (Buxton, Drummond et al. 1997). The disadvantages of this approach include the possibility that the intermediate outcomes may not be valid proxy measures of the final outcomes and there are concerns that these 'meta-analyses' suffer from clinical heterogeneity and bias (Sheldon 1996).

Generalising results from one specific context

This can be broadly categorised into generalising from clinical trials to practical settings and generalising from one setting to another (Buxton, Drummond et al. 1997).

Modelling to inform research strategy and design

This is one of the key roles of modelling used by both government agencies and pharmaceutical companies. This can help to generate hypotheses that can be tested by trials and to decide on the key outcome variables to be measured. By quantifying the potential added value of the information, models can help inform research priorities and design issues.

Modelling uncertainties in the knowledge base

All economic evaluations have some degree of uncertainty that should be explored by modelling, usually in the form of a sensitivity analysis (Briggs 2000).

Additional values of modelling

In addition to its primary role, there are other benefits to modelling. As a communication tool, models are explicit and therefore provide a framework for consensus and a tool for dissemination once a policy is made. In addition they are valuable for conceptualising problems in order to identify key variables and to postulate the relationship between them.

2.1.4 Types of models

The modelling techniques traditionally used in economic evaluation have been decision-analytic models and Markov chain models. However for practical purposes, a combination of techniques and adaptations are often used.

2.1.4.1. Decision-analytic models

These are based on the construction of a decision-tree, a graphical representation of probable pathways and consequences. The advantages are that they are simple to construct, they separate fact from value, they can include data from different sources and it is easy to identify what information is needed and where data are missing. The main disadvantages are that they can quickly become unwieldy conceptually and practically, that they use *average* values and that they are static. They are also said to be prone to errors of logic and structure (Sonnenberg, Roberts et al. 1994) and are therefore most appropriate for short time periods and for well-defined specific decisions.

2.1.4.2. Markov chain models

These attempt to overcome the static nature of decision-tree models by introducing feedback loops and the ability to change the probabilities of events occurring over time. They are therefore useful when there is a relatively long time frame, when the time-dependant nature of the events needs to be considered (Sonnenberg and Beck 1993; Briggs and Sculpher 1998). The main disadvantage is that they require a strict assumption of zero memory so that the probability of moving from one health state to another is independent of how that health state was reached or how long it was in existence for. This is a potential disadvantage of using this approach for the modelling of antimicrobial resistance (Smith, Coast et al. 2000a).

2.1.4.3. Monte Carlo (Stochastic) Simulation

Monte Carlo simulations have increasingly been used for conducting sensitivity analyses (Goodman, Coleman et al. 2001). This involves programming a computer to run a model several hundred or thousand times in which parameters may be input at random from a pre-specified probability distribution. The underlying model is usually based on a decision-trees or Markov chains. This results in an average predicted value with confidence intervals and allows a more robust prediction of likely outcomes.

2.1.4.4 Other modelling approaches based on decision trees and Markov chains

Both decision-tree models and Markov chain models are based on populations and therefore do not allow heterogeneity between individuals to affect model outcomes. In addition Markov chains make the assumption of "zero memory". With the advent of advanced computational ability, it is now possible to programme computers to track individuals through different health states, assigning them various attributes and recording their individual histories. The advantage of such models is that they allow complex and dynamic systems to be modelled, however the

resulting complexity can make them opaque and they require a significant input of time and resources.

2.1.4.5. Mathematical models

Although mathematics is at the core of all modelling, mathematical modelling as applied to solve epidemiological problems, macroeconomic and some microeconomic questions, implies the use of differential equations. These equations are programmed into a computer and then solved for a given input of data. The advantage of mathematical modelling is its great flexibility and the ability to handle complex interrelationships. The disadvantage is that the models can be highly complicated and therefore difficult to interpret and use. Recent macroeconomic models have demonstrated the wider economic implications of malaria (Gallup and Sachs 2001) and to more fully capture the economic benefits of averting infectious disease in children through immunisations (Bloom, Canning et al. 2005). With reference to their place in the modelling of resistance, Smith et al. comment that:

“It is possible that the mathematical approach may be adapted or built upon in developing a cost model for the economic impact of resistance in terms of emergence and spread within populations. An alternative is for mathematical models of epidemiology of emergence and spread of resistance to be used to generate data to input into one of the other forms of model which may be applied to the economics of resistance.” (Smith, Coast et al. 2000a)

2.1.5 General problems with economic models

As well as disadvantages mentioned with specific methodologies, there are problems inherent to any modelling approach. These range from the initial selection of data, which may be inappropriate or biased, through concerns with extrapolation and generalising, to overall doubts about the lack of transparency and validity of the approach. Some of this concern arises from a fundamental discomfort with attempts to quantify human health. However, as argued by Williams, in the absence of a perfect measure, there is still a desire to improve peoples' health and therefore it is still necessary to measure and aggregate health. He identifies this process, clarity and explicitness as a means to allaying some of the criticisms (Williams 1995).

2.1.6 Validation of economic models

Ideally models should be validated either by cross validation against the results of other models or by comparing predicted results with real outcomes (Buxton, Drummond et al. 1997; Brennan and Akehurst 2000). The model should match the result of the source data to ensure internal

validity and predictions should agree with non-source data. Other means of increasing the validity of economic evaluations and the models used in them include making them transparent and explicitly exploring uncertainty. Validity is assisted if there is expert concurrence that the right factors have been chosen and that the relationships intuitively make sense. Finally they should be presented in a way that is as simple as possible but not over-simplified.

2.2 Economics and malaria

2.2.1 The economic burden of disease

The human cost of malaria is high. In a recent study on the cause of 10.6 million annual global deaths of children under the age of five, malaria ranked 4th after neonatal causes, pneumonia and diarrhoea, causing 8% of deaths overall (Bryce, Boschi-Pinto et al. 2005). In endemic African countries, malaria accounts for 25–35% of all outpatient visits, 20–45% of hospital admissions and 15–35% of hospital deaths (WHO 2005b). Malaria was estimated to be the 8th largest contributor to DALYs lost worldwide and 2nd in Africa (WHO 2002b). In addition to the direct costs due to malaria, there are also the indirect costs due to the loss of productivity and schooling. Beyond this, the presence of malaria in societies has had a fundamental influence on their economic development that can only be appreciated from a macroeconomics perspective (Gallup and Sachs 2001; Sachs and Malaney 2002).

In recognition of the magnitude of the burden, many studies have attempted to quantify it in economic terms. This body of literature has recently been the subject of a number of reviews (Chima, Goodman et al. 2003; Malaney 2003; Arrow, Panosian et al. 2004) and is summarised here in brief. In this section all costs have been converted to US\$2002 to aid comparison.

2.2.1.1. Macroeconomic studies

Malaria and poverty are inextricably linked through multiple relationships. Where the burden of disease is the highest, economic development is lowest. In order to quantify this relationship, Sachs et al. recently analysed cross-country datasets of malaria and economic indices. Malaria burden was estimated using a “malaria index” derived from the fractional land mass with endemic malaria, the population estimates and the risk of *P. falciparum* malaria. They estimated that the average-per-capita gross domestic product (GDP) of malaria-endemic countries in 1995 was about one-fifth as much as the average across the rest of the non-malarious world. Between 1965 and 1990, annual economic growth in malaria endemic countries averaged 1.3% less than countries without malaria in terms of per-capita GDP,

controlling for other standard growth determinants. A 10% reduction in malaria was associated with a 0.3% higher growth rate. The association therefore is clearly significant and the authors detail a number of mechanisms through which this link may operate. These include effects on fertility, population growth, savings, investment, worker productivity, absenteeism, missed schooling, premature mortality and medical costs (Gallup and Sachs 2001; Sachs and Malaney 2002). A similar study was conducted by McCarthy to explore the impact of malaria on average per capita growth rate between 1983 and 1997 and using malaria incidence as the indicator of malaria burden. A significant negative association between malaria and economic growth was also found in this study although the impact was smaller than in the Gallup and Sachs study, averaging a 0.55% lower growth rate due to malaria, in sub-Saharan Africa (McCarthy, Wolf et al. 2000).

2.2.1.2. Microeconomic studies

Most microeconomic studies that attempt to capture the cost of malaria use a "human capital" approach in which the costs borne by providers and privately by households are aggregated. The direct cost of treating or preventing malaria includes money spent on drugs, diagnosis, transport, consultation and bed nets. The indirect costs represent the loss of income due to lost days of productivity and are discussed later¹⁴.

Direct costs to households of malaria-related treatment include out-of-pocket expenditure for consultation fees, drugs, transport and the cost of subsistence at distant health facilities. Estimates vary significantly between settings depending on epidemiological and socio-economic factors, illness-related beliefs and methodology. Estimates of monthly per capita expenditure on malaria treatment in Africa range from \$0.33 and \$4.19. This is equivalent to \$2.03 and \$28.08 per household (Chima, Goodman et al. 2003). The available evidence suggests that spending on malaria treatment is highly regressive. For example, in Malawi, it was estimated that the direct cost of malaria treatment amounted to 28% of household income in very poor households and 2% amongst others (Ettling, McFarland et al. 1994). Direct costs of prevention include the cost of bed nets and different types of mosquito repellents. Estimates of monthly expenditure range between \$0.05 and \$2.27 per capita, equivalent to between \$0.26 and \$16 per household (Chima, Goodman et al. 2003). In their review, the authors note that most estimates have been based on household studies that report expenditure within the previous month and therefore do not reflect the variation in spending through the year.

↳ why is it a problem?

¹⁴ The human capital theory regards investment in human health as akin to investment in physical assets with the benefits measured in increased output in the economy.

There are few data on the direct costs to the government of malaria prevention and treatment. This is in part because costs are borne both by vertical malaria control programmes, such as the cost of provision and distribution of bed nets, and also by the general health service who fund the outpatient and inpatient treatment of malaria. These treatment costs should ideally be based on estimates of the number of patients seeking care for suspected malaria and the unit costs of treatment. Both the number of patients and the unit costs vary significantly between studies. The number of patients mainly depends on transmission intensity and the unit cost on the health care setting, age of patient, severity of disease and methodology. Estimates for the cost of outpatient consultations vary from \$0.44 (Jackson, Sleigh et al. 2002) to over \$12 (Goodman, Coleman et al. 2000). Estimates of the cost of an inpatient admission vary from \$4.60 to \$277.5 per admission (Goodman, Coleman et al. 2000), with the average length of stay being around four to five days (Ettling, Thimasarn et al. 1991; Goodman, Coleman et al. 2000).

Estimates of the indirect cost of malaria based on the human capital approach attempt to value the loss in economic output as a result of ill health. Most studies are based on the wage-rate method, which multiplies estimates of the time lost by sick individuals and their carers, by some monetary value for that lost time, to represent lost productivity. However, there is considerable variation in estimating both of these elements leading to an enormous variation in actual estimates (Attanayake, Fox-Rushby et al. 2000). Average estimates for number of days of lost productivity for an adult range from one to five days but in some studies go up much higher to as much as 18 days (Jackson, Sleigh et al. 2002; Chima, Goodman et al. 2003).

Some studies include additional morbidity costs and most studies do not include the cost of mortality in terms of lifetime income foregone. There are also significant differences in the definitions of the economically active workforce; the value of the marginal product of labour; the value given to carers' time; whether or not lower levels of activity are allowed for; and seasonal variation in productivity. In addition, there are difficulties in capturing the complexity of the effect of illness in one individual on other members of the household and community (Sauerborn, Adams et al. 1996). In their review of studies in Africa, Chima et al. found that estimates varied for indirect costs ranged from \$0.73 per case in children under 10 years in Malawi, to \$24.8 for an adult episode in Ethiopia (Chima, Goodman et al. 2003).

The total economic cost of malaria, estimated by adding together the direct and indirect costs, has been estimated in a number of studies. At a household level, the total annual cost was estimated to be equivalent to 32% of household income in very low income households in Malawi (Ettling, McFarland et al. 1994). From the perspective of both the household and the

government, the mean total per capita cost per malaria episode was estimated at US\$4.18 in Rwanda and US\$1.67 in Burkina Faso (including indirect mortality costs). In Rwanda, direct costs made up 22%, indirect morbidity costs 20% and indirect mortality costs 58%. In Burkina Faso, direct costs accounted for 23%, indirect morbidity costs 9% and mortality costs 69% (Ettling and Shepard 1991; Sauerborn, Shepard et al. 1991).

Shepherd et al. attempted to bring together data from these two studies and from studies in Chad and Congo, in order to estimate the overall cost of malaria morbidity and mortality in Africa (Shepard, Ettling et al. 1991). They estimated that in 1987 the total cost of malaria was \$10.63 per capita - \$1.98 in direct costs and \$8.65 in indirect costs (2002 prices). This led to a total cost of over \$1 billion for sub-Saharan Africa or 0.6% of GDP. They predicted that due to projected increases in population, malaria incidence and the cost of antimalarials, this would rise to 1% of GDP by 1996.

Another approach to assessing the burden of malaria is to assess how much individuals are willing to pay to avoid malaria. The “willingness to pay” or “contingent valuation” approach was originally used to estimate the value of goods and services to consumers (Donaldson 1990). There are a number of studies of “willingness to pay” in the context of malaria, mostly limited to patient’s willingness to pay for insecticide treated nets (Onwujekwe, Chima et al. 2001; Sauerborn, Gbangou et al. 2005) with one published study on malaria vaccines (Sauerborn, Gbangou et al. 2005).

Finally household datasets can be used to explore the impact of malaria on households through econometric methods. For example Laxminarayan conducted an empirical study in Vietnam, in which household consumption data was compared to malaria incidence data. He found that a 60% reduction in malaria cases was associated with a 1.8% increase in household consumption. When this was extrapolated up to the national level, he estimated that this translated into an aggregate benefit of US\$183 million per year (Laxminarayan 2004b).

2.2.2 Economic evaluations of antimalarial treatment

In framing the thesis within the context of these analyses, it is useful to start with the framework provided by Phillips et al (Phillips, Mills et al. 1993) This specifies the application of cost-effectiveness analysis in malaria control depending on objectives and choices (See Table A5-2). Within this framework, the study is mainly concerned with objectives III (The choice of first-line treatment) and IV (The choice of implementation strategy).

An extensive review of the literature on the economic analysis of malaria control, by Goodman et al. in 2000, identified only one CEA and one CBA on the case management of uncomplicated malaria. Since then, a number of other studies have been published. In most studies, antimalarial drug resistance plays a part by influencing the effectiveness of one of the drug choices. These studies have either been based on facility-based data, predictive modelling or a mixture of both.

Sudre et al. used a probability-based decision-tree analysis and mortality estimates based on a Delphi survey to compare the cost-effectiveness of chloroquine, amodiaquine and SP for the treatment of children in sub-Saharan Africa, at different levels of chloroquine resistance (Sudre, Breman et al. 1992). Only the cost of the drugs was considered, with the SP costing 1.4 and 1.7 fold more than chloroquine¹⁵ and outcomes were measured in cost per death averted. Adherence was shown to be a key determinant of the cost-effectiveness. Assuming 80% adherence to chloroquine and amodiaquine, and 95% to SP, they found that SP was more cost-effective than chloroquine in terms of cost per death averted when the level of RIII resistance to chloroquine was over 14%. At this level of adherence, 34% of deaths were associated with poor adherence. By increasing adherence to chloroquine to 100%, the threshold at which SP was more cost-effective than chloroquine was increased to 30%. If the value of a death prevented was assumed to be less than US\$2.38 (in 1992 US\$), then SP was more cost-effective than chloroquine even in the absence of drug resistance.

Schapira et al. also used a modelling approach to predict the optimal time of switching drugs through a series of four increasingly costly first-line drugs (chloroquine - \$0.03, SP -\$0.05, mefloquine -\$0.60 and then halofantrine - \$1.75) in a 27-year period (Schapira, Beales et al. 1993). The proportion of treatment failures was assumed to grow exponentially at 11% per annum for each drug from the time of introduction. With deaths valued at US\$800 (in 1993), the minimum economic costs were achieved when chloroquine was used for five years (corresponding to a resistance level of 42%), SP and mefloquine for 10 years, then halofantrine for two years.

In a review on making antimalarial drug policy in the presence of drug resistance, Phillips and Phillips-Howard illuminated the important factors that need to be considered in the process. These include the relative costs of first-line drugs, the costs and accuracy of diagnosis, and the cost of the drugs relative to the "cost of failure" (Phillips and Phillips-Howard 1996).

¹⁵ For 100,000 episodes the costs were assumed to be US\$1,812 for chloroquine, US\$2,622 for SP and US\$3,044 for amodiaquine (in 1992).

The last issue – the importance of the cost of treatment failure relative to the incremental cost of drugs - was illustrated in a post-hoc hospital based study in India and a CEA from South Africa. In the hospital-based study, Gogtay et al. compared the total expenditure (direct and indirect costs) of patients who had received either chloroquine or mefloquine as first-line treatment during a clinical trial (Gogtay, Kadam et al. 2003). The cost of mefloquine per patient was 12-fold higher than chloroquine (120 versus 10 rupees), however only 15 out of 76 patients treated with chloroquine were completely cured compared to all 55 patients treated with mefloquine. As a result, it was found that the total expenditure on patients who fail chloroquine would exceed the excess expenditure on mefloquine when the RII and RIII resistance to chloroquine exceeded 9%.

Wilkins et al. analysed the cost-effectiveness of SP compared to chloroquine as first-line treatment for *P. falciparum* malaria in Mpumalanga, South Africa, from the perspective of the public health care provider (Wilkins, Folb et al. 2002). A “resistance variable” (R) described the proportion of patients who returned for treatment following treatment failure with the first-line drug. This was derived from a “probability of drug resistance” based on the proportion of RI, RII and RIII resistance from *in vivo* studies and the likelihood that patients would return for treatment. This probability of drug resistance to chloroquine was assumed to be 48%, and to SP 5.5%, giving R values of 0.335 and 0.039 respectively. Based on local cost data, the direct provider costs of first-line treatment and subsequent recrudescence and severe infections were used to compare the two drug alternatives. SP was found to have an average cost-effectiveness ratio of 4.83 compared to chloroquine, despite being almost 20 fold more costly (US\$4.02 versus \$0.22 in 1997).

Agnamey et al. in Senegal explored the importance of diagnosis in determining the cost-effectiveness of different strategies including the use of an ACT (Agnamey, Brasseur et al. 2005). The direct costs of malaria diagnosis and treatment were compared between a policy of presumptive treatment with oral chloroquine or intramuscular quinine and a switch to artesunate-amodiaquine (AS-AQ) based on biological confirmation. The average slide positivity rate was 34-44% and the cost of diagnosis by microscopy was US\$0.3 and US\$ 1.0 by rapid diagnostic test (RDT). The assumed failure rates were 50% for chloroquine and 5% for both quinine and AS-AQ. They found that the single most important determinant of cost saving was the switch from clinical to parasitological diagnosis and that even with RDT diagnosis, AS-AQ reduced overall costs by 22% compared to use of chloroquine presumptively.

With the increasing number of countries starting to switch to an ACT, there are a growing number of economic evaluations estimating the cost of switching to ACTs and their cost-effectiveness following implementation.

Snow et al. estimated the total drug cost of providing ACTs for malaria case management in Africa, based on national surveys and population projections. Assuming the current practice in which a large number of non-malarial fevers are treated empirically as malaria, they calculated that the annual cost of ACTs would be between US\$1.6 billion and 3.4 billion (Snow, Eckert et al. 2003).

Estimates of the “willingness to pay” for ACTs was assessed, using a bidding-game technique in a recent study in Tanzania. Mothers whose children had been recruited into a clinical trial of different ACTs were interviewed about their willingness to pay for the drugs, two weeks after treatment. The authors found that mothers were willing to pay significantly more for the more effective ACTs than for the ineffective amodiaquine. This was between \$0.65 – 0.75 for artemether-lumefantrine or artesunate-SP compared to US\$0.47 for amodiaquine alone. Interestingly, there was no association between willingness to pay and socio-economic status (Wiseman, Onwujekwe et al. 2005).

Muheki et al. undertook an economic evaluation of the change of first-line treatment in KwaZulu-Natal (KZN) in South Africa from SP to artemether-lumefantrine (AL) (Muheki, McIntyre et al. 2004). It showed that treatment with AL at US\$3.24 per adult dose was not only more cost-effective than SP monotherapy at US\$1.65, but also resulted in substantial cost savings. They estimated that the average cost per life saved with AL was US\$18 compared to \$158 with SP. Cost-savings for the sub-district (population not stated) were estimated to total US\$201,065 (\$115,801 from outpatients and \$85,254 from inpatients). The evaluation was performed from the perspective of the government provider, which in South Africa reflects the reality of a well performing public health sector from which most patients receive treatment.

In the studies presented thus far, the level of drug resistance has either been fixed or assumed to grow at a fixed rate independent of the actual drug. Therefore the actual effects of different drugs on the development of drug resistance itself have not been explored. In addition, the effects of drug resistance have been measured in terms of costs to the individual patient and provider, but not as a negative “externality”. In economic terms, externalities are the effects felt on the overall welfare of a community, rather than the individual consumer (or patient) and their supplier (or provider) (Coast, Smith et al. 1998). The prevention of the development of drug

resistance and reduction of disease transmission are both positive externalities. As both are important in the rationale for switching to ACTs in the treatment of malaria, it is essential that they are incorporated into any long-term economic evaluations of ACTs.

Goodman et al. explored the effect of drug choice on the dynamics of resistance in a model examining the optimal time to switch first-line drug from chloroquine to SP, within a 10-year time frame (Goodman, Coleman et al. 2001). Drug resistance to SP was assumed to grow twice as fast as resistance to chloroquine, which was assumed to grow exponentially between 7-15% per year. The approach placed a decision-tree based model into a dynamic framework with Monte-Carlo simulations to explore uncertainty. Outcomes were expressed as disability adjusted life years (DALYs) averted. The cost of SP was assumed to be only slightly higher than chloroquine and, as in the model by Sudre et al., it was assumed that adherence and therefore the cure rate was higher with SP. Therefore an immediate switch to SP from chloroquine was more cost-effective than continuing with chloroquine, if drug resistance was not considered. However, if the development of drug resistance was incorporated, then it was more cost-effective to use chloroquine for some years and then to switch to SP. The actual timing of switch was dependant primarily on the relative growth rates of resistance, the coverage rates, the time frame and the discount rate used. If the starting level of resistance to chloroquine was 20%, then the optimal time of switch was at four years, using a 10-year time frame. It was noted that there is a trade-off between the cost-effectiveness in the long-term and higher rates of mortality in the short and medium term.

In a related report, the authors extended the analysis to compare the cost-effectiveness of the ACT of artesunate and SP with the continued use of SP on its own, varying the growth rate of drug resistance to SP in both scenarios. They found that in a high transmission setting, if using the ACT reduced the growth rate of resistance to SP by greater than 58% compared to the continued use on its own, then the cost-effectiveness would be under \$25 per DALY. In low transmission areas, the intervention was less cost-effective, with a reduction in the growth in resistance to SP of at least 47% being required, to be reasonably certain of a cost-effectiveness ratio less than \$150 per DALY. In their discussion they note the importance of the coverage and adherence rates in affecting results (Goodman, Coleman et al. 2000). In a later paper, the model is used to undertake a threshold analysis of ACTs versus monotherapy. It was found that ACTs were more than 95% likely to be cost-effective (at a threshold of US\$150 per DALY averted) except when a short (five-year) time frame was used and when the initial resistance to the monotherapy was less than 20% (Coleman, Morel et al. 2004).

In a more recent study, Morel et al. used the WHO approach of a generalised framework to compare the relative cost-effectiveness of implementing combinations of interventions for prevention or treatment of malaria, taking into consideration interaction between different interventions. This included the cost-effectiveness of chloroquine, SP, non artemisinin-based combinations and ACTs as first-line treatment. Each drug was assigned different cure rates based on expected levels of adherence and different starting levels of drug resistance and linear growth rates. A 10-year time- frame was used and effectiveness was expressed in terms of a reduction in incidence, a reduction in case fatality rates and DALYs averted. They found that of all single interventions, first-line treatment with ACT at high (>80%) rates of coverage was the most cost-effective overall. They estimated that the incremental cost-effectiveness of ACT at 85% coverage in Africa D region was \$9, and \$10 at 95% coverage, and \$12 at 95% coverage in Africa E region¹⁶ (Morel, Lauer et al. 2005).

Although these models did allow resistance to spread at different rates with different drugs or drug combinations, they did not incorporate a number of important aspects of the epidemiology including host immunity and the effect of drug resistance on transmission intensity. In an attempt to incorporate some of these factors, Laxminarayan (Laxminarayan 2004a), proposed a model based on a basic compartment model of malaria transmission described by Koella (Koella 1991). In this model, the spread of drug resistance was dictated by the ratio of reproductive numbers, based on the relative duration of resistant and susceptible infections and the proportion of infections treated. Patients not treated with the drug in question were assumed to receive another effective drug. The model was used to compare the cost of illness resulting from a switch from chloroquine monotherapy to a non-chloroquine containing ACT, with and without an intermediate step through SP monotherapy. The results suggested that the cost of illness generally decreased with increasing coverage with ACTs, whether or not there was an intermediate switch to SP. It also suggested that an intermediate switch to SP was less costly in certain circumstances, in particular when only a short time horizon (five years) was considered and at the extremes of coverage rates. Though useful for its qualitative findings, the model did not incorporate some biological and economic factors important for the realistic predictive modelling of drug resistance and combination therapy. In particular immunity was treated unrealistically as a binary phenomenon and the transmission of malaria was not made explicit. In economic terms, neither clinical outcomes nor treatment failures were included.

¹⁶ Afr D countries are mainly in West Africa and Afr E countries mainly in East and Southern Africa.

In the Institute of Medicine report “Saving Lives, Buying Time” (Arrow, Panosian et al. 2004), the findings of Laxminarayan’s model were discussed. In addition, the model by Goodman et al. was adapted to compare no treatment versus treatment with an ACT, with and without rapid diagnostic test (RDT) diagnosis. The cost of an ACT is assumed to be US\$1 for an adult and US\$0.50 for a child and the cost of an RDT, US\$0.50. The proportion of patients who actually have malaria was assumed to be 45%. Treatment with ACT was found to be very cost-effective for the treatment of children under the age of five years, whether treatment is presumptive or given only to those with a positive RDT result – US\$8 per DALY averted and US\$6.23 respectively. The cost per life saved was calculated to be US\$209 or US\$171 respectively. For the treatment of older children and adults, the costs per DALY averted were much less – US\$112 with presumptive treatment and US\$81.61 with an RDT.

In order to explore other possible approaches to incorporating antimalarial drug resistance into an economic evaluation, the literature on economics of antimicrobial drug resistance was reviewed.

2.2.3 Economics of antimicrobial resistance

For over 20 years there has been rising global concern about anti-microbial resistance (AMR). Across the industrialised world, *methicillin resistant staphylococcus aureus* (MRSA) infections and other hospital acquired multi-drug resistant bacterial infections have reached the top of the political agenda (Batty 2005; White and Carvel 2005). Much less is known about the problem of antibiotic resistance in developing countries. However a recently published review of the literature shows that the most common pathogens are becoming increasing resistant to the most commonly available antibiotics (Okeke, Laxminarayan et al. 2005). Despite this, relatively little has yet been published on the impact of interventions against antimicrobial resistance (Smith, Coast et al. 2000; Wilton, Smith et al. 2002; Okeke, Klugman et al. 2005). Since the literature has recently been extensively reviewed, only the relevant findings will be summarised here.

2.2.3.1. Interventions to control antimicrobial drug resistance

From the earlier reviews, it was suggested from the available studies involving combination therapies (none of which were antimalarials), that the use of combination drugs did generally show an effect on AMR. However it was noted that the duration of this effect was unknown. The overall conclusions of the reviews were that most of the studies were from the developed world, were hospital-based and inadequately measured the impact of interventions in terms of costs. The authors identify four further areas for research: the need for more effectiveness data, the need for “macro” level studies rather than studies based on the “closed hospital

environment”); studies in developing countries; and studies that examine cost implications (Smith, Coast et al. 2000; Wilton, Smith et al. 2002).

The more recent review focuses on the evidence from developing countries (Okeke, Klugman et al. 2005). In addition to the use of combination therapies, the authors suggest that antimicrobial cycling may have a place in antimicrobial strategy. The argument is largely based on evidence from the studies of antimalarials which have shown that cessation of the use of chloroquine in some well-controlled settings has resulted in a return of susceptibility in the parasite population (Kublin, Cortese et al. 2003).

As found in the previous reviews, although there was evidence that strategies aimed at modifying prescribing practice through training and guidelines could be effective, there was little evidence on the outcome in terms of the level of drug resistance. Recognising that in developing countries, the public health care infrastructure is often weak and the role of informal providers important, the authors also explored a number of other interventions. These included improving patient adherence, improving the drug supply, eliminating the availability of substandard and counterfeit drugs and improving the surveillance of antimicrobial drug resistance. The authors concluded that although data are lacking, especially on the cost-effectiveness of different interventions, based on the available information there are a number of feasible interventions that should be prioritised.

2.2.3.2. Methodological issues

The possible reasons for the failure to consider drug resistance in economic evaluations comparing management strategies of infectious disease was first approached by Coast et al. (Coast, Smith et al. 1996). The authors explore why this is the case, despite the fact that drug resistance is an important social externality. They identify the implicit assumptions that are made in ignoring AMR¹⁷ and conclude that the exclusion is due to practical difficulties in measurement rather than based on methodological justification. Noting the diffuse and uncertain nature of the problem, and the fact that decisions regarding the choice of antibiotic therapy are usually made at the level of individual doctors and patients, they queried whether the inclusion of drug resistance in economic evaluations could in fact lead to a policy response.

The difficulties in dealing with antimicrobial resistance in economic evaluation, and the possible policy responses were explored further in a later paper (Coast, Smith et al. 1998). The

¹⁷ These include assumptions that either the absolute costs of AMR are too small to be considered; or that the future costs are too small in current values, either due to “time preference”, or due to uncertainty about future costs.

authors identify important aspects of AMR which make it particularly challenging - mainly the intergenerational and interregional nature of the problem as well as the inherent uncertainties involved. The latter include not only uncertainties surrounding the biology of drug resistance and effectiveness of controls, but also uncertainties regarding the future development of new drugs and more diverse issues such as international travel, co-morbidity and economic growth. Drawing from the area of environmental economics in which there is more experience with dealing with externalities, such as pollution, three policy options are proposed - regulation, permits and charges. Each have their pros and cons but all seek to limit the use of antimicrobials based on the assumption that this would lead to a reduction in resistance and an overall positive effect on society as a whole.

In a more recent paper, the authors discuss four key difficulties with evaluations incorporating AMR: diffuse impacts, comparing current and future impacts, uncertainty and difficulties in measurement and valuation (Coast, Smith et al. 2002). They note these difficulties result in a bias towards undertaking studies of interventions with short time horizons, in closed environments and where the spread rather than the emergence of drug resistance is targeted. In view of these uncertainties, they explore some other possible approaches to dealing with the emergence of drug resistance. Drawing from the natural resources literature, the idea of considering antibiotics as a non-renewable resource is explored. Given the uncertain but catastrophic nature of the emergence of drug resistance, it is possible to regard policies undertaken now to reduce the risk of resistance, as a form of insurance. Their recommendations for future research include focusing on modelling, in particular combining economic and epidemiological aspects as a means of evaluating different policy responses to drug resistance.

The importance of considering the macroeconomic impact of antimicrobial resistance was recently explored by Smith et al (Smith, Yago et al. 2005). Using a static, closed-economy, competitive equilibrium model, the impact of methicillin-resistant *staphylococcus aureus* (MRSA) on 10 sectors of the UK economy is described. The key finding is that the impact of MRSA acting through higher healthcare costs is proportionately smaller in terms of adverse macroeconomic impacts compared to the impact of MRSA acting through labour quantity and productivity. An MRSA level of 40% was estimated to increase the government transfers to households by between 0.7% and 2.8%, unemployment by between 4 and 18% and lead to the loss of GDP of 0.4% to 1.6% (equivalent to £3-11 billion in monetary terms). The authors note the complementary nature of the "macro" and "micro" approaches and conclude that the former is dependant on the latter for data on the long-term impact of resistance in large-scale settings. In particular they identify the need for epidemiological studies of the factors affecting drug

resistance and studies that elucidate the relationship between drug resistance and health outcomes.

The literature on the modelling of antimalarial drug is therefore now explored.

2.3 Mathematical models of malaria

Models of drug resistance have traditionally come from either an epidemiological perspective, which analyses the infected hosts, or a population genetics perspective, which analyses individual genes or clones.

2.3.1 Mathematical modelling of infectious disease epidemiology

“Epidemiology is the study of the spread of disease in space and time, with the objective of tracing the factors that are responsible for, or contribute to their occurrence” (Diekmann and Heesterbeek 2000). The founding father of modern epidemic theory is probably Sir Ronald Ross who first attempted to provide a quantitative understanding of the dynamics of malaria transmission and later extended this to develop a general theory of disease transmission. Thus the history of the mathematical modelling of infectious disease is closely entwined with the modelling of malaria transmission.

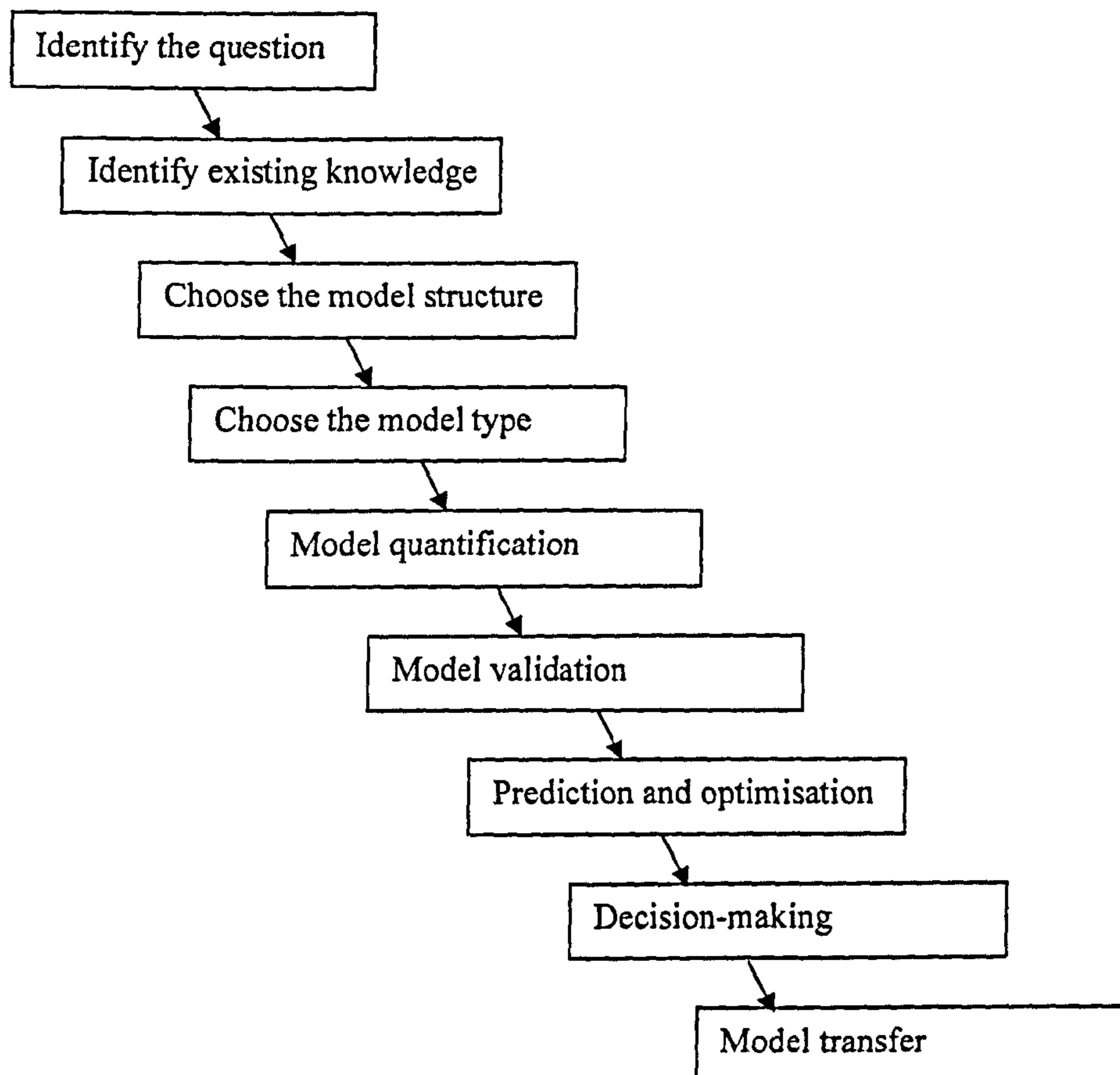
Before focusing on the modelling of malaria specifically, it is useful to review steps involved in infectious disease models. An exhaustive list was drawn up by Habbema et al after their experience of the development of large micro-simulation models for the control of infectious diseases, with the aim of providing a tool for use by policy makers and programme makers (Habbema, De Vlas et al. 1996). Although they emphasize that the whole process highly iterative and may take years, it is a useful framework in which to situate this current study (Figure 2-1).

2.3.2 Modelling malaria transmission

The cornerstone to any infectious disease model is the basic reproductive rate, R_0 , which is essentially the average number of successful offspring that a parasite is intrinsically capable of producing or the average number of secondary infectious cases resulting from each infectious case in a totally susceptible population. Clearly for infections to spread, the R_0 must be greater than one. Generally, once an individual is infected, they are no longer susceptible, thereby decreasing the pool of susceptible hosts. Eventually an equilibrium may be reached when the

rate of susceptible hosts becoming infected is balanced by the appearance of newly susceptible hosts (for example through birth or the loss of immunity). In other words, each infection will on average produce exactly one secondary infection and the $R_0=1$.

Figure 2-1: Steps in the development and use of models



Source: Habbema, de Vlas et al. 1996

The early models by Ross were essentially compartment models in which changes in the density of susceptible and infected people, and susceptible and infected mosquitoes, were described by a number of differential equations (Ross 1911). In the early 1950s, Macdonald refined the models by focusing on the interpretation and estimation of parameters (Macdonald 1957). Subsequent models of malaria transmission have largely been based on the “Macdonald-Ross model” with refinements aimed at improving the realism of the model. Early adaptations focused on the effect of immunity. In the original model, the simplest assumption was made about immunity – that on recovery from first exposure an individual acquires sterile immunity for life, similar to the simple compartment models of viral infections. This resulted in estimates of the duration of infection being much too long, up to 30 years!

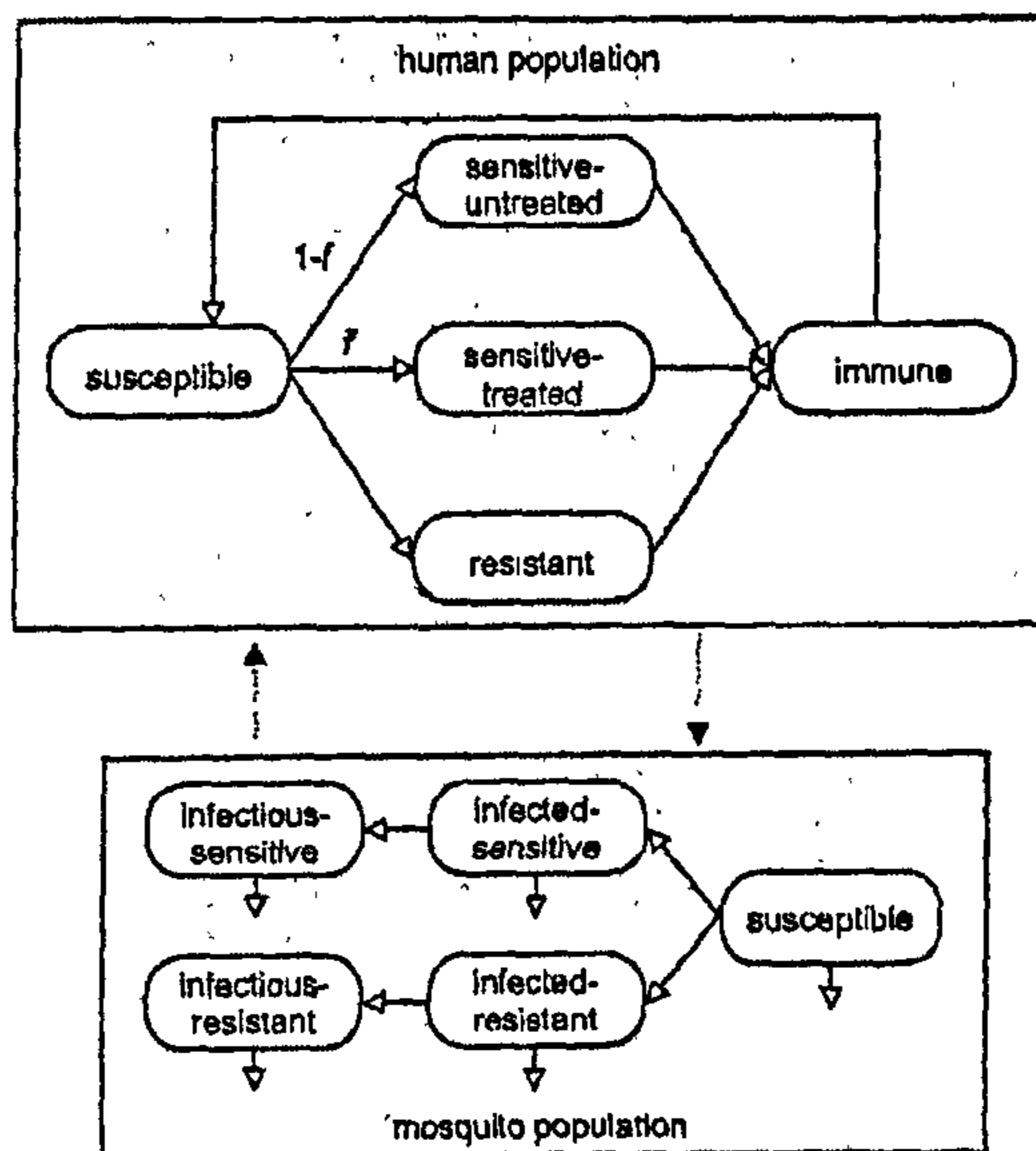
In Dietz's and related models, humans are divided into a relatively non-immune group with a slow recovery rate and more immune group with a fast recovery rate and lower chance of detection (Dietz, Molineaux et al. 1974). There is a fixed rate of transition from slow recovery to fast recovery class. Infection induces immunity by increasing the threshold level of parasitaemia necessary of acute episode. The parameter estimates were largely based on the results of the Garki project, an extensive study of malaria in Nigeria. Unsurprisingly there was therefore a good fit between the model and actual estimates (Molineaux, Storey et al. 1980). One of the main limitations with the model was that it did not address all aspects of immunity. Aron and May attempted to address the problem of immunity directly by introducing three classes of individuals: susceptibles, infecteds and immunes (Aron and May 1982). Immunity was assumed to last for some fixed period of time in the absence of re-exposure and infection was assumed to occur at a fixed rate per capita.

However, the categorisation of the host into three categories still lacked realism and the constraints of using a compartment-based model were made clear. As remarked by Anderson and May:

“These observations combine to suggest that an accurate mathematical description will need to abandon the compartmental or prevalence based structure of conventional microparasite models and move toward a more detailed description of the growth and decay of parasite abundance within individuals.” (Anderson and May, 1991, p 417)

In addition, none of these models deal specifically with the competition between two parasite populations, in order to explore the phenomenon of the spread of drug resistance. This was undertaken recently by Koella and Antia. This model is based on the traditional compartment model of malaria transmission with modifications to incorporate competing drug sensitive and drug resistant parasite populations, which are assigned different basic reproductive rates (Figure 2-2) (Koella and Antia 2003). The parasite with the higher basic reproductive number R_0 , drives the number of susceptible hosts below the threshold density necessary to maintain the parasite with the lower basic reproductive number. A “cost of resistance” (or “fitness cost”) is incorporated, which describes the reduced reproductive capacity and therefore transmission intensity of resistant parasites compared to sensitive parasites in the absence of drug treatment. In this paper, an arbitrary value of five is used.

Figure 2-2: Schematic diagram of Koella's model of malaria transmission adapted to incorporated resistant and sensitive parasites



Source: Koella and Antia 2003

By varying proportions of infections which are treated, they explore the effect of drug treatment and observe that there is a threshold level of drug use below which resistance cannot spread and above which resistance spreads and eventually becomes fixed. This threshold level is determined by the duration of infection in treated sensitive infections and by the “cost of resistance”. They also find that by allowing super-infection of hosts with both types of parasites, both parasite populations can coexist even in the absence of treatment under some conditions. Finally, they observe that the migration of mosquitoes from an area of malaria treatment to an untreated area can swamp the local effects of selection. Whilst the model is informative in exploring the factors affecting the spread of resistant infections in relation to sensitive infections, it is based on little empirical data and does not incorporate a number of important factors including pharmacokinetics, pharmacodynamics, clinical outcomes and most importantly host immunity. In addition, transmission is assumed to occur at a fixed rate so that drug resistance and treatment has no feedback effect on transmission intensity. In order to use the model in economic analysis, Laxminarayan adapted an earlier model by Koella and in doing so addresses some of the limitations (Laxminarayan 2004a). However, as discussed in the previous section, as a basic model, it lacks realism and a more comprehensive model is required.

2.3.3 Modelling antimalarial drug resistance

The development of drug resistance requires the initial emergence of a *de novo* genetic mutation and its subsequent survival and spread. In order for drug resistance to emerge, first a genetic

event¹⁸ that confers antimalarial drug resistance has to spontaneously occur *de novo* in a single parasite, independently of any drug. Mutation frequencies vary depending on the drug, because individual drug targets in the parasite differ in their vulnerability to mutations. Based on *in vitro* studies of atovaquone (Rathod, McErlean et al. 1997) and the *DHFR* mutation in SP (Paget-McNicol and Saul 2001), estimates for the frequency at which mutations occur vary from one in 10^5 to 2.5 in 10^9 . Estimates calculated from observations from *in vivo* studies and from retrospective calculations are significantly lower (White and Pongtavornpinyo 2003).

In humans, infections become microscopically detectable at a density of about 50 parasites/ μ l of blood. This corresponds to a total of between 10^8 and 10^9 parasites in an adult. In this context, it can be seen that if the *in vitro* estimates are accurate, the occurrence of the mutations themselves are probably not that rare. It can also be appreciated that the higher the parasite density in an individual, the more likely it is that they will harbour a mutant parasite. Therefore it is a non-immune patient who remains untreated and develops a high parasitaemia that has the highest chance of being the source of a new mutant (White and Pongtavornpinyo 2003).

From field evidence, it has now become apparent that the actual emergence of a resistant infection is an extremely rare event and that most of the antimalarial drug resistance in existence today is the results of spread of a few original mutants. It is also clear that these mutants arose in low transmission areas and spread to high transmission areas. It is likely that the rarity of emergence reflects the infrequency at which spontaneous mutation that do arise, actually manage to survive and multiply at the expense of non-mutants within the initial host, to reach sufficient density of gametocytes in order to infect an inoculating mosquito (Hastings 2004).

Models have been extensively used to examine the factors affecting the spread of resistance through the parasite population. There has been particular interest in exploring the effect of transmission intensity, clonal multiplicity and drug pressure on the evolution of drug resistance.

In a pioneering work by Curtis and Otoo, a deterministic compartmental model was used to study the spread of drug resistance in a population where two drugs were used in sequence or in combination (Curtis and Otoo 1986). Their findings suggested that the use of combinations was advantageous provided that the resistance genes were rare, that free recombination could occur between them and that only a small proportion (<20%) of the parasite population remained untreated. Subsequent models which have used different approaches have confirmed that using

¹⁸ Although the genetic event can be an amplification or mutation, for simplicity it will be referred to as a mutation.

drugs in combination is likely to slow the development of drug resistance (Mackinnon and Hastings 1998; Hastings and D'Alessandro 2000).

In the model by Curtis and Otoo it was also predicted that drug resistance is more likely to evolve in low transmission areas. Modelling by Dye and Williams suggests that recombination between different parasite clones in multiclonal infections is more likely to result in outbreeding resistance, especially when resistance is determined by two or more genes which are initially both rare and subject to low selection pressure (Dye and Williams 1997). Emergence should therefore be less likely to occur in high transmission areas where superinfection is more likely.

However other mathematical models have predicted that resistance would be more likely to survive and spread in areas of high transmission (Mackinnon 1997; Mackinnon and Hastings 1998). In Mackinnon's earlier model, branching theory was used to examine the probability of survival of one- and two- locus new mutants as a function of drug pressure, transmission rate and fitness cost. Crucially, it was unrealistically assumed that the frequency of treatment is independent of transmission rate. Therefore in high transmission settings not only did new resistant mutants have a greater chance of being transmitted, but they were as likely as in low transmitting settings to be subjected to selection by drugs. In the later model, the positive force of effective selection on the parasite population is modelled against the negative force of recombination. The results suggest that high transmission rates promote the spread of drug resistance (Mackinnon and Hastings 1998).

Hastings explained these discrepancies by comparing the implicit assumptions made by the analysts about whether host immunity was clone specific or generalised (Hastings 1997). He argues that in models which analyse individual genes or clones, there is an implicit assumption of specific clonal immunity and that this results in predictions that the evolution of resistance tends to be faster in low transmission areas where the chance of recombination is less. Models that analyse infected hosts are more likely to make the implicit assumption that immunity is generalised and may conclude that evolution is more rapid at low or high infection levels depending on the choice of parameters.

Hastings and D'Alessandro explore this further in a model of the evolution of drug resistance in which they examine the effect of clonal multiplicity, intrahost dynamics and starting frequency (Hastings and D'Alessandro 2000). Making assumptions of complete independence and complete non-independence of transmission of malaria clones from the same host, they suggest that as clone multiplicity increases, so does the recombination rate between resistant and

susceptible forms, with a corresponding decrease in the probability that resistance will be retained. Therefore the increasing number of clones seen in higher transmission areas slows the spread of resistance.

Talisuna et al. used empirical data to describe the relationship between chloroquine resistance, as measured by the frequency of *pfcr-76* and *pfmdr-86* mutants, and transmission intensity, as measured by prevalence, in six Ugandan populations (Talisuna, Erhart et al. 2005). They found that the frequency of the resistant *pfcr-76* mutant was universally high (86 to 100%). However the frequency of the resistant *pfmdr-86* mutant appeared to be higher at the extremes of transmission for that study. They provide an eloquent explanation for this observation in terms of the interplay of factors affecting the spread of drug resistance. In brief, in a high transmission setting, immunity results in lower parasite mass and decreased drug pressure. It is also associated with increased parasite diversity. As a result of the latter, there is increased sexual recombination, which leads to a break down in mutant parasites but also leads to a boosting of intrahost dynamics which can contribute to the selection of mutant parasites.

Gatton et al. focused on the relationship in the rate at which mutants arise, that *var* gene switch rate, the host antibody response and the timing of drug treatment (Gatton, Hogarth et al. 2001) and predicted that drug resistance is more likely to be initiated in a malaria-naive host compared to someone who is relatively immune.

A number of models have focused on pharmacokinetics and the development of drug resistance. By incorporating an intermediate partially-resistant class of parasites, Hastings et al. were able to describe the importance of long elimination half-life in selecting for resistance. They emphasize the difficult policy dilemma which requires the balancing of minimizing the risk of the development of resistance by minimizing drug usage against the benefit of having drugs readily available (Hastings, Watkins et al. 2002).

The disadvantage of these models based on population genetics is that the consequences of different epidemiological circumstances cannot be examined. Ideally therefore, both the epidemiological and genetic models should be merged. This has been attempted in a number of models (Cross and Singer 1991; Dye 1991).

Cross and Singer describe a closed model in which the infected human and mosquito populations are each identified by a log(tolerable dose) distribution of the parasites they are harbouring (Cross and Singer 1991). The human population is stratified into three age groups

with different durations of untreated infections and different levels of parasite density and therefore infectivity. The human and mosquito populations are exposed to each other on a daily basis resulting in a transformation of the distribution depending on a number of factors including infectivity and biting rate. The log(tolerable dose) distribution of parasites in humans is affected by drug treatment which acts by clearing or reducing parasite density depending on drug resistance. The model was calibrated with field data of pyrimethamine resistance in Tanzania. The important qualitative conclusion was that to maximize the length of time that an anti-malarial is effective in a community under holoendemic conditions, the curative doses should be administered to 25% or less of the infected population – posing an interesting ethical dilemma. The main disadvantages of this model are that immunity in the human population remains static and the effect of combination therapy is not incorporated, aspects that the authors suggest as priorities for future research.

2.4 Conclusions

From the literature reviewed in this chapter, it is clear that there are significant gaps in both the economic literature and the literature of malaria modelling with regards to the study of the economic impact of drug resistance and of drug policy options. The review of the literature on economic evaluations provided a framework for the analysis and clarified the possible approaches in this study. With a couple of notable exceptions, most economic evaluations of antimalarial treatment have taken a traditional microeconomic approach in which drug resistance has either been ignored or has been incorporated as a fixed phenomenon. The literature on the economics of antimicrobial resistance has also had limited reference to the study of antimalarials in community settings, with most focused on the use of antibiotics in hospital settings in developed countries. Macroeconomic analyses of the economic impact of malaria and of antimicrobial drug resistance highlight the importance of taking a broader societal view. However the accuracy of these analyses are dependent on the quality of information produced from “micro” economic studies which in turn are dependent on biological models of disease transmission.

Reviewing the literature on the modelling of malaria transmission and drug resistance revealed the limitations of existing models. Although different approaches address different factors affecting disease transmission and the evolution of drug resistance, none of them incorporate them all. Epidemiological models, based on Ross and Macdonald’s original model of malaria transmission, have focused on the dynamics of transmission between the human and mosquito

population where the implications of host immunity on the density and dynamics of the parasite population have not been realistically incorporated. Population genetic models have focused on the factors affecting the evolution of resistance in the parasites population but have also either ignored host immunity or treated it unrealistically and have not included other important behavioural, clinical and drug-related factors.

There is therefore a clear need for a new model of antimalarial drug resistance, one that can be easily placed in an economic framework and that is as biologically accurate as possible. In particular the model needs to track both the human and the parasite populations and to incorporate immunity, drug characteristics and human behavioural factors. The realism of such a model depends on an extensive amount of empirical data, obtained mainly from secondary sources in order to reflect a range of settings. The literature reviewed in the process of developing the model, and the data extracted, is covered mainly within Chapters 4 and 5 and in table format in Annex 6.

CHAPTER 3

AIMS, OBJECTIVES AND METHODOLOGY

This chapter summarises the aims and objectives of the thesis and outlines the methodologies used. The overall approach and the economic analytic framework is first described, followed by a brief description of the methods used to achieve the objectives. More detailed descriptions of the methods are provided in the separate chapters with additional information in the annexes.

3.1. Aims and objectives

Aims

The overarching aim is to conduct an economic analysis of combination therapy for the treatment of malaria in order to contribute to the current debate on the role of combination therapy in malaria control policy. There are two main elements to this study: the development of a bio-economic model of transmission and antimalarial drug resistance, and the collection of model parameters.

Objectives

- (1) To develop a comprehensive bio-economic model of antimalarial drug resistance and combination therapy.
- (2) To collect and synthesize secondary data for such a model.
- (3) To collect and analyse primary data on the implementation of artemisinin-based combination therapy (ACT) from Cambodia, for input into the model.
- (4) To use the model in a low transmission context to predict the cost-effectiveness of ACTs under different conditions.
- (5) To discuss the implications for antimalarial drug policy based on these findings.

3.2. Overall approach and study framework

As discussed in the previous chapters, it is clear that despite significant changes in global antimalarial drug policy, uncertainty still exists on the benefits of switching and when and how to switch from monotherapy to an ACT.

There are a number of ways of dealing with this uncertainty. There is the “natural experiment approach” in which ACTs are introduced in only a few controlled settings and the impact on transmission and drug resistance is closely observed. However, this is clearly not feasible as there is an urgent need to act now.

An alternative approach, and the one proposed here, is to use what information there is available to produce a model to predict what will happen in the future, given certain assumptions. In the process, the assumptions are made explicit, the gaps in knowledge are revealed and, if necessary, primary data obtained. Models have increasingly been used to help explore policy options where risks and benefit outcomes will be incurred in the future and where there are inherent uncertainties. They are ideally suited to exploring both biological and economic influences on outcomes. Moreover, models can be used to produce the estimates of the cost-effectiveness of policy options, which are now accepted to be a vital input to decision making in the health sector.

As explored in the literature review, static economic models of malaria, which do not capture the change in disease transmission or antimalarial drug resistance, ignore the externality benefits and importance of both the reduction in the number of cases and prolonging the useful life of antimalarial drugs. The development of sound economic analysis is dependent on the robustness of the underlying biological model of malaria that predicts these changes. Although there have been a number of mathematical models of malaria and antimalarial drug resistance, none have comprehensively incorporated all the relevant biological and economic factors.

It is the aim of this thesis to develop such a model. Critical steps in this process have been, firstly, the elucidation of the individual steps involved, defining these as “parameters” and determining their relationship to each other within the model. Finally, primary and secondary data needed to be gathered, to support the actual value inputs in the model. It was felt that producing such a comprehensive database of values would also be useful to others who wish to develop alternative models. During this process, gaps in knowledge were made apparent and decisions were made on how they should be handled. In general, the resulting uncertainties were incorporated into the model with the aim of testing them with sensitivity analysis. However, there were gaps that were thought likely to have a significant impact on the model outcomes and where it was possible to obtain primary data from the field. One such gap that emerged early on in the process pertained to the actual pattern of drug usage once ACTs were deployed, in terms of coverage rates and adherence. As it was possible to collect the information from Cambodia, the first country to switch to an ACT, this became an important part of the thesis.

The intensity of malaria transmission in Cambodia is generally low and therefore this work mainly focuses on low transmission settings. The model was run to illustrate how it functions and to explore the spread of drug resistance and the effect of ACTs, using inputs for different scenarios in a low transmission setting. However the model can be applied high transmission settings and this is illustrated in Annex 10.

Table 3-1 shows the relationship between objectives and methods and Figure 3-1 describes the study framework.

3.3. Economic analysis – Conceptual framework

The primary purpose of the thesis was to produce a model that could be used to perform an economic analysis and to generate outcomes of direct policy relevance. The development of the biological model was therefore underpinned by the economic framework in which it was situated.

Several guidelines on the application of economic evaluation in the health field have been published (Drummond et al 1993; Drummond and Jefferson 1996; Tan-Torres Edejer 2003; Weinstein 1996). There is broad agreement on most of the important aspects of analysis, and in this thesis, they have been followed as far as possible. However, there are still some areas of controversy, for example in the handling of DALYs, and where these are relevant the alternatives and choices are discussed here.

In presenting an economic analysis it is important to state, at the outset, a framework that includes the perspective taken, the intended audience, geographical boundary, time-frame, outcomes and alternatives. As the intention was to develop a model that could be used to answer different questions, some of the specifics are left to be defined when the model is applied to particular scenarios in the results chapter (Chapter 8).

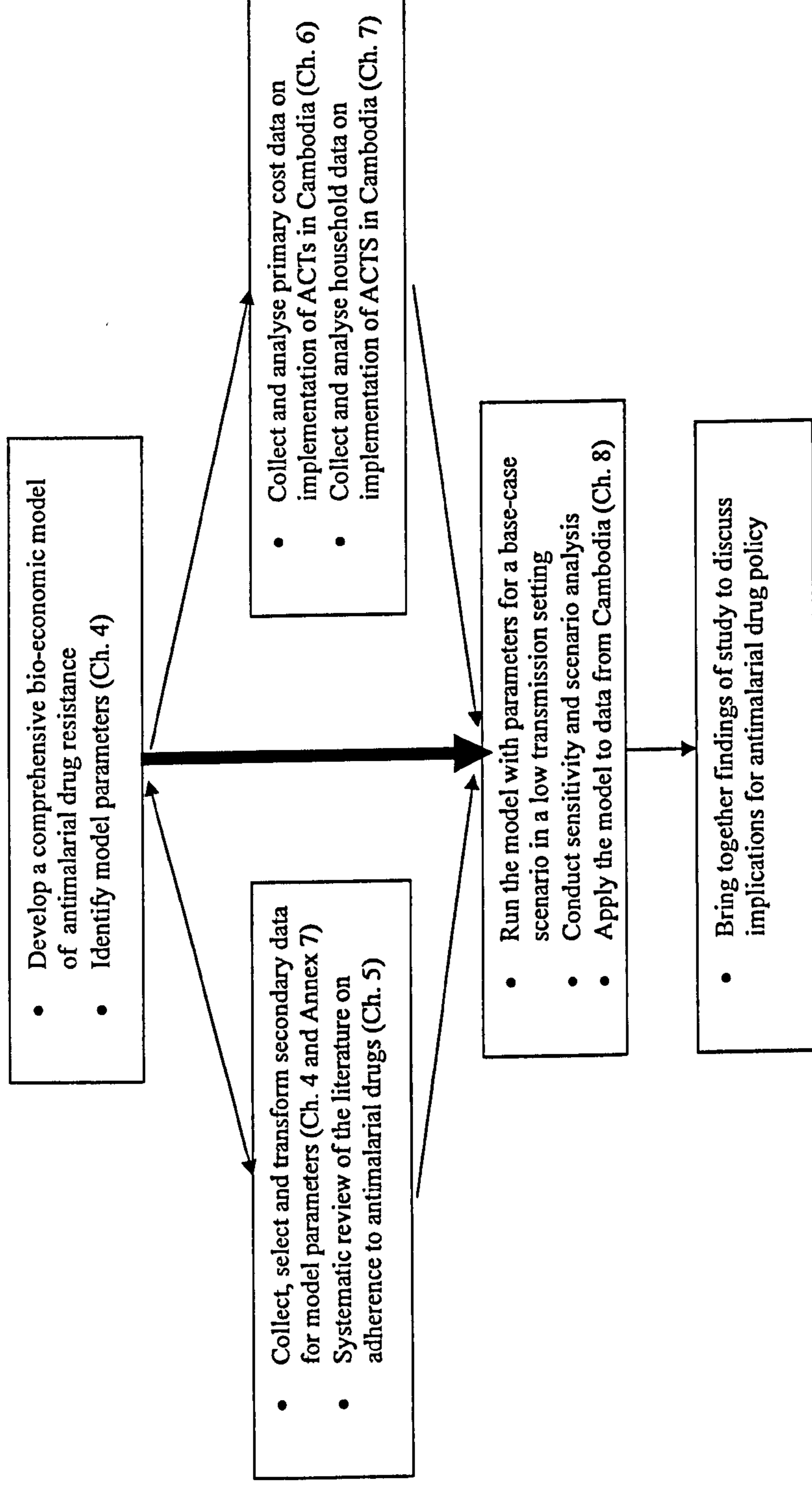
3.3.1. Goals and perspective

The overall goal of antimalarial drug policy is assumed to be a reduction in morbidity and mortality. This includes a reduction in the morbidity and mortality occurring in the future as a result of the reduction in drug resistance. The audience for this analysis is chiefly policymakers and malaria programme managers.

Table 3-1: Relationship between objectives and methodology

Objective	Methodology
To develop a comprehensive bio-economic model of antimalarial drug resistance and combination therapy	<ul style="list-style-type: none"> • Collaboratively develop a mathematical model of the development of antimalarial drug resistance that incorporates clinical, behavioural and economic factors • Identify model parameters
To collect and synthesize secondary data for such a model	<ul style="list-style-type: none"> • Collect, select and transform model parameters from secondary sources • Systematically review the literature on adherence to antimalarial drugs
To collect primary data on the implementation of artemisinin-based combination therapy from Cambodia, for input into the model	<ul style="list-style-type: none"> • Collect costs of the implementation of ACTs using the ingredients approach • Conduct a household survey of treatment seeking behaviour, drug usage behaviour and patient costs to study the implementation of ACTs
To use the model to predict the cost-effectiveness of ACTs under different conditions	<ul style="list-style-type: none"> • Run the model with parameters for a base-line scenario and scenario analysis in a low transmission setting • Apply the model to data from Cambodia
To discuss the implications for antimalarial drug policy based on these findings	<ul style="list-style-type: none"> • Bring together findings from the research to discuss their relevance to antimalarial policy

Figure 3-1: Study framework



The potential benefits can be categorised into three separate policy desirable outcomes: 1) effective patient cure, 2) preventing the emergence and spread of resistance, which benefits future generations (a positive externality), and 3) in low transmission areas, reducing transmission which reduces the incidence of malaria and benefits the public, both now and in the future (a positive externality).

The analysis is undertaken from a societal perspective, including that of the patient, because in the treatment of malaria, most of the cost of illness has traditionally fallen on patients and their families rather than the government, because most treatments are not obtained in the public sector. However, it has now been generally accepted that if the more expensive ACTs are to be used, then they must be highly subsidised or made free, shifting the cost of illness from patients to governments and donors.

To try to dissect out who benefits and when, and who pays, the outcomes for the economic model are expressed in terms of current and future malaria cases and therapeutic failures, and the associated costs and cost savings. Costs and benefits to current and future patients are therefore considered as well as the costs to the government implicitly including donors. These include all the treatment costs associated with both the initial malaria infection and subsequent treatment for recrudescence and severe infections.

3.3.2. Time-frame and population

The actual time-frame over which costs and effects are considered is a critical part of the analysis as much of the benefit is expected to be reaped in the future, in terms of fewer cases and reduced drug resistance. Therefore, the time-frame of the analysis is allowed to vary in order to explore questions such as the length of time a policy needs to run before it starts becoming cost-effective, and at which time point it is most cost-effective to switch from a cheaper failing drug to a more expensive combination therapy.

The population included in the analysis are all people living in a single geographical region with uniform malaria transmission, healthcare delivery and treatment seeking behaviour. This can be a whole region, country or specific area within a country. Key characteristics of the population that are assumed to affect the outcome of any policy change are the level of transmission and the proportion of patients who are likely to be covered by any change in drug policy. These parameters therefore form an integral part of the biological and the combined bio-economic model.

3.3.3. Costs

The costs included and measured must be relevant to the objectives of the study. In this case, the focus is the incremental health impact of switching to a combination therapy. Given the importance of high coverage, the analysis is done with and without additional interventions to increase coverage. In addition, the overall cost of treating malaria, inclusive of treatment failures, is important. Therefore, the types of costs presented in this thesis are, firstly, the net incremental cost of the first-line drug inclusive of any delivery costs and, secondly, the total cost of treating malaria.

Incremental costs consist of the costs that would be incurred based on the new resources needed to deploy combination therapy. In this case, for the cost-effectiveness analysis the incremental costs comprise the cost of drugs and of any interventions to increase coverage. The other costs of treatment such as the cost of consultation and diagnosis are not included as it is assumed that these would be incurred irrespective of the choice of drug. The costs of the policy change process itself are also not included as it is assumed that these would be incurred independent of the drug choice.

In order to capture the consequences of antimalarial resistance in monetary terms, the total costs (direct and indirect) of malaria illness, to providers and patients, are considered. In this case average recurrent and capital costs are used, as there is an expectation that in the long term, treatment resources saved by the health sector and patients can be relocated away from malaria treatment. Details are provided in the next chapter.

3.3.4. Outcomes

In order to reflect the priorities of the audience for whom this analysis is intended, a number of different outcomes are presented. For affected communities and those involved specifically in malaria control, the cost per case of severe malaria or death averted is most relevant. For policy makers involved in making allocative funding decisions across the health sector and who have a longer term outlook, the cost per DALY averted is used. Finally, for policy makers at this level and above, the monetary implications of different alternatives are included.

3.3.4.1. Number of clinical cases

In a low transmission area, using any effective drug should reduce the malaria incidence because people who are treated for malaria do not continue to be parasitaemic and therefore do not transmit malaria. Using combinations that contain an artemisinin derivative has the potential to reduce transmission further, because of their specific effect on gametocytaemia. This reduction in the number of clinical cases in the future is therefore an externality benefit. In high transmission areas, effective treatment is not expected to reduce malaria incidence, as only a

small proportion of those who are parasitaemic take any treatment, as immunity is higher and many people are parasitaemic but not symptomatic.

3.3.4.2. Number of treatment failures

Where levels of resistance to the current drug are already high, switching to ACTs or any effective drug reduces the number of treatment failures. Thus, in the short term (<5 years), the number of failures simply reflects the efficacy of the drug. In the long term, the continued effectiveness of the drug reflects how efficiently the development of resistance has been delayed by using ACTs. Therefore, treatment failures averted in the future reflect the externality benefit of controlling drug resistance.

3.3.4.3. The consequences of treatment failure

In itself, “treatment failure” has limited usefulness as an outcome measure in terms of policy relevance. To make this a more tangible concept, there is a need to estimate the clinical and economic consequences of the treatment failures. In other words, in order to quantify the “cost of resistance” there is a need to estimate the consequences and costs of treatment failure in terms of repeated or more expensive second-line drugs and their administration (parenterally rather than orally), prolonged illness, hospitalization, severe disease, death and lost productivity. Estimates of the likelihood that a patient who fails treatment will go on to develop severe malaria, and the likelihood of death, are therefore required, as are the associated costs as discussed above.

3.3.4.4. Total costs

As discussed above, in order to compare the cost-benefit of different strategies in monetary terms, the total costs of malaria, including the costs of first-line treatment and the subsequent cost of treating recrudescence infections and severe malaria, need to be considered. In this analysis, both the direct costs of treatment and the total costs inclusive of indirect costs are shown.

3.3.4.5. DALYs

Effectiveness is also expressed in terms of DALYs based on the number and age of averted deaths and the disability weights and durations assigned to uncomplicated and severe infections. This is discussed in more detail in the next chapter.

3.3.5. Comparators

The selection of alternative scenarios is an important step in setting up the economic analysis. In traditional cost-effectiveness analyses where two different treatment choices are being compared, the choice of comparator is reasonably straightforward. However, in this case, the

aim was to develop a generic model, which can be used to explore different scenarios. In this case, the base-case comparator is the continued use of a monotherapy and the alternatives are the switch to a combination therapy under different conditions.

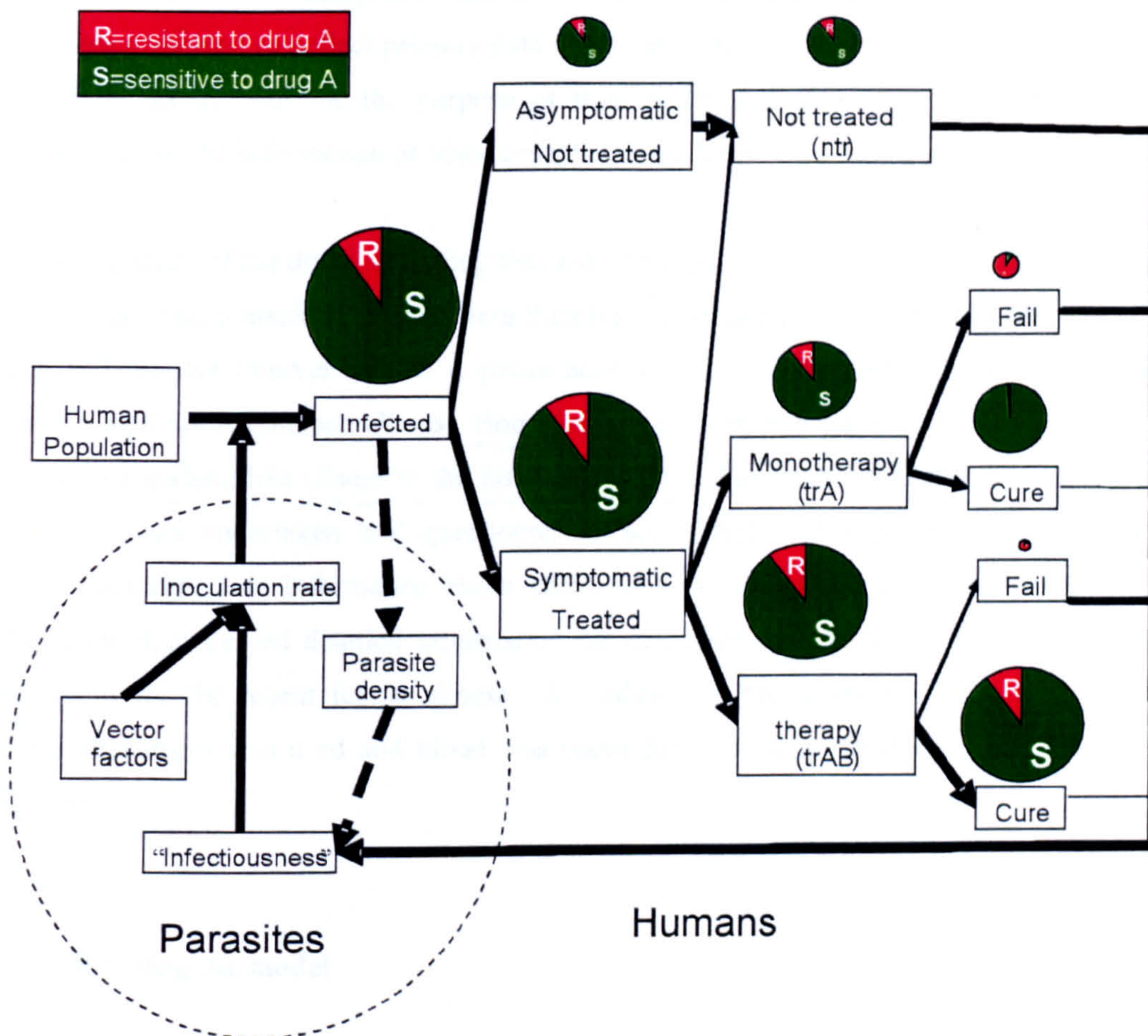
3.4. The development of the bio-economic model

The biological model attempts to incorporate all the factors considered relevant to the development of drug resistance. These factors include host immunity, vectorial factors, drug characteristics and human behaviour. As discussed Chapter 1, drug resistance essentially develops in at least two distinct phases: firstly the “*de novo*” emergence of a resistant infection and then the spread of this infection through the population. In this thesis, only the spread of antimalarial drug resistance is explored. Emergence of drug resistance is a stochastic process and there is much more uncertainty involved in predicting its occurrence. It therefore requires modelling separately, and whilst this is now being undertaken with the aim of eventually interlinking it with the “spread” presented here, it was beyond the scope of this thesis. Consequently, the full benefits of ACT are not incorporated in this current model.

The biological model evolved from a simple binary probabilistic model to an iterative dynamic model in which the total number of people and the age structure of the population remains fixed but other key features such as number of infections, level of resistance and cure rate are allowed to vary according to the outputs of the previous iteration. A cartoon of the model is illustrated in Figure 3-2.

Essentially, this is a deterministic age-stratified population-based model that keeps track of the number and type of infections in humans and of parasites. The type of infections are monitored in terms of whether or not they are sensitive or resistant to a given drug (Drug A). At the beginning of each model iteration, a certain proportion of humans in each age group are infected by malaria, depending on their level of immunity and the transmission intensity. The outcomes of these infections, in turn, depend on whether they are resistant, whether and what type of treatment is received and the level of human immunity. The outcomes at the end of each iteration are the number and type of human infections, the number and type of parasites, and the level of drug resistance. The number of parasites determines the number of gametocytes, which in turn determines the infectiousness of humans to mosquitoes and therefore the transmission intensity in the next iteration. Input parameters and the costs of drugs, diagnosis and other treatment costs are varied in order to explore different scenarios.

Figure 3-2: Schematic diagram of one iteration of the model



3.5. Parameter estimates

One of the key steps in the development of the model was the description of the chain of events leading from a person getting malaria to receiving treatment and the consequent outcomes in terms of cure/failure, transmission and the development of resistance. This was necessary in order to elucidate the parameters and define the relationships between them. This was an iterative process so that as the model was being developed, it would become apparent which data were necessary. Conversely, new data could be found which would inform the development of the model. This chain of events is simplified and shown in Table 3-2. For most of the parameters, data were gathered from published sources and put in a collated table format (Annex 6). Data on drug usage was thought to be particularly important and was systematically reviewed and is presented separately. Some gaps in the data became apparent early on, in particular information on the actual implementation of ACTs and the level of expected coverage and adherence. The primary collection of this data was therefore undertaken in Cambodia.

3.6. Primary data collection in Cambodia

Cambodia was the first country to switch to ACTs, and in making the change, also utilised a number of innovative strategies to improve coverage and adherence. An ideal opportunity was therefore presented to collect primary data on the implementation of ACT, the results of which would be useful both for the purpose of this model and also as a documentation of the experience for the information of other countries considering a switch in policy.

A costing study of the drugs, including the cost of pre-packaging and delivery interventions, and a cross-sectional household survey, were therefore undertaken. The latter took place in villages with and without interventions to improve access to diagnosis and treatment through village malaria workers or outreach clinics. Households were screened for individuals who had had an episode of malaria-like illness in the last three weeks. For households that were included, an interview was undertaken and questionnaires completed. This consisted of a household component capturing information about socioeconomic status and an individual component. The latter documented detailed information on treatment seeking behaviour and drug taking behaviour for the recent febrile illness. In addition to the questionnaire, a drug board for identifying drugs was used and blood was taken for microscopy and rapid diagnostic testing (RDTs).

3.7. Running the model

When the model had reached a stage at which it was felt sufficiently robust to use, it was run with different input parameters in order to explore the spread of drug resistance and the impact of combination therapy, under different scenarios.

For each scenario, the main biological model was run for 12 years, with the initial two years being the time taken for the model to reach a “steady state”, giving a time-frame of 10 years for actual comparison between scenarios. Selected outputs were then placed in clinical outcome and costs “sub-models” in order to generate outcomes in terms of actual number of cases of severe malaria, deaths, DALYs and costs.

Running the model therefore entailed three steps:

- 1) For each scenario, assigning values for the biological model and running this for 12 years.

- 2) Placing the outputs from the biological model into the clinical outcomes model in order to generate policy-relevant clinical outputs.

- 3) Placing the outputs from the clinical outcomes model into an Excel®-based spreadsheet. For each scenario, this results in the generation of the predicted levels of resistance, number of cases, failures, severe malaria and deaths, and costs. The results of these scenarios are then compared in a final spreadsheet in which cumulative costs, effects and cost-effectiveness ratios are calculated.

Table 3-2: Chain of events for clinical outcomes

Event	Indicator	Data availability	Note
X gets bitten by infected mosquito	Inoculation rate	Some data available	
X develops a patent parasitaemia	Likelihood of developing patent parasitaemia	Limited data	Prevalence data also reflects susceptibility
X transmits to person Y	Transmission rate		Core part of modelling transmission Actually depends on many steps ¹⁹
X develops symptomatic malaria	% of patent cases which are symptomatic	Some data available	Depends on immunity
X develops severe malaria	Likelihood of developing severe malaria	Some data available	Depends on immunity, treatment and drug resistance
X seeks treatment	Treatment rate	Data available	Depends on accessibility
X has a biological diagnosis	Biological diagnosis rate	Data available	Depends of type of provider
X is not correctly diagnosed	Sensitivity/specificity	Some data available	Depends on type of provider, type of test
X receives appropriate therapy	% correctly prescribed drug	Some data available but not for ACT	Depends on provider and drug availability and cost
X completes full course	Adherence rate	Data available but little on ACT ²⁰	
X fails treatment	Parasitological cure rate (Recrudescence rate)	Plenty of drug efficacy data Little effectiveness data	Depends on immunity, treatment, drug resistance and adherence
X receives 2 nd line therapy	Treatment rate	Limited data available	
X develops severe malaria after failing treatment	Likelihood of developing severe malaria	Some data available	Depends on immunity, treatment and drug resistance
X dies	Case fatality rate for severe malaria	Some data available	Depends on immunity, treatment and drug resistance

¹⁹ These steps are explained in detail in Chapter 4.

²⁰ There were little data on the use of ACT at the start of this study but a number of studies have been published since.

CHAPTER 4

DEVELOPMENT OF A BIO-ECONOMIC MODEL

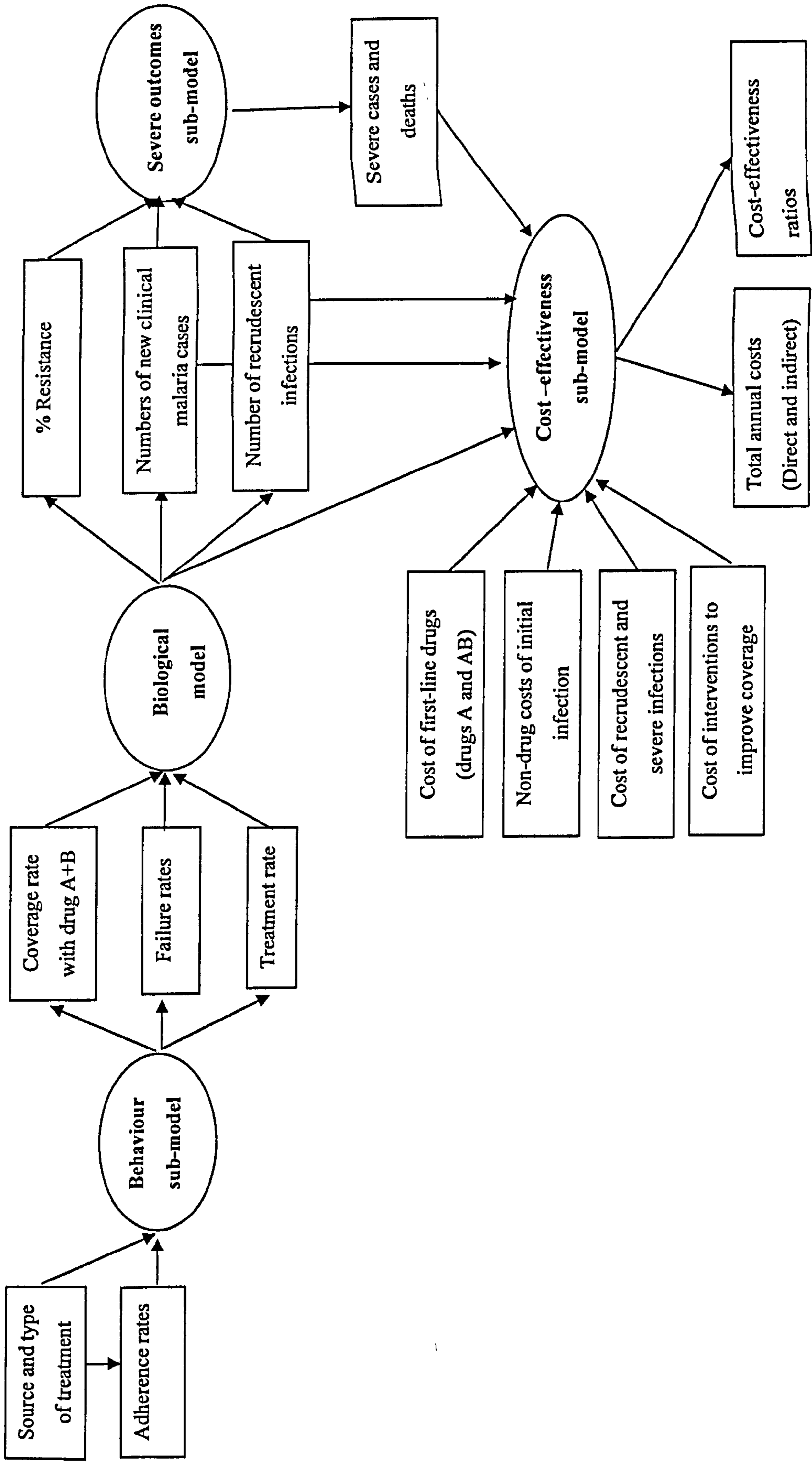
4.1 Introduction

In this chapter the development of the model is discussed. Firstly, there is a description of the overall structure, explaining how the core biological model and the behavioural and cost sub-models are integrated. The second section is devoted to the development of the biological model starting with a brief outline of its evolution, followed by a description of the model structure with a detailed explanation of the underlying concepts and data used. The third section describes how behavioural and economic sub-models were developed and integrated with the biological model. The chapter ends with a summary of the assumptions made. Annex 6 contains the parameter estimates.

4.2 The overall structure of the bio-economic model

Central to the overall bio-economic model is a dynamic biological model of malaria epidemiology, which describes the transmission of drug-resistant parasites through human hosts via the mosquito vector. It attempts to incorporate the vector, parasite, drug and human factors likely to affect malaria transmission and the spread of drug resistance. Linked to this core model are three sub-models based on simple decision trees that form the user-end of the model, which allow the integration of operational and behavioural factors and costs that enable economic analyses to be undertaken. The first sub-model – the behaviour sub-model – calculates the coverage rate and patient adherence rates to monotherapy and drug combination therapy according to whether patients seek treatment in the formal or informal sector. Based on this combined adherence rate, a maximum failure rate for each drug is assigned according to drug type and whether or not the infection is “drug resistant”. These maximum failure rates and the coverage rate are then used as inputs into the biological model. The second sub-model – the severe outcomes sub-model – calculates the annual number of severe malaria cases and deaths based on annual number of cases, treatment failures, and level of drug resistance output from the model. The final sub-model – the cost-effectiveness sub-model – introduces the cost of drugs, other illness costs and the costs of implementation strategies and uses the outputs from all three models to calculate the costs and cost-effectiveness of different scenarios. The relationship between these components is illustrated in Figure 4.1.

Figure 4-1: Diagram illustrating the relationship between the different components of the bio-economic model



4.3 The core biological model

4.3.1 An outline of the preceding models

The biological model was developed in the following steps, going from an initial simple exploration of the effect of immunity on the emergence and spread of resistance, “Model 1”, to a sophisticated model which attempts to incorporate all known factors affecting the development of antimalarial drug resistance in “Model 3”. In models 1 and 2, many of the key concepts in the final model were developed. However, because these earlier models were developed separately from the economic analysis and were superseded by model 3, only the latter model is described in detail. A table summarising the progressive sophistication of the models is shown below (Table 4-1).

Model 1 was a simple closed model, which explored how the spread of rate of resistance was affected by varying the relative reproductive advantage of resistant over sensitive infections and by varying the level of immunity in infected humans. Immunity was treated unrealistically, as a binary factor where hosts are either completely immune and therefore do not receive treatment, or they are completely non-immune in which case they do receive treatment. It was a static model, in which the output was the proportion of resistant infections out of a fixed total number of infections, and therefore effects on transmission and the actual number of infections could not be explored. In addition, the ability to explore the effect of different treatment options was limited. It was therefore not a suitable model upon which to base an expanded policy-relevant model.

Model 2 was a population-based dynamic model exploring the emergence and spread of resistance where immunity was incorporated as a function of age and was allowed to affect parasite density as well as the proportion of symptomatic and therefore treated infections.

Immunity was represented more realistically as a continuous function based on age-stratified rates of severe malaria (Yeung, Pongtavornpinyo et al. 2004). The emergence of drug resistance was incorporated simplistically by assigning every infection a fixed, albeit very small, probability of being a new resistant mutant infection. As the model ran, the immunity of the population was allowed to change in response to the change in transmission intensity. The output at the end of each annual iteration was the absolute number of infections, as well as the proportion of infections that were resistant. These values change from iteration to iteration according to the relative “reproductive rates” assigned to sensitive and resistant infections. These “reproductive rates” were simplified terms that encompassed a number of steps involved in human to mosquito to human transmission with vector factors being assumed to remain constant. In attempting to use the model to predict absolute numbers of infections year to year, it was found that this oversimplification of transmission proved problematic, especially in high transmission areas. In addition, because of the simplistic deterministic handling of the

emergence of drug resistance, there was an unrealistic constantly accumulating proportion of drug resistance.

In order to address some of the limitations of the second model, a third and final model was developed. In this model transmission is dealt with explicitly, with infectiousness based on the actual number and distribution of gametocytes through the human population and the incorporation of vector dynamics. In addition, durations of infection, which were ignored in the previous model, are incorporated and more facets of immunity are included and are described by separate immunity functions. In addition to the outputs in model 2, the numbers of cured and recrudescence infections, and the age groups in which they occur, are also produced. The emergence of drug resistance is separated from the spread in order to focus on the latter, as it was not possible to model both within the given time constraints and because it was felt that there were more data available to create a reliable model of the spread of resistance.

The remainder of this thesis relates only to the third and final model.

Table 4-1: Summary of the refinements of the biological models, from model 1 to model 3

	Model		
	1	2	3
Emergence of resistance included	0	√	0
Spread of resistance under drug pressure	√	√	√
Output as total number of infections	0	√	√
Immunity as a simple binary phenomenon	0	√	0
Immunity as a continuous phenomenon with multiple effects	0	0	√
Recrudescence infection included	0	0	√
Integration of cure rates within biological model	0	0	√
Infectiousness quantified as gametocyte carriage	0	0	√
Feedback loop between transmission intensity and immunity	0	√	√
Duration of infection included	0	0	√
Iteration frequency	√	Yearly	Daily
Vector factors dynamic included	0	0	√
Migration allowed	0	0	√
Seasonality allowed	0	0	√
Effects of chemoprophylaxis allowed	0	0	√
Different characteristics of drugs included	0	√	√

4.3.2 Computer programming

The biological models and severe outcomes model were programmed and run in S-plus® (version 7). The decision-trees and calculations of coverage and cure rates based on patient treatment-seeking and adherence behaviour were performed in Excel®, with the inputs being fed into the biological model. The cost-effectiveness sub-model was also undertaken in Excel® by cutting and pasting spreadsheets produced in S-plus®.

4.3.3 A general description of the core biological model

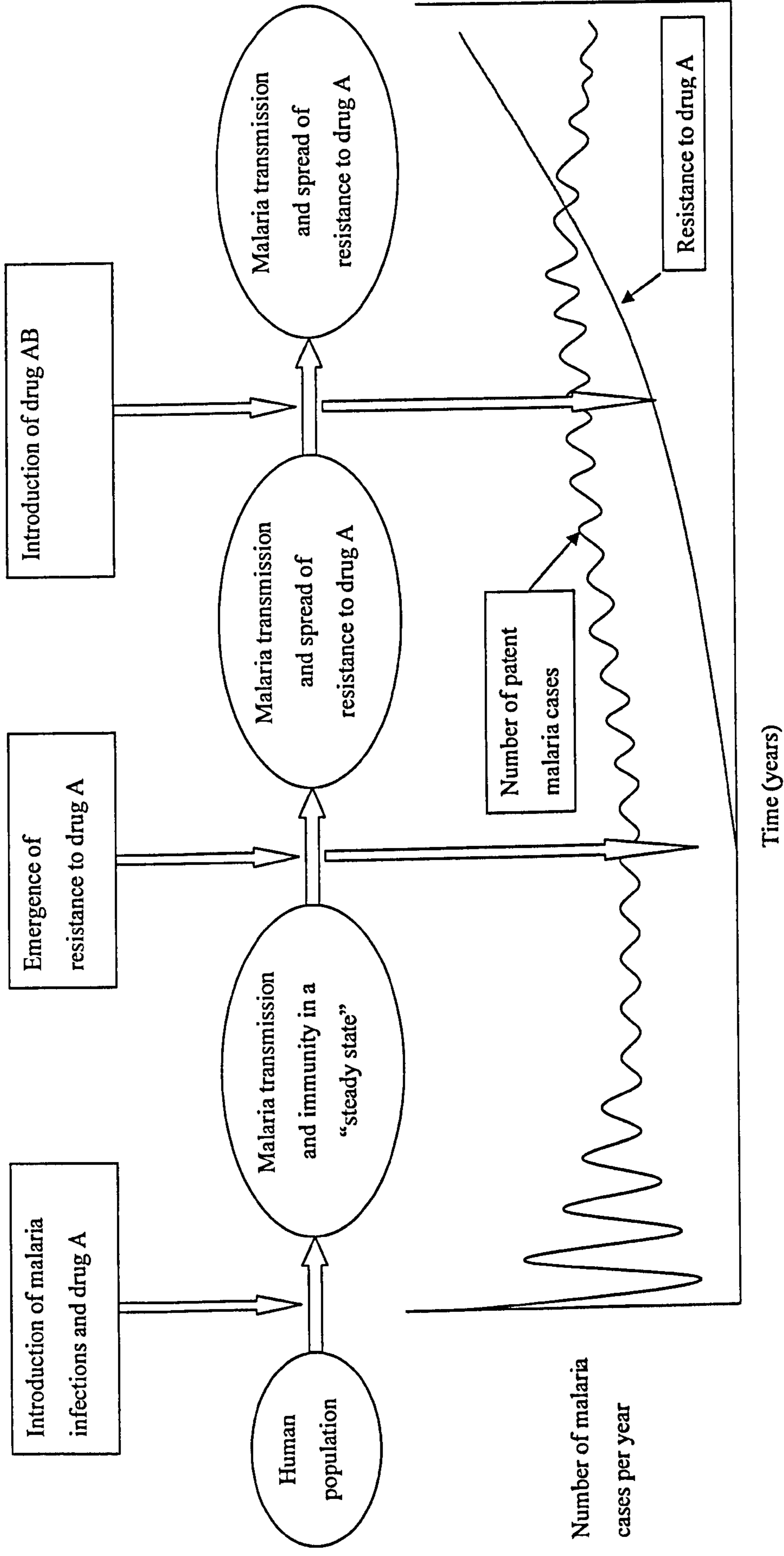
As explained earlier, the biological model is primarily a dynamic model of malaria transmission and the spread of drug resistance. The model iterates by the day. The main body of the model is deterministic except for the introduction of new (“migrant”) infections, which is allowed to vary stochastically daily²¹. The model involves, firstly, the introduction of malaria infections into a non-immune human population, which is stratified by age and where treatment of a fixed proportion of the population is with a monotherapy (drug A). This model is initially run with no resistance, until a stable level of transmission and human immunity is reached – a process that was found to take approximately two years. At this point, infections that are resistant to drug A are introduced at a user-defined starting level of resistance. A change in drug policy can be made from the monotherapy to a combination therapy (drug AB or BC) at any time²². This is shown schematically in Figure 4-2. This is a population-based model; therefore outcomes and changes are observed at the level of age-stratified groups and not in individuals, and the population in any one age-group is assumed to be homogenous. The total population and the age-structure are assumed to remain fixed. This means that the influx into the population in terms of births and immigrants is assumed to be balanced by the efflux out, in terms of deaths, due to malaria and other causes, and migrants.

Key inputs into the model include vector factors, drug characteristics, human behaviour factors (such as time-to-treatment and the proportion taking combination therapy versus monotherapy), treatment failure rates and costs. The model can then be used to compare alternative policies in different epidemiological settings by varying any of the input parameters and comparing the outcomes over the desired time period.

²¹ The sensitivity analysis, done by WP, was also stochastic, using Monte Carlo simulations.

²² The model also allows resistance to drug B or drug BC to be introduced at any time.

Figure 4-2: Schematic diagram of the biological model progression from steady state through to the introduction of resistance and changes in drug policy

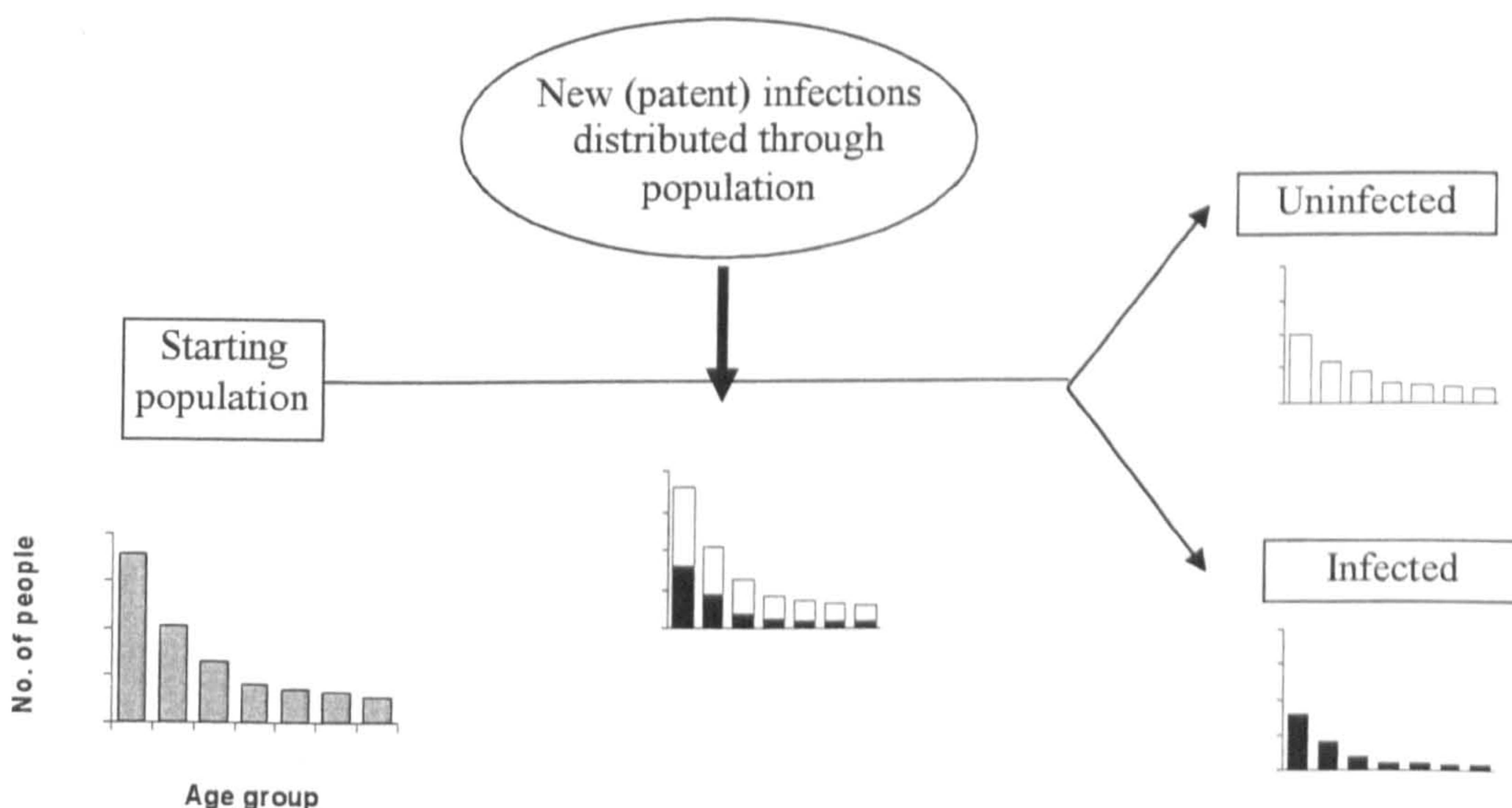


4.3.4 One iteration of the biological model

The model starts with a population of humans stratified by age. A specified number of new patent or transmissible infections are introduced into this population. For the very first iteration this number of infections is specified as an input value. Thereafter, the number of new infections is determined by the infectiousness of the population based on the previous iteration, as described later. The actual distribution of patent infections through the age groups is determined by the susceptibility to infection, which depends on the level of immunity. In the model, the level of immunity is expressed through the use of “immunity functions” which describe the relationship between age, transmission intensity and different facets of immunity. These are central to the model and are described in more detail later. This initial step is illustrated in Figure 4-3.

At this stage, an additional refinement to the model accommodates the possibility that some people, when bitten by a mosquito, will have recently taken antimalarial treatment for a fever presumed to be malaria (“presumptive therapy”) and this exerts a selective pressure that results in a fixed proportion of the potentially patent *sensitive* infections being extinguished.

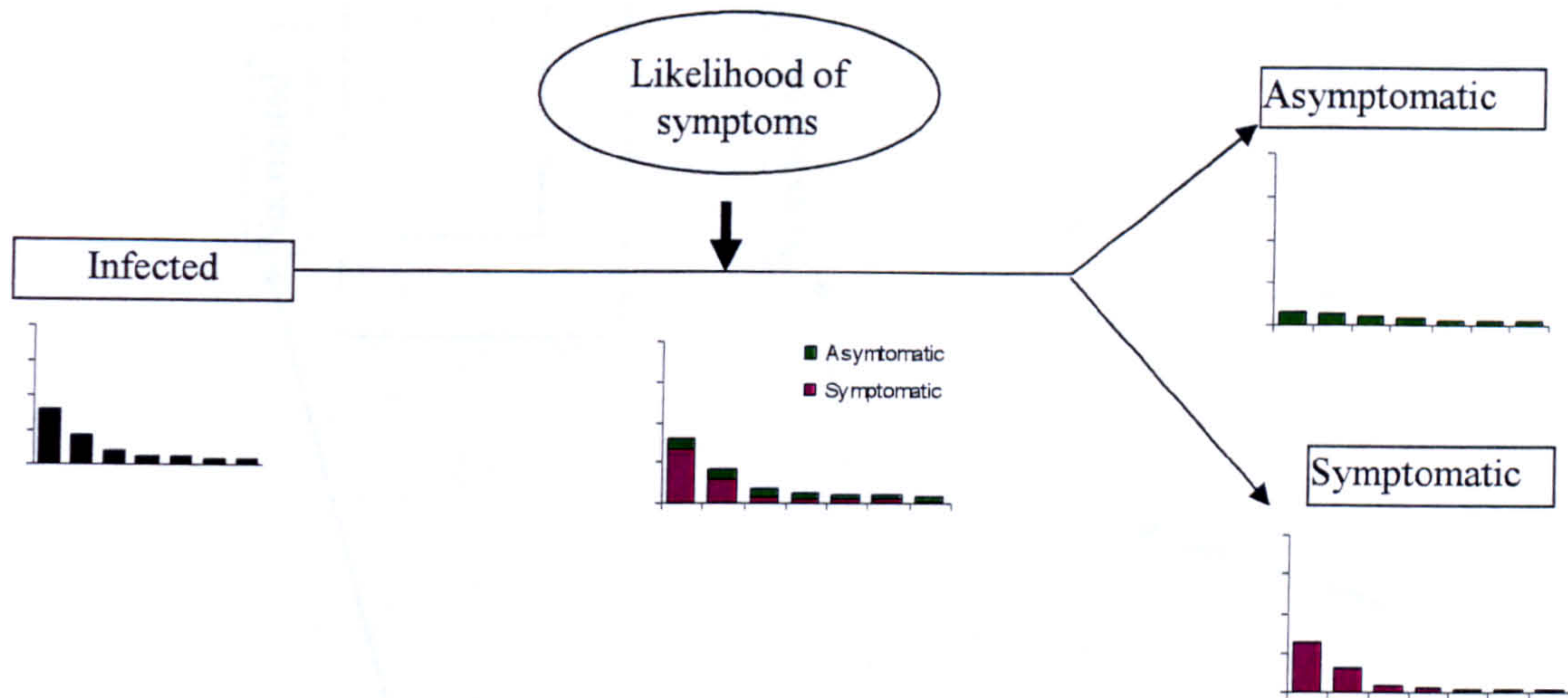
Figure 4-3: Introduction of patent infections into first iteration of model



Not all patent infections in humans will be symptomatic, as “anti-toxic” immunity allows immune patients to tolerate parasitaemias without apparent effect. Therefore, in high transmission settings the majority of infections, especially in adults, will be sub-clinical. This is important to capture accurately in the modelling of drug resistance, as it is patients who are symptomatic and take antimalarials who contribute to the drug pressure that selects for resistant

infections. In this model, the proportion of patent infections that are symptomatic depends on age and transmission intensity as determined by the immunity function based on age-stratified likelihood of clinical malaria (Figure 4-4).

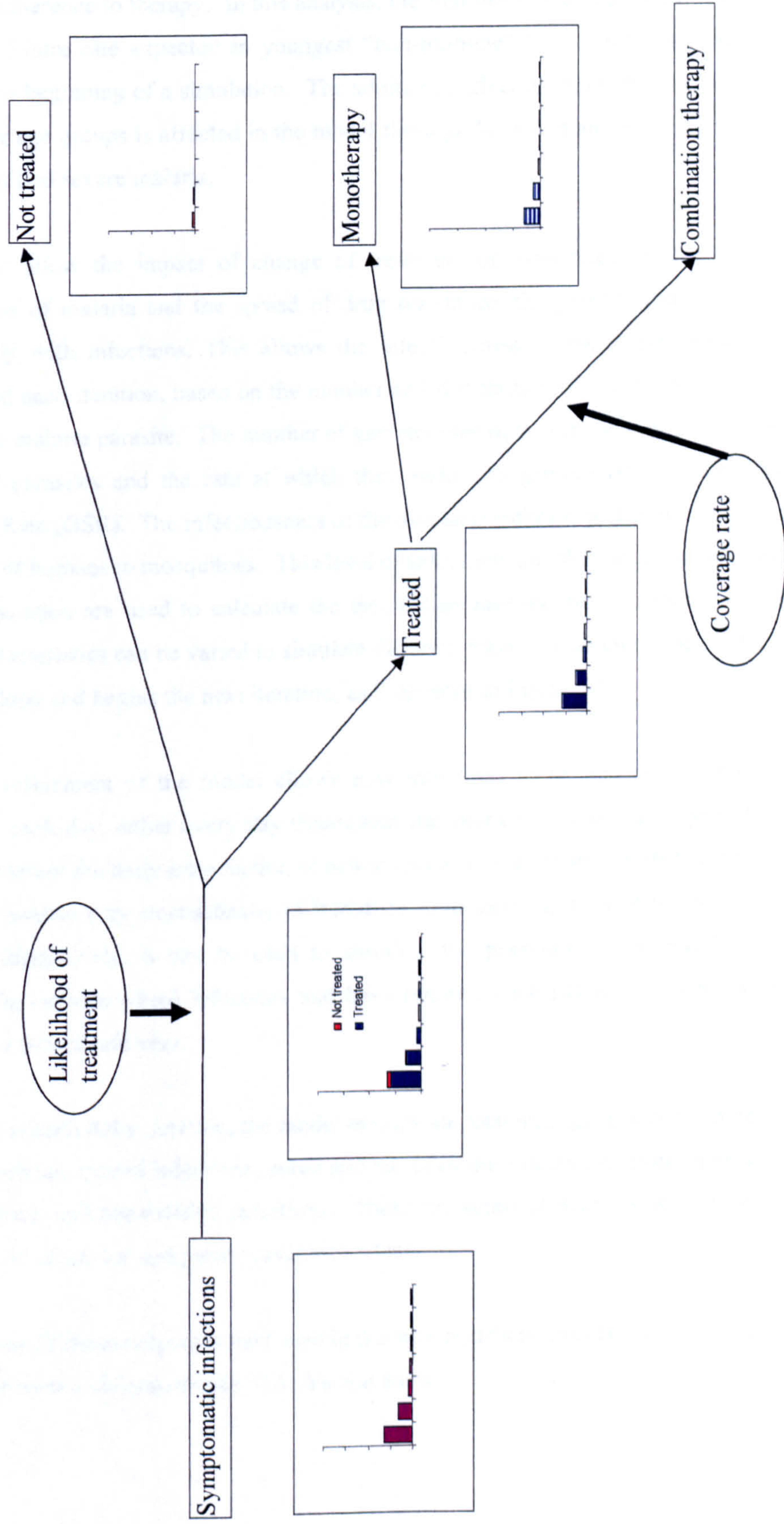
Figure 4-4: Determination of likelihood of symptoms by age



Most symptomatic patients seek treatment sooner or later, depending on accessibility to treatment. In this model, it is assumed that the likelihood of seeking treatment and time to receiving treatment is independent of age and both these values are assigned at the beginning of a simulation. In reality, patients take a variety of antimalarial drugs and drug combinations, and both the type and timing of treatment, may be dependent on age. However, for the purpose of this model, they are allowed to receive either a combination therapy (drug AB) or a monotherapy (drug A), and the proportion receiving combination therapy is termed the “coverage rate” and is varied as an input value (Figure 4-5).

The model is initially run without drug resistance in order to allow malaria transmission to reach a steady state. Infections that are resistant to drug A are introduced into the population as a proportion of the number of new infections. Resistant infections are more likely to recrudesce than sensitive infections if treated with a failing drug, and it is this that is the main driver of the spread of drug resistance. Resistance to other drugs can also be introduced later.

Figure 4-5: Assignment of treatment type



Untreated infections resolve after a certain amount of time, depending on the level of immunity. Treated infections may either be completely cured or may recrudescence if treatment is unsuccessful. The likelihood of recrudescence also depends on patient immunity, as well as the type of treatment, whether or not the infection is sensitive to the treatment received and the level of patient adherence to therapy. In this analysis, the first three factors are used to determine the maximum failure rate expected in youngest “non-immune” hosts, and this is input into the model at the beginning of a simulation. The additional effect of immunity in clearing infection in the older age groups is affected in the model through the use of an immunity function based on age-stratified severe malaria.

In order to allow the impact of change of treatment on cure rates to feed back into the transmission of malaria and the spread of drug resistance, the parasite population is tracked concurrently with infections. This allows the infectiousness of the human population to be estimated at each iteration, based on the number and distribution of gametocytes, the infectious form of the malaria parasite. The number of gametocytes is, in turn, determined by the number of asexual parasites and the rate at which they switch to gametocytes - the Gametocyte Switching Rate (GSR). The infectiousness of the human population is then used to work out the infectivity of humans to mosquitoes. This level of infectivity and the input characteristics of the vector population are used to calculate the inoculation rate for the next iteration. The input vector characteristics can be varied to simulate different transmission intensities. This therefore closes the loop and begins the next iteration, as illustrated in Figure 3-2.

A further refinement of the model allows new infections to be introduced into the human population each day, either every day throughout the year or for a specified period. It can be used to represent the daily introduction of new infections by a group of infected “migrants” and is programmed to vary stochastically to introduce some heterogeneity in transmission into the model. Alternatively, it can be used to simulate the phenomenon observed in some low transmission settings where infections that have remained sub-patent during a dry season re-emerge in a subsequent year.

At the end of each daily iteration, the model outputs the total and age-group stratified number of patent infections, treated infections, cured and recrudescence infections, taking into account both new infections and pre-existing infections. These are summed over a year to produce annual age-stratified incidence and point-prevalence rates.

A data-frame of these outputs is then used in the sub-models to calculate annual and cumulative numbers of severe malaria, deaths, DALYs and costs.

4.4 Parameter estimates

A large number of data were required at various stages in the development of the model. The process of developing the model, identifying what data were needed, and obtaining and transforming data, was iterative. There was a substantial amount of data that were useful in informing the development of the model but where actual values could not be used directly. The data that were collected and used are presented in table format in Annex 6 and are cross-referenced in the text in parentheses.

4.4.1 Uses of data

Data were applied in a number of ways:

- *Development of the overall framework.* For example, early on, evidence suggesting that the development of resistance was highly dependent on immunity ensured that this formed a core part of the model structure.
- *Input values.* The data were used to guide the values of inputs used in the base-case scenario and to determine the range and distribution of values to be used in the sensitivity analysis. For example, drug prices are known fairly precisely whereas the data on duration of infection in the immune individual are less certain and estimates covered a wide range.
- *Relationship between parameters.* Most often this was in the form of the likelihood of a given outcome; for example, the likelihood that a symptomatic patient would receive treatment or that a patient with severe malaria would die.
- *Construction of immunity profiles.* Immunity functions were constructed and extensively used in the model. Their construction required age-stratified data on malaria parasite density, morbidity and mortality from different transmission settings.
- *Validating the model.* The model produced outputs that could be validated against existing data, which had not been used directly in constructing the model. These data were therefore useful for checking whether the model outputs were within reasonable limits and refining the model. For example, the rich data from Senegal were used to check that in high transmission intensity areas, the model predicted the number of clinical attacks correctly (Trape, Rogier et al. 1994).
- *Scenario analysis.* Where basic data are available from one particular setting, this can be substituted and the model adapted in order to make predictions relevant to that setting under different intervention scenarios. This was applied to data from Cambodia.

4.4.2 Sources of data

Several approaches were taken to obtain parameter estimates. The available scientific literature was initially searched electronically using PubMed®. Bibliographies of relevant papers and reviews were searched for literature missed in the original search and for unpublished sources.

In addition, archived papers, pre-dating electronic bibliographies, were obtained from personal collections. Experts in the field provided an invaluable source of unpublished data or raw data, especially for use in the construction of the immunity functions. In addition, where data were insufficient or unobtainable, expert opinion was sought; for example, for estimates of the failure rates for untreated symptomatic infections. In the case of data on the implementation of ACTs, primary data on costs, coverage and adherence were collected in Cambodia.

4.5 Details of the biological model

4.5.1 Measuring parasites

Background

One of the most important characteristics of this model is that it handles malaria like a “macro” parasite by quantifying the density of infection in the human host. This is important in the modelling of malaria epidemiology and antimalarial drug resistance for a number of reasons. It is the distribution and density of infections in humans that determines both morbidity and infectiousness (Anderson and May 1991). In addition, the *in-vivo* effect of drugs on parasite density can be measured, creating the unique ability to quantify the pharmacodynamic properties of drugs on parasites (White 1997).

Modelling

The model is based on parasite biomass in terms of number of parasites per person, whereas most data available in the literature refer to parasite density in terms of parasites per μl of blood. Therefore, the biomass of human infections was calculated using data on estimated blood volume per kilogramme (kg) of body weight and the estimated weight-for-age (M1 and M2). In fact, the blood volume/kg changes vary by age (from 80 to 70ml/kg) and the weight-for-age for a population depends on a number of factors including race and nutrition.

4.5.2 Infections in the human host

Background

The meaning of “infection” is not straightforward in malaria, as the relationships between receiving a potentially infectious bite (being “inoculated”), developing a detectable parasitaemia, developing symptoms and transmitting to other people (“infectious”) are not fixed. A patient may receive an infectious bite after which the parasite may or may not multiply and the resulting parasitaemia may or may not be “patent” and may or may not be associated with symptoms. It is therefore important to define what is meant by infection depending on the perspective and outcome of interest.

From the perspective of the patient and health worker, an infection is relevant if it causes symptoms for which a patient might seek treatment. Symptomatic infections also matter from a public health perspective as whether or not patients are treated successfully has implications in terms of both transmission and the development of drug resistance. However, infections that do not cause clinical symptoms may still be transmissible or “patent” and are therefore important from a public health perspective. As we are interested in transmission, drug resistance *and* clinical outcomes, the model handles “patent”, “symptomatic” and “treated” infections.

→ Patent infections are those where the asexual parasite density is high enough to generate enough gametocytes to cause a transmissible infection in a biting mosquito. Normally, in order for a mosquito to develop a transmissible infection it must take up at least one female and one male gametocyte in one blood meal. Because in human infections with malaria, there are normally four females for one male (Smalley and Sinden 1977; Smalley and Sinden 1977; Robert, Sokhna et al. 2003), the mosquito must take up on average five gametocytes in one meal. One blood meal is usually 2-3 μ l. Therefore, the density must be on average at least three per μ l equivalent to a total parasite biomass of approximately 10^7 parasites in an adult²³.

← This true?

Modelling

For the purpose of this model, the equivalent of 10^7 parasites in an adult is therefore considered to be the minimum parasite density for patent infections. This works out to be around the parasite density that can be detected by light microscopy, which is fortuitous in our interpretation of field data, as it allows us to assume that all detectable parasitaemias from cross-sectional prevalence studies are potentially transmissible and therefore to use such data directly.

All uninfected humans have an equal chance of being inoculated by an infective mosquito but whether or not the inoculation results in a “patent” infection is dependent on the immunity profile based on the age-stratified susceptibility of infection. This is discussed later in the section on immunity.

← This is not true!
Like other models of malaria transmission, we do not consider super-infection (Hastings 1997; Koella and Antia 2003). Therefore, only non-infected humans are susceptible, and while infected, another infection is not allowed.

²³ There is some evidence to suggest that the gametocyte density picked by a mosquito from a skin capillary may not reflect that in a blood smear and that the ratio of gametocyte may vary according to drug treatment, but for this model these are ignored. There must also be an absence of factors which inhibit the development of viable sporozoites in the mosquito.

Individuals who have sub-patent infections where the parasite density is less than the detectable limit are assumed to have a low enough transmission potential that their contribution to the overall infectiousness of the population can be ignored. However, in reality there is some evidence that in low transmission settings, chronic low-density infections may survive through the dry season and be an important source of new infections at the beginning of the next high transmission season. As discussed later, the model allows for this phenomenon to be simulated.

4.5.3 Period of chemoprophylaxis

Background

At any point in time, a certain proportion of the human population will have detectable levels of antimalarial drugs in their blood stream as a result of having taken antimalarial drugs, for example a recent episode of fever. A few of these will have a high enough drug concentration to inhibit the growth of sensitive parasites emerging from the liver 10 days after inoculation, effectively providing patients with chemoprophylaxis and exerting drug pressure that favours the selection of resistant parasites. Drugs with long half-lives, such as mefloquine, are particularly vulnerable to this type of drug pressure. As parasites become increasingly more resistant, they are able to tolerate and survive through higher levels of drug. In addition, the likelihood that a new infection becomes established in the presence of presumptive therapy is dependent on the amount of drug taken, the half-life of the drug, the time elapsed since being taken and the degree of drug resistance of the parasite.

The likelihood that individuals will take antimalarial drugs in the absence of infection depends on epidemiological and behavioural factors. It is particularly high where the population habitually treat any fever with antimalarial drugs and historically during programmes of mass drug administration. In high transmission areas, it has been estimated that some 40% of children receive antimalarial treatment prior to seeking treatment at a clinic (Nshakira, Kristensen et al. 2002) and that 24% of children with fever in the community had received an antimalarial in the previous two weeks (Talisuna, Langi et al. 2002). A recent study by Eriksen et al. in Tanzania found that 18% of children in the community had detectable levels of sulfadoxine in their blood (Eriksen, Nsimba et al. 2005).

Modelling

In order to incorporate this phenomenon into the model, we simplified this relationship so that humans either have an inhibitory level of drug A in their blood or not, and if they do then potentially patent "sensitive" infections are extinguished whereas "resistant" infections survive.

The value input into the model is the fixed proportion of the potentially patent *sensitive* infections that are extinguished before the infection reaches. In the base-case scenario this is assumed to be 10% of the population (M10).

4.5.4 Symptomatic infections

Background

Patients with patent infections may be asymptomatic or may develop fever and other symptoms depending on their age, parasite density and level of immunity. For non-immune patients, nearly all patent parasitaemia result in symptoms. Estimates range from 84–100% from studies based on adults and children in low transmission settings (Luxemburger, Thwai et al. 1996; Barnes 2003) and 95% in adult malaria therapy patients (Ciuca, Ballif et al. 1934).

Numerous studies have attempted to establish the relationship between fever, age, immunity and parasite density. A number of studies have found that there is a significant negative correlation between age and pyrogenic density (Petersen, Hogh et al. 1991; Cox, Kum et al. 1994). In Senegal, the age dependent threshold parasitaemia was five times higher for a one year old than in a 60 year old (Rogier, Commenges et al. 1996). Petersen and colleagues suggested that this indicated there was no evidence of a separate “anti-disease immunity” independent of parasitological immunity, arguing that immunity results in less parasites and as a consequence less severe symptoms (Petersen, Hogh et al. 1991).

Modelling

In this model the proportion of patent infections in each age group that manifest symptomatically is determined by the immunity profile based on age-stratified prevalence of clinical malaria (Im 1 and Im6)). An alternative approach would have first determined the parasite density of infections and then used a parasite-density dependent “pyrogenic threshold” to determine the number of symptomatic and asymptomatic infections. However, this was not undertaken for two reasons. Firstly, as described above, the exact relationship between age, immunity and pyrogenic threshold is still uncertain. Secondly, this is a population-based model in which each age group is assigned an average parasite density. Therefore, in age groups where the average parasite density falls below the pyrogenic threshold, *all* individuals in that age group would be assumed to be asymptomatic and vice versa. To enable this approach to be taken, the model would need to be adapted so that each age group was assigned a parasite density profile rather than an average parasite density, and then determining a pyrogenic threshold for each group dependent on the parasite density and possibly transmission intensity.

4.5.5 Parasite growth and maximum parasite density

Background

Humans with previous and sustained exposure to malaria develop an anti-parasitic immunity that enables them to control the level of parasitaemia and to clear parasites without treatment. Therefore, in high transmission settings, the mean parasite density falls with age (Trape, Rogier et al. 1994; Akim, Drakeley et al. 2000). Patients without such immunity are more likely to

develop higher density infections and to take longer to clear their infections without treatment. In reality, once the parasite density reaches a certain threshold that causes symptoms, they are likely to seek treatment that modifies the duration of infection.

The parasite multiplication rate prior to treatment is approximately eight-fold (90% CI, 5-12.3) per 48-hour cycle (Simpson, Aarons et al. 2002). The maximum parasite density in a non-immune host can reach almost $10^7/\mu\text{l}$. The relative parasite density in asymptomatic infections varies in relation to symptomatic infections from 0.01-0.03 in Vanuatu (Maitland, Williams et al. 1996) to 0.55 in Mali (Sagara, Sangare et al. 2002) and 0.7 in adults in Ghana (Owusu-Agyei, Koram et al. 2001).

Modelling

The parasite density in all infections is allowed to increase at the same rate of one log every 2 days (M9). However, the maximum density that they are allowed to reach is higher in symptomatic infections, which occur in relatively non-immune patients, compared to asymptomatic infections. The actual value for each age group is determined by an immunity function derived from age-stratified parasite density (Immunity Function 3 (Im3)) as described later. At the start of the model the maximum parasite biomass in the non-immune symptomatic infections is assumed to be equivalent to 10^{12} in adults. The parasite mass in asymptomatic infections is assumed to be 0.5 relative to that in symptomatic infections (A1).

For symptomatic infections, it is assumed that patients become symptomatic when they reach this maximum parasitaemia. The length of time from this point to when they receive treatment depends on a number of factors including the patients' access to treatment and is varied as an input factor (S3). During this time, it is assumed that the parasite density remains at the maximum parasite density.

4.5.6 Likelihood of treatment

Background

The likelihood that patients with symptomatic malaria receive antimalarial treatment depends on their treatment-seeking behaviour and access to antimalarial drugs. There is a substantial literature on the subject, including a review by McCombie (McCombie 1996) which suggested that although estimates varied substantially, the majority of patients seek treatment outside the home (>90%). This is corroborated by subsequent studies (Munguti 1998; Nuwaha 2002; Eriksen, Nsimba et al. 2005) which have found rates of 84–96%. However, the percentage actually receiving antimalarial treatment may be slightly less at around 80% (Espino and Manderson 2000; Deressa, Ali et al. 2003).

Modelling

The likelihood of treatment is an input variable into the model and is termed the “treatment rate”. The base-case scenario is given a value of 0.95 (S1).

The actual drugs that patients receive depend on a number of factors including whether they receive treatment in the formal or informal sector and the current recommendations. For simplification in the biological model, patients are allowed to either receive combination therapy (drug AB) or monotherapy (drug A), and the proportion that receives combination therapy is termed the “coverage rate”²⁴. The coverage rate is an aggregate value, calculated separately using simple decision-tree based models as described later in this chapter.

4.5.7 “Migrant” or dormant infections

Background

In areas where the level of local transmission is low, infected immigrants from high transmission areas can be important in the maintenance of malaria infection in the population (Craig, Kleinschmidt et al. 2004; Zhou, Sirichaisinthop et al. 2005). In other areas where transmission is highly seasonal, there is evidence that infections in humans can remain at a sub-patent level through the dry season to become reactivated at the beginning of the next wet season. Such infections may therefore be an important reservoir of infections, enabling transmission to continue year to year (Roper, Elhassan et al. 1996; Babiker 1998).

Modelling

The model allows the possibility of introducing new infections either at a constant rate or over a specified number of days. Introducing infections at a constant rate can be considered to represent the inward migration of an infected population. The size and the characteristics of this sub-population can be adjusted so that when introduced, they have a different immunity profile and level of resistance from the main population. When the model was run to simulate low transmission settings, it was found that these “new” infections were important for the maintenance of infection in a population. Without them, it was possible to eradicate malaria in certain situations. Although not the focus of this thesis, this is an interesting finding and may be explored further using the model. In the base-case scenario, it is assumed that rate of introduction of migrant infections is around 5% of the population per year. This is allowed to vary from 3 to 7% of the population on a daily basis.

²⁴ In reality, patients receive any number of different drugs and combinations but this was too complex to be modelled.

4.5.8 Duration of infection

Background

The duration of parasitaemia in the human host is important in determining infectiousness – the longer an individual carries a patent parasitaemia, the longer they are potentially infectious to mosquitoes²⁵. Duration is influenced by the maximum density of parasites attained and the rate at which they are cleared from the blood, which both depend on host immunity and drug treatment. The effect of immunity on the duration of infection is uncertain. It is likely that duration of infection is reduced by immunity and this has been assumed by most mathematical models (Molineaux, Storey et al. 1980; Cross and Singer 1991).

Few data are available for the duration of *untreated* infections, and estimates vary widely. This is because, for obvious ethical reasons, one cannot nowadays observe the natural course of infection in symptomatic patients without terminating the infection. However, estimates are available from the early observational studies of malaria therapy in adult patients with neurosyphilis and more recent longitudinal studies on asymptomatic infections.

In an early study on malaria therapy patients, Eyles and Young estimated the average duration of an initial infection to be 121 days (s.d. 9 days). In a more recent retrospective analysis of similar data, the duration of primary treated infections varied from 79 to 132 days depending on parasite strain and from 89 to 185 days in infections that remained untreated (Collins and Jeffery 1999).

In more recent years, molecular techniques have been used to detect persistence of parasitaemias that are undetectable by microscopy. In Sudan, in an area of highly seasonal malaria transmission, it was shown that multiclonal infections could be maintained throughout the dry season and into the next wet season (Babiker 1998; Babiker, Abdel-Muhsin et al. 1998). These would be supplanted by a novel genotype when transmission restarted. Franks et al. longitudinally studied 143 newborns in coastal Ghana, with monthly blood tests for the first two years of life, and found a median duration of an asymptomatic infection was less than four weeks and the longest period of continuous infection was 64 weeks. However, the transmission intensity was moderately high (5-10 infectious bites/year) and the duration of infection would have been influenced by immunity derived in-utero (Franks, Koram et al. 2001). But the problem with using the molecular-based data in the model is that because the infections are

²⁵ There is a difference between the “duration of infection” and the duration of illness experienced by patients. Duration of illness is important from the patient’s perspective, both in terms of morbidity and costs in terms of days of lost productivity. The duration of illness is generally shorter than the duration of infection as symptoms are only experienced when a certain level of parasitaemia is reached. Average durations of symptomatic uncomplicated and severe episodes of malaria are used in the calculation of the cost of illness.

his?
me?
undetectable by light microscopy, they do not fall into our category of "patent" infections and are not considered transmissible.

Modelling

At a population level, the daily rates at which different infections are cleared from the human population are calculated as the inverse of the duration in days. This overall rate of conversion of "infecteds" to "non-infecteds" represents the population recovery rate.

To describe the relationship between age and duration of infection, the immunity function based on age-stratified parasite density (Immunity Function 3 (Im3)) was used with specification of the maximum durations of treated and untreated infections in the non-immune host.

The maximum duration of *treated* infections varies within the model according to the parasite reduction ratios for each drug (Im8). These were obtained from work by White and are based on the parasite clearance times provided in clinical trials (White 1997). This is described in more detail in the section on drug characteristics.

For the purpose of the model, the maximum duration of an untreated infection is assumed to be 80 days (Im7). This "untreated" group is predominantly made up of "immune" patients. However, for model simplicity and because of the lack of data, symptomatic non-immune patients were placed in the same group.

4.5.9 Immunity

Background

Immunity clearly plays a central role in malaria epidemiology and in the development of antimalarial drug resistance. Immunity to malaria is acquired slowly following repeat and sustained infection. However, few individuals ever become completely immune and malaria infection continues throughout life despite repeated inoculation, with adults in high transmission areas tolerating a low-density parasitaemia without symptoms (a phenomenon known "premunition"). The level of immunity attained depends on a number of factors including the pattern of exposure, natural maturation of the immune system, parasite variability and variation between individuals and ethnic groups.

As mentioned earlier, two main facets of immunity have been recognized: "clinical" or anti-toxic immunity, which acts to ameliorate the exhibition and severity of clinical symptoms, and anti-parasite immunity, which limits parasite numbers, replication and burden in the human host. These facets can be further broken down into the following:

- Reduction in host susceptibility to infection;
- Reduction of the level of parasitaemia in infected patients;
- Reduction in likelihood of fever and other symptoms in infected patients;
- Reduction in the therapeutic failure rate for all levels of antimalarial drug resistance;
- Reduction in severe disease and mortality.

The relationship between age and frequency of infection and the rate of acquisition of immunity is complex and has not been clearly defined. From the neurosyphilis studies, adult patients developed both anti-parasitic and clinical immunity after one infection (Collins and Jeffery 1999). However, the different facets of immunity appeared to be acquired at different rates at different transmission intensity.

In high transmission settings, infants and young children are particularly susceptible to severe and fatal malaria (Marsh 1992). Clinical immunity is gradually acquired through childhood (Rogier and Trape 1993) and this manifests as lower rates of disease and decreased severity of disease despite parasitaemia. Therefore adults are much less likely to develop infections (Beier et al 1994), to develop high parasitaemias (Beadle, McElroy et al. 1995) and to present with clinical symptoms (Bloland, Boriga et al. 1999; Owusu-Agyei, Koram et al. 2001). Infants in their first six months of life appear to be relatively protected against infection and severe clinical episodes of malaria (Kitua, Smith et al. 1996) due to acquired immunity from their mothers in-utero (Edozien, Gilles et al. 1962).

Anti-parasite immunity which results in eliminating parasites or limiting their replication and burden also increases with age (Rogier, Commenges et al. 1996). The peak in age-stratified prevalence appears to occur later than the peak in incidence of clinical attacks (Smith, Genton et al. 1994). However, there is some evidence that of the two components only anti-parasite immunity plays a major role as age increases and not "anti-toxic" (clinical) immunity (Petersen, Hogh et al. 1991; Rogier and Trape 1993).

At low transmission intensities, older children and adults have little immunity. There is some evidence that in epidemic situations, adults may be even more susceptible to infection and severe disease. Baird found that the prevalence of parasitaemia soon after onset of exposure was similar in non-immune migrants adults compared to children (Baird 1998) and that the risk of severe malaria was almost 2.7 times higher (95% CI=1.8-4.2) (Baird, Masbar et al. 1998). Similarly, Soni and Gouws found that the odds ratio for severe malaria in those over 12 years compared to under 12 years was 4.8 in the KwaZulu-Natal (Soni and Gouws 1996).

At intermediate levels of transmission, the relationship between transmission intensity and the epidemiology of severe malaria is therefore not straightforward. As the entomological inoculation rate (EIR) falls below 10 to 20 infective bites per year, the incidence of clinical malaria episodes and paediatric severe malaria appears to be higher than at higher levels of transmission intensity (Marsh and Snow 1999), and there is a shift from severe malarial disease in children younger than five years toward severe disease in older age groups (Snow, Omumbo et al. 1997).

However, it has been widely observed that age is an important risk factor for treatment failure (Fontanet and Walker 1993; Dorsey, Kamya et al. 2000). In Uganda, children under the age of five years were found to be 3.4 times (95% CI = 1.8-6.3) more likely to be unsuccessfully treated with chloroquine than older patients (Dorsey, Kamya et al. 2000) and to require fewer *dhfr/dhps* mutations for treatment failure with SP (Staedke, Sendagire et al. 2004).

The effect of immunity of infectiousness – i.e. the existence of transmission-blocking immunity – is still uncertain. There is some evidence that there is a specific immunity that results in the suppression of gametocyte production independent of the number of asexual parasites (Baird, Jones et al. 1991; Bousema, Gouagna et al. 2004).

Loss of exposure results in loss of immunity over a period of time that varies from host to host and depending on the type of immunity. African expatriates lose some immunity over two to three years while remaining protected from severe disease (Carter and Mendis 2002).

Modelling

Unfortunately there is no *ex-vivo* correlate for immunity against malaria, meaning that there is no single blood test that accurately reflects the level of functional immunity. However, it is possible to measure some of the *effects* that immunity has on clinically relevant outcomes. Therefore, by mathematically describing the relationship between age, transmission intensity and these outcomes, the resulting functions could be used in the model as proxy measures of immunity. The three functions for which sufficient data were obtained are:

- Likelihood of symptomatic malaria (Immunity Function 1)
- Mean parasite density (Immunity Function 2)
- Likelihood of severe malaria (Immunity Function 3)

These immune functions took the form of multiple regressions using EIR and age as independent variables. Detailed information on the sources of the original data, the functions and graphs themselves can be found in Annex 7.

These three immunity functions were used directly in the model and were also used as proxies for the other facets of immunity for which there were insufficient data. It is assumed that immunity does not have any specific effect on the infectiousness of gametocytes – that is, there is no transmission-blocking immunity – due to the uncertainty in the data.

The immune function described the *change* in an outcome with age but not the actual outcome itself. In order to generate actual values, the functions were “zeroed” by specifying the value in the youngest (under one year old) age group, who were assumed to be the most “non-immune”. The facets of immunity, the immune function and data on which they are based are shown in Table 4-2. Where the functions are incorporated into the model is illustrated in Figure 4-6 and the facets and functions are discussed below.

Host susceptibility

Host susceptibility determines the likelihood that an inoculation results in a patent infection in a human. This cannot be measured directly and therefore the function based on age-stratified parasite density (Immune Function 2) is used as a proxy. This assumes that the anti-parasite immunity limiting the number of parasites in patent infections is similar to the immunity that eradicates parasites so that patency is never reached.

The maximum likelihood of infection in the non-immune host is specified at the beginning of the model and the immune function is then used to describe the likelihood of infection in other age groups. From experiments on non-immune volunteers, it is apparent that several infective bites are required to get reliable infection (Peters, Fowler et al. 2002), showing that susceptibility to any single bite is below one. From a study on malaria therapy patients, Ciuca observed that after a single inoculation 75% of patients developed symptomatic parasitaemias and 4% developed asymptomatic parasitaemias (Ciuca, Ballif et al. 1934). A value of 0.8 was therefore used as the model input for the maximum likelihood of host susceptibility in the base-case scenario (Im4).

Likelihood of symptomatic infection

In order to answer the question “given a patent parasitaemia (of any level), what is the likelihood of clinical symptoms?”, individual level-data were required. Authors were therefore contacted directly and four data sets were obtained which contained adequate and comparable data on age-stratified parasitaemia and clinical outcomes²⁶.

²⁶ As mentioned in the methods section, it was done this way round, rather than first determining the distribution and level of parasitaemia in each age group then separating asymptomatic from symptomatic cases, because in this population-based model it would have meant whole age groups either being symptomatic or not.

The best fit was with a bi-exponential non-linear regression model and the resulting function (Immunity Function 1) is used directly in the model to determine the proportion of patent infections in each age group that are symptomatic. The maximum likelihood that a patient with a patent parasitaemia is symptomatic in a non-immune host is specified as an input parameter and in the base-case scenario was assumed to be 0.8 (Im6).

Parasite density

Immunity Function 2 is based on the age-stratified parasite density at different transmission intensities. Eight sets of age-stratified cross-sectional data were obtained. The data from Thailand, Laos and two areas in Kenya were in the form of patient-level raw data and the remaining four sets of data were in the form of mean age-stratified densities. As the model tracked actual parasite numbers rather than density, the mean age-stratified parasite biomass was calculated²⁷. It was assumed that the detectable limit in all studies was 20 parasites/ μ l (parameter M8) and the average blood volume was 75ml of blood per kg of body weight (M2).

A number of non-linear regression models were fitted onto the data with the best fit being described by a two-term exponential decay function with an interaction term. This function is used directly in the model to calculate the parasite density in each group. The function is also used to as a proxy measure of the effect of immunity on host susceptibility and duration of infection.

Duration of treatment

It was assumed that the mechanism of host immunity that limits parasite density is the same as the mechanism that clears existing parasites. Therefore, the immunity function based on parasite density was also chosen to describe the relationship between duration and immunity. The maximum durations of different types of untreated infections and minimum parasite reduction ratios in treated infections are therefore assigned as input parameters (Im7 and Im8).

Likelihood of treatment failure

Age-stratified data on treatment failure are not widely available but obviously form a key component of the model. Fortunately, data suggest that in a low transmission setting the relationship between age and treatment failure rate is very similar to the relationship between age and severe malaria. It is therefore assumed that the immune mechanism protecting a human from developing severe malaria is the same or very similar to that which clears infection. Therefore, the immune function based on the age-stratified likelihood of severe malaria

²⁷ Where raw data were used, this was calculated using the mean log (parasite density).

(Immunity Function 3) is used in the model to determine the effect of age and transmission intensity on the likelihood of treatment failure. The “maximum failure rate for a non-immune patient” is specified depending on treatment type, drug resistance and level of patient adherence to therapy (Table A6-14). During the running of the model, the actual value used for a given age group is determined by the immunity function relative to this maximum rate.

Likelihood of severe malaria

The data used in order to construct the immunity function based on age-stratified severe malaria came from prospectively recorded paediatric admissions with severe malaria from five discrete communities in The Gambia and Kenya (Snow, Omumbo et al. 1997), and from one study on adults and children in Thailand (Luxemburger, Ricci et al. 1997).

A number of non-linear regression models were fitted onto the data with the best fit being described by a two-term exponential decay function. This function is used in the severe outcomes sub-model to describe the likelihood of severe malaria in the absence of drug resistance after specifying the maximum likelihood in a non-immune host. The increase in likelihood of severe malaria due to increasing drug resistance is then calculated. It is also used as a proxy for the effect of immunity on clinical failure based on evidence that there is a similar relationship between age and the two outcomes in a low transmission setting.

Figure 4-6: Schematic diagram of where immunity influences age-stratified likelihoods in the biological model.

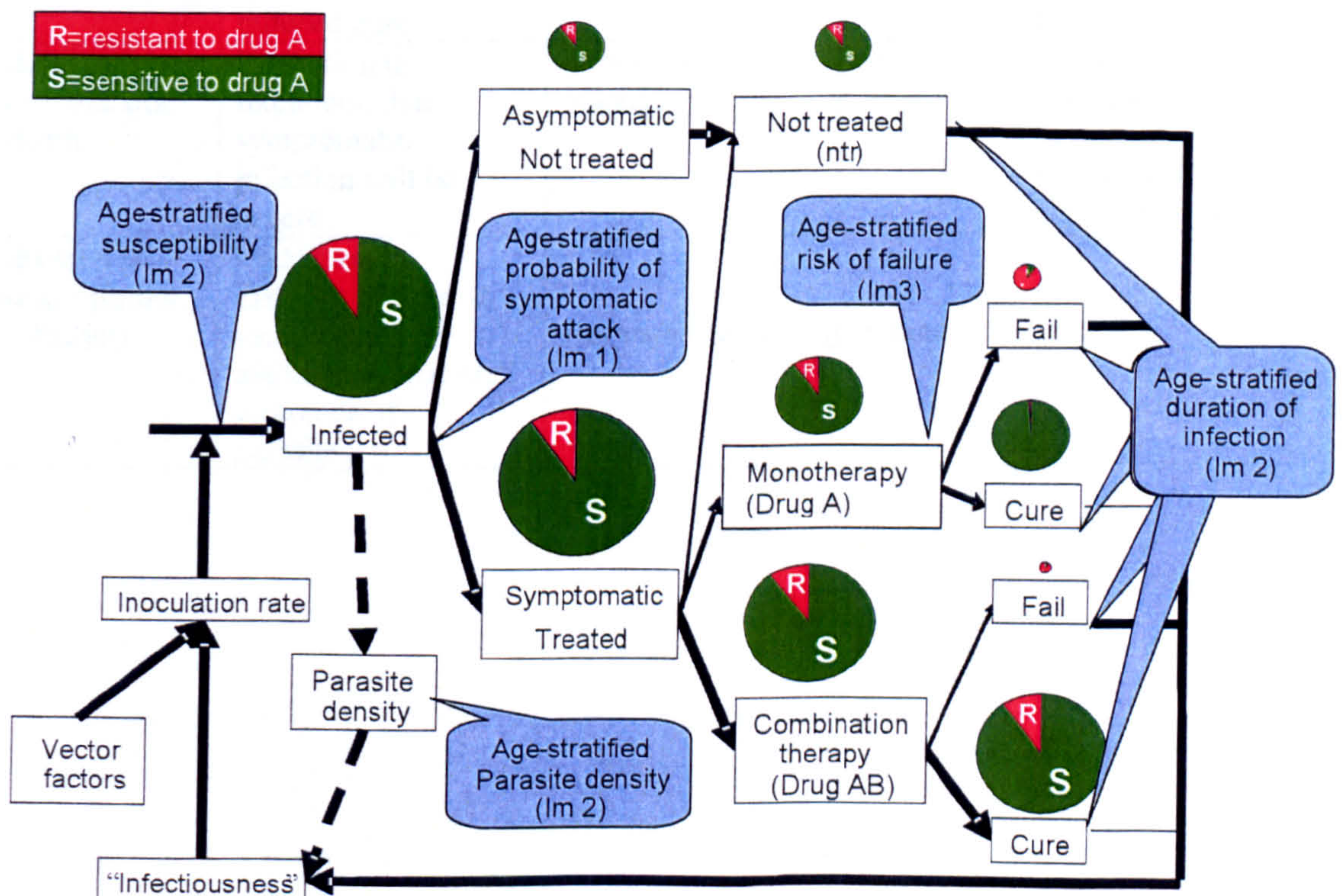


Table 4-2: Facets of immunity and data used in model

Facet of immunity	Explanation	Age and EIR stratified data used in immunity function	Immunity function (Im)	Parameter for "zeroing" immunity function
Reduction in "Susceptibility"	Reduction of the probability that an inoculation becomes a detectable and viable infection (pre-erythrocytic or liver stage immunity)	Mean parasite density	Im 2	Maximum susceptibility of a non-immune host
Reduction in maximum parasite density	Reduction in the probability that viable merozoites released from the liver will multiply during the blood stage of infection to reach high densities	Mean parasite density	Im 2	Maximum parasite density in non-immune host
Reduction in duration of infection	Increased rate of clearance of parasites	Mean parasite density	Im 2	Maximum durations of different types of infection in non-immune host
Reduction in symptomatic disease	Reduction in the likelihood that a patent infection will be symptomatic	Likelihood of symptoms infection	Im 1	Maximum likelihood of symptoms in non-immune host
Increase in self-cure and cure rate	Increased clearance of parasites and therefore likelihood of self or drug induced cure	Risk of severe malaria	Im 3	Maximum failure rate in different types of infection in non-immune host
Reduction in severe malaria or death	Reduction in likelihood that symptomatic infection will be severe	Risk of severe malaria	Im 3	Maximum likelihood of developing severe malaria in non-immune host
Reduction in transmissibility of infection	Reduction in viability of formed gametocytes (in addition to increased clearance of parasites)	Not included directly in model		

4.5.10 Gametocytes and infectiousness

Background

Gametocytes are the entity responsible for transmitting malaria from humans to mosquitoes. One of the key characteristics of this model is that by quantifying infectiousness in terms of gametocyte carriage, the details of transmission are handled explicitly. It is known that recrudescence infections are associated with a higher gametocyte density, with important consequences for the spread of drug resistance (Price, Nosten et al. 1999; Sowunmi and Fateye 2003; Suputtamongkol, Chindarat et al. 2003). Drug treatment and drug efficacy affect the gametocyte density by decreasing the asexual parasite density. Drugs can also alter the rate at which asexual parasites switch to gametocytes, the “gametocyte switching rate (GSR)” and, in some instances, can have a direct effect on the gametocytes (Price, Nosten et al. 1999; Suputtamongkol, Chindarat et al. 2003; Pukrittayakamee, Chotivanich et al. 2004). Other factors which have been associated with gametocyte carriage include age, asexual parasite density (Akim, Drakeley et al. 2000), duration of illness, anaemia and gametocytaemia prior to treatment (Price, Nosten et al. 1999). However, our understanding of the gametocyte dynamics and infectiousness is still incomplete.

Gametocytes take about 10 days to mature before they are infectious. Estimates for gametocyte circulation time vary from 3.4 days (Smalley and Sinden 1977) to 7.4 days (Eichner, Diebner et al. 2001), depending on underlying assumptions about gametocyte survival.

Thomson, under the direction of Ronald Ross, compared the density of asexual parasites and gametocytes (known as “crescents”) in partially immune and non-immune patients over time (Thomson 1911). In the former, an average of 172,300 asexual parasites/mm³ produced 3,343 crescents per/mm³, giving a ratio of 52 parasites to one crescent. In the latter, the findings were 724,000 asexual parasites to 1,354 crescents, giving a ratio of 535 to one. Almost 100 years later, Eichner et al. fitted a dynamic model to individual data from adult malaria-therapy patients, taking into account the gametocyte life-cycle. The authors estimated average conversion probabilities of between 0.0039 and 0.0068 (mean 0.0064) (Eichner, Diebner et al. 2001).

Modelling

The infectiousness of humans is determined by the density of and duration that mature gametocytes remain in circulation, and can be expressed as the Area Under the Curve of time versus gametocyte density (AUC_{gam}) as shown in Figure 4-7. This, in turn, is dependent on the number of asexual parasites, the GSR and the duration that mature gametocytes remain in circulation. The number of asexual parasites on any one day is dependent on the number of infected individuals, their age-stratified parasite density and the rate at which infections are

cleared (the population recovery rate). This process is shown schematically in Figure 4-8. In the model, gametocyte half-life was assumed to be 2.4 days (M7). The actual parameter input for the model for asymptomatic (untreated) infections is given as a value relative to the GSR of infections treated with the monotherapy and the base-case scenario is set at one (A2).

Figure 4-7: Course of parasite and gametocyte density in a single infection

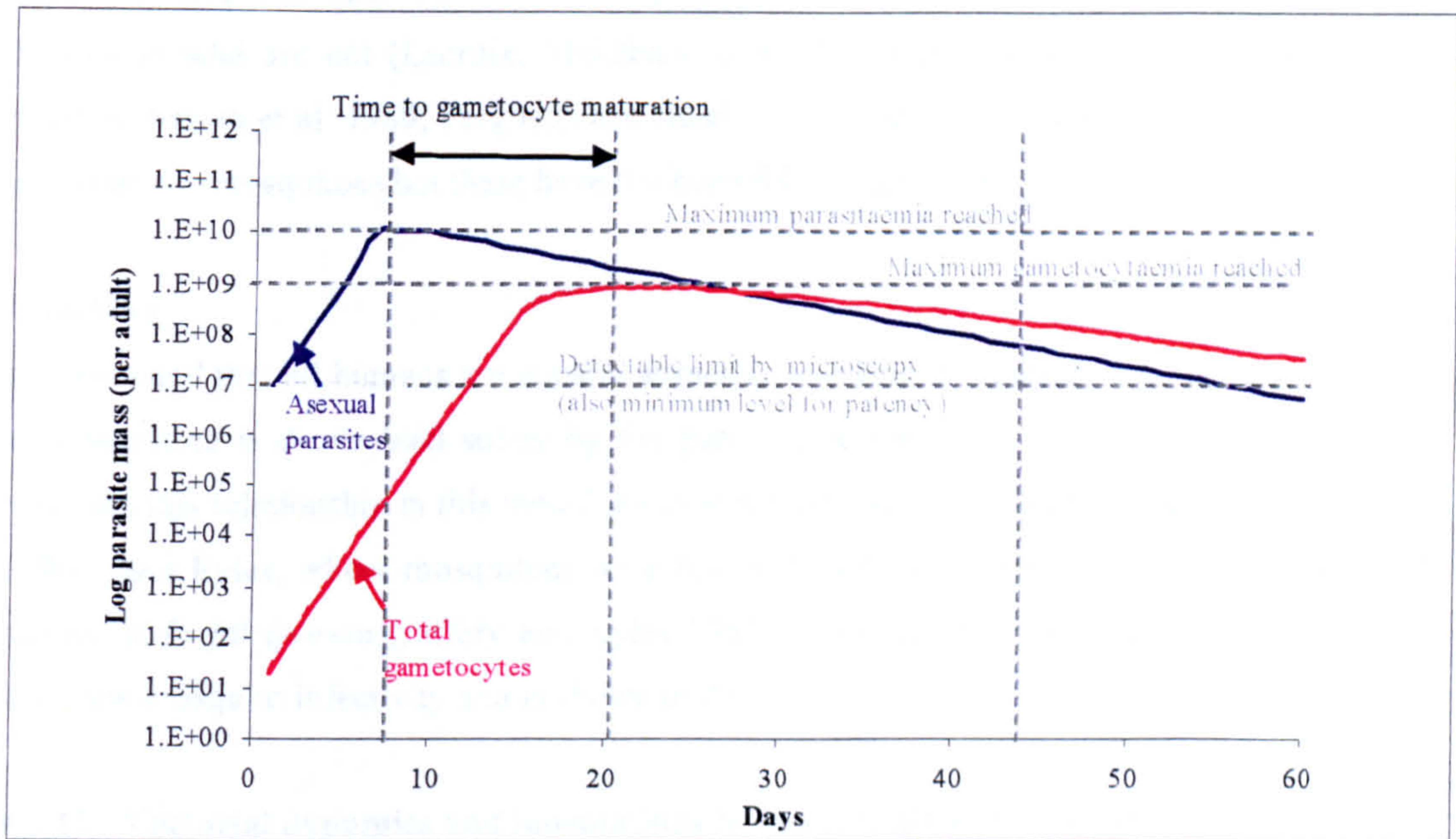
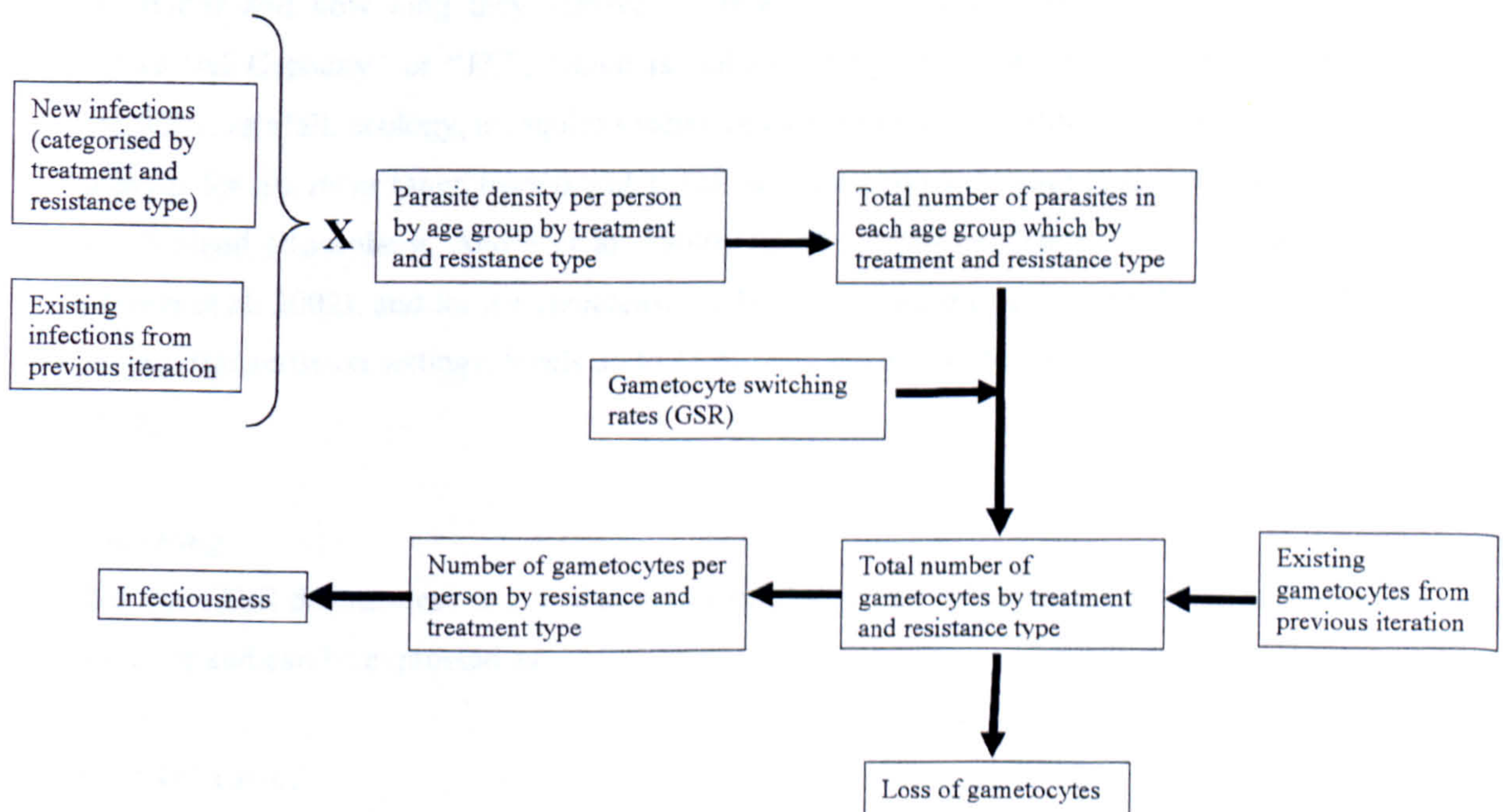


Figure 4-8: Diagram illustrating the calculation of infectiousness of the human population to mosquitoes at each iteration



4.5.11 Infectivity to mosquitoes

Background

The likelihood that a mosquito will develop a transmissible infection following a bite on an infected human generally increases in relation to the gametocyte density of the human host (Jeffery and Eyles 1955; Drakeley, Secka et al. 1999; Bonnet, Gouagna et al. 2000). There is some evidence that children who are carrying gametocytes are more attractive to mosquitoes than those who are not (Lacroix, Mukabana et al. 2005) but this is not a consistent finding (Burkot, Narara et al. 1989; Ferguson and Read 2004). Other factors may affect the infectivity of humans to mosquitoes but these have not been fully elucidated.

Modelling

It is assumed that all humans are equally attractive to biting mosquitoes and that the infectivity to mosquitoes is determined solely by the gametocyte density in humans (V_2). In order to calculate this relationship in this model, an exponential model was fitted to data from a study by Jeffrey and Eyles, where mosquitoes were fed on blood from patients infected with different strains of *P. falciparum* (Jeffery and Eyles 1955). This function is used at each iteration to calculate mosquito infectivity and is shown in Annex 7.

4.5.12 Vectorial dynamics and inoculations from mosquitoes to humans

Background

The intensity of malaria transmission from mosquitoes to humans is usually expressed as an annual Entomological Inoculation Rate (EIR). The EIR is determined by the infectiousness of the human population and by vectorial characteristics, namely mosquito density, their biting behaviour and how long they survive. These vectorial characteristics are captured in the “Vectorial Capacity” or “ VC ”, which is influenced by many factors including temperature, humidity, rainfall, ecology, mosquito species and vector control. Estimates in low transmission settings for *An. dirus* range from 0.009–0.428 in Laos (Toma, Miyagi et al. 2002) to 0.48–1.28 in Thailand (Rosenberg, Andre et al. 1990); for *An. Minimus*, 0.048–0.186 in Laos (Toma, Miyagi et al. 2002); and for *An. Arabiensis*, 0.34–1.42 in Tanzania (Ijumba, Mosha et al. 2002). In high transmission settings, levels up to 15 of have been recorded (Garrett-Jones and Shidrawi 1969).

Modelling

The daily EIR determines the inoculation rate of mosquitoes to humans at the beginning of each iteration and can be expressed as:

$$\text{EIR} = VC \times P \times i$$

where P is the proportion of the human population who are infected and i is the probability that a mosquito feeds on an infected human.

The value for VC is an input parameter and is chosen to reflect high or low transmission intensity ($V1$). The model also allows for data on the component parts of the VC to be fed into the model to enable the exploration of vector dynamics, in particular the daily survival rate of mosquitoes (Smith and McKenzie 2004). It can be programmed to fluctuate from month to month in order to reflect seasonal changes that might be observed ($V4$ and $V5$) (Prakash, Bhattacharyya et al. 2001). In the base-case scenario, a value of 0.1 is used for the vectorial capacity and it is assumed that transmission is constant throughout the year.

4.5.13 Drug characteristics

Background

The biological characteristics of drugs are described in terms of their pharmacokinetic and pharmacodynamics properties. Pharmacokinetics refers to how drugs are affected by humans, that is, their absorption, metabolism, distribution and excretion. Pharmacodynamics refers to how the drug affects its target.

The most important pharmacokinetic property of antimalarial drugs is how long they remain in the blood stream, as expressed by the drug half-life. This determines the frequency and duration of drug administration and also the likelihood that new infections will be exposed to inhibitory drug levels from the prior consumption of an antimalarial drug. The former is important in influencing the likelihood of patient adherence and the latter has important implications for the development of drug resistance. Artemisinin has the shortest half-life, of an hour or less, and chloroquine and mefloquine have the longest half-lives, of several weeks. Other drugs such as pyrimethamine and quinine lie in between with half-lives of several days.

Another important pharmacokinetic property of drugs is whether or not they are water-soluble. If they are not, for example lumefantrine, their absorption is dependent on concurrent consumption of fat in the diet, which affects their effectiveness outside of clinical trial conditions.

The pharmacodynamics effect of antimalarial drugs is to kill malarial parasites. Different drugs have different levels of killing ability and target different stages of the parasite life cycle. The killing ability can be expressed as the maximum parasite reduction ratio (PRR), which is the fixed proportion of the parasite mass, which is removed per two-day life cycle. This varies from a parasite reduction ratio of 10-fold for the antibiotics such as tetracycline, to over 10,000-fold for artemisinin derivatives. Adult patients with acute malaria have up to 10^{12} parasites

circulating in their blood. Therefore, even with a 10,000-fold reduction in each cycle, the complete eradication of the parasite load requires at least three cycles or six days, and therapeutic drug levels need to be present for four cycles to ensure cure (White 1997).

The stages of the parasite life cycle that are vulnerable to drug attack are important in determining the range of effectiveness of the drug. Drugs that prevent the maturation of asexual forms to schizonts decrease sequestration and are therefore useful for treating severe malaria. Drugs that inhibit the development of gametocytes can help to decrease transmission. Artemisinins have the broadest stage-specificity of all antimalarial drugs, preventing the maturation of asexual forms to both schizonts and gametocytes. Their inhibitory effect on the production of gametocytes has important implications in terms of transmissibility, especially in low transmission settings (Chen, Li et al. 1994; Price, Nosten et al. 1996; Pukrittayakamee, Chotivanich et al. 2004). In contrast, other studies show increased carriage of gametocytes following treatment, especially with SP (von Seidlein, Drakeley et al. 2001; Sowunmi and Fateye 2003) and possibly chloroquine.

Modelling

The characteristics that can be varied in order to explore the affects of different drug choices on model outcomes are: the parasite reduction ratio (PRR), the gametocyte switching rate, the failure rates and the cost.

The PRR is altered to reflect the rapidity of drug action, which effects the duration of treated infections. It is dependent on the type of drug and drug resistance. In the base-case scenario, the PRR in sensitive infections treated with monotherapy (SP or mefloquine) is 1,000-fold reduction in parasite mass per 48 hours and is reduced to 100-fold in resistant infections. The PRR in infections treated with an ACT is assumed to be 50,000 to reflect the rapid efficacy of the artemisinin component (Im8).

The GSR is varied to simulate the effect that drugs have on the production of gametocytes. These were estimated from clinical studies reporting data on the density of asexual parasite and gametocytes densities before and after treatment with different drugs. It was assumed that the GSR was reflected by the change in gametocyte density after treatment relative to the pre-treatment asexual parasite density. In the base-case scenario, the values used were 0.003 for the monotherapy and 0.0009 for ACTs (S4) (Price, Nosten et al. 1996; Robert, Awono-Ambene et al. 2000; von Seidlein, Drakeley et al. 2001).

The failure rate with different drugs is varied by altering the maximum likelihood of cure in non-immune hosts depending on the resistance and adherence, as discussed below. Finally, the

cost of the drugs is varied in the costs model, so that the cost-effectiveness of different drugs and drug combinations can be explored.

4.5.14 Drug resistance

Background

For most drugs, drug resistance is acquired in a step-wise fashion so that as a parasite acquires an increasing number of resistant mutations, the rate at which they are cleared by the drug decreases. Clinically, this results in longer parasite clearance times, an increased likelihood of recrudescence and a decrease in the time to recrudescence, until eventually there is no initial reduction in parasites at all, as if the infection is untreated. This results in an increased likelihood of severe malaria and death. Epidemiologically, this results in a shift from RI type failures to RII and RIII type failures, with the changes first occurring in children and pregnant women due to their relative lack of immunity. These different aspects of drug resistance are illustrated in Table 4-3.

Table 4-3: Aspects and manifestations of drug resistance

Aspect of drug resistance	Manifestation of increasing drug resistance
Genotype	Increase in number of resistance mutants per resistant infection
Clinical outcome (phenotype)	<ul style="list-style-type: none"> • Increase in parasite and fever clearance time • Increase in likelihood of treatment failure • Decrease in time to recrudescence • Increase in likelihood of severe infection and death
Epidemiology (model outcomes)	<ul style="list-style-type: none"> • Increase in proportion of population carrying resistant mutants • Shift from RI through to RIII type failures • Increasing incidence of severe infections, especially in young children and pregnant women

Modelling

For the purpose of the model, the most important relationships to define are the relationships between genotypic resistance and clinical outcomes in terms of treatment failure and severe malaria. For simplicity, the duration of infections and the time to recrudescence are fixed²⁸.

There were several possible approaches for handling the relationship between drug resistance and treatment failure and severity of disease in the model. The first, and most realistic, would have been to increase genotypic resistance in a step-wise fashion and to link this to a step-wise change in clinical outcomes, in particular failure rate and severity of illness.

²⁸ Although, on a population level, because the same factors increase both duration and likelihood of failure, an increasing number of failures is associated with an increase in the duration of the initial infection.

In an early model, this was attempted by creating an intermediate state of drug resistance between fully sensitive and fully resistant – termed “partial resistance”. Clinical outcomes were expressed as complete cure, complete failure and “intermediate failure”. However, as the model grew in complexity it became apparent that tracking three levels of resistance in both the human infection and parasite population was too unwieldy and that this was not a practical approach. Therefore, an alternative approach was required, which assumed that resistance was a binary phenomenon of either “resistant” or “sensitive” infections.

The challenge was, therefore, how to link the likelihood of failure, a continuous phenomenon, to “drug resistance” as a binary phenomenon. One possible approach was to modify the structure of the biological model so that the failure rate did actually change as the proportion of resistant infections increased. This would have meant that although on an individual level, parasites were either resistant or not, at a population level, as the number of infections with “final mutant” increased, the consequence of the increasing number of “partially resistant” infections would be reflected in an increasing failure rate. This complexity could not be incorporated into the biological model but was applied to the proportion of recrudescence infections resulting in severe malaria in the “severe outcomes” model, and has therefore resulted in one of the key clinical consequences of drug resistance being shown as a continuous phenomenon.

Within the biological model, the likelihood of treatment failure therefore had to be treated as a binary phenomenon and the failure rate resulting from the single genetic event conferring “drug resistance” had to be defined. This genetic event could have been chosen to represent an initial or intermediate step in the series of genetic events that lead to complete treatment failure. However, this would have been an arbitrary level and difficult to interpret. This genetic event was therefore assumed to be the “final step” conferring complete drug resistance and resulting in a recrudescence rate equivalent to that of an untreated symptomatic patient.

4.5.15 Failure rates

Background

The likelihood that an infection recrudescence depends on whether it is treated, the efficacy of the drug, whether or not the infection is sensitive to the drug, and the level of host immunity. These have been discussed in detail in the sections on immunity and drug resistance.

Modelling

To describe the *relationship* between immunity and treatment failure, the immunity function based on the age-stratified risk of severe malaria (Immunity Function 3) is used, as explained earlier. In order to obtain the actual treatment failure rate for each age group, the relationship between drug resistance and the maximum failure rates in a non-immune host had to be defined,

depending on type of infection and treatment. This results in six possible resistance/treatment type scenarios:

Sensitive to both A and B:	treated with A	→	Maximum failure rate 1
Sensitive to both A and B:	treated with AB	→	Maximum failure rate 2
Resistant to A / Sensitive to B:	treated with A	→	Maximum failure rate 3
Resistant to A / Sensitive to B:	treated with AB	→	Maximum failure rate 4
Resistant to both A and B:	treated with A	→	Maximum failure rate 5
Resistant to both A and B:	treated with AB	→	Maximum failure rate 6

? | However, it is assumed that infections that are *only* treated with the drugs to which they are resistant are essentially untreated and therefore have a fixed maximum failure rate. The maximum failure rates 3, 5 and 6 are therefore assumed to be all the same. The cure rates of infections sensitive to monotherapy and combination therapy depend on the efficacy of the drugs and are reflected in different failure rates (Maximum failure rates 1 and 2 respectively). If an infection, which is resistant to drug A but sensitive to drug B, is treated with a combination therapy of AB, it is much more likely to be cured than if treated with drug A alone. However, it is still compromised by the resistance to drug A, and therefore the failure rate is higher than in infections with a parasite sensitive to drug A or infections treated with drug BC. In the base-case scenario, it is assumed that the monotherapy is mefloquine (drug A) and that the combination therapy is mefloquine and artesunate (drug AB).

The other key determinant of failure is whether patients take a sufficient amount of the drug at frequent enough doses and for long enough duration in order to reduce the level of parasitaemia sufficiently for the remaining parasites to be cleared by host immunity. Patient adherence is therefore taken into account when calculating the input value used for the maximum failure rate in a non-immune host. This is explained in detail in a later section.

4.5.16 Characteristics of recrudescence infections

Background

Recrudescence infections are important not only because of the associated morbidity and costs but because they are the main source of the spread of resistance. Infections recrudescence because the infecting parasite is resistant to the treatment used or because of inadequate dose or duration of an efficacious drug, or both. Infections that recrudescence once are more likely than initial infections to recrudescence again, resulting in several recrudescence peaks separated by periods without detectable parasitaemia (Collins and Jeffery 1999).

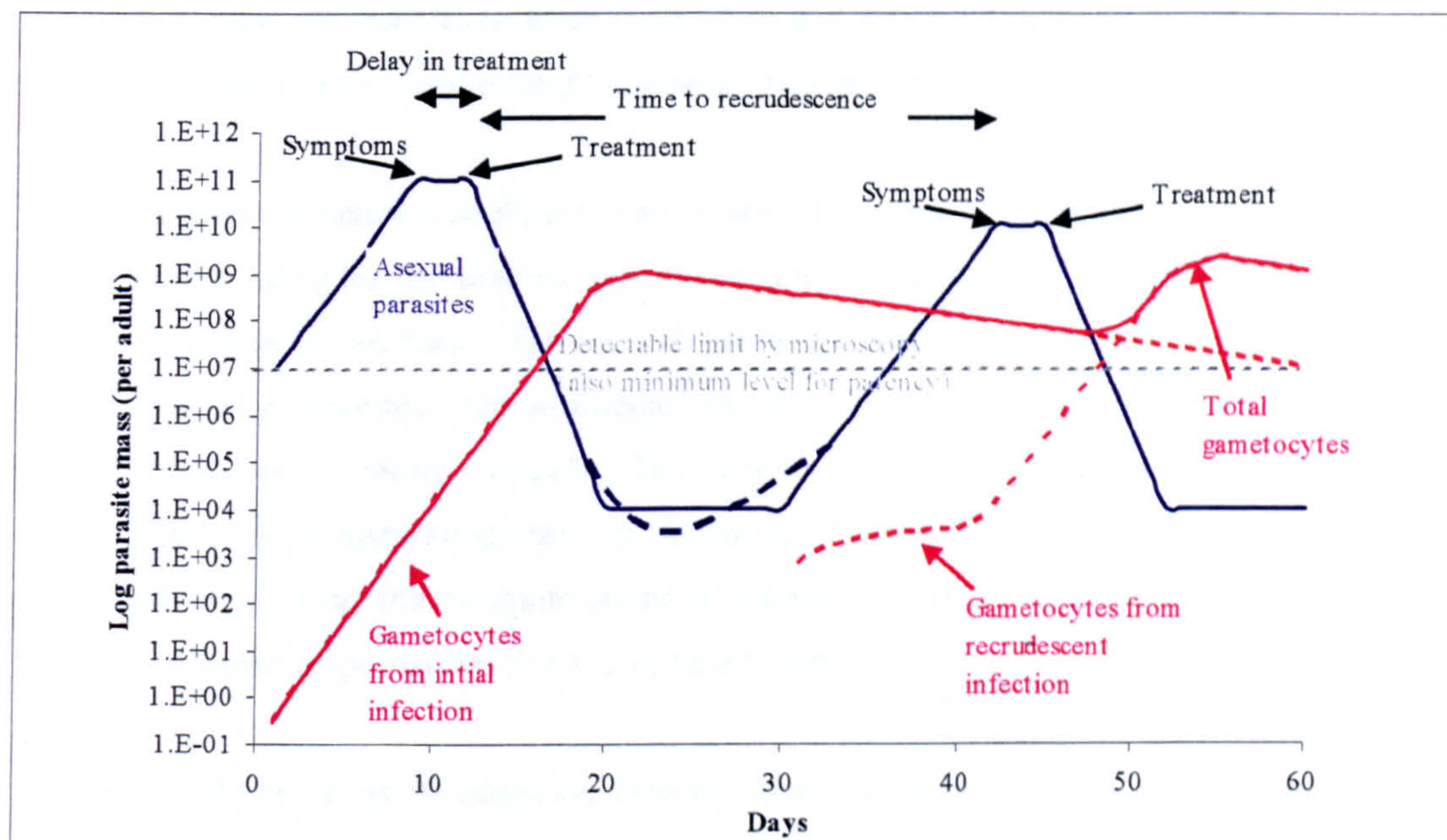
Recrudescence infections tend to have a lower parasite density but relatively more gametocytes than initial infections and are potentially more infectious than initial infections (Handunnetti, Gunewardena et al. 1996; Sowunmi and Fateye 2003). Suputtamongkol et al. suggest a relative risk of developing gametocytaemia of 49.8 (CI 14.4-171.9) and 39.8 (CI 9.1-173.4) in patients with recrudescence and re-infection compared with patients who are cured (Suputtamongkol, Chindarat et al. 2003). Price et al. found that patients who had a recrudescence infection had an adjusted odds ratio (AOR) of 2.3 of being gametocytaemic after adjusting for asexual parasite density (Price, Nosten et al. 1996). Sowunmi compared primary with recrudescence infections following chloroquine treatment in children in Nigeria. Expressing the gametocytes load as the Area Under the Curve of time versus gametocyte density (AUCgam), sensitive infections were found to have an AUCgam approximately 14 times higher for sensitive compared to resistant infections (Sowunmi and Fateye 2003) (R1). Drakeley found that infections which recrudescence following chloroquine treatment were 11 times more likely to result in transmissible infections in membrane-fed mosquitoes than those that were successfully treated (Drakeley, Jawara et al. 2004).

Modelling

The course of asexual parasitaemia and gametocytaemia is illustrated in Figure 4-9. For model simplicity, multiple recrudescence peaks are treated as one long recrudescence and the total duration, the parasite density and gametocyte switching rates are determined so that the resulting area under the time/gametocyte density curve is equivalent to multiple recrudescence peaks.

In the base-case scenario, the parasite density of recrudescence infection relative to initial infections is assumed to be 0.5 ~~in the base-case scenario~~ (R2) and the GSR is assumed to be 20-fold that of initial infections (R3). The time interval between initial and recrudescence infections input into the model is the time interval between disappearance of parasites in the initial and reappearance of parasites in recrudescence infections, and was assumed to be 14 days (R5). This is based on the mean "time to recrudescence" which is the time between and first- and second-line treatments. This varies depending on drug half-life, with an overall mean of 24 days (95% CI 21-27) (Stepniewska, Taylor et al. 2004).

Figure 4-9: Schematic diagram of the course of parasitaemia and gametocytaemia during the course of a recrudescent infection. Note that the y-axis uses a logarithmic scale; therefore gametocytes during recrudescence add little to the total gametocyte mass until they reach a density of above $1 \times 10^7 / \mu\text{l}$. For cured infections only, the asexual parasites in the first peak (ie above the minimum level of patency) are assumed to produce gametocytes.



- Total gametocytes
- - - Gametocytes for initial or recrudescent infections
- Total asexual parasites (modelled)
- - - Total asexual parasites (actual)

4.5.17 Time intervals

The model iterates by the day; however, some processes take days, weeks or months and therefore the appropriate input values for a particular iteration are not based on the output from the immediately preceding iteration, but from an iteration some time previously. These time-intervals include the interval between inoculation and infectiousness and the interval between a change in transmission intensity and the change in immunity profile of the population.

The time taken for patent infections in one iteration to be translated into potential new infections is the time it takes for the malaria parasite to complete its asexual period in humans and its sexual period in mosquitoes. The asexual period in humans refers to the period from initial inoculation of sporozoites from an infected mosquito into a human host to the time when that host is infectious to a biting mosquito. This is equivalent to the pre-patent period (M5) plus the time to gametocyte maturation (M6) and is around 20 days. The sexual cycle in the mosquito refers to the time from the mosquito taking up gametocytes in a blood meal to the point when it is ready to transmit sporozoites to a susceptible human – this is around 12 days (V3). *Transmission?*

As explained earlier, as transmission intensity changes, so does the level of immunity of the human population. Obviously, this does not occur immediately and is related to the rapidity of change and actual transmission intensity. However there is a lack of suitable data on which to base this estimate, therefore for simplicity, in the model immunity is updated every 90 days based on the mean transmission intensity in the previous 90 days.

4.6 Sub-models

4.6.1 Severe outcomes sub-model

In order to estimate the “cost of resistance”²⁹ it is necessary to extrapolate from “drug resistance” to the clinical and economic consequences in terms of prolonged and severe illness and deaths. Because these consequences do not affect transmission directly³⁰, their calculation was done in a simple separate model as explained at the beginning of the chapter.

Background

Even in the absence of drug resistance, a certain proportion of malaria cases will progress to severe malaria and death. The likelihood of this occurring depends on age, immunity, access to

²⁹ The term “cost of resistance” in this case should not be confused with its other use to describe the “fitness cost” to a parasite of having a genetic mutation that confers resistance!

³⁰ However, in the model those patients more likely to develop severe malaria are also those more likely to have a higher parasite density and therefore be more infectious.

first-line treatment and treatment-seeking behaviour. In non-immune patients, the likelihood of severe malaria in treated symptomatic drug-sensitive infections is probably around 5% and of mortality around 0.2% (Luxemburger, Ricci et al. 1997). The mortality rate of severe malaria in non-immune adults in clinical trials is around 15-20% depending on the efficacy of the treatment (Newton, Angus et al. 2003; Dondorp, Nosten et al. 2005).

The mortality of untreated malaria in non-immune patients is less certain. From observations of Europeans in Africa in the 19th century, the untreated mortality rate varied from 9.4 to 57% in French troops in Senegal from 1819-1831 (Curtin 1994). Sudre et al. used the Delphi method to gather expert opinion on the effect of resistance on case fatality rate (CFR). For children under two years old, estimates ranged from between 0.00045 and 0.007 in those with RI resistance to between 0.02 and 0.05 in for those with RIII resistance in a high transmission setting (Sudre, Breman et al. 1990). Brinkman, in a review of epidemiological studies in Africa, estimated that the CFR was between two and 24% depending on age and drug resistance (Brinkmann and Brinkmann 1991).

Modelling

It is assumed that as the proportion of drug resistant infections rises, there is a sigmoid relationship with the likelihood of severe infection or death. This is because when the proportion of infections that carry resistant genotypes is low, the intensity of resistance is also low, resulting mainly in recrudescence infections. However, as drug resistance rises, the time to recrudescence decreases until it is as if the initial infection is untreated. As a result, once this threshold occurs, there is an exponential increase in the rate of severe infections and death. There is therefore a fixed likelihood of severe malaria in a treated infection (initial or recrudescence) in a symptomatic host. This is the “baseline” likelihood of severe malaria, and referred to as $p(\text{“baseline” severe})$ in Figure 4-10. Those that are symptomatic but *untreated* are much more likely to develop severe malaria and are assigned a maximum likelihood of severe infection – $p(\text{maximum severe})$. The effect of immunity on these likelihoods is estimated by using the immune function based on severe malaria (Immunity Function 3). It is assumed that once a patient develops severe malaria, the likelihood of death is fixed and there is no additional effect of immunity³¹.

To incorporate the increased likelihood of severe malaria in those who are drug resistant, there is an additional risk on top of the “baseline” likelihood for recrudescence infections. This probability increases according to the level of drug resistance in the population and reaches a maximum at 100% resistance, at which point it is assumed that the treatment is useless and the

³¹ The CFR of malaria infections of course still varies by age because severe malaria varies by age according to immunity.

mortality rate is equivalent to an untreated symptomatic infection. The overall likelihood of severe infection for recrudescence is expressed as $p(\text{severe if recrudescence})$. This relationship is assumed to be a sigmoid relationship and is described by Equation 1-1 and illustrated in Figure 4-11.

Equation 1-1:
$$y = Y_{\min} + ((Y_{\max} * x^a) / (x^a + (X_{50})^a))$$

where y = likelihood that recrudescence infection would become severe, x = level of resistance, Y_{\min} is the likelihood of severity with no resistance, Y_{\max} is the likelihood of severity with 100% resistance, a gives the slope of the curve and X_{50} is the level of resistance at which the likelihood of severity is half the maximum.

The data on which the estimates were based are shown in the parameters tables and can be seen to vary widely depending on location, definition and methodology. In the base-case scenario, the maximum likelihood of developing severe malaria for a non-immune treated infection is estimated at 5% and the untreated infection at 15%, with a mortality rate of severe malaria of 15% (O1, O2 and O3).

4.6.2 Behaviour sub-model

4.6.2.1. Coverage

Background

The coverage rate is important as it has obvious cost implications and is assumed to have major implications on effectiveness in terms of clinical cure and drug resistance. In many settings the majority of patients seek treatment in the informal sector, where prescribing practices often differ from the public sector³². Many patients do not receive the correct treatment, let alone the correct dose or drugs of good quality. A significant proportion of patients who receive treatment may not actually have malaria. The latter is important because of the cost of unnecessary treatments and because the number of people exposed to the risk of adverse events is increased. These practical concerns have been a major deterrent to changing first-line drug policy to ACTs. Although data were available on the coverage rate and adherence rate to the older monotherapies, there was little data on ACTs.

Is this true?

³² The terms "public" and "formal" sector are used interchangeably to mean providers who have received some formal training for the treatment of malaria and who are funded by the government. This includes the outreach workers and village malaria worker discussed later. The terms "private" and "informal" sector are also used interchangeably to denote all other providers of healthcare.

Figure 4-10: Diagram illustrating severe cases as a consequence of initial infections and recrudescence infections

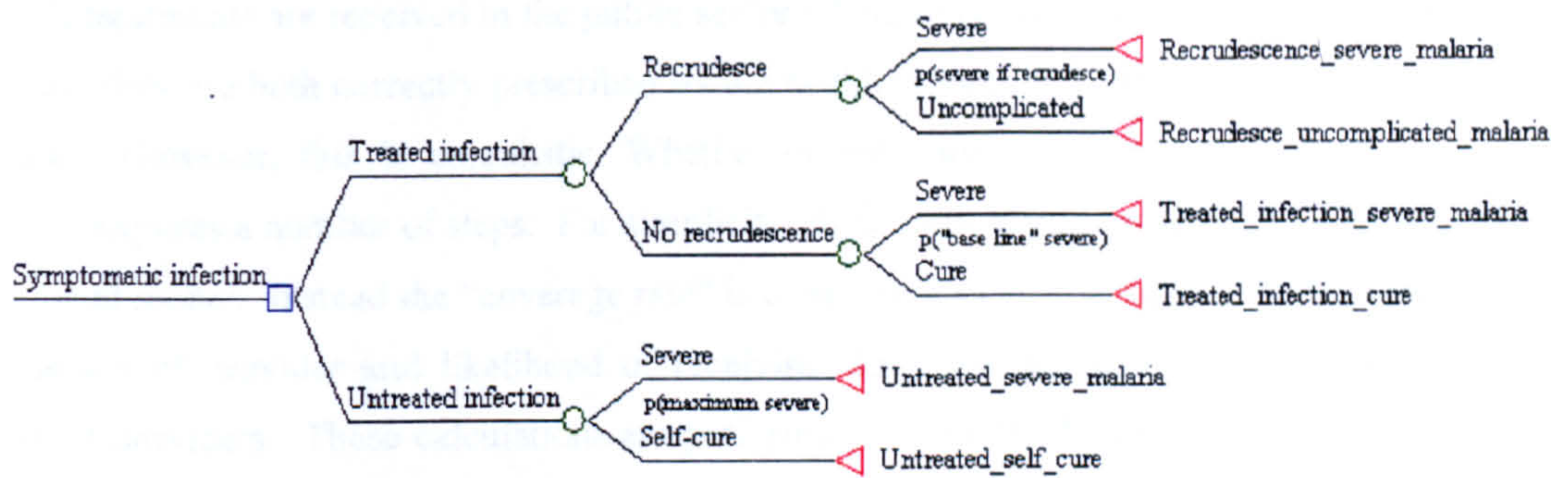
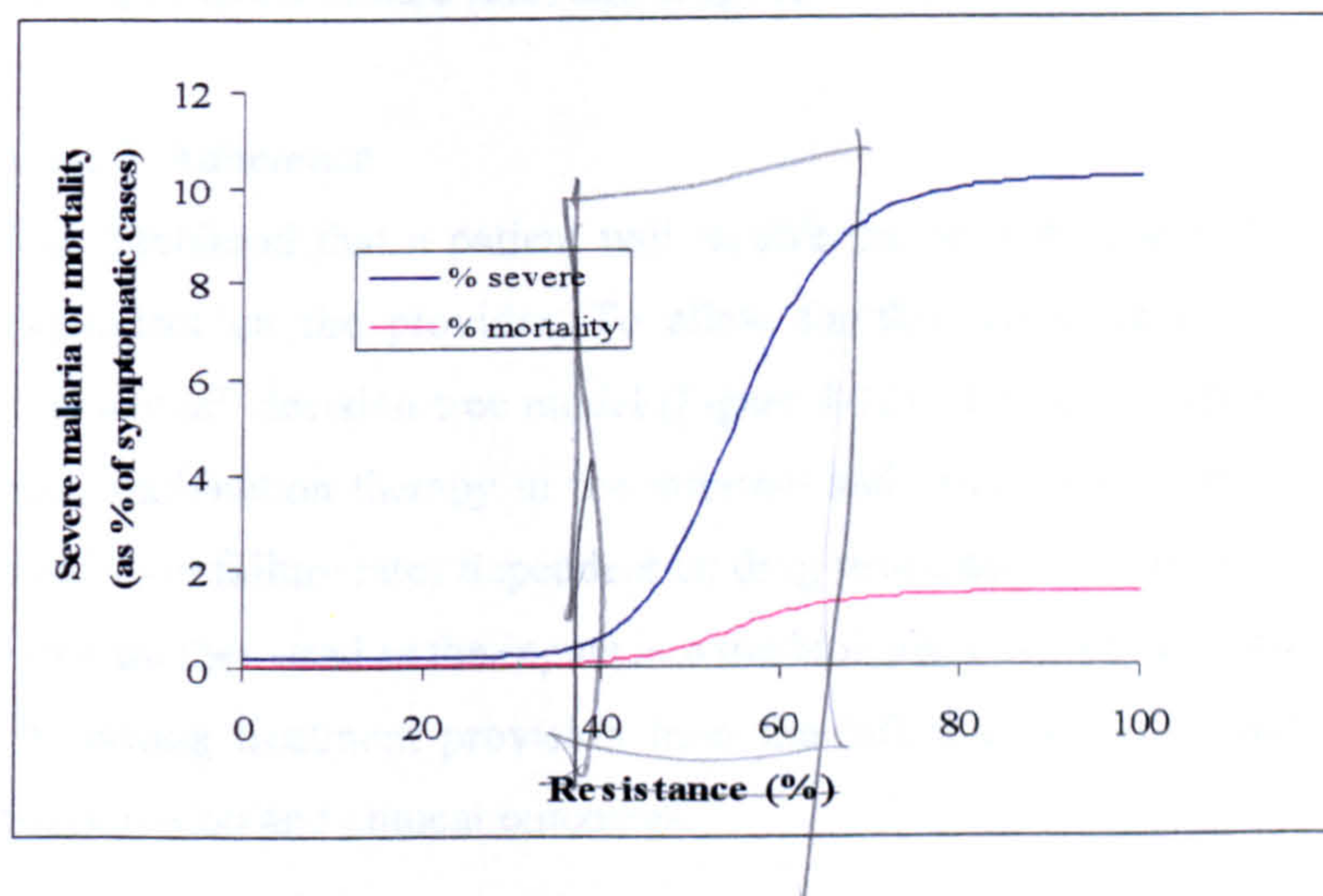


Figure 4-11: Diagram showing the sigmoid relationship between resistance and severe malaria or mortality



Modelling

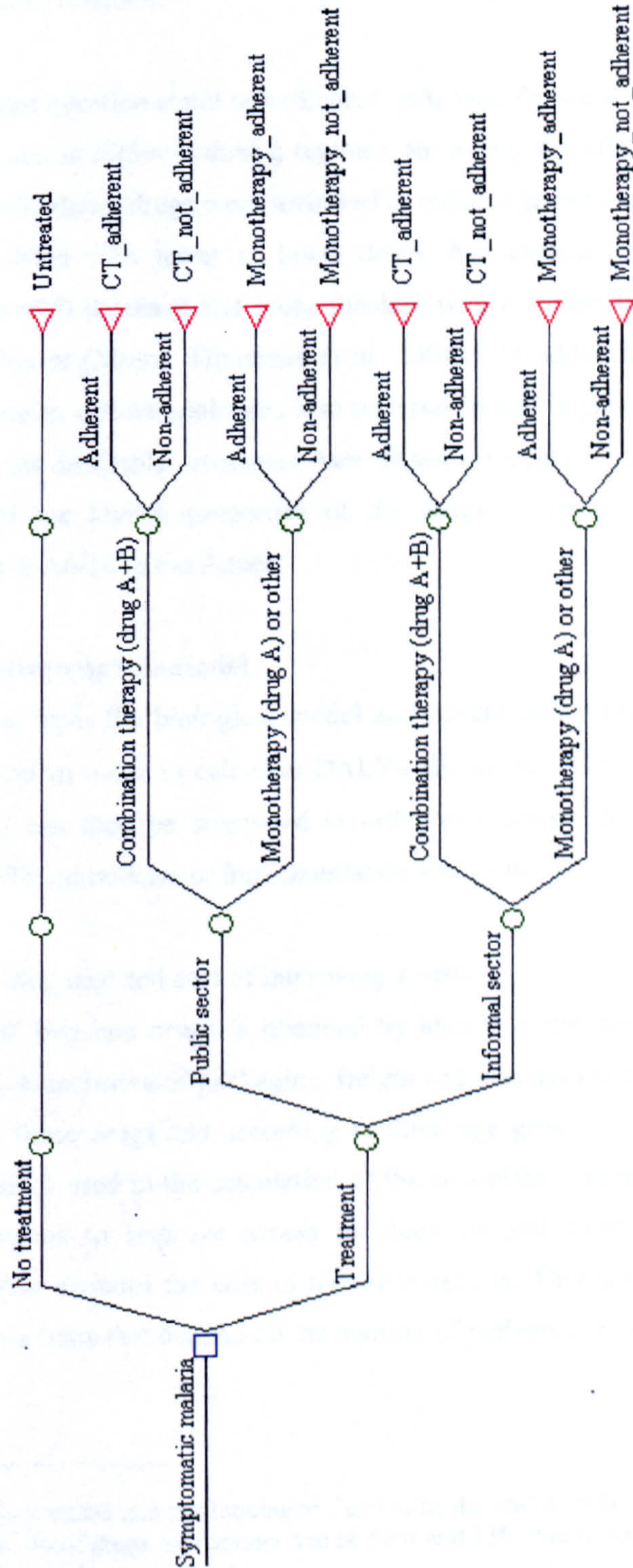
In the biological model, the “coverage rate” is the likelihood that treated patients receive the combination therapy (drug AB or drug BC). It is assumed that all those not treated with the combination are treated with the monotherapy (drug A). In the base-case scenario, it is assumed that all treatments are received in the public sector where only good quality drugs are available, and that they are both correctly prescribed by the health worker and correctly adhered to by the patient. However, this is unrealistic. Whether or not patients receive the correct first-line therapy requires a number of steps. For simplicity, these individual steps are not included in the biological model. Instead the “coverage rate” is considered as an aggregate parameter based on the choice of provider and likelihood of receiving diagnosis and combination therapy from different providers. These calculations are performed outside the biological model in a simple decision-tree “behaviour” sub-model. This allows the calculation of treatment rates, coverage rates and adherence rates, given inputs of the proportion of patients going to the private and public sector (B1) and the likelihood that they will receive a monotherapy or combination therapy (B2). The decision-tree on which these calculations were based is illustrated in Figure 4-12. In this way, the costs and effect of implementing changes to the coverage rate can be explored. For example, if an intervention to provide combination therapy through village malaria workers results in a higher coverage rate, then the cost of the intervention and the effects in terms of cure rates and drug resistance can be estimated.

4.6.2.2. Adherence

The likelihood that a patient will receive the correct dose and be adherent to therapy is also dependent on the provider. To allow for this, an extra level of branches is added to the “behaviour” decision-tree model (Figure 4-12). The likely adherence rates to the monotherapy and combination therapy in the informal and formal sector are input along with the estimated maximum failure rates dependent on drug resistance. The resulting aggregate maximum failure rates are then used as the inputs into the biological model. This allows examination of the effect of shifting treatment provision from the informal to the formal sector on treatment failure, transmission and clinical outcomes.

As mentioned earlier, the two main factors affecting treatment failure rate are drug resistance and adherence. Unfortunately, there are very little quantitative data linking adherence rates to cure rates. Further, the relationship is not simple or linear and depends on the pharmacokinetics and pharmacodynamics of the drug and how the drug is taken in terms of frequency and dosing.

Figure 4-12: Diagram of the decision tree used to calculate costs of first-line drugs in the economic analysis and the “untreated” and the “CT coverage” rates used in the biological model



Because this is an important relationship in the model, estimates were made based on the following approach:

- What is the known or estimated adherence rate to different antimalarial drugs?
- If not adherent, how is the drug most likely to be taken (e.g. a duration of three instead of seven days for quinine)
- What is the likely cure rate given the non-adherent behaviour if the infection is a) sensitive or b) resistant?

Some data on the last question could be estimated quite well for some drugs where clinical trials have been carried out on different dosing regimes, for example mefloquine. A large number of clinical trials of antimalarial drugs were reviewed in order to gather the available information on failure rates associated with fewer or lower doses than currently recommended. This was entered into an Excel® database and cross-checked with a systematic review of antimalarial trials by Dr Hla Myint (Myint, Tipmanee et al. 2004). In addition, a systematic review of studies of adherence to antimalarials was also undertaken and is presented in the next chapter. Where data were not available, estimates were based on expert opinion and estimated from available data and the known properties of the drugs. The result, of this exercise are summarised in Table A6-14 in the Annex.

4.6.3 Cost-effectiveness sub-model

The annual outputs from the biological model and severe outcomes model are placed in an Excel®-based model in order to calculate DALYs and costs. The results from two or more different scenarios can then be compared in order to examine the relative costs and cost-effectiveness of different policies or implementation strategies.

4.6.3.1. First-line drug cost and cost of improving access

The annual cost of first-line drugs is obtained by attaching the cost of the monotherapy or combination therapy (inclusive of packaging, freight and wastage) to the annual number of new cases treated with those drugs and according to three age groups³³. The incremental cost of drugs is the numerator used in the calculation of the cost-effectiveness ratios. In the scenarios in which interventions to improve access to diagnosis and treatment are introduced, the incremental cost also includes the cost of the interventions. This consists of the annual fixed cost and the variable costs that depend on the number of patients seen and treated, and comprise

³³ For pre-packaged artesunate and mefloquine in Cambodia, the cost of different age-group packages was used. Otherwise the cost of drugs was assumed to be 50% and 25% that of adults for the 6-12 year old and the <6 year old categories respectively.

the cost of rapid diagnostic tests, in addition to the costs of antimalarial drugs. This is explained further in Chapter 6.

4.6.3.2. Total cost of malaria treatment

The total costs of malaria include the costs of the initial infection and the costs of treatment failure in terms of the recrudescence infections and severe infections. In the base-case scenario, it is assumed that all malaria cases go to a public health facility for the initial, recrudescence and severe infections.

For patients, the main direct costs are of transport for the patient and carer to the health facility and for food and other consumables during their time at the health facility (UC2). For severe infections, the average in-patient stay was estimated to be five days (IC3). Although user fees are often charged, as this does not represent a net change in overall “societal” costs, for simplicity, it is assumed that the cost of consultations is borne by the provider.

For the provider, the cost of the outpatient treatment of the initial infection includes the cost of consultation (UC1) and microscopic diagnosis (UC5), in addition to the cost of the first-line drug. It is assumed that uncomplicated recrudescence cases are treated as outpatients and the costs include the cost of more costly second-line drugs. For severe infections, it is assumed that patients require five days in-patient treatment and receive three days of parenteral quinine, four days of oral quinine and seven days of oral tetracycline (IC8). Other in-patient costs include the cost of investigations, consumables (IC4) and the hotel costs of staying in hospital based on the average cost per in-patient day (IC6). The cost of death *per se* is not included.

In addition, the total costs inclusive of the indirect costs are also estimated – although as noted previously, indirect costs are notoriously difficult to estimate reliably. In this analysis, it was assumed that the total number of lost days of productivity (inclusive of carers’ loss) was five days for uncomplicated episodes (PC1) and 10 days for severe episodes (PC2). The loss was assumed to be the same whether the patient was a child or an adult, based on the assumption that an adult would not be able to work while looking after a sick child. The daily loss of income was estimated at US\$1.5 based on the daily labourer’s wage in Cambodia (PC3).

The costs and benefits to private, or “informal”, sector providers are not included as this was felt to fall beyond the scope of this analysis. However, where the informal sector is an important source of malaria treatment, the successful implementation of drug policy is dependent on involving them in the process. This requires an understanding of the sector and implementing strategies that will impact on their prescribing behaviour, for example subsidising the cost of drugs and rapid diagnostic tests. Thus, it is an important area for future analysis and

the overall model structure has been developed to enable the incorporation of costs and benefits to the informal sector in later analysis.

4.6.3.3. DALYs

Effectiveness is also expressed in terms of Disability Adjusted Life Years (DALYs) averted. In this analysis, the years of life lost were based on the life expectancy tables for West Africa, which are typical of developing countries³⁴, and disability weights were taken from the Global Burden of Disease study (Murray and Lopez 1996). Initial and recrudescing infections were assigned a weight of 0.211, with an average duration of 0.01 years. Neurological sequelae were given a weighting of 0.473 if untreated and 0.436 if treated, with an average duration of 35.4 years. The likelihood of neurological sequelae for severe malaria was assumed to be 0.0093. This was based on the likelihood that severe malaria is associated with cerebral malaria and the likelihood that cerebral malaria would result in neurological sequelae. However, estimates of the frequency, duration and severity of different types of neurological sequelae vary enormously. Although effects of low birth weight, chronic anaemia and effect on co-morbidity were not included, which therefore results in an underestimate of the actual burden of disease, by far the largest contribution to DALYs in malaria are the childhood deaths (Snow, Korenromp et al. 2004).

DALYs were discounted at a rate of 3% to aid comparison with other studies in the field (Goodman, Coleman et al. 2001). This was varied to 0% in the sensitivity analysis. This results in health benefits in the future accounting for less than those occurring currently, although this has been criticised as being inequitable. This is particularly the case in an analysis such as antimalarial resistance where the major effects of an intervention are expected in the future (Coast, Smith et al. 1996). However, this has now become accepted as standard practice in economic evaluations. Age weighting of DALYs has been advocated by some authors (Murray and Lopez 1996). This is where more weight is given to the years lived between the ages of 9 and 54 years than those outside of this range in an effort to capture some value of the notion of “productive years”. This remains controversial and, counter-intuitively, actually results in more importance being placed on deaths occurring in the 0-27 age group than in the 9-54 age group (Barendregt, Bonneux et al. 1996). In addition, weighting would not be expected to make any difference to the cost-effectiveness in the analysis and therefore was not incorporated in the base-case scenario, but was explored in the sensitivity analysis

³⁴ West Africa was chosen rather than the table available for Cambodia because the values were very similar but were not available down to one-year age groups for the latter.

4.7 Assumptions

Although a more comprehensive model than previous models of antimalarial resistance, as in any model there was a trade-off between realism and simplicity and a number of assumptions were made, many of which are unlikely to make a material difference to the outcomes of the model. The important assumptions are described below, with a more detailed discussion on the possible implications for policy and future research in the final chapter.

The population of humans was fixed in total number and in age-structure over time. Therefore, it was assumed that the number, age and level of immunity of humans that entered (as births or in-migrations) balanced those that exited (as deaths or out-migrations). Although immunity varied by age group, some other characteristics were assumed not to be affected by age, in particular the likelihood of inoculation, the likelihood and type of treatment, adherence to treatment and death in the case of severe malaria. In addition, within each age group the population was homogenous, so variations between individuals and groups were not allowed. Therefore, the effect of individual differences in immunity and of differences in immunity between ethnic groups or due to genetic differences such as sickle cell trait, could not be explored.

The vector population was also assumed to be homogenous, although monthly vectorial capacity was allowed to vary to simulate seasonal changes.

In terms of human immunity, it was assumed that there was no refractory period, thus patients could receive a new infection at any time after being cured of an infection. However, once infected, it was assumed that further infection was not possible - that is, that there was no super-infection - and all infections were therefore single clonal. Clearly, the use of the immunity functions themselves is based on the assumption that they accurately represent the relationship between age and EIR and the intermediate outcomes in the model. Children aged one year or less were the least immune, although it is known that in high transmission settings infants under six months are afforded some protection from the in-utero transfer of maternal antibodies. However, attempting to incorporate this into the immunity functions was not possible and it is unlikely to make a material difference to the overall results. It was also assumed that there was no specific transmission-blocking immunity.

If infections were treated, there were only two treatment choices, the monotherapy or combination therapy, and if infections were not treated then the human hosts were assumed to have the same immune characteristics as immune non-symptomatic individuals.

Like most other models, a number of simplifying assumptions were made about drug resistance and treatment failure. It was assumed that resistance was a binary phenomenon and that complete drug resistance that rendered a drug completely ineffective was encoded by a single genetic event. It was also assumed that there was no fitness disadvantage of being a resistant mutant and there was no cross-resistance between drugs. It was assumed that treatment failures are uniform in character and consist of a recrudescence infection that becomes detectable 14 days after the initial infection.

The model does not take into account *var* switching which would act to decrease the susceptibility of parasite infections to clearance by the human immune system (Peters, Fowler et al. 2002).

Finally, in the cost-effectiveness modelling, it was assumed that the cost of drugs were the same whether or not patient was adherent to therapy. However, this could be varied in the sensitivity analysis if necessary.

4.8 Summary

In summary, this is a deterministic, age-stratified, population-based, dynamic bio-economic model of the spread of antimalarial drug resistance in the human and parasite population. It iterates on a daily basis and incorporates a large number of factors that are thought to be important in the transmission of drug resistance. In addition to epidemiological factors such as vectorial capacity and the potential for seasonality, which allow the spread of drug resistance in different transmission settings to be explored, it has at its core the effect of human immunity and treatment on the outcome of potential infections, both in terms of clinical failure and infectiousness. This feeds back into the model to ensure that changes to either are reflected in the future in terms of transmission intensity and the spread of drug resistance. It incorporates drug characteristics including rapidity of action and effect on gametocytes, and also takes into account the possible effect on drug resistance of chemoprophylaxis due to prior exposure to an antimalarial drug. The model was developed within an economic framework with an intention of being able to generate tangible clinical and economic outcome to help address policy-relevant questions using data such as coverage rates, failure rates, rates of adherence, cost of drugs and interventions to maximise access. As these data were clearly important in determining the outcomes of the model, the comprehensive collection of secondary, and in the case of coverage and adherence rates to artemisinin-based combination therapy – primary, data was made a priority and is covered in the next three chapters.

CHAPTER 5

SYSTEMATIC LITERATURE REVIEW: ADHERENCE TO ANTIMALARIAL DRUGS³⁵

The objectives of this review are to summarise the current knowledge on adherence, the effectiveness of interventions to improve antimalarial drug usage, and the effects of patient adherence on therapeutic response.

5.1. Material and methods

5.1.1. Search strategy

The medical literature was searched using PubMed under the following terms (“malaria” OR “antimalarial”) AND (“compliance” or “adherence” or “prescri* or” or “drug usage”). Studies in all languages were considered.

The bibliographies from studies and reviews were then searched manually for relevant references. In addition, the International Network for Rational Use of Drugs (INRUD) database was screened for unpublished work and a further search was carried out using the Scirus™ search engine, which combines Medline and Embase and also searches websites for unpublished material. Finally, we solicited materials of interest from individuals known to be active in the field.

5.1.2. Criteria for inclusion

Studies that were clearly irrelevant were first discarded. The remaining studies were examined for information about use and/or effect of antimalarial drugs in the treatment (not prophylaxis) of malaria. These were included for further analysis if they fulfilled the following criteria:

- Studies with original quantitative data on patient “adherence” to a prescribed regime of antimalarials or comparing “self-treatment” with recommendations.
- Studies of interventions to improve antimalarial usage where patient or carer behaviour were assessed.

³⁵ Published as Yeung S., White N.J. (2005). How do patients use antimalarial drug? A review of the evidence. *Trop Med Int Health* 10(2): 121-138.

- Clinical trials reporting objective measure(s) of effectiveness of unsupervised treatment either in comparison with supervised treatment or with an assessment of adherence.

The following categories of study were excluded:

- Studies conducted in populations in which malaria is not endemic.
- Studies/reviews on chemoprophylaxis or mass treatment.
- Clinical trials with no data on effectiveness of unsupervised treatment or patient adherence.
- Studies of knowledge, perceptions or behaviour with no quantitative data on drug usage for specific and recent illness episodes.
- General reviews with no original data.

Two reviewers undertook the initial search and sorting independently. Where there was discordance over whether or not a paper should be included in the review, this was resolved through discussion.

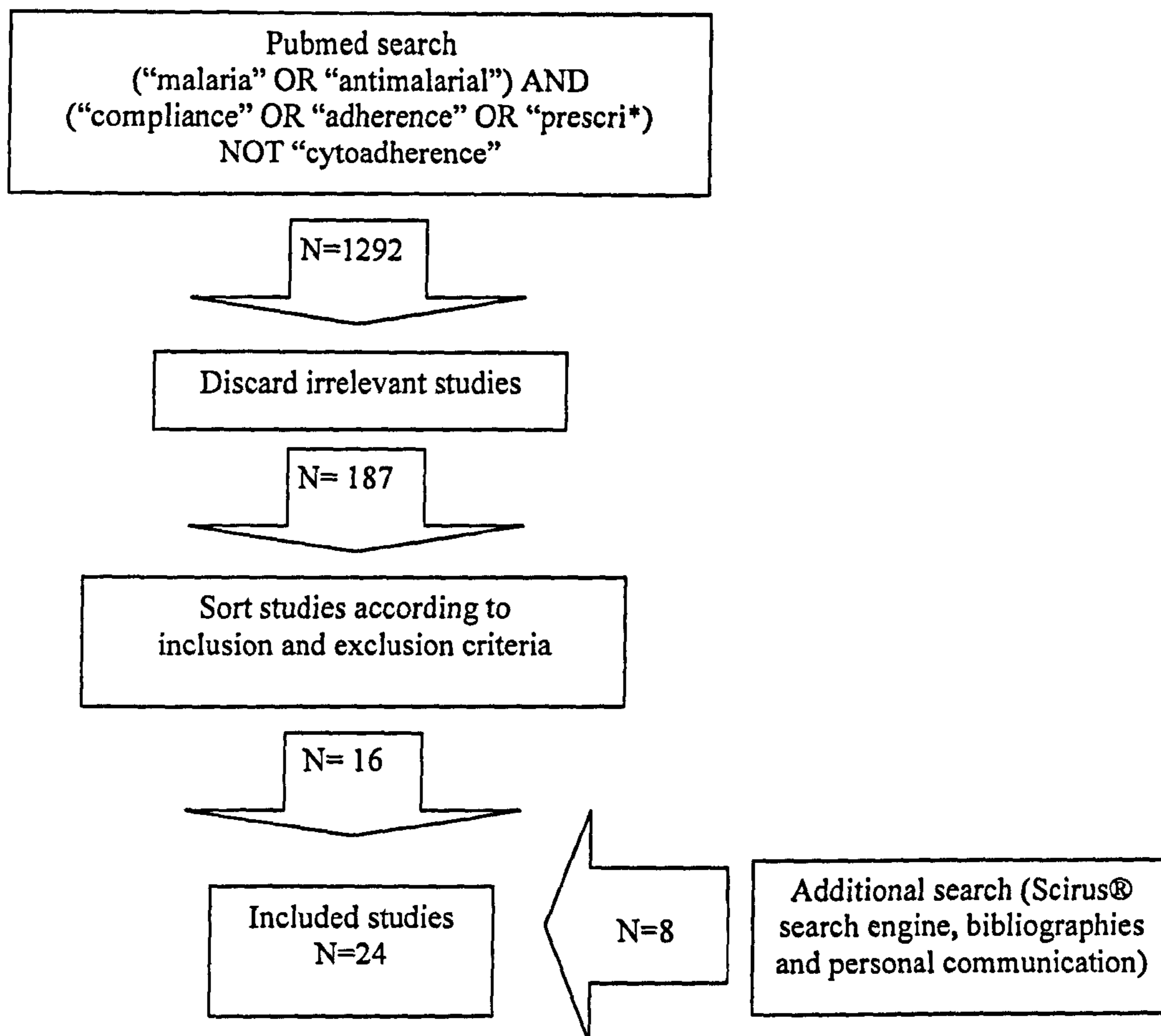
5.2. Results

5.2.1. Studies identified

The initial search using PubMed resulted in 1292 hits. Many of these studies were irrelevant, referring to the use of antimalarials or antibiotics in the treatment of non-malaria conditions such as the quinine for leg cramps or cardiac arrhythmias, chloroquine for the treatment of rheumatoid arthritis, or dapson for leprosy. There were also a large number of articles of general travel advice, adverse effects of antimalarials and general reviews.

The search of bibliographies, hand searching journals and personal communication resulted in eight additional studies. Finally only 24 studies that fulfilled the inclusion criteria were identified. Of the excluded studies, two thirds were on chemoprophylaxis or mass treatment, 6% were clinical trials (often of short course regimens in which adherence was mentioned but not measured), and 7% were reviews about adherence that did not contain any original data. The remaining 8% of the studies were an assortment of studies on economics, treatment seeking and diagnosis. The result of the search process is shown in Figure 5.1.

Figure 5-1: Result of literature search



5.2.2. Types of study

The search captured a wide variety of studies, which for ease of description are presented as follows:

- (1) Descriptive studies of "How do patients actually take antimalarial drugs?"
 - a. When they are prescribed by a trained provider
 - b. When bought in the community
- (2) Intervention studies which looked at "How can drug usage be improved?"
- (3) Clinical outcome studies which examined "Does non-adherence matter?"

Of the 24 studies, there were eight "purely descriptive" studies (four clinic based and four community based), nine "interventions" studies and seven "outcome" studies. There was obvious overlap between these categories in that intervention studies and some clinical outcome studies included descriptions how drugs were used by patients.

5.2.3. Study populations

Thirteen studies were undertaken in Africa, nine in Asia and two in South America. Of the 13 studies in Africa, 10 were on children only and three were on both adults and children. In Asia, four of the eight studies were on adults only and the other four on both adults and children. Both studies in South America included adults and children.

5.2.4. Definitions

By default, the definition of malaria differed by the location and type of study so that in all the community based studies the diagnosis of malaria was self-defined whereas in most clinic-based studies, diagnosis was confirmed biologically.

There was wide variation in definitions for the terms “home or self-treatment”, “compliance” and “adherence” which reflected the range of study approaches and methodologies. The terms “home treatment” or “self treatment” imply that treatment was obtained without consultation with a formal sector provider, however studies differed in whether treatment from private providers was included or not.

A wide range of definitions of full adherence, non-adherence, under- and overdosing were used, with a minority of studies using detailed definitions of adherence that included dose, duration and frequency (Yepez, Zambrano et al. 2000; Ansah, Gyapong et al. 2001; Depoortere, Guthmann et al. 2003). Definitions such as “bought and used full course” were not uncommon and even where doses were specified, the criteria for adherence differed from study to study. However, the implications of failing to take one of the 70 tablets in an adult course of treatment with quinine and tetracycline are considerably different to those of not taking one of the three tablets in a treatment with SP, or one of the five tablets in a mefloquine treatment. Clearly there is a considerable subjective element to both the definition and its assessment. For the purpose of comparing different studies in this review, a standardised operational definition of “full adherence” was used and the term “compliance” was replaced by the currently more acceptable term, “adherence”. This meant that the antimalarial was taken at a dose and duration that was considered to be within a range that would result in the same efficacy as the recommended regime. As few studies reported the actual frequency of administration, this was not included in the definition. Where the authors themselves had used a similar definition, their categorisation was used directly. In other cases, the data reported were used to obtain the best estimate e.g. if the only data available was on “non-adherence” defined as “failing to take the full course” then it was assumed that everyone else was “adherent”.

5.2.5. Measurement of drug usage or adherence

Patient drug usage can be assessed by a number of means including self- or carer report, pill counts or container inspection, electronic counters and blood or urine drug assays.

5.2.5.1 Drug assays

Drug assays were used in six studies, either as the sole measure of adherence (Na-Bangchang *et al.* 1997; Shwe *et al.* 1998) or as a supplement to reported behaviour and container inspection (Qingjun, Jihui *et al.* 1998; Marsh, Mutemi *et al.* 1999; Kofoed, Lopez *et al.* 2003; Fogg, Bajunirwe *et al.* 2004).

Blood mefloquine levels on day 2 were used to assess adherence to a two-day course of artemether and mefloquine in Thailand. Patients were considered fully adherent if the mefloquine level was within or above the 95% confidence interval of the same regime supervised. Using this definition, 87% of patients were considered fully adherent, 11.3% were partially adherent, and 2% had undetectable levels (Na-Bangchang, Congpuong *et al.* 1997).

In another study of adherence to a five-day regime of artesunate with mefloquine, one tablet each of chloroquine and quinine were added to the blister-packages of artesunate and mefloquine on day 3 and day 5, respectively. The presence of both chloroquine and quinine in the urine was taken to mean full adherence and was reported to be 99.5% (Shwe *et al.* 1998).

The other studies mainly relied on drug histories with or without tablet inspection and selectively used drug assays to complement or validate this information.

In the study of adherence to artemether-lumefantrine in Uganda, adherence was assessed by interview and inspection of the blister-package, and this was compared to plasma levels of lumefantrine on day 4. Although levels were lower in the non-adherent patients than in the adherent patients, this difference did not reach significance (Fogg, Bajunirwe *et al.* 2004).

Marsh *et al.* found that blood chloroquine levels in children whose carer reported full adherence to a 25mg/kg dose taken unsupervised at home, were not significantly different from levels in children who had received 25mg/kg under supervision (Marsh V.M. *et al.* 2004). A similar finding, suggesting that carers' reports of adherence were reliable was reported by Kofoed *et al.* who found that the median day 7 chloroquine levels in children whose mothers had retained empty medicine bags did not differ significantly from those who had thrown them away (546 nmol/l versus 644 nmol/l respectively, $P > 0.05$) (Kofoed, Lopez *et al.* 2003).

Comparability between drug assays and self-reported adherence in adults was also found in the study by Qingjun et al.. In this two-phase study adherence to blister-packaged chloroquine and primaquine was reported to be 97% both when assessed by self-report in one set of patients and when assessed by the presence of urinary phenobarbital, which had been added to the blister-packages as a marker drug, in another set of patients (Qingjun, Jihui et al. 1998).

5.2.5.2. Other measures

In the remaining studies, adherence was measured using drug histories with or without pill-counting or container inspection and in one study was not assessed at all, being purely a comparative study of effectiveness of drugs taken with and without supervision (Smithuis *et al.* 2003).

Several studies also included qualitative assessments such as focus group discussions and key informant interviews to validate the results of household surveys (Marsh, Mutemi et al. 1999; Ansah, Gyapong et al. 2001; Yeboah-Antwi, Gyapong et al. 2001; Reilley, Abeyasinghe et al. 2002).

5.2.6. Adherence to clinic-prescribed antimalarial drugs

Thirteen studies gave details of adherence to antimalarial drug regimes prescribed in clinics prior to any intervention either as purely descriptive studies (n=3), as a baseline in intervention studies (n=5) or as part of a clinical effectiveness study (n=5). These results are pooled and discussed by drug regime.

5.2.6.1. Chloroquine

Three studies which reported adherence to three-day chloroquine regime using syrup in children prior to any intervention, all showed poor levels of adherence of 33-42% (Ansah *et al.* 2001 (Ansah, Gyapong et al. 2001; Okonkwo, Akpala et al. 2001; Yeboah-Antwi, Gyapong et al. 2001) although one further study suggested no difference in chloroquine levels between supervised and non-supervised patients (Kofoed, Lopez et al. 2003). Overdosing was reported to be around 40% for a three-day regime (Nshakira, Kristensen et al. 2002), and 1% in the single study of a one-day regime (Deming *et al.* 1989).

5.2.6.2. Chloroquine and primaquine

Interestingly, despite generally longer and more complicated regimes, clinic based studies of adherence to chloroquine and primaquine conducted in Asia and South America showed generally higher levels of adherence. Thus, adherence rates varied from 58% to a three-day course of chloroquine and seven-day course of primaquine in Ecuador (Yepez, Zambrano et al.

2000), to 82% to a three-day course of chloroquine and eight-day course of primaquine in a study in Sri Lanka (Reilley, Abeyasinghe et al. 2002).

5.2.6.3. Quinine and tetracycline or doxycycline

Only one study, by Fungladda et al., documented adherence to a seven-day regime of quinine (three doses/day) and tetracycline (two doses/day). Self-reported adherence was surprisingly high at 72% (Fungladda, Honrado et al. 1998). One further study reported adherence levels of 84%, but did not differentiate between the three-day chloroquine and 14-day primaquine regime for vivax malaria and the seven-day quinine and doxycycline regime for falciparum malaria and suffered from potential recall bias as patients reported on their last malarial episodes, some of which had occurred more than two years earlier (Duarte & Gyorkos 2003).

5.2.6.4. Artemisinin monotherapies and combination therapies

The study by Fungladda also reported adherence levels of 98% to a five-day artesunate monotherapy regimen. Other studies reported adherence to three-day artemisinin combination therapies with mefloquine or SP and co-formulated with lumefantrine. When mefloquine tablets were not provided together at the same time and place, very few (<5%) patients reportedly bought and took both components (Shwe, Lwin et al. 1998). Much better levels of adherence were reported when both component drugs were provided together, with adherence levels of 78% for a three-day course of artesunate and SP in Zambia (Depoortere, Guthmann et al. 2003) and 87% for a two-day course of artesunate and mefloquine in Thailand (Na-Bangchang, Congpuong et al. 1997). In an excellent study in Uganda which used self-report, pill counting and blood drug levels, adherence to a three-day course of co-formulated artemether-lumefantrine (Co-artem®) was reported to be even higher at 90-93%, even though twice daily dosing was required (Fogg, Bajunirwe et al. 2004).

5.2.7. Antimalarial drug usage in the community

Seven studies described use of antimalarial drugs for treatment of malaria-like illness in the community. Of these three were purely descriptive studies (Table 5-1 and 5-2) and four were from the pre-intervention phase of intervention studies (Table 5-3). Five of the studies documented the use of chloroquine use in Africa. For a standard three-day course the median reported correct usage was around one third (Thera, D'Alessandro et al. 2000; Nshakira, Kristensen et al. 2002), with a wide range from less than 10% (Marsh, Mutemi et al. 1999) to 68% (Krause and Sauerborn 2000). However the settings and methodologies varied considerably. In particular the type of provider accessed by the study populations differed considerably. For example in the study in Mali, even though only 8% of respondents sought treatment at health centres, over half of the remainder obtained their treatments through pharmacies or drug shops linked to health centres where they were more likely to receive

antimalarials at the correct dose. This compares to the two studies by Marsh et al., where the main source of treatment was small general shops with untrained shopkeepers where the type and duration of treatment is largely determined by the client's ability to pay. The relatively high adherence rate from the Burkina Faso study may be explained in part by the fact that follow-up was conducted mid-way through the treatment course rather than after completion. In addition the results represent only the small proportion of clients who were successfully followed-up.

Even when compared to a recommended one-dose regime of chloroquine, only 29% reportedly took the right dose. Overdosing rates were similar to those in the clinic based studies (Marsh, Mutemi et al. 1999; Thera, D'Alessandro et al. 2000).

The two remaining community based studies were conducted in Cambodia, the first in 1998 when the recommended treatment was seven days of quinine (three doses/day) and tetracycline (two doses/day). Only one to 10% of those who bought quinine and tetracycline, bought and used the full course (Denis 1998). In the second study in 2002, of those who took the new recommended first-line therapy of blister-packaged artesunate and mefloquine, over 77% were adherent (i.e. completed the blister-package over three days). However, less than 10% of the respondents actually received the recommended therapy in the first place and that artesunate monotherapy in inadequate doses was one of the most popular options (Yeung, Socheat et al. 2004).

5.2.8. Interventions to improve adherence

Table 5-3 and 5-4 summarise the four community-based and five clinic-based studies that assessed interventions aimed at improving patient drug usage. In all studies the authors found that at least one intervention had a significant effect in improving patient drug usage.

Of the clinic based studies, four were randomised control trials (RCTs), three based on 3-day chloroquine treatment in African children, examining the effect of packaging (Yeboah-Antwi, Gyapong et al. 2001), formulation (Ansah, Gyapong et al. 2001), and patient or carer education (Okonkwo, Akpala et al. 2001) and one RCT of blister-packaging of chloroquine and primaquine in China. All the community based studies were of a pre- and post- intervention observational study design except one in which two types of study design were used (Sirima, Konate et al. 2003).

5.2.8.1. Clinic based interventions

Drug formulation and packaging

For children, adherence to chloroquine in tablet form was found to be significantly better than syrup in two RCTs (Ansah, Gyapong et al. 2001; Yeboah-Antwi, Gyapong et al. 2001). Pre-

Table 5-1: Descriptive studies of adherence to prescribed regime-health centre (HC) based

Drug regime	Country, (Author, Year)	Study design (No. of patients assessed)	Assessment of adherence*	Level of adherence
Artesunate & SP – 3 days (Artesunate: 4mg/kg/dose 1x/day for 3 days, SP: 2.5mg/day single dose on day 0)	Zambia (Depoortere et al. 2003)	Clinic follow-up (n=162)	A1 = Gave exactly as prescribed A2 = No drugs remaining on day 3 but not given exactly as prescribed U = Drugs remaining on day 3	A1 = 39% A2 = 39% U = 22%
Artemether & lumefantrine (Co-artem®) – 3 days (twice daily for 3 days)	Uganda (Fogg et al. 2004)	Clinic follow-up (n=210)	A1 = No drugs remaining on day 4 and drug taken as prescribed A2 = No drugs remaining on day 4 but not given exactly as prescribed U = Drugs remaining on day 4	A1 = 90% A2 = 3% U = 7%
Chloroquine & primaquine – 5 days (Chloroquine: 4mg/kg day 0-1, 2mg/kg day 2 to 4; primaquine: once daily for 5 days, dose not stated)§	Sri Lanka (Reilly et al. 2002)	Clinic follow-up (n=132)	A = Took the full course and took over a 5-day period	No significant difference in day 3 lumefantrine levels between adherent and non-adherent A = 74%

* A, adherent; U, under dose; O, overdose; N, not adherent.

§ *P. falciparum* and *P. vivax*.

Table 5-2: Community based studies comparing antimalarial drug usage to national drug policy

National recommended first-line drug	Country, (author, year)	Study design (number of observations)	% of patients consulting health centre (HC)	% of patients receiving first-line drug	Assessment of patient adherence*	Patient adherence to first-line drug (of those who receive it)	Provider adherence
Chloroquine – 1 day (10 mg/kg)	Togo (Deming et al. 1989)	Household survey (n=370 children)	20%	94% of home treatments	A = 10-20 mg/kg U = <10 mg/kg O = >20mg/kg	A = 29% U = 70% O = 1%	
Chloroquine – 3 days (dose not specified)	Mali (Thera et al. 2000)	Household survey (n=152 children)	8% (but 32% bought from shop linked to HC)	90% of home treatments	A = <¼ of a tablet (100mg) difference between recommended and actual dose U = > ¼ tablet less than recommended O = > ¼ tablet more than recommended	A = 34% U = 36% O = 30%	
Chloroquine – 3 days (25 mg/kg over 3 days)	Uganda (Nshakira et al. 2002)	Clinic and drug shop follow-up n=463 children, two clinics, two drug shops)	Part of selection criteria	94% (98% for clinics, 92% for drug shops)	A = 20-30mg/kg U = <20mg/kg O = >30mg/kg	A = 38% U = 24% O = 38%	A = 34%§ U = 39.5% O = 26.4%
Chloroquine (dose not specified)	Burkina Faso (Krause & Sauerborn 2000)	1. Household survey (n=204 adults and children) 2. Clinic and drug outlet follow-up (n=47) 3. 155 provider consultations observed at 9 HC	21% of 204	58% (90 of 155 of provider consultations	A = "Drugs taken correctly according to count of remaining pills in middle of treatment period"	A = 68% of 47	Correct dose prescribed in 37 of 57 (65%) of children and 74 of 79 (94%) of adults (p<0.001)
Artesunate & mefloquine - 3 days (artesunate: 12mg/kg over 3 days, mefloquine: 25mg/kg over 2 days)	Cambodia (Yeung et al. 2004)	Household survey (n=361)	8%	9%	A = Blister-package taken over 3 days	A = 77%	

* A, adherent; U, under dose; O, overdose; N, not adherent.

§ 39% for clinics, 28% for drug shop.

packaging drugs in age-specific quantities, resulted in a reported increase in adherence of about 20%, from 33% to 54% for syrup and from 61% to 80% for tablets (Yeboah-Antwi, Gyapong et al. 2001).

Only one study directly compared the effectiveness of blister-packaging with conventional dispensing. In this RCT, Qingjun et al., showed that adherence to a regime of chloroquine (three days) with primaquine (eight days) for the treatment of *P. vivax* infections, was already high (81-83%) when provided in traditional paper envelopes from clinics (Qingjun, Jihui et al. 1998). By replacing this with blister-packaging, adherence was reported to increase to 97%. Although one other study did report remarkably high levels of adherence (99.5%) to a blister-packaged five-day regime of artesunate with either mefloquine or a placebo (Shwe, Lwin et al. 1998), the non-intervention group were not even provided with the drugs concurrently and were expected to go to a different outlet in order to obtain the mefloquine.

Patient/carer information and education-clinic

One study, an RCT, specifically studied the effectiveness of instructions for carers on the correct use of drugs; this was for the use of chloroquine syrup in children in Nigeria (Okonkwo, Akpala et al. 2001). At baseline, with no intervention, adherence was only 37%. With pictorial instructions alone, this increased significantly to 52% and with both pictorial and verbal instructions adherence increased further to 73%.

5.2.8.2. Community based interventions

Behaviour change communication

In Kenya a pilot programme was undertaken during which drug vendors were trained to treat childhood fevers with chloroquine and provided with age-specific dosing charts. Pre- and post-intervention assessments showed that the number of childhood fevers treated with chloroquine increased and in those who received it, adherence to the correct age-specific dose increased from 4% to 75% and correct duration from 23% to 47% (Marsh, Mutemi et al. 1999). Following a switch in national drug policy to SP (which has the advantage of a single dose) and the further scaling up of this programme, this improvement in drug usage has been sustained (Marsh, Mutemi et al. 2004).

Community education appeared to improve drug usage in a pre- and post-intervention observational study in Cambodia at a time when the recommended regime was quinine and tetracycline (Q+T) for seven days (Denis 1998). In villages with posters only, adherence in those who bought Q+T reportedly increased from one to 15% and the proportion of patients buying Q+T increased from 47 to 54%. In villages using both videos and poster the corresponding increases were from 10 to 38% and 57 to 74%. The evaluation was only

conducted immediately before and after the 10-week intervention, and so the long-term impact of the campaign is unknown.

Clinical outcomes and interventions

Four of the clinic based studies reported some measure of outcome. However because follow-up was very short and relied on carer reports and was unlikely to identify most recrudescing infections, it is not possible to comment accurately on the relationship between interventions to improve adherence and clinical outcomes from the data presented. These reported “recovery rates” were uniformly high and did not differ significantly between groups.

In the community based study (Sirima, Konate et al. 2003) in Burkina Faso, the measure of clinical outcome was the incidence of probable severe malaria. The intervention was a community malaria control programme which involved a number of integrated strategies including the training of community health workers and providing them with pre-packaged antimalarial drugs (PPAM). Unfortunately, no pre-intervention data are presented, however, post-intervention, the incidence of probable severe malaria in children who had received PPAM for a malaria-like episode was reported to be 5%, compared to 11% for those who had not (adjusted odds ratio of 0.47 (95% CI 0.35,0.64;P<0.0001). Interestingly, receiving the incorrect age-specific package or taking incorrect duration was not shown to make any difference to the outcome (P=0.64 and P=0.23 respectively).

5.2.8.3. Cost of interventions

Some information on the cost of interventions was available from six studies. Only one study on pre-packaging of chloroquine gave detailed financial and economic costs from both the government and caregivers perspective (Ansah, Gyapong et al. 2001).

Cost of pre-packaged drugs was also reported in the study by (Yeboah-Antwi, Gyapong et al. 2001), who found that the average cost to the patient who received treatment in intervention dispensaries (with pre-packaging) was almost half that in non-intervention dispensaries (US\$0.38 versus US\$0.72). From the patients perspective, Sirima found that if patients bought pre-packaged antimalarial drugs (PPAM) from the community health worker (CHW), the cost of treatment was US\$0.05-0.12 compared to the standard practice of buying 20 tablets each of chloroquine and paracetamol for US\$0.70 (Sirima, Konate et al. 2003). However, Yeboah-Antwi et al. noted that some patients preferred to have extra medication in order to treat future episodes, and it may be that some would be willing to pay more for this option. In the study by Okonkwo inserting a pictorial insert added US\$0.01 to the mean cost of a bottle of syrup (US\$0.30) (Okonkwo, Akpala et al. 2001).

Table 5-3: Studies of interventions to improve community antimalarial drug usage

Intervention Study design	Country (author, year)	Number of patients	Assessment A=adherent	Adherence		P- value	Outcome
				Pre- intervention	Post- Intervention		
Shopkeeper training: Training and provision of drug dosage charts for chloroquine (25 mg/kg over 3 days)	Kenya (Marsh et al. 1999)	109 (pre- and 6 months post)	A1 = correct dose by age- specific band	A1 = 4% A2 = 3%	A1 = 75% A2 = 47%	<0.001	Mean cost of treating a child with fever US\$0.15 to US\$0.21 Also provider adherence***
Pre- and post-household survey		-	A = taking adequate dose	SP not available prior to intervention A = 8% for chloroquine (12/160)	A = 63-65% (of those who received SP)	-	-
Shopkeeper training: Training on how to use new first-line policy SP (single dose of tablet by age-group)	Kenya (Marsh et al. 2004)						
Pre- and post-household survey							
Community education, delivery and packaging: Community based intervention with IEC and pre-packaged antimalarial (PPAM) according to 4 age-specific categories for chloroquine (3 days)	Burkina Faso (Sirima et al. 2003)	3203	A1 = correct age specific dose A2 = 3 days (of patients who took PPAM)	Pre- intervention: Not available	Post- intervention: A1=52% A2=59% Over dose=17%	-	% of patients developing severe malaria (not laboratory confirmed), 5% if took PPAM versus 11% if did not take PPAM (adjusted OR = 0.47, 95% CI 0.35,0.64, P<0.0001) ** Pre-packaged treatment from CHW = US\$ 0.05-0.12 Standard treatment in drug store = US\$0.7
Post-intervention household survey							
Facility based health education: Display of posters alone (I) or poster and videos (II) on correct use of quinine and tetracycline (7 days)	Cambodia (Dennis 1998)	325	A = bought and used full course of those who bought Q+T	(I): A = 1% (II): A = 10%	(I): A = 15% (II): A = 39%	-	-
Follow-up of clinic and drug outlet patients							

** No difference if received correct rather than insufficient age-specific dose or duration.

*** Of antimalarials sold, % selling adequate dose = 31.8% before and 89.9% 1 year after intervention and % who gave advice on use=2% before and 97.5% after 1 year)
RCT, Randomised control trial; IEC Information, education and communication.

Table 5-4: Studies of interventions to improve patient adherence – health centre based

Intervention Study design	Country (author, year)	Number of patients	Adherence			Outcome and cost
			Assessment A = adherent	Pre-intervention	Post-Intervention	
Formulation: RCT of chloroquine tablets versus syrup (25mg/kg over 3 days)	Ghana (Ansah et al.2001)	299	A = correct dose, duration, and frequency	Syrup: A=42%	Tablets: A = 91% (or 74% if include vomiting and spitting)	<0.001 No difference in carer reported recovery on day 4 Tablets = \$0.08/pack Syrup = \$0.36/bottle
Packaging: RCT of pre-packaging of chloroquine syrup and tablets (3 days) according to 7 age-weight categories	Ghana (Yeboah-Antwi et al. 2001)	509	A = drug taken for 3 days as prescribed	Tablets: A=60.5% Syrup: A=32.5%	Tablets: A = 82% Syrup: A = 54.3%	Average cost paid by patient: Pre-packaged drug = US\$ 0.72 “Usual” = US\$ 1.38
Carer instructions: RCT of chloroquine syrup (3 days) dosing instructions for carer: (I) No instruction (II) Pictorial insert (III) Pictorial insert and verbal instruction	Nigeria (Okonkwo et al. 2001)	632	A = correct amount and dosing schedule	(I) A= 36.5%	(II) A = 51.9% (III) A = 73.3%	“Recovery” assessed by carer (day 2 and 7) and day 2 parasitaemia (I) 93.7% improved (II) 89.9% improved (III) 96.8% improved* Syrup = US\$0.3 Pictorial insert = US\$0.01
Packaging: RCT blister-packaging (versus paper envelopes)	China (Qingjun et al. 1998)	596	Phase I (1994): A1 = correct dose and duration	Phase I: A1=83%	Phase I: A1 = 97%	Day 9 cure rate not significantly different with or without packaging
Chloroquine (3 days) and primaquine (8 days) for PV			Phase II (1996): A2 = level of urinary phenobarbital	Phase II: A2=81%	Phase II: A2 = 97%	<0.001
Packaging and delivery: Provision of pre-packaged drugs to health centres Artesunate (5 days) and mefloquine or placebo (3 tablets on day 1)	Myanmar (Shwe et al. 1998)	(455 post-intervention)	Pre-intervention: A1 = bought mefloquine as well as artemisinins Post-intervention: A2 = positive urine test for biological markers	A1=<5%*	A2 = 99.5%	With blister-packaging, day 28 cure rate = 99.6% for artesunate plus mefloquine and 95.6% for artesunate alone

*Mefloquine *not* provided by provider in pre-intervention study.

From the private vendors' perspective, treating childhood fevers with chloroquine as well as antipyretics increased the mean cost per treatment from US\$0.15 to US\$0.21 and this increased profitability was perceived as a benefit by the vendors (Marsh, Mutemi et al. 1999).

5.2.9. How much does adherence affect clinical outcome?

Seven clinic-based studies reported parasitological outcome in relation to unsupervised or non-adherent antimalarial drug taking. Only one of these studies was conducted in Africa (using chloroquine in children) (Kofoed, Lopez et al. 2003). There were three RCTs comparing supervised versus unsupervised treatment, one RCT comparing the outcome of different drug regimens both given unsupervised (effectiveness), two observational follow-up studies relating patient adherence to outcome, and one longitudinal cohort study relating adherence with therapy to subsequent incidence of malaria attacks (Table 5-5).

5.2.9.1. Chloroquine

There was one RCT of supervised versus unsupervised treatment with chloroquine in children in Guinea-Bissau in 1996 (Kofoed, Lopez et al. 2003), where the cumulative failure rate up to day 35 was high in both the unsupervised group (47%) and in the supervised group (36%) (Cumulative relative risk =1.26; 95% CI 0.76-2.10, Logrank test, P=0.37). Day 7 chloroquine levels were not significantly different between the two groups.

5.2.9.2. Chloroquine and primaquine

In Ecuador, Yopez et al. compared 14-day cure rates in self-reporting non-adherent and adherent patients. For patients who were adherent to the three-day course of both drugs for falciparum malaria, cure in adherent patients was 90% compared to non-adherent patients in which it was 69%; adherence was reported to be 74%. For patients with vivax malaria for whom recommended treatment consisted of three days of chloroquine and seven days of primaquine, adherence was significantly lower at 58%. Cure rates were "high" in both adherent and non-adherent groups at 100% and 94% respectively, however with only 14 days of follow-up, few failures would have been detected.

Adherence and outcome with chloroquine and primaquine (14 days) treatment of *P. vivax* infection was also studied in Brazil (Duarte and Gyorkos 2003). Patients in the community were asked when they had received their last treatment for vivax or falciparum malaria infection and whether they completed the course. They were then followed-up to record the incidence of malaria episodes. Unfortunately the results for patients treated for vivax malaria are not presented separately from those who were treated for falciparum malaria, who should have received quinine for three days and doxycycline for seven days. Overall, the authors conclude

that poor adherence was an important predictor of subsequent malaria episodes, but only in individuals who were “less immune”.

5.2.9.3. Quinine and tetracycline

In a comparative trial of the effectiveness of five-day artesunate monotherapy and seven-day quinine and tetracycline in Thailand (Fungladda, Honrado et al. 1998), “cure rates” were assessed very early, at the end of the treatment (i.e. days 5 and 7 respectively). The cure rate to the quinine and tetracycline regime was reported to be 77% in the 53 out of 60 (88%) patients followed up. Adherence was reported to be 72% with cure rates of 73% in the non-adherent and 79% in the adherent group.

5.2.9.4. Artemisinin derivative monotherapy

In the other arm of the Fungladda et al. study, the five-day “cure rate” to artesunate monotherapy was reported to be 100% in the 61 out of 77 (79%) patients followed up. Adherence to this regimen was reported to be 98.4%.

Efficacy and effectiveness were compared with five-day regimens of either artesunate or artemisinin monotherapy in Vietnam (Le, Pham et al. 1999). With artemisinin, the 14-day parasitological cure rate in the supervised “efficacy” group was reported to be 100%, significantly higher than the unsupervised “effectiveness” group, in which it was 83.3%. With artesunate a difference was not seen; corresponding values were 100% and 97.1%, respectively. However treatment groups were small and again follow-up was too short at only 14 days, which is insufficient to define the true treatment failure rate.

5.2.9.5. Artesunate and mefloquine

Fortunately the most rigorous “outcome” study may also have the most relevance to countries contemplating a switch in drug policy to ACTs. In this health centre based RCT in Myanmar (Smithuis, van de Broek et al. 2003), four artesunate and mefloquine regimes were compared including a supervised and unsupervised regime of artesunate 4mg/kg/day for three days and mefloquine 25mg/kg, where the only dose to be supervised was the first day’s dose of artesunate. After 42 days of follow-up, there were no recrudescences in the 177 patients who received the three-day regime under supervision and only seven (polymerase chain reaction (PCR) confirmed) recrudescences in the 180 unsupervised patients, giving a cure rate with unsupervised treatment of 96% (95% CI: 93 to 99%). Although this difference was significant, unsupervised treatment was still extremely effective.

The effectiveness of a two-day course of artesunate and mefloquine was also studied by Na-Bangchang. However, only 43% of the patients were followed up to day 42. The cure rate

Table 5-5: Studies examining the clinical outcomes in unsupervised patients (effectiveness)

Drug regime	Country (author, year)	Number of patients	Days FU	Study design	Outcome (parasitological cure rate unless otherwise specified)			Adherence	
					Supervised	Un-supervised	P-value	Assessment	Adherence rate
Artesunate & mefloquine-3 days (Artesunate: 4 mg/kg daily; mefloquine: 15 mg/kg day 1 and 10 mg/kg day 2)	Myanmar (Smithuis et al. 2003)	803 in four arms	42	RCT of supervised versus unsupervised	100%	94%	0.01	Not measured	
Chloroquine – 3 days (25 mg/kg over 3 days)	Guinea-Bissau (Kofoed et al. 2003)	140	35	RCT of supervised versus unsupervised	64%	53%	P=0.37	Median blood chloroquine levels on day 7	No difference between supervised and unsupervised treatment (P>0.05)
Artesunate - 5 days (50 mg tablets, six tablets/day 0, then two tablets/day)	Thailand (Fungladda et al. 1998)	77	5	RCT of different unsupervised regimes	NA	100%		A = "Adherence to protocol" or "not missing as single dose or absence of residual pills"	A = 98%
Quinine & tetracycline-7 days (Quinine: 300 mg tablets, two tablets thrice daily; tetracycline; 250 mg capsules, two capsules twice daily)	Thailand (Fungladda et al. 1998)	60	7	RCT of different unsupervised regimes		77% overall (73% if non-adherent. 79% if adherent)		A = "Adherence to protocol" or "not missing as single dose or absence of residual pills"	A = 72%
Artemisinin - 5 days (10mg/kg twice daily on day 0, then 5mg/kg twice daily)	Vietnam (Le et al. 1999)	75	14	RCT of supervised versus unsupervised	100%	83%	0.02	Not available	
Artesunate – 5 days (2mg/kg twice daily on day 0, then 1 mg/kg twice daily)	Vietnam (Le et al. 1999)	74	14	RCT of supervised versus unsupervised	100%	97%	0.58		

Table S-5 continued

Drug regime	Country (author, year)	Number of patients	Days FU	Study design	Outcome (parasitological cure rate unless otherwise specified)			Adherence	
					Supervised	Un-supervised	P-value	Assessment A=Adherent	Adherence rate
Chloroquine & primaquine – 7 days for <i>P. vivax</i> (Chloroquine: 150mg tablets, 4 tablets on day 0, then 3 tablets daily on day 1 and 2; primaquine: 75mg daily for 7 days*)	Ecuador (Yepez et al. 2000)	129	14	Observational follow-up of patients	NA	94% if not adherent 100% if adherent		A = "Recommended dose for recommended duration and frequency and on empty stomach"	A=58%
						69% if not adherent 90% if adherent			A=74%
Chloroquine & primaquine – 3 days for <i>P. falciparum</i> (Chloroquine: as above primaquine: 75mg daily for 3 days)	Ecuador (Yepez et al. 2000)	121	14	Observational follow-up of patients					
Artemether & mefloquine – 2 days (Artemether: 300 mg (50 mg tablets) as a single dose day 0; mefloquine 750 mg (250mg tablets) at 24 hours and 500 mg at 30 hours)	Thailand (Na-Bangchang et al. 1997)	126	42	Observational follow-up of patients	NA	93% (Only 43% followed up) 96%**		A = mefloquine level within reference range	A = 87%
						Incidence rate (episodes/100 person days) 0.141 if non-adherent 0.079 if adherent		Self-reported Not defined	A=83.8%***
Quinine & doxycycline – 7 days for <i>P. falciparum</i> (dose not stated)	Brazil (Duarte & Gyorkos 2003)	550 in total	NA	Prospective open cohort study of patients who received antimalarials in the past	NA				
Chloroquine and primaquine – 14 days for <i>P. vivax</i> (chloroquine: 3 days and primaquine 14 days, dose not stated)									

NA, not available.

** Not in this study but refers to published study.

*** Self-reported adherence to last episode occurring any time in the past.

reported for these patients was high (92.6%), and thought to be similar to the 96.4% cure rate reported with supervised treatment in a previous efficacy studies at the same site (Na-Bangchang, Congpuong et al. 1997).

5.3. Discussion

In recent years there has been considerable interest and concern in translating antimalarial efficacy (documented usually with observed treatment in randomised controlled trials) into effectiveness, when these drugs are taken unsupervised in “real life” settings in malaria-affected communities. The importance of understanding how antimalarial drugs are used in the community, how their use might be improved, and the effect on clinical outcome are reflected in the growing number of studies in this area. Of all the studies reviewed, all except one were published in the last 10 years, and 13 were reported in the last five years. The utility and quality of studies has improved with more recent publications, reflected as clearer definitions of adherence, an increasing number of randomised control trials, and longer periods of follow-up for patients in effectiveness trials. However, the overall quality and quantity of information available to date is still seriously inadequate and results are so variable that it certainly does not justify generalisations on how good or bad adherence is to currently available drugs in different settings.

There are a number of limitations to this review. Although the search strategy involved more than one electronic database and personal communications, it is possible that we failed to identify studies that would have fulfilled the inclusion criteria. We did not include unpublished work such as project reports, theses, and local surveys, although a substantial amount of information is available from these sources, because we could not be sure of either the completeness of the search or the quality of the data. The review was limited to studies that provided quantitative information related to the use of antimalarial drugs by patients for specific episodes of malaria. We did not attempt to include studies of treatment seeking behaviour, qualitative studies, or evaluations of provider behaviour. These studies contribute greatly to our understanding of the factors underlying the drug usage behaviour of patients. These include assessment of socio-economic factors (Kaewsonthi and Harding 1986; Snow, Peshu et al. 1992; Molyneux, Mung'Ala-Odera et al. 1999; Biritwum, Welbeck et al. 2000; Kamat 2001), the prescribing behaviour of providers in the public and private sector (Ndumbe 1989; Feller-Dansokho, Ki-Zerbo et al. 1994; Ofori-Adjei and Arhinful 1996; Ongore and Nyabola 1996; Sharma, Gupta et al. 1996; Yousif and Adeel 2000; Font, Alonso et al. 2001; Rowe, Onikpo et al. 2001; Agyepong, Ansah et al. 2002), and the underlying community beliefs and attitudes (Ahorlu, Dunyo et al. 1997; Miguel, Tallo et al. 1999; Williams, Kachur et al. 1999; Baume, Helitzer et al. 2000; Tarimo, Lwihula et al. 2000; Kilian, Tindyebwa et al. 2003). Without such

an understanding, attempts to influence behaviour are unlikely to succeed. Nor, did we include community or informal provider intervention studies that did not include information on patient drug usage. As a result, a number of studies with useful information for the implementation of such programmes were excluded (Kafle, Gartoulla et al. 1992; Oshiname and Brieger 1992; Kidane and Morrow 2000; Tavrow, Shabahang et al. 2003). Of particular note are the studies of retailer training in Nepal by Kafle et al. and Kidane and Morrow's RCT in Ethiopia where mothers were taught to recognise and treat malaria and were supplied with chloroquine, resulting in a significant reduction in under-five mortality.

Despite the limitations and the disparity in locations, study designs, drug regimens, and health environments, it is still possible to draw some broad conclusions from the studies in this review. As might be expected, descriptive community based studies indicated generally low levels of conformity to national recommendations for malaria treatment. This is unsurprising as treatments are often bought over the counter from untrained shopkeepers where the choice of drug and amount purchased are limited by the cost of the drugs and the training of the provider. However, when patients were given free drugs at the correct dose by a trained health provider, levels of adherence were much higher, especially if careful verbal instructions had been given. Patient adherence to a recommended drug regime represents the final step in a pathway from first developing symptoms to receiving curative treatment (Krause & Sauerborn 2000) and the problem of patients not taking drugs as recommended, may be more a result of the patient not having access to affordable treatments and not receiving the correct instructions rather than "patient non-adherence" *per se* (Nshakira *et al.* 2002) (Kofoed *et al.* 2003). Identifying where problems lie in this complex pathway is important so that interventions to improve drug usage can be tailored accordingly.

It is generally assumed that adherence to antimalarial regimens is inversely proportional to the duration of treatment and the frequency of dosing, although there are few data to support this. Certainly the treatment of malaria (between one to seven days) cannot be compared with the treatment of HIV (lifelong with poorly tolerated drugs) or tuberculosis (six months). Seven day regimens with quinine, a generally poorly tolerated drug, are generally considered to be poorly adhered to – although this has not been well documented. Although adherence with unobserved three-day regimens is likely to be less than single dose treatments, the very limited available data suggested that with attention to patient or care education and packaging, cure rates approached those with observed treatment.

There appears to be a trend towards higher rates of adherence to drug regimes known to be efficacious than those that are ineffective. In particular, evidence in this review and other studies in South Africa and Laos (Dr K Barnes and Dr Mayxay, personal communication)

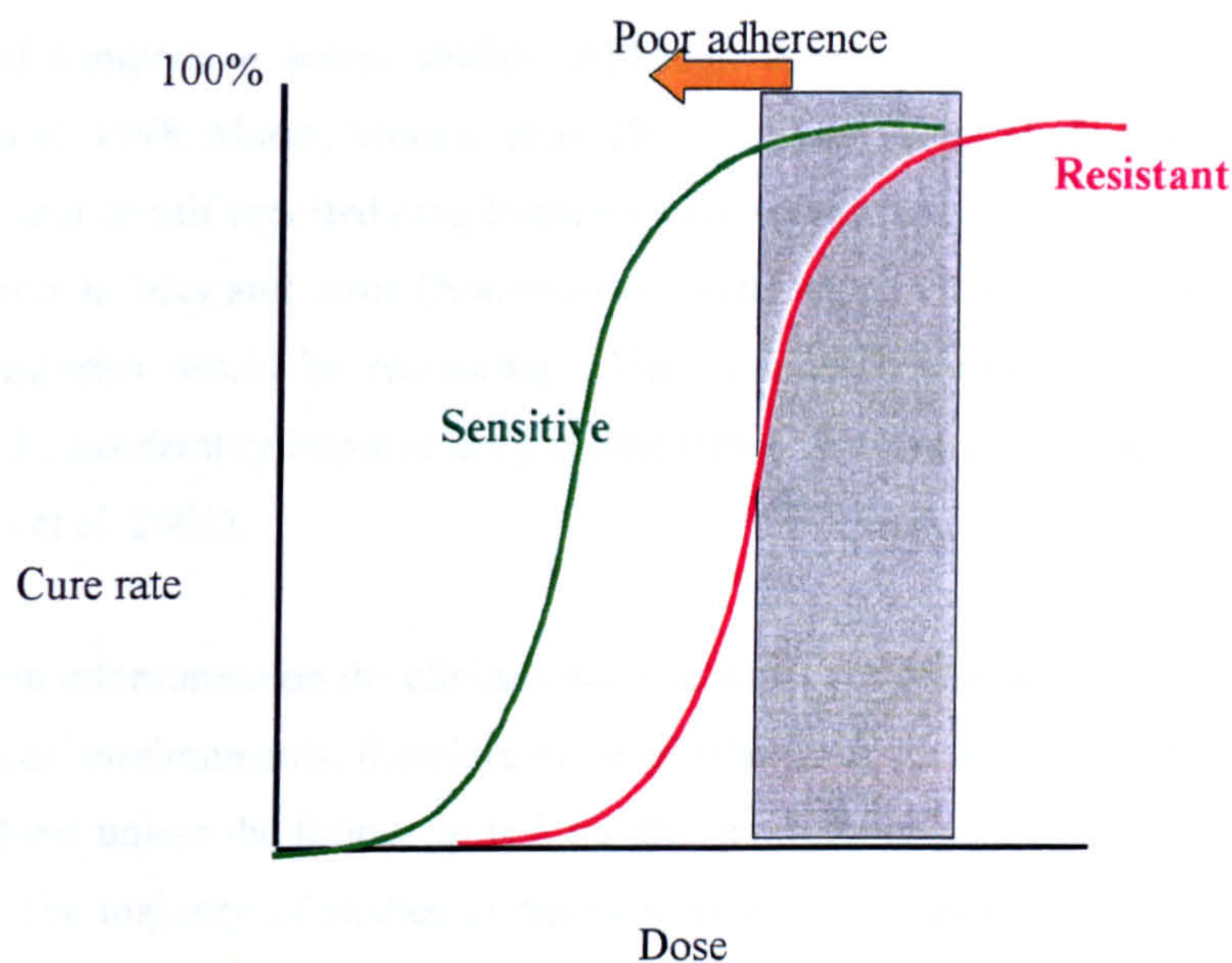
suggest high levels of adherence and effectiveness to 3-day regimes of artemisinin combinations which are known to be both very well tolerated and highly effective (Price, van Vugt et al. 1999; McGready, Cho et al. 2001) compared to the three-day regime of chloroquine which is increasingly ineffective. This finding should help allay fears that the rapidity of action of ACTs would actually encourage poor adherence.

Although there are significant logistic constraints to improving antimalarial drug usage, the limited interventions studies presented here, suggest that there are a number of simple practical interventions both at the community level and clinic level which are effective. This includes making sure that patients and carers understand both how and why drugs should be taken correctly and providing patients with pre-packaged drugs (Ross-Dengan, Laing et al. 2003). However, in order to improve community drug usage both for malaria and other common diseases, the most effective approach is an integrated one in which affordable diagnosis and effective treatment are made accessible, community awareness is raised, and health care providers are trained and supported appropriately.

In terms of the relationship between actual antimalarial drug-taking and clinical outcome, the data were sparse. Despite this, the effects of incomplete adherence were most evident where the antimalarial used was relatively ineffective. This is related to the shape of the dose-response curve as shown in Figure 5-2. Poor adherence reduces the dose taken and therefore increases the chance of therapeutic failure if the dose is reduced to the steep part of the dose-response curve. The closer the dose is to the steep part of this curve the greater is the reduction in cure rate with incomplete treatment. Thus as cure rates with observed treatment fall, the greater is the effect of poor adherence on treatment outcomes. As cure rates fall further the differences reduce again.

Highly efficacious treatments are more likely to be adhered to, and if they are not, the consequences in terms of efficacy are less, than with poorly efficacious treatments. Where an effective antimalarial is used or the patient is partly "immune", unsupervised treatment or incomplete adherence usually still results in a good outcome in terms of clinical cure. However, there are two caveats to interpreting these data. Firstly, nearly all of the "outcome" studies were facility-based where drugs are prescribed by trained staff and the "non-adherence" is probably less extreme than the "non-adherent" behaviour in the informal sector. Secondly, these studies only measured clinical outcomes (and often with inadequate follow-up) and did not assess the negative impact of poor adherence on the development of antimalarial resistance.

Figure 5-2: *The relationship between dosing (dose and duration of dosing) and therapeutic response to antimalarial drug treatment in sensitive (green) and resistant (red) infections. Treatment failures result from resistance (shaded area).*



The relationship between drug usage and antimalarial drug resistance has not been well characterised. Partially effective treatment which results in recrudescence of the infection encourages the selection of resistance (White 2004). Taking little or no drug does not select for resistance (but will not cure the illness either!). Where resistance to the recommended antimalarial regime is high, the first-line drug is by definition ineffective, and so it is entirely rational for the patient or carer to choose not to use the drug or to use it for a short time before looking for a more effective alternative. This may reinforce the behaviour of trying out many different drugs for short durations, and is most likely to reduce trust in that medicine, the dispensing healthcare provider, and the health care system. Strategies to improve delivery and adherence are likely to have ~~to have~~ limited effectiveness if ineffective drugs are used and the poor results from such studies should not deter deployment of effective antimalarials. Interpretation and judgement of the community's drug usage behaviour must be done in light of the known efficacy of the recommended regime.

The review revealed other gaps in knowledge and areas in which future studies could be improved. Community drug usage studies are constrained by not knowing whether a patient actually had malaria or not and therefore whether the choice of treatment was in fact appropriate. Microscopy at time of interview is not useful, as patients who genuinely may have had malaria will often have undetectable parasitaemias soon after starting treatment. The wider user of rapid diagnostic tests both operationally and for research purposes, especially in low transmission areas may be one approach to addressing this problem.

There were wide discrepancies in the definition and measurement of “adherence”. A patient may not take the regimen exactly as prescribed, but still receive adequate treatment. Clearer definitions of adherence in terms of dose, duration and frequency would greatly assist interpretation and comparison across studies. Although the results of studies in this review (Qingjun, Jihui et al. 1998; Marsh, Mutemi et al. 1999; Kofoed, Lopez et al. 2003) suggest that in these settings carer or self-reported drug histories were reliable, other studies have shown that they can be subject to bias and error (Nwanyanwu, Redd et al. 1996). More studies which validated drug histories would be reassuring. Use of modern population pharmacokinetic approaches would considerably improve drug concentration interpretation in adherence studies (Simpson, Aarons et al. 2001).

There is inadequate information on the clinical outcome when antimalarial drug are used outside of controlled clinical environments, therefore more effectiveness studies are needed. But these will be of limited use unless the follow-up is for sufficient duration to detect treatment failures (i.e. ≥ 28 days). The majority of studies in Africa were on chloroquine use in children (often where the drug was failing) whilst studies of ACTs and other drugs were largely performed in Asia and South America. As the majority of the world’s malaria occurs in Africa, where countries are increasingly switching to combination treatments, there is a need to document how well the drug is being used by both adults and children in the community and how effectively specific interventions can improve drug usage and therapeutic outcome in these settings. This includes evaluation of the effectiveness of strategies such as the use of rectal artemisinins in children, the blister-packaging of tablets, co-formulations, and working with the informal sector to improve diagnosis and treatment. Finally future intervention studies should include more information on costs and how they are calculated in order for policy makers to make informed decisions around policy change and implementation.

CHAPTER 6

PRIMARY DATA COLLECTION IN CAMBODIA: COSTING STUDY

From early on in this study it was apparent that there was a lack of data on the actual implementation of ACTs, the adherence and coverage rates and the costs in trying improve either or both. In this and the next chapter the primary data collection that took place in Cambodia is described and the results presented. The chapter starts with a background section describing the key components of the implementation of ACT in Cambodia including blister-packaging, rapid diagnostic tests (RDTs) and delivery through village malaria volunteers (VMVs) and outreach. The cost methodology for each strategy is then presented followed by the results.

6.1 Specific aims

The aim of the costing study was to estimate the provider costs of interventions involved in the implementation of “Early Diagnosis and Appropriate Treatment” (EDAT) with artesunate and mefloquine to obtain the appropriate input values to assess the cost-effectiveness of introducing ACTs. These included the incremental cost of commercially available blister-packaged ACT, RDTs and the cost of delivery with VMVs and outreach clinics.

6.2 Background

6.2.1 Blister-packaged artesunate and mefloquine

When Cambodia became the first country to switch to an ACT for the first-line treatment of *P. falciparum* malaria in 2000, it was clear that there were a number of obstacles to successful implementation. These included the unavailability of co-formulated or blister-packaged ACTs, the low utilisation of public health facilities; the high usage of antimalarials without biological confirmation of malaria; and the wide-spread availability of fake artesunate and mefloquine. In order to address these problems, the change in policy was accompanied by a number of innovative strategies.

Initially the artesunate and mefloquine were distributed and prescribed separately. However the dosing regime is relatively complicated and it was recognised early on that there would be problems with ensuring that the drugs were correctly prescribed by health providers, and

correctly taken by patients. In addition, in view of the problem with fake drugs, it was felt that pre-packaging drugs would also enable both patients and health workers to be assured of the drug quality.

However, at the time there were no local pharmaceutical companies with the capacity to produce blister-packages. Therefore a decision was made by the National Malaria Centre (CNM) with the support of WHO, to pre-package the drugs themselves. A room in the Central Medical Stores building was extensively renovated, including the installation of specialist air-conditioning and ventilation; the separation of packaging and storage rooms; and the construction of a special staff toilet. New packaging and printing machines were purchased and staff were given the appropriate training.

Artesunate and mefloquine tablets were bought separately and then pre-packaged together into three different age-packages: for children aged from 6-11 years, 12-15 years and adults (See Annex 4 for details). Packages for the public sector ("A+M") were packaged simply with a warning of "not for sale". In recognition that the majority of patients would continue to seek treatment in the private sector, the two older age group regimes were also packaged for sale in the private sector ("Malarine") in more attractive packaging (Figure 6-1). These were marketed in the private sector through a social marketing initiative that was initially piloted in two districts, and then was launched nationwide in March 2003.

The local blister packing of the ACT was only ever intended as an interim measure until commercially produced ACT became available or until local production of the blister-packages could be taken over by a more appropriate organization. The process is now being contracted out to the Food and Drugs Administration (FDA) who have established a blister-packaging facility.

The original system was reported to have a capacity of up to 2,500 tablets per day but actual maximum technical efficiency was estimated at 2,000 tablets/day or 40,000 blisters per month. In reality only 56,794 packages were officially produced in 2001 (CNM 2001). Once the production is taken over by the FDA, the maximum technical efficiency is more likely to be reached.

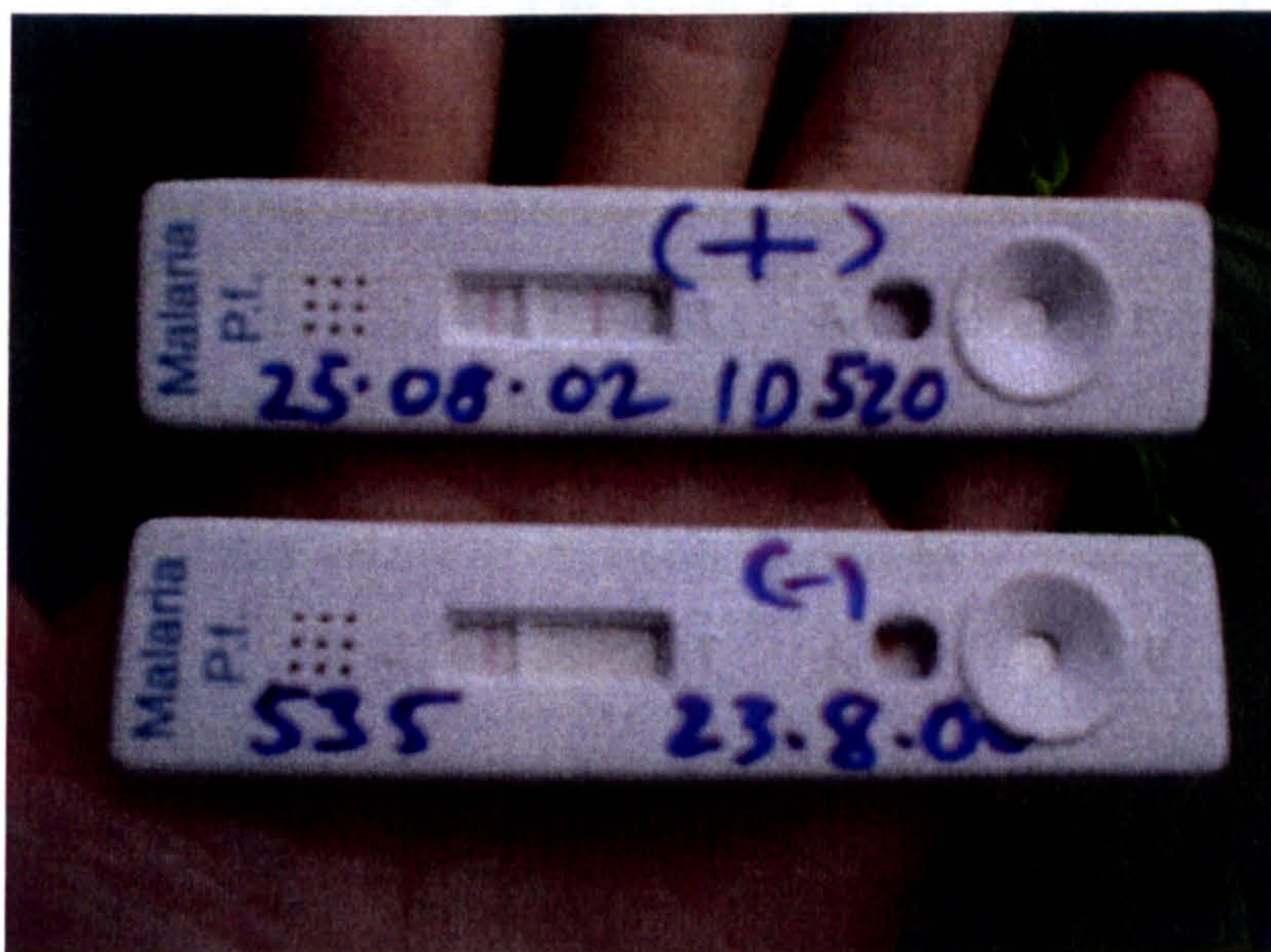
6.2.2 Rapid diagnostic tests (RDTs)

One of the keystones to the EDAT approach was the provision of accurate biological diagnosis to replace the inaccuracies of clinical diagnosis. The broad intention was to ensure that patients with malaria-like symptoms, who did not have access to microscopic diagnosis, should receive diagnosis by an RDT prior to receiving antimalarial treatment. Paracheck®, a *P. falciparum* -

Figure 6-1: The blister-packaged A+M4 and Malarine®



Figure 6-2: The Paracheck® rapid diagnostic test



specific RDT (Figure 6-2), was introduced with the intention that it should be used in health centres without microscopes and also in the private sector alongside Malarine®. However, actual implementation was patchy, and there was a lack of information on the extent to which the RDTs were actually being used in the either sector. To add to the confusion, a shipment of Optimal®, an RDT which can detect non-*falciparum* malaria, also started to be distributed³⁶. However initial problems with quality as a result of deterioration during storage in field conditions resulted in haphazard introduction and use.

6.2.3 Interventions to improve access to early diagnosis and appropriate treatment

In addition to the change in national policy, there were a number of initiatives aimed at increasing access to early diagnosis and treatment at the village level including Malaria Outreach Teams in Anlong Veng district and VMVs in Rattanakiri and Ko Kong provinces. These are described below.

6.2.3.1. Outreach clinics

The malaria outreach activities in Anlong Veng District, Oddor Meanchey province were set-up, run and funded by Médecins Sans Frontières (MSF) as part of their programme of support in that area. The area is in the Northwest of Cambodia, heavily forested and had remained a Khmer Rouge (KR) stronghold until 1999 and therefore lacked government-supported health facilities. MSF first arrived in 1998 and took over the running of the previously KR-run Anlong Veng Health Centre³⁷ in 1999.

The collapse of KR power resulted in an influx of non-immune migrants from all over Cambodia who came in search of farmland and to collect forest products. The population of the district estimated by MSF in 2001 was 19,029 in 64 settlements (Goubert L, personal communication)³⁸. This figure is continuously changing as new settlements appear and sometimes “older” ones disappear in response to local political problems, superstitions or rumours of new roads being built.

One of the major health problems as new settlers moved into areas was an epidemic of malaria. Between May and August of 1999, in the health centre alone, there were over 2000 confirmed malaria cases, 400 hospitalisations and 18 deaths with malaria accounting for one third of all outpatient and two thirds of all inpatient cases (Van Engelgem 2001).

³⁶ The current recommendation is for Optimal® be used in health centres without microscopes and for Paracheck® to be used by VMVs and for outreach activities.

³⁷ Anlong Veng health centre is classified as a “Health centre with beds” and is the only bedded health facility in the district. It actually functions somewhere between a health centre and a hospital.

³⁸ There was no census data available as the area had been under KR control during the time of the census.

At the time, the national antimalarial guidelines for uncomplicated *P. falciparum* malaria in that area was single dose mefloquine, and for complicated malaria, quinine and tetracycline. In response to the epidemic and the known problem of drug resistance, MSF switched first-line treatment to an ACT of artesunate and mefloquine (A+M). A malaria control project was also set up with a core component being malaria “outreach” clinics. These consisted of teams of two people who went out each day from the health centre to the settlements, in order to diagnose and treat malaria using RDTs and A+M. There were initially two teams, expanding to four teams with the aim of visiting each settlement once or twice per week depending on population movement, road conditions and information about suspected malaria outbreaks.

6.2.3.2. Village Malaria Volunteers (VMVs)

The first experience of using village malaria volunteers in Cambodia came from a community based trial for insecticide treated bed nets (ITNs) in 30 villages in Rattanakiri in the Northeast of the country in 2001. This is a remote heavily forested area, sparsely populated by ethnic minorities with low access to any kind of health service. Malaria transmission is high with prevalence rates of 5 and 57% (Sochantha, Hewitt et al. 2005). The trial aimed to assess the impact of ITNs by comparing *P. falciparum* prevalence rates in intervention versus control villages. However, in order to address ethical concerns about having an exposed group without any interventions, village malaria volunteers (VMV) were introduced in all villages. The VMVs were trained to perform RDTs on any villagers suspected of having malaria and to provide treatment as per the national guidelines. They were supervised and re-supplied monthly by the provincial malaria staff. The resulting data from this passive surveillance system exposed the scale of the problem of malaria in these communities and demonstrated that VMVs provided a practical means of access to biological diagnosis and appropriate treatment. A further piloting project was therefore undertaken in 10 ethnic Khmer villages in Ko Kong province in the South (Sedano 2002). A grant application was successfully made to the Global Fund to expand the VMV programme to 300 villages in 10 provinces and is now in the process of being implemented (Cambodia Coordinating Committee 2002).

6.3 Methods

The costing in this chapter was performed from the perspective of the provider. The household costs of treating malaria were obtained during the community based study described in the next chapter. Throughout this chapter, capital costs are annualised at a rate of 3% and all costs converted into US\$2002³⁹.

³⁹ US\$1= 3900 Cambodian riel

6.3.1 Cost of blister-packaged artesunate and mefloquine

The cost of the blister-packaged drugs was separated into capital costs and recurrent costs. Costs were obtained from receipts and where these were not available, from estimates by the WHO and CNM staff.

The capital costs included were: the building renovations (\$20,000), the blister-packaging and printing machinery (\$40,000), and the consultancies and training (\$15,000). The useful life of these inputs was assumed to be five years. The costs involved in the decision-making process were not included. These discussions were mainly carried out by e-mail and telephone conversations between WHO staff and experts but were considered a routine part of their work and a reliable estimate of the time and money allocatable specifically to blister-packaging was not available.

The recurrent costs were separated into fixed and variable costs. The fixed costs were the overhead costs for electricity, water and building maintenance (\$1,600/month) and staff salaries and wages. The staff consisted of a pharmacist (\$800/month), a maintenance technician (\$200/month) and 12 machine operators who were paid a daily wage of \$12.50 per working day. Actual expenditure on salaries was not available but according to the administrator, all operators were paid to work full-time. The average monthly earnings in the manufacturing industry in Cambodia were approximately \$195 (\$ 228 for men and \$161 for women), giving an estimated total monthly payout of \$2,340 per month for labour.

The cost of packaging and drugs are shown in Table 6-1 and Table 6-2. At the time of the analysis, 50mg tablets of artesunate were being used for all products except adult Malarine® where the 200mg tablets were used instead, partly to ensure differentiation of the product *inside* the packaging from A+M, in order to discourage leakage of the latter into the informal sector. The choice of drug varied over time according to the availability and cost of different products.

Table 6-1: Cost of packaging⁴⁰

	Cost per blister (US\$)
Aluminium foil	0.0267
PVC	0.0115
Individual boxes	0.0340
Large boxes (for 100 individual boxes)	0.0048
Ink for printing on box ⁴¹	0.0020
Package insert	0.0010

⁴⁰ The cost of the aluminium foil and PVC included freight and storage. Other products were available locally and the cost is the price paid inclusive of delivery and storage.

⁴¹ Although the printing costs for the Malarine® products was higher than A+M because of the amount of coloured ink used, only an average cost of ink was available

Table 6-2: Cost of antimalarial drugs

	Cost per tablet (US\$) ⁴²
Mefloquine 250mg (Mepha®)	0.3696
Artesunate 50mg (Gui Lin®)	0.0725
Artesunate 200mg (Mepha®)	0.3323

6.3.2 Cost of rapid diagnostic tests

The data on the costs of the tests, and the training and supervision of healthcare staff were obtained from the CNM. In addition information was obtained on the rate of positive tests under routine use. This is necessary as the cost-effectiveness of the RDTs themselves and of ACTs depends on the relative costs of the tests and drugs, the likelihood that a febrile illness is truly due to malaria, and the cost of drugs used when the diagnosis is negative for malaria. The cost of the tests are shown with and without the inclusion of the training and supervision costs.

6.3.3 Costing interventions to increase access

The costs of the delivery interventions consisted of variable costs and fixed costs. The latter included the capital costs and recurrent costs of the intervention. These were divided into staffing; transport; computers and other equipment; and office overheads. Fixed costs were estimated with and without the inclusion of the start-up costs and the cost of project coordinators, in order to facilitate comparison with other settings. The variable costs were those directly associated with diagnosing and treating patients with malaria and essentially included the costs of RDTs and drugs as calculated above. In addition, in order to take into account the cost of performing tests on patients who presented with malaria-like symptoms but did not have malaria, data on the proportion of tests taken which were positive were also noted.

The costing of these two interventions was carried out separately. Detailed information was available for the year 2001 from the expenditure accounts, budgets, logbooks and reports from the MSF outreach programme and an ingredients approach was therefore used. Actual cost data from the project were used where possible and in particular for the vehicles and computers. Costing of the VMV intervention was based on the budget granted by the GFATM.

The level of activity in terms of number of suspected malaria patients tested and number of patients with *P. falciparum* malaria treated was gathered from the statistics kept from the two projects in order to estimate the cost per case seen and treated for each intervention.

⁴² Including 5% wastage and 3% freight.

6.3.3.1. Outreach clinics

Start-up costs

Start-up costs were based on discussions with project staff and involved estimates of the time and resources spent in the months leading up to the launch of the project. It was estimated that the project co-ordinator spent about three months in preparation, at which time it took up about 80% of his time. During the month preceding the launch the supervisor (80% allocation) was recruited and the lab technician became involved in assessing different RDT (20% allocation). Salary, transport and overhead costs were allocated accordingly.

Staffing

The staff directly involved in the outreach activities in 2001 consisted of four, six and then eight outreach workers, a local supervisor, a local laboratory technician and an expatriate project co-ordinator. Outreach workers each spent on average two or three days per week on outreach. They were officially ministry of health (MOH) employees from whom they received a salary of \$8.20 per month but they also received a salary supplement from MSF (average \$17.50 per month) and a per diem for each day of outreach work. The per diem paid out from MSF was \$2 (of which half went to the worker and half went into a common staff fund). For the cost analysis the actual cost paid out monthly by MSF was used.

Both the supervisor and laboratory technician were MSF employees receiving a monthly salary of \$250. The supervisor was dedicated to the malaria control activities in Anlong Veng and estimated that 60% of his time was spent on outreach activities, mainly collecting and entering data, organising supplies and repairs and direct supervision of the outreach teams. The laboratory technician was mainly occupied with providing microscopic diagnosis for inpatients and outpatients but also provided training and quality control for the RDTs and estimated that about 10% of his time was spent on outreach activities.

The expatriate project co-ordinator was based in Siem Riep town and was responsible for overseeing the established Anlong Veng malaria control project, setting up new projects elsewhere and liaising with central headquarters in Phnom Penh. In addition to a monthly salary of \$380, there were costs associated with housing and a malaria project driver. The proportion of the co-ordinators time dedicated to the outreach activities in Anlong Veng was estimated at 20% and was allocated accordingly.

Other staff indirectly involved included the MSF medical co-ordinator and assistant co-ordinator and the support staff in the Siem Riep office and the Phnom Penh headquarters. Data on these costs were only available as part of the gross cost of operating and staffing costs at these two levels. These costs were not included in the costing as they are very context specific.

Table 6-3: Cost of staffing for the outreach intervention

Staff	Monthly salary (US\$)	Additional costs	% allocated to outreach
Outreach workers (x6 ⁴³)	25.70	US\$2/day per diem for each outreach day worked	100%
Supervisor	250	-	60%
Laboratory technician	250	-	10%
Expatriate project co-ordinator	380	Housing, food, air tickets (approximately US\$750/month)	20%
Project driver	225	-	20%

Vehicles

The annual costs of the vehicles consisted of maintenance and fuel taken from receipts plus the capital cost of the vehicles assuming a useful life of five years for motorcycles and six years for the car⁴⁴. The eight motorcycles were bought locally at an average price of \$1,400. Total annual cost for maintenance was \$1796 and for fuel, \$428. There was also a Toyota Hilux car used by the project co-ordinator for other business and therefore 20% of the costs associated with the car and driver were allocated to outreach. The capital cost of the car was \$27,300, inclusive of freight and radio equipment and the annual cost of maintenance and fuel was \$2,380.

Equipment and office overheads

The other capital costs were for a laptop computer (US\$2,000), motorcycle helmets, weighing scales and bags. These were assumed to have a useful life of five years. The cost of office overheads were estimated for the MSF office in Anlong Veng where the malaria project had desk space in a building built by MSF next to the health centre. The accounts did not differentiate between the costs of the health centre and the office cost; however it was estimated that about 10% of the costs of maintenance and electricity to the health centre and 20% of the office related to outreach activities. This worked out to approximately \$20 per month.

6.3.3.2. Village malaria volunteers

Start up costs

The start up costs that were budgeted for in the first year included the cost of initial training, monthly meetings with the newly trained VMVs and an initial screening survey. The latter involved visiting villages in the 10 provinces to choose the 300 villages with the highest proportion of children with palpable spleens (the "spleen rate") as an indication of malaria prevalence. Each province was estimated to take about 10 days to cover and involved three

⁴³ Four workers from January to March (three months), six workers from April to August (four months) and then eight workers (four months).

⁴⁴ Based on estimates provided by the logistics co-ordinator.

CNM staff (with a per diem of \$30) and their transport costs to and around the province at \$500/province and two provincial health staff (with a per diem of \$20) and their transport costs at \$300/province. The initial training involved ten two-day courses for 10 health staff from each of the 10 provinces and 25 separate four-day training courses for the 20 VMVs (at a per diem of \$5/day). Training materials were estimated to cost \$5 per provincial health staff and \$10 per VMV. Total transport costs were estimated at \$80 and \$100 for the provincial staff and VMV training sessions respectively and refreshments \$1 per person per day.

Staffing

The budget for the salary of the project co-ordinator was \$ 24,000 per annum. The other costs were associated with the supervision, monitoring and evaluation and were estimated at \$30, 000 per year. This was to cover the per diems of two teams of two CNM staff employed to supervise the project, with an aim of visiting each village twice each year, taking about 100 days working days at \$20 per diem. At the provincial level, support was budgeted for monthly meetings (nine per year) between provincial health staff and VMVs with per diems of \$5 and \$2 respectively. In addition salary support was budgeted for local monthly data collection, data entry and reporting of data.

Vehicle and transport costs

The project budgeted for the purchase of four new 4-wheel drive vehicles and 10 motorcycles. The cost of maintaining the vehicles was estimated at a total of \$5,000 per year for the first two years and then \$10,000 per year thereafter. In addition there were transport costs associated with monitoring and supervision activities.

Other costs

The other costs included the capital costs of two computers and annual administrative costs estimated at \$10,000 per year. The office overheads in the CNM headquarters in Phnom Penh were not estimated.

6.4 Results

6.4.1 Blister-packaging and drugs

The results of the costing of the blister-packaging are shown in Table 6-4. It can be seen that the total costs inclusive of capital costs of the blister-packaged drugs were between \$2.60 for the package for the A+M2 and \$3.77 for A+M4. The cost of Malarine® was slightly more than A+M4 because of the higher cost of the artesunate used. The cost of packaging material was \$0.089 per package for all packages and at actual productivity, salary and overhead costs per

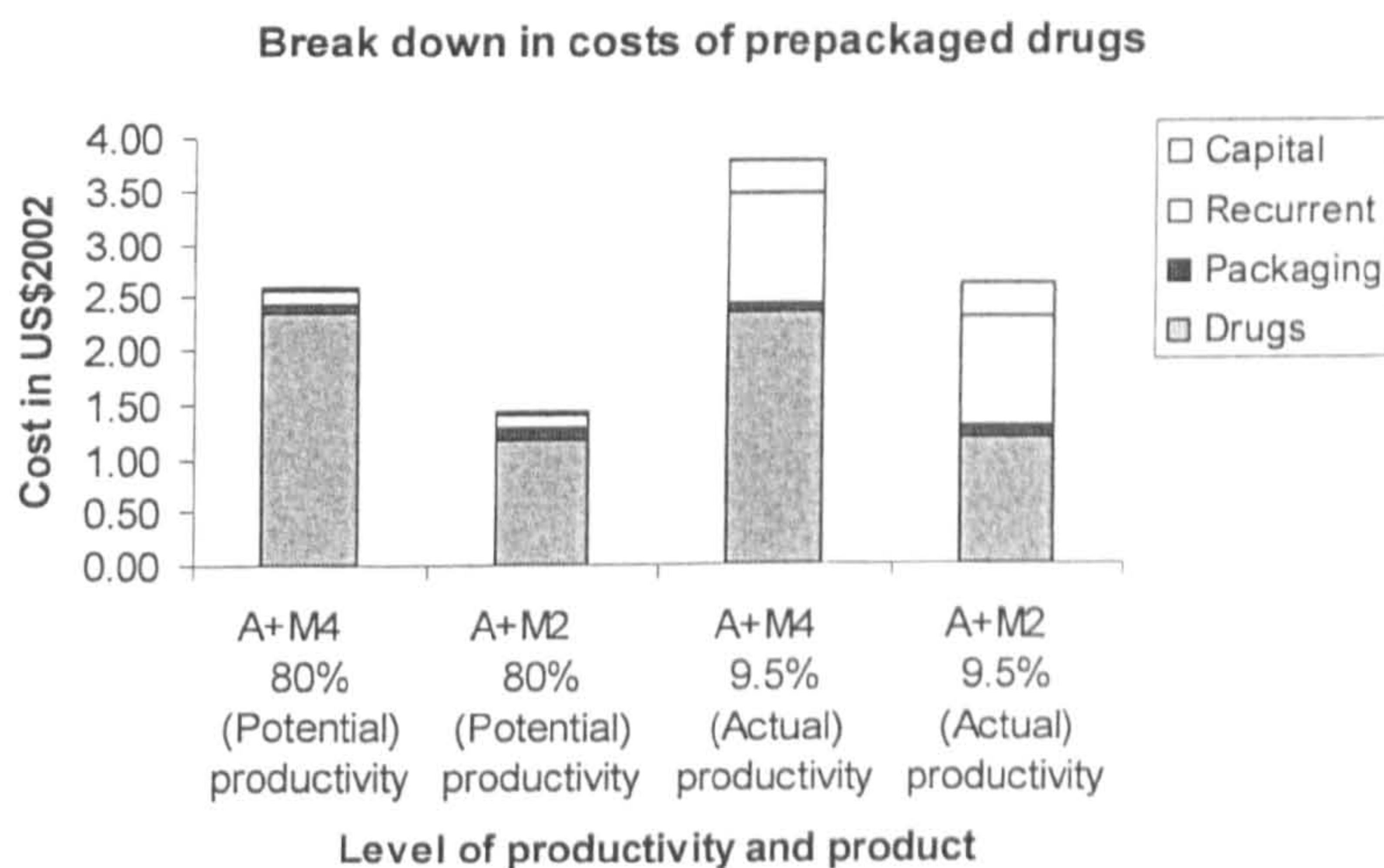
package were \$0.338 and \$0.706 respectively, resulting in a total packaging cost per package of \$1.133! If production were increased to 80% of the potential capacity, then packaging costs would be reduced more than 5-fold to \$0.188, resulting in the cost of A+M2 and A+M4 being considerably lower, at \$1.42 and \$2.59 respectively. Figure 6-3 shows that when the costs of the product are broken down, at the current level of productivity, the drug costs only accounted for 45% and 62% of the cost of A+M4 and A+M2 respectively, compared to 83% and 90% at the anticipated level of productivity.

Table 6-4: Cost of blister-packaged artesunate and mefloquine

Drug package	Actual cost (at 9.5% productivity)		Potential cost (at 80% productivity)	
	Recurrent costs	Recurrent and capital costs	Recurrent costs	Recurrent and capital costs
A+M2 (Art 50mg x 6 + Mef 250mg x 2)	2.307	2.595	1.386	1.420
A+M3* (Art 50mg x 9 + Mef 250mg x 3)	2.894	3.182	1.973	2.007
A+M4 (Art 50mg x 12 + Mef 250mg x 4)	3.480	3.769	2.560	2.594
Malarine® (adult) (Art 200mg x 3 + Mef 250mg x 4)	3.608	3.896	2.688	2.722

*Same cost for Malarine junior ®

Figure 6-3: Breakdown in costs of blister-packaged drugs



6.4.2 Rapid diagnostic tests

The basic cost of RDTs inclusive of freight, storage and wastage was \$0.83 for Paracheck® and \$2.75 for Optimal®. When used in the health centres, the cost of training and supervision of health centre staff added an additional \$0.12 to each RDT assuming that a health centre performed an average of 200 tests per year.

6.4.3 Interventions to improve access

Table 6-5 and Table 6-6 summarise the results of the cost analysis for the MSF malaria outreach project and the VMV scheme.

Table 6-5: Summary of the annual fixed costs of the outreach and VMV interventions

	Cost (US\$)	
	Outreach	VMV
Basic annual running costs (without expatriate co-ordinator)		
Salary	5,422	20,270
Transport	2,224	37,850
Other (equipment, overheads)	739	10,738
Sub-total	8,385	68,858
Additional costs		
Cost of expatriate co-ordinator	4,643	24,000
Initial start-up cost	4,710	40,000
Total annual cost	13,898	100,243

Table 6-6: Estimated activity and fixed cost of interventions per capita, per patient seen and per patient treated

	Outreach	VMV (based on estimates from pilot project)
Population	19,029	100,000
Number seen	3,152	57,360
Number <i>P. falciparum</i> cases treated	658	13,407
<i>P. falciparum</i> positive rate	20.9%	23.4%
Basic annual fixed cost*/capita	\$0.44	\$0.69
Basic annual fixed cost*/patient seen	\$2.66	\$1.20
Basic annual fixed cost*/positive case	\$12.74	\$5.14
Total annual fixed cost/capita	\$0.73	\$1.00
Total annual fixed cost/patient seen	\$4.41	\$1.75
Total annual fixed cost/positive case	\$21.12	\$7.48

(*Without start-up and co-ordinator costs)

6.4.4 Inputs for modelling

The costs obtained from this analysis were used as inputs into the model. In the base-case scenario the cost of the drugs based on the cost of monotherapy and ACT are assumed to be the cost of mefloquine and blister-packaged artesunate and mefloquine. For mefloquine monotherapy the cost is \$1.11 for an adult cost, \$0.56 for a child aged six to twelve years and \$0.28 for a child aged one to five years. The age-grouping of the blister-packages did not match the age-grouping used in the model. For the purpose of the model it was assumed that those above twelve years received A+M4 (aimed at those 15 years and above), at \$3.77 per course. Children aged six to 12 years were assumed to receive A+M2 (aimed at children aged six to ten

years), at \$2.60 per course. Children aged five years and under were suppose to receive five days of rectal artesunate (or artemether) suppositories and mefloquine but in reality, usually received artesunate tablets with or without mefloquine from blister-packages. The cost of five suppositories and one tablet of mefloquine at \$2.40 was similar to the cost of A+M2 and in the model the cost input for the ACT in this age group was assumed to be \$2.60.

For the cost of the intervention to improve access the basic fixed annual costs were used, exclusive of the cost of the expatriate co-ordinator and the start-up costs as it was felt that these costs are highly context specific making it difficult to generalise to other settings. The actual annual fixed costs used in the base-case scenarios with a population of 10,000 was therefore \$4406 for outreach and \$6886 for the VMV scheme. The variable costs were the costs of the drugs and the RDTs as described above.

6.5 Discussion

The costing of the blister-packaged drugs shows that at the actual level of productivity in 2001, an adult course of pre-packaged A+M4 cost around \$3.80. This compares with \$2.40, the current price of artemether-lumefantrine (Co-artem®) supplied by Novartis to WHO). By increasing the productivity, the cost of A+M4 can be lowered to almost the same as artemether-lumefantrine.

From the cost analysis of the interventions, it can be seen that the basic per capita running costs of the schemes was estimated to be around \$0.44 from outreach and \$0.69 for the VMV scheme. Inclusion of the cost of a project co-ordinator and (20% allocation for the outreach project and full-time for the VMV scheme) and annualised start-up costs increased this to \$0.73 and \$1.00 respectively.

Although the fixed cost per capita of outreach is less than that of the VMV scheme, the costs per case tested and per positive case treated are almost double. This is because the prevalence of malaria was higher in the area covered by the VMV scheme in Rattanakiri from where the estimates for the projected number of visits and cases came. It is also probably because the VMVs were more convenient and accessible than outreach and were more often consulted. It is estimated that over half the population are likely to visit their VMV in a year compared to fewer than 20% in the area covered by outreach.

However, as explained earlier, the populations covered by these two interventions was quite different and it is unlikely that VMVs would have operated successfully in the Anlong Veng district. It can therefore not be assumed that VMVs are the more cost-effective option in all

settings. Nonetheless the cost of the outreach programme, at \$12.74 per positive case, appeared to be considerably more than that estimated by Ettlting et al. for a similar intervention in Mae Sot, Thailand, where diagnosis was by microscopy and treatment was with a single dose of mefloquine (Ettlting, Thimasarn et al. 1991). Despite the slide positivity rate in Thailand being only 5%, the average institutional cost per positive case was \$2.57 (90 baht) and \$0.13 (4.4 baht) per smear⁴⁵. The community cost inclusive of the indirect costs of lost earnings, was \$0.06 (2.26 baht) per positive case. In terms of institutional costs alone adding a mobile clinic in addition to a central clinic was less cost-effective, in terms of costs per positive case treated, than adding a peripheral clinic, partly because the slide positivity rate was higher (17.5%) in the latter.

There have been a number of other descriptive studies of village malaria volunteers, however in most, costing data were not available. One cost-minimization analysis was performed on a small community based intervention in Brazil. Volunteer bar owners in a remote mining town were trained to use the ParaSight-F® test (a similar test to Paracheck®) to diagnose malaria and to treat positive cases with mefloquine monotherapy. The study compared the direct costs (patient and provider) incurred with the intervention compared to the costs prior to the intervention, when the main source of treatment was the government clinic and hospital located 32 km away. It was found that net savings were \$60,900 or \$81 per person per year⁴⁶ (Cunha, Piovesan-Alves et al. 2001; Pang and Piovesan-Alves 2001).

However there are little published data that includes both the costs and the effect of these interventions from the community perspective. In the next chapter the treatment seeking and drug usage behaviour in areas with and without VMVs and outreach clinics is compared.

⁴⁵ \$US1 (2002) = 35 baht (1990).

⁴⁶ They also established from interviewing, that the average willingness to pay for RDT diagnosis alone was \$5.60 (average monthly income of \$250).

CHAPTER 7

PRIMARY DATA COLLECTION IN CAMBODIA: COMMUNITY-BASED STUDY OF TREATMENT SEEKING BEHAVIOUR AND DRUG USAGE

In this chapter, the specific aims of a community-based study on treatment seeking behaviour and antimalarial drug usage are presented. This starts with the aims of the study and is followed by the methods used, results and discussion of the findings. For the purpose of the model, it was important to have data on adherence to ACTs and the coverage rate with the policy following a switch from monotherapy. Cambodia had been commended for its early switch to ACTs, however there was no reliable documentation of this process or its success in terms of whether or not patients with malaria actually received the recommended drugs or took them correctly. It was therefore decided that it would be useful to collect data to assess the coverage and adherence rates to ACTs, with and without interventions to improve access. Not only would this serve to fill gaps in the data needed to apply the model, but it would also serve as a useful resource for other countries earlier on in the process of changing policy.

7.1 Specific aims

The aims of this community-based study were:

- 1) To document the coverage rate of the new antimalarial drug policy i.e. the proportion of people with malaria-like symptoms who received a biological diagnosis and the proportion who received artesunate and mefloquine for *P. falciparum* malaria.
- 2) To quantify the effectiveness of providing outreach clinics and village malaria volunteers in increasing coverage of the policy.
- 3) To measure the adherence to artesunate and mefloquine (A+M) when given in an operational setting.
- 4) To obtain the household costs of treating malaria.

7.2 Methods

7.2.1 Study design

This was a cross-sectional household survey carried out in three different types of intervention areas: with village malaria volunteers (VMVs), outreach clinics and no specific interventions. In addition to household and individual questionnaires, a drug board for identifying drugs was used and blood was taken from a finger-prick for rapid diagnostic testing (RDT) of *P. falciparum* malaria. RDTs were performed in an effort to estimate very approximately, the proportion of respondents who actually had *P. falciparum* malaria in the previous two weeks. This relies on one of the usually unwanted characteristics of tests based on Histidine Rich Protein 2, (HRP2) which is that it persists in the majority of treated cases for at least two weeks following effective treatment⁴⁷ (Mayxay, Pukrittayakamee et al. 2001).

7.2.2 Sample size calculation

From the preparatory work it was estimated that the presence of outreach and VMVs increased coverage of biological diagnosis and ACTs by at least 60%. A sample size of 200 people in each group was therefore chosen, which had a 90% probability of detecting a difference in coverage or adherence rates in two groups of 60% and 75% at the 5% level on a two-sided test. In the event, due to problems in the intervention area with VMVs and generally lower than expected levels of malaria, it was not possible to achieve samples of 200 in the intervention groups. However the differences between intervention areas were large enough to infer significance for most key outcomes.

7.2.3 Site selection

Sample selection was pragmatic because the main purpose was to describe the behaviour of people with malaria and to include areas in which the interventions were carried out. The district of Anlong Veng, which was covered by the outreach programme, was therefore purposefully selected as were the 10 villages in the Ko Kong VMV pilot project. The latter was selected rather than the villages with VMVs in Rattanakiri for a number of reasons. Ko Kong is ethnically Khmer whereas the population in Rattanakiri is from many different ethnic minority groups, which are culturally and linguistically distinct from the majority Khmer population. This would have made the conduct of the household survey very difficult and the results could not be extrapolated to elsewhere in Cambodia. In addition a qualitative and quantitative study of treatment seeking behaviour had recently been conducted in villages in the province (Brown, Montavy et al. 2002).

⁴⁷ 61% in uncomplicated malaria and 89% in severe malaria.

Villages in the Sampalouen district, where Malarine® was being supplied directly to market retailers in a social marketing pilot project, were also selected. However, early on in the field work and subsequently in the initial data analysis it was apparent that Malarine® had ceased to be stocked by a number of the market retailers and had not penetrated into the villages, resulting in no difference between pilot and non-pilot areas and a subsequent absorption of these villages into the “non-intervention” group. The study sites are shown in Figure 7-1. A detailed description of the interventions was given in the previous chapter and a table comparing the characteristics of all areas is given in Table A9-1.

Figure 7-1: Map of study sites in Cambodia. The orange dots ● identify the areas studied in this study. The red dots ● are the areas covered by the national drug usage survey carried out in 2002.



Within single districts there were areas or villages severely affected by malaria and others that were completely malaria-free. Therefore, in the first instance, districts and health centre catchment areas within them were chosen that qualitatively most closely matched the intervention areas. This was done in terms of risk of malaria; ecology; access to roads, health centres and markets; and the socio-economic status of the communities in terms of livelihood, poverty and level of migration⁴⁸. Selection of villages took place at the health centre with the assistance of local health care staff (Figure 7-2). After identifying all the villages covered by the health centre, those in which no malaria cases had been seen or reported and those that were

⁴⁸ However this matching was not done with the intention of matched analysis.

deemed too dangerous (because of landmines or bandits) were excluded. The remaining villages were stratified into two groups according to accessibility. Villages were then randomly selected from each stratum⁴⁹. Selected villages were visited one or two days prior to the day of the survey in order to inform and discuss the study with the local community.

7.2.4 Screening of households

On the day of the survey, all households in the selected villages were visited and if an adult was present, screened for inclusion. The inclusion criteria was anyone in the household who in the last three weeks had either taken an antimalarial drug or who had symptoms consistent with malaria⁵⁰. Interviewers were instructed to return to empty households twice if possible, before recording them as absent.

7.2.5 Questionnaire development and piloting

Prior to the questionnaire, in-depth interviews were carried out with villagers, migrant workers, drug vendors, and private and public health centre staff. On the basis of this information and from previous surveys carried out in Cambodia (Bury 1999; 2000; Brown, Montavy et al. 2002), an instrument was developed, translated, back-translated, piloted in the field on three separate occasions and revised a number of times.

7.2.6 The questionnaire

The questionnaire had two modules: a household module and individual module. One household module was filled out for each included household. This contained questions on the household socio-economic status in order to explore whether this had any impact on treatment seeking behaviour. The individual module was filled out for each member of a household who fulfilled the inclusion criteria. This module included sections on the details of the illness episode, with questions on the most recent and preceding episodes of fever in an attempt to capture information about chronic infections and possible treatment failures. The questions were designed to capture some of the key indicators of antimalarial drug usage as shown in Table 7-1. Questions were asked about the illness itself; where treatments were sought; whether any diagnostic tests were undertaken; what kind of drugs were bought or prescribed; how exactly they were taken in terms of dose, frequency and duration; and how much they cost. The questionnaires are appended in Annex 8.

⁴⁹ In Sotnikum and Sampalouen districts there were insufficient numbers of malaria-affected villages within the official boundaries of the chosen health centre areas, therefore two villages from the neighbouring health centre area were selected.

⁵⁰ This was defined as fever +/- headache +/- chills excluding other localizing infection e.g. bloody or profuse watery diarrhoea, or cough productive of coloured sputum as the predominant symptom.

Table 7-1: Possible drug use indicators derived from questionnaire

Objective of malaria drug policy	Indicator	Denominator	Question no.	Variable type	Binary categories
Increase treatment from trained provider	% of people who went to public trained provider	People who took modern drugs	17,117,2 17	Categorical	Formal (Health centre, VMV, outreach)/ Informal (Simple seller, private provider)
Increase use of biological diagnosis	% of people who have a biological diagnosis before treatment	People who took modern drugs	8	Binary	Yes/No
Reduce delay in treatment	% of people who receive modern medicine within 48 hours of symptoms	People who took modern drugs	10	Continuous	≤ 2 days / > 2 days
Correct drug choice	% of people diagnosed with <i>P. falciparum</i> malaria who take artesunate and mefloquine	People diagnosed with <i>P. falciparum</i>	11 19,119,2 19	Categorical	A+M / not A+M (with or without other antimalarial)
Decrease use of artemisinin monotherapy	% of artemisinin treatments without mefloquine	All treatments containing artemisinins	19,119,2 19	Categorical	
Adherence to ACT	% of people who take artesunate and mefloquine for at least 3 days	People who took A+M or Malarine	19,119,2 19	Continuous	$\Rightarrow 3$ days/ < 3 days
Reduce patient costs	Mean (s.d.) drug cost of treatment	People who took antimalarials	44	Continuous	$\Rightarrow \$1 / < \1

7.2.7 Drug identification board

One of the key difficulties in community-based drug usage studies is the accurate identification of drugs. Patients and even providers may not know the name of the drugs in question. This is particularly a problem where mixtures of drugs are bought in unlabelled plastic bags, as they are in Cambodia (Figure 7-3). In order to assist in this identification process a drug identification folder was developed which aimed to enable patients to correctly identify drugs. This is illustrated in Figure 7-4. Patients were first asked to name the drugs they thought that they had been given, prior to being shown the drugs identification folder as a prompt to help them recall the identity of drugs they may have forgotten (Figure 7-5).

7.2.8 Blood testing

For each individual who fulfilled the inclusion criteria, blood was taken by finger prick for a RDT (Paracheck®) for *P. falciparum* malaria and was read at 15 minutes⁵¹. If patients were symptomatic and RDT positive they were treated with artesunate and mefloquine according to national guidelines.

7.2.9 Ethics and consent

Ethical approval was granted by the Cambodian Ministry of Health, the research ethics committee of the London School of Hygiene and Tropical Medicine, and the research ethics committee of the Oxford Tropical Medicine Network. Informed consent was obtained from the community and individual participants (Annex 8).

7.2.10 Data entry and analysis

Data were double-entered into EpiInfo 2000, cleaned and analysed using STATA® (Version 8 and 9). The STATA survey commands were used to adjust for stratification by intervention area and to adjust for clustering between individuals in the same village⁵². Observations were not weighted as there was no sampling within villages. Differences in proportions were tested for significance using the Pearson chi-squared statistic adjusted for the survey design. Regression models were used for multivariate analysis of variation in key outcomes using the STATA survey logistic (*svy logistic*) commands, which enable adjustments to be made for clustering and stratification.

⁵¹ From patients who reported having taken mefloquine and 30 “controls”, 200ul of blood was also collected onto filter paper and kept in a desiccated container. The intention was to later measure drug levels in order to estimate the actual amount of mefloquine taken by comparing with population pharmacokinetic data. In the event, due to the small numbers it was not feasible to carry out this part of the study.

⁵² Clustering should normally have been taken into account in the sample size calculation, however the necessary information should be captured in the width of the confidence intervals (Smith & Bates 1992).

Figure 7-2: Identifying villages in the health centre catchment area

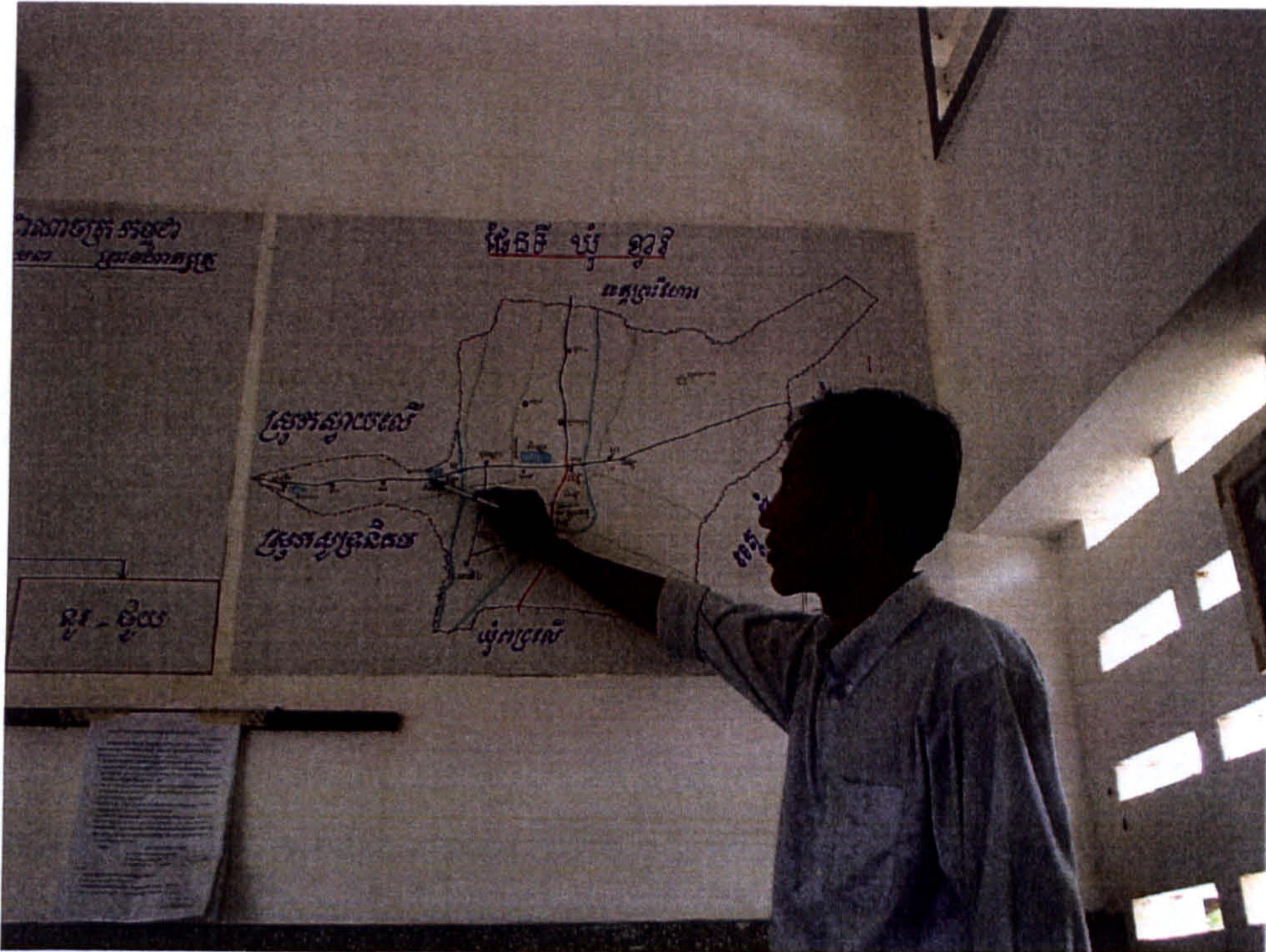


Figure 7.3: Packages of tablet mixtures, as commonly bought for the treatment of malaria



Figure 7.4: Drug identification board



Figure 7.5: Sokhoen, one of the research assistants interviewing a respondent



7.3 General analytical approach and definitions

7.3.1 General approach

The first step in the analysis involved identifying the key indicators for each stage of the process leading up to the point where patients with malaria take the recommended antimalarial drugs in the recommended fashion. The indicators were chosen because they represent important steps in the process and are a specific measure of whether key objectives of improving malaria case management are being reached (Table 7-1). These were both process indicators, such as the proportion of cases seeking treatment from a trained provider, and outcome indicators, such as the proportion of patients diagnosed with *P. falciparum* malaria taking the first-line therapy.

7.3.2 Provider type

Providers were grouped into “formal” or trained provider (public, VMV, outreach) and informal providers (simple sellers, private health worker, other). As described in the background chapter, most of the population obtained treatment from the informal sector and this sector included a range of providers - from village vendors who sold simple drugs including antimalarials, to providers who either had or were perceived to have had some training in prescribing, including doctors, nurses and pharmacists and medical assistants trained by the Khmer Rouge or by NGOs in border camps. The Khmer term “phet” was used by villagers to describe those providers whom they perceived to have some relevant prescribing knowledge. This term was used in the questionnaire and is referred to as “private health workers” in this study.

7.3.3 Drug categories

To simplify the analysis of treatment types, drug treatments were grouped into mutually exclusive categories that were felt to be most informative and useful for comparing with recommendations. Thus, there were separate groups for treatments that contained combinations of artesunate with mefloquine, quinine with tetracycline and separate groups for chloroquine and for artemisinin derivatives alone and partnered with ineffective drugs. The latter group, where artemisinin derivatives are in effect used unprotected by a partner drug is important as their widespread misuse as a monotherapy in a short course is ineffective and theoretically increases the risk that resistance may arise. Where a treatment regime could belong to more than one group, it was grouped according to whether any of its components belonged to a recommended combination and if not, then by its most efficacious contents e.g. a mixture of artesunate, quinine and tetracycline was grouped as “quinine and tetracycline +/- other antimalarial” and the combination “artesunate plus tetracycline” was grouped as “artemisinin alone (without mefloquine) + other antimalarial”.

7.3.4 Adherence

Although correct duration, dose, frequency and timing may be important for effective treatment, in this survey duration of treatment was used as a proxy measure for adherence. This is due to the difficulty of determining with any accuracy, the dose and timing of treatment. In addition, the adequacy of treatment duration is particularly important in determining cure and decreasing the likelihood of resistance arising to the most efficacious and commonly used antimalarials (artemisinin and quinine)⁵³.

In order to define adherence, the duration of treatment taken was compared to the minimum recommended duration. For artemisinin derivatives without an effective partner drug, the most commonly available artesunate tablets are sold as a five-day regime and this is widely thought to be adequate. However, the evidence suggests that cure rates are lower (down to 72%) compared to a seven-day regime (cure rate >95) (Bunnag, Viravan et al. 1991a; Bunnag, Viravan et al. 1991b; Hassan Alin, Ashton et al. 1996)⁵⁴. Therefore for monotherapy with an artemisinin derivative, adequate duration was assumed to be seven days. For simplicity, if the antimalarial drugs were taken for longer than the recommended duration, the respondent was regarded as “adherent” rather than creating an extra category for prolonged duration⁵⁵.

7.3.5 Socio-economic status

Households were defined as the number of people regularly living and eating together under one roof and often included more than one family. In order to compare the level of poverty between households within the sample, a poverty rank was established by performing a principal component analysis (PCA) on the socio-economic indicators collected in the survey. This method was chosen due to the problems associated with collecting reliable and meaningful household income or expenditure data and the acceptance of such an index as a reasonable measure of household wealth in similar settings (Filmer and Pritchett 2001).

In brief, PCA is closely related to factor analysis and is a technique of data reduction where there is an attempt to explain the total variability of a large number of correlated variables through the weighted linear combinations of the original variables, known as “components”. Thus the first principal component is the weighted linear combination that captures the largest

⁵³ From patients who reported having taken mefloquine and 30 “controls”, 200µl of blood was also collected onto filter paper and kept in a desiccated container. The intention was to later measure drug levels in order to estimate the actual amount of mefloquine taken by comparing with population pharmacokinetic data. In the event, due to the small numbers it was not feasible to carry out this part of the study.

⁵⁴ Five days may be adequate if a higher dose is taken (Looareesuwan, Wilairatana et al. 1997).

⁵⁵ Although prolonged duration does have implications both for the patient in terms of adverse events, costs and possibly for the development of resistance due to the increased likelihood that malaria parasites from new infections are exposed to levels of drug in the bloodstream that inhibit the growth of sensitive parasites but not resistant ones.

amount of information common to all the variables. If each variable is a household asset or other indicator of wealth, then the principal component analysis produces a poverty index for each household (P_j) based on the formula:

$$P_j = f_1 \times (a_{j1} - a_1) / (S_1) + f_2 \times (a_{j2} - a_2) / S_2 \dots + f_N \times (a_{jN} - a_N) / (S_N)$$

Where f_1 is the Eigenvalue or "scoring factor" for the first asset as determined by the procedure, a_{j1} is the j th households' value for the first asset, and a_1 and s_1 are the mean and standard deviation of the first asset variable over all households. Using this index each household is then ranked and assigned into quintiles.

In this study information was collected on the following indicators: building material for the roof and walls; ownership of land, livestock, means of transport and telecommunications; source of water, years of schooling; and number of months of borrowing money for food.

7.4 Results

In this section the results are presented according to non-intervention and intervention areas. In order to compare the effect of the interventions and other factors on the key outcomes, multivariate regressions are also included where appropriate. The general characteristics of the sample are first described, followed by the findings from the household module of the questionnaire and then the findings from the individual module. Annex 9 contains additional tables.

7.4.1 General characteristics

In all, 1491 households in 23 settlements in six administrative districts were visited in the survey. The description of the sample resulting from the screening process is presented in Table 7-2. Of the households visited, there was an adult present in 1143, which were therefore included in the screening. In 290 households, at least one person fulfilled the inclusion criteria resulting in a total of 361 individuals completing the individual questionnaire and being included in the analysis. Unfortunately the sample size from the VMV intervention area was small. This was due to unfortunate political reasons that necessitated the withdrawal of the survey from these villages early on in the study. In the majority (82%) of households only one person was included, in 35 (12%) two people, in 17 (6%) three people or more.

Table 7-2: Summary description of sample

	Overall	Intervention area		
		None	Outreach	VMV
No. of districts	6	4	1	1
No. of villages	23	14	7	2
Total population of screened villages	10,120	8,325	1,401	394
No. of households in screened villages (covered by intervention)	2,093	1,767	252	74
No. of households visited	1,491	1,185	232	74
No. of households with adults present (% of those visited)	1,143 (77%)	884 (75%)	198 (85%)	61 (82%)
No. of households included (as % of those screened)	290 (25%)	208 (24%)	63 (32%)	19 (31%)
No. of individuals included	361	251	88	22
Mean age in years	-	25.2	22.0	21.8
% male	-	57%	58%	55%

7.4.2 Results from the household module

In total, 290 households were included in the analysis. Half the respondents of this part of the questionnaire were the head of the households (85% male), and a third were their spouses. Overall, 57% of households had been in-situ for less than five years, with marked difference between villages. The length of stay was noticeably short in Anlong Veng and Sampalouen districts, where around one third of households had been in-situ for less than a year (Table 7-3). Overall the mean number of people per household was 6.3, median six (range 1-25) with a median of three children (under the age of 12 years) per household.

Table 7-3: Median duration of stay by district

District (Intervention type)	n	Median duration in years (range)	% of households who had been in-situ less than 1 year (n)
Anlong Veng (Outreach)	64	1 (0.2-30)	33% (21)
Chik Phat (VMV and non-intervention)	72	11 (0.5-30)	4% (3)
Malai (Non-intervention)	36	6 (0.3-30)	11% (4)
Sampaleoun (Non-intervention)	50	3 (0-25)	28% (14)
Sotnikum (Non-intervention)	25	25 (2-57)	0 (0)
Thmar Bang (Non-intervention)	39	3 (0.5-6)	3% (1)
Total	286	4 (0 - 57)	15% (43)

7.4.2.1. Socio-economic status

The population was predominantly farmers and many were very poor. Level of educational attainment was generally low, with 42% of the respondents reporting having had no schooling at all, giving a median of one and mean of 2.5 years of schooling overall. The median size of land

ownership was one hectare with one quarter of households being completely landless. This did not vary significantly by district (Table A-9.2). Although detailed information was collected on crop production, it proved difficult to analyse because of differences in measurements (descriptions in sackfuls but different size sacks) and areas where maize or beans were grown rather than rice. These data have therefore not been analysed. The number of months of food shortage, reflected by the borrowing of rice or money to buy rice, appeared to be more reliable. One third of the 264 respondents to the question of borrowing said that they had to borrow rice, or borrow money for rice in the last year (Table 7-4). Over one third reported that the food shortage lasted for more than half the year (Table A9-3). There was a significant difference between districts with over 40% of households in the two districts in Ko Kong (Chik Phat and Thmar Bang) reporting having to borrow, compared to only 10% in Malai ($p=0.014$). Most (86%) households received some form of income, the most common being selling forest-related products (33%) or working as hired labour (20%).

Table 7-4: Proportion of households who had to borrow money last year

District	n	% who have to borrow (n)
Anlong Veng	62	36% (22)
Chik Phat	66	42% (28)
Malai	29	10% (3)
Sampalouen	48	27% (13)
Sotnikum	22	18% (4)
Thmar Bang	37	43% (16)
	264	33% (86)

$p=0.014$

7.4.2.2. Poverty indicators

Details are provided in the Tables A9-4 to A9-10, but in summary the findings confirmed that the level of poverty in the sampled population was high. Housing materials were of poor quality with 70% of roofs and over 40% of walls being made of leaves or bamboo, and the majority of households (85%) not owning any draft animals or any means of transport (66%). Access to clean water was poor with only 7% having access to water from a drilled well with most people relying on a dug well (72%) or surface water (21%). In terms of telecommunications, only 26% of households owned a radio and 64% owned neither a radio nor television.

7.4.3 Individual data

Altogether 361 individuals fulfilled the inclusion criteria. The median age was 22 years, with 6% of the sample being five years or younger (Table A9-11). Of the sample, 57% were male. Age and sex distributions did not differ significantly between different intervention areas.

7.4.3.1. General description of illness

Commonly reported symptoms included fever (97%), headache (85%) and chills (71%) with only two respondents reporting to have had convulsions. The median duration of fever was four days (range 1-60). Of the sample, 70% (254) reported having only one episode of fever in the previous two months, where an episode was described as a period of fever separated from a previous fever by more than three days. The remainder reported having had two episodes except for two individuals who had three episodes.

7.4.3.2. Treatment with modern drugs

Modern drugs were taken by 85% of the respondents for the most recent episode of fever. Surprisingly, the treatment rate was significantly lower in the VMV area with only 14 out of the 22 (63%) respondents reporting to have received modern treatment compared to 84% in outreach areas (χ^2 $p=0.054$). By univariate analysis the odds ratio (OR) of receiving modern drugs was 0.34 (95% CI 0.13 – 0.87) if in a VMV area and on multivariate analysis, this remained the only significant factor when adjusted for age, sex, distance from health centre, poverty and clustering in the survey design (Table 7-5).

Table 7-5: Proportion and likelihood of receiving modern drugs for most recent episode of fever

Intervention	n (N=361)	% who received modern treatment (n)	Odds ratio (OR) (95% CI)	p	Adjusted odds ratio* (AOR) (95% CI)	p
None	251	85% (213)	1	-	1	
Outreach	88	84% (74)	1.03 (0.52- 2.00)	0.09	0.70 (0.33-1.48)	0.34
VMV	22	63% (14)	0.34 (0.13- 0.87)	0.02	0.28 (0.10-0.80)	0.03

*Adjusted for sex, age (<6 and 6-14 years), distance from health centre (>2 hours by motorcycle), poverty rank (poorest 40% and richest 20%) and survey design.

7.4.3.3. Timing of treatment

Overall, the median time to modern treatment from the onset of symptoms was two days. "Delay in treatment" was defined as time to treatment of more than two days and was found to be significantly different between intervention areas. In non-intervention areas, the delay in treatment was 37% (107), compared to 25% (19/75) in outreach areas and 57% (8/14) (χ^2 $p=0.026$) in VMV areas. When adjusted for clustering, this difference was no longer significant ($p=0.1536$). This suggests that clustering may have contributed to the significance of the result and that the sample may have been underpowered to detect the difference between intervention. By multivariate analysis the only factor to correlate with delay in treatment was age five years or under (OR 0.58, 95% CI 0.35-0.98, $p=0.044$).

7.4.3.4. Number of treatments

Altogether there were 466 treatment contacts in the previous two months, with 369 of those being for the most recent episode. The majority (78% of 298), of respondents only received one treatment for their most recent episode, 20% (60) received two treatments and 2% (6) received three. The likelihood of having more than one treatment did not differ between intervention areas ($p=0.38$).

7.4.3.5. Source of treatment

First provider

In non-intervention areas, the single most common source of initial treatment was a “simple seller”, accounting for 54% of first providers. This was followed by private health workers, either at the providers’ place in 24%, or seen at the patient’s home in 6%. This was significantly different by intervention such that in VMV areas 10 out of 14 (71%) of cases first went to the VMV. However in the outreach area only 17% first went to the outreach team, the majority (63%) still choosing to go to a simple seller first (Table 7-6).

Table 7-6: First source of treatment by intervention (n)

Intervention	n (N=317)	Simple seller	Went to private health worker	Public health facility	Private health worker came to home	VMV	Out-reach	Traditional ⁵⁶	Other ⁵⁷
None	224	54% (121)	24% (54)	6% (13)	6% (13)	1% (2)	0.5% (1)	3% (7)	6% (13)
Outreach	76	63% (48)	7% (5)	3% (4)	1% (1)	0	17% (13)	0	8% (6)
VMV	17	12% (2)	6% (1)	0	0	71% (12)	6% (1)	0	6% (1)

Use of formal providers

For the most recent episode, only 8% of cases in non-intervention areas who sought treatment received treatment at some time from a formal provider (as defined in the Methods section). This was much higher in both outreach villages (31%) and particularly VMV villages (93%) ($p<0.001$) (Table 7-7). Children under the age of 14 were three times more likely to be taken to see a formal provider, but neither distance from the nearest health centre, sex, or level of poverty made any difference (Table A9-12).

⁵⁶ Although a number is given for provider contacts which were considered “Traditional” this is likely to be an underestimate and limited to those cases where traditional remedies were sought from outside the household. In reality patients often used local remedies early on in an illness and often at the same time as modern medicines. These included drinking concoctions made from local plants, rubbing with coins or cupping.

⁵⁷ “Other” included the military, de-mining organisations and forest rangers.

Table 7-7: Proportion and likelihood of patients seen by a trained or "formal" provider for the most recent episode

Intervention	n (N=294)	% seen by formal provider (n)	OR (95% CI)	p	AOR* (95% CI)	p
None	206	8% (17)	1	-	1	-
Outreach	74	31% (23)	5.1 (2.5-10.0)	<0.01	4.0 (1.2-13.2)	0.023
VMV	14	93% (13)	144.5 (17.8-1173)	<0.01	147.5 (8.46-2570.7)	0.002

*Adjusted for sex, age (<6 and 6-14 years), distance from health centre (>2 hours by motorcycle), poverty rank (poorest 40% and richest 20%) and study design.

7.4.3.6. Diagnosis

Overall rates of biological diagnosis were very low. Of the 251 respondents in non-intervention areas, only 17% of 251 reported having had a biological diagnosis for their most recent episode of illness. This was significantly higher in the areas with VMVs and outreach, at 63% (14/22) in the former and 35% (31/88) (p=0.009) in the latter. By univariate analysis the odds ratio of having a test were 8.5 (95% CI 3.3-21.4) if the respondent was from a VMV area and 2.6 (95% CI 1.5-4.5) if they were from an outreach area (Table 7-8). Adjusting for the same factors as described previously, the odds ratio of having a test was increased 11-fold in VMV areas and two-fold in outreach areas but adjustment for clustering reduced the level of significance, so that only the former reached significance. This reflects the amount of variance between villages with 2% of respondents from villages in Chik Phat reporting to having had a biological diagnosis compared to 46% in Malai (Table A9-13). Children aged six to 12 years were three times more likely to have a test (95% CI 1.1-7.8, p=0.035), however sex, distance from health centre and level of poverty did not have any effect (Table A9-14).

Table 7-8: Proportion and likelihood of having a biological diagnosis for most recent episode of fever

Intervention	n (N=361)	% having biological diagnosis (n)	OR	p	AOR*	p
None	251	17% (42)	1	-	1	
Outreach	88	35% (31)	2.6 (1.5-4.5)	0.001	2.4 (0.83-6.9)	0.102
VMV	22	63% (14)	8.5 (3.3-21.4)	0.00	10.7 (4.7-24.3)	<0.001

*Adjusted for sex, age (<6 and 6-14 years), distance from health centre (>2 hours by motorcycle), poverty rank (poorest 40% and richest 20%)

The difference seen in intervention areas is mainly explained by the fact that consultations with VMV or outreach workers resulted in a biological test 96% and 94% of the time, respectively. This compares to around half the consultations in public health facilities (52%) and private health workers (42% to 52%) and only 3% when treatment was sought from the most popular source of treatment, the simple seller (Table 7-9). The type of test provided also varied

significantly by intervention area so that tests performed by VMV or outreach workers were reportedly always by RDT. In contrast, only 15-25% of tests by informal providers and 63% of tests at public health facilities reportedly included an RDT (Table 7-9). Overall, the test positive rate was 77% and was significantly lower (χ^2 p=0.009) if performed by RDT (67%) compared to microscopy only (88%). This difference is reflected in the decreased likelihood of having a positive test if performed by a VMV or an outreach worker. This is at least in part explained by the fact that Paracheck®, the RDT used, only detects *P. falciparum* malaria, whereas all species can be detected by microscopy.

Table 7-9: Frequency of biological diagnosis by provider type (all contacts)

Type of provider	No. of contacts	No. (%) of contacts resulting in biological diagnosis (B)	No. of RDTs (as % of B)	No. of tests reported positive (as % of B)
Simple seller	232	8 (3.4%)	3 (37.5%)	4 (50.0%)
Went to private health worker	98	41 (41.8%)	6 (14.6%)	36 (87.8%)
Public health facility	31	16 (51.5%)	11 (62.5%)	13 (81.3%)
Private health worker came to home	24	4 (16.7%)	1 (25.0%)	3 (75%)
VMV	18	17 (94.4%)	17 (100%)	11 (64.7%)
Outreach	23	22 (95.7%)	22 (100%)	17 (77.3%)
Other	26	4 (15.4%)	3 (75.0%)	3 (75.0%)
Unknown	23	12	4 (33.0%)	6* (66.7%)
Overall	452	124 (27.4%)	65 (52.4%)	93* (76.9%)

*3 unknown results

7.4.3.7. Drug treatment

The common practice in the selling of drugs in Cambodia is for a selection of different coloured tablets and pills to be packaged together in little plastic bags or wrapped in paper, often one dose per packet (Figure 7-3). In this study respondents reported receiving altogether 464 treatments in the previous two months. Of these, 23% of treatments contained four or more different drugs with a mean and median of 2.6 and 2.0 respectively. Of these treatments 63% (296) were known to contain antimalarials, 13% possibly contained antimalarials (“unknown”) and 23% did not. Overall the mean number of antimalarial drugs per treatment was one.

There were at least 28 different combinations of antimalarials of which 15 contained an artemisinin derivative. These different combinations were placed into mutually exclusive groups for analysis (as described in the Methods). In non-intervention areas, the most commonly received treatment was one containing artesunate without mefloquine, which accounted for 40% of all treatments containing antimalarials. These treatments can be

effectively considered as artemisinin derivative “monotherapy” because even if they contained other antimalarial drugs, the latter were generally either ineffective against *P. falciparum* malaria (e.g. chloroquine) or taken for insufficient duration (e.g. quinine). The proportion of artemisinin derivatives that are taken as monotherapy rather than in effective combinations has grave implications for the potential development of drug resistance. In non-intervention areas this accounted for 78% (102/131) of all artemisinin derivative use whereas in outreach and VMV areas this was 36% (10/28) and 7% (1/14) respectively (Table 7-10).

Table 7-10: Percentage of different antimalarial treatments received in the last two months, by intervention area (n)

Treatments received in last 2 months	Intervention		
	None	Outreach	VMV
Artesunate + mefloquine (+/- other antimalarial)	11.3% (29)	23.1% (18)	52.4% (13)
Artemisinin derivative alone	16.7% (43)	7.7% (6)	0
Artemisinin derivative with other drug	16.0% (41)	2.6% (2)	4.8% (1)
Artesunate+ tetracycline (+/- other antimalarial)	7.0% (18)	2.6% (2)	0
Chloroquine	14.8% (38)	26.9% (21)	0
Chloroquine + tetracycline	4.3% (11)	5.1% (4)	0
Other antimalarial combination	5.1% (13)	6.4% (5)	0
Quinine (+/- other antimalarial)	8.6% (22)	11.5% (9)	0
Unknown	16.3% (42)	14.1% (11)	33.3% (7)
Total	257	78	21

p<0.001

In order to compare coverage with the first-line ACT, artesunate and mefloquine, information on antimalarial treatments taken for the most recent episode were compared (Table 7-11). In non-intervention areas only 8% of patients received artesunate and mefloquine compared to 22% and 64% in outreach and VMV areas respectively (p<0.001). The adjusted odds ratio of receiving A+M was 2.7-fold higher in outreach areas and 7.7-fold higher in VMV areas. No other factor was significantly associated with a change in likelihood of receiving A+M (Table A9-15).

Table 7-11: Proportion and likelihood of treated patients receiving A+M for most recent episode

Intervention	n (N=298)	% receiving A+M	OR	p	AOR* (95% CI)	p
None	210	8% (17)	-			
Outreach area	74	22% (16)	3.05	0.003	2.73 (0.99-7.59)	0.053
VMV area	14	64% (9)	9.53	0.000	7.72 (1.84-28.2)	0.007
	298	14% (42)				

* Adjusted for sex, age (<6 and 6-14 years), distance from health centre (>2 hours by motorcycle), poverty rank (poorest 40% and richest 20%) and survey design.

7.4.3.8. Adherence

Most antimalarial drugs were taken for a median of two to three days with a range of one to 14 days (Table A9-16). Patient adherence to the recommended treatment regime was defined according to duration as explained in the methods section. This analysis was carried out on the most recent treatment, as this was less likely to be subject to recall bias than earlier treatment taking episodes. The results are summarised in Table 7-12. Adherence was noticeably better to the three-day regime of A+M than to the three-day regime of chloroquine (77% versus 35%). However when artemisinins were not taken as part of pre-packaged artesunate and mefloquine, adherence was poor with only 13-28% taking at least seven days of treatment. Adherence was even poorer with quinine-based regimes with none of those taking quinine and tetracycline taking it for the recommended seven days and only 13% taking quinine on its own for seven days or more.

In order to compare adherence across interventions and to examine the factors affecting adherence, a binary variable of “adherent to treatment” or “not adherent” was created. In non-intervention areas adherence was 37% (80/218), in outreach areas 44% (34/78) and in VMV areas 90% (17/19). By univariate analysis the OR of being adherent was 15-fold greater in VMV areas (95% CI 3.3-65.1) but not significantly greater in outreach areas. By multivariate analysis adherence was not affected by age, sex, distance from closest public health facility, schooling or level of poverty.

Of particular interest was the likelihood of adherence to A+M and whether this was affected by whom it was obtained from. The results are shown in Table 7-13. Unfortunately as only three patients obtained A+M from a public health facility the result is unlikely to be representative. However if A+M was obtained from a VMV or from the outreach team, adherence appeared to be better than if obtained in the informal sector.

Table 7-12: Adequate duration of treatment (for most recent treatment)

Regime (recommended duration)	n	% achieving recommended durations
A+M (+/- other antimalarial) (3 days)	44	77% (34)
Artemisinin alone (7 days)	29	28% (8)
Artemisinin with other drugs (including quinine) (7 days)	31	13% (4)
Chloroquine (+/- tetracycline) (3 days)	63	35% (22)
Quinine (+/- other excluding artemisinins) (7 days)	24	13% (3)
Quinine + tetracycline (+/- other excluding artemisinins) (7 days)	13	0
Overall	204	46% (94)

P<0.001

Table 7-13: Proportion "adherent" to artesunate and mefloquine regime by type of provider

Type of provider	N	% adherent (n)
Public health facility	3	33% (1)
VMV	13	85% (11)
Outreach	15	87% (13)
Informal provider	17	59% (10)
	48	73% (35)

7.4.3.9. Rapid diagnostic test results

Overall 355 study RDTs were performed at the time of interview, of which 28% were positive. There was no significant difference in positivity rate between intervention areas and non-intervention areas. There was however a significant difference *within* the non-intervention areas such that in Malai only one out of 44 people (2%) tested positive compared to 40 out of 91 (44%) in Chik Phat. There was no significant difference in the result if the analysis was limited to the 215 who began treatment recently (in the last three weeks) and who therefore might have been expected to still be RDT positive had they been parasitaemic before starting treatment. By multivariate analysis, in the model adjusted for study design, the only factor significantly associated with an increased likelihood of having a positive RDT on the day of the study was being a child less than five years of age (AOR 2.5, CI 1.44 – 4.21, p<0.001). Being further than two hours by motorcycle from the nearest health centre halved the likelihood of a positive test.

Table 7-14: Likelihood of positive study RDT

Variable**	AOR (95% CI)*	p
Outreach area	1.62 (0.88-3.01)	0.12
VMV area	1.06 (0.32-3.49)	0.92
Did not receive A+M in last 2 months	1.95 (0.97 – 3.91)	0.06
Did not receive any antimalarial received in last 2 months	1.04 (0.54 -2.02)	0.90
Female	1.26 (0.77-2.07)	0.36
Child 6-14	2.46 (1.44-4.21)	0.00
Child <6	0.64 (0.18-2.34)	0.50
Far	0.45 (0.26-0.79)	0.01
Poorest 40%	1.20 (0.67-2.15)	0.54
Richest 20%	1.14 (0.57-2.32)	0.71

Number of obs=354

* Adjusted for sex, age (<6 and 6-14 years), distance from health centre (>2 hours by motorcycle), poverty rank (poorest 40% and richest 20%) and study design.

**Results in bold highlight variables that significantly affect the AOR.

7.4.4 Patient costs

The table below summarises the household costs for the most recent treatment. All costs have been converted to US\$ 2002 (US\$=3900 Cambodian riel).

Table 7-15: Costs for most recent treatment episode by intervention area

Intervention (n)		Cost (US\$)		
		Drugs	Travel	Total including other costs ⁵⁸
None (205)	Mean (s.d.)	3.24 (6.23)	0.38 (1.18)	4.31(8.07)
	Median (range)	0.88 (0 – 41.0)	0.00 (0-11.1)	1.28 (0 – 54.9)
Outreach (71)	Mean (s.d.)	2.01 (3.22)	0.26 (0.89)	2.92 (5.32)
	Median (range)	0.77 (0 – 17.9)	0.00 (0-6.41)	0.90 (0 – 33.7)
VMV (16)	Mean (s.d.)	0.52 (1.28)	0.00	0.68 (1.37)
	Median (range)	0.00 (0-5.13)	0.00 (0-0)	0.00 (0-5.13)

Much of the difference in cost between intervention areas is explained by the difference in the cost of drugs from different types of providers and the proportion of treatments sought from each. Drugs from simple sellers and private providers, the most popular source of treatment in non-intervention areas, cost a median of \$0.77 and \$2.95 respectively. This compares with a median of zero from VMVs and \$0.64 from outreach workers. As can be seen from Table 7-16 there was a large variation in the cost of drugs ranging up to \$41 from a private health worker.

⁵⁸ Other costs included food and drink.

Table 7-16: Cost (US\$) of drugs (for most recent treatment episode) by provider type

Provider	n	Median (Range)	Mean (s.d.)
Simple seller	151	0.77 (0 - 12.82)	1.28 (1.86)
Went to private health worker	65	2.95 (0 - 41.03)	7.35 (9.56)
Public	17	0.95 (0 - 9.23)	2.41 (2.83)
Private health worker came to home	15	6.44 (0.44 - 15.38)	5.73 (4.23)
VMV	12	0 (0 - 1.78)	0.23 (0.54)
Outreach	18	0.64 (0 - 1.28)	0.51 (0.41)
Traditional	1	0.77	0.77
Other	13	0 (0 - 1.54)	0.30 (0 - 0.57)
Total	292	0.77 (0 - 41.03)	2.79 (5.51)

Cost of drugs

Overall, households spent a median of \$0.77 for A+M compared to a median of \$2.05 for artemisinin derivatives without another antimalarial, and \$1.67 for artemisinin derivatives given in combination with another (non-mefloquine) antimalarial. Treatments that did not contain any antimalarial cost \$0.38 and the most common non-artemisinin antimalarial treatments cost a median of \$0.67 (for both chloroquine and/or tetracycline and quinine without tetracycline) (Table 7-17).

Table 7-17: Cost of different treatments for most recent episode (US\$)

Treatment for most recent episode (n)	Mean (s.d.)	Median (range)
A+M (+/- other antimalarial) (42)	2.00 (3.27)	0.77 (0 - 12.82)
Artemisinin alone (25)	5.00 (7.35)	2.05 (0.38 - 26.7)
Artemisinin with other antimalarial (31)	4.01 (7.04)	1.67 (0.22 - 38.9)
Chloroquine and/or tetracycline (61)	1.08 (1.66)	0.67 (0.11 - 11.11)
Quinine (+/- other antimalarial) (21)	2.15 (3.70)	0.67 (0 - 11.1)
Quinine + tetracycline (+/- other antimalarial) (13)	3.01 (4.65)	1.11 (0.35 - 17.3)
Other antimalarial combination (6)	2.76 (3.48)	1.53 (0 - 9.23)
No antimalarial (55)	0.76 (0.94)	0.38 (0 - 4.44)
Unknown (36)	7.43 (9.9)	3.59 (0 - 41.03)
Total (290)	2.79 (5.5)	0.77 (0 - 41.03)

In order to compare costs across interventions and to investigate factors other than intervention type that might influence costs to households, a binary indicator variable of “cost of treatment greater than \$1” was created (Table 7-18). There was no difference by intervention area and increasing the threshold to \$2. By multivariate analysis, only the level of poverty affected the likelihood of paying more than \$1 for drugs with those in the poorest 40% being less likely than those in the middle 40% AOR 0.38, 95% CI 0.21-0.68).

Table 7-18: Proportion and likelihood of spending greater than \$1 treatments for malaria

Interventions	n (N=298)	% spending more than \$1 (n)	OR	p	AOR*	p
None	210	52.% (110)	-	-	-	
Outreach	74	46% (34)	0.93 (0.55-1.59)	0.795	1.15 (0.63-2.12)	0.525
VMV	14	29% (4)	0.42 (0.14-1.23)	0.126	0.55 (0.16-1.85)	0.107

* Adjusted for sex, age (<6 and 6-14 years), distance from health centre (>2 hours by motorcycle), poverty rank (poorest 40% and richest 20%) and study design.

7.4.5 Inputs for modelling

The values for input into the model were estimated from the data collected. Most values could be used directly but for some estimates, adjustments had to be made, in particular to that the model tracked *P. falciparum* infected patients whereas the study was on patients with malaria-like symptoms.

Treatment rate

In this study, in the absence of interventions, the treatment rate for malaria-like symptoms was only 83%. However, as explained in the next chapter, for the purpose of the model, the treatment rate is assumed to be 95%.

Formal or informal provider

The type of provider determined the likelihood of receiving the ACT, likelihood of adherence and cost. In non-intervention areas, of those who received modern treatment, an estimated 8% were seen in public health facilities with the remainder being seen in the informal sector only (Table 7-7). Dues to the small sample size in the outreach and VMV areas and for ease of comparison, it is assumed this was the same proportion in intervention areas. It is therefore assumed that in outreach areas 23% were seen by outreach workers and in VMV areas 85% were seen by VMVs⁵⁹. It is assumed that choice of provider is the same irrespective of whether the malaria-like illness is actually due to *P. falciparum* malaria or not.

Likelihood of receiving combination therapy

For the model, the likelihood that patients with *P. falciparum* malaria receive the ACT needs to be known. From the survey it is not possible to know whether patients actually had *P. falciparum* malaria, except if treatment was sought from outreach workers or VMVs, where all patients were tested with an RDT and treated with A+M if positive. However for patients who went to the private sector it is only known that 8% received A+M. Therefore it is assumed that the likelihood of receiving A+M is independent of actual diagnosis and that the likelihood of

⁵⁹ the proportion seen in the formal sector as whole was 31% in outreach and 93% in the VMV areas.

receiving A+M is 8%. In public health facilities, biological diagnosis is more likely, a choice of antimalarials are available and prescription of antimalarial drugs is presumably more rational. It is therefore assumed that patients who received chloroquine had non-*falciparum* malaria and that those who did not receive an antimalarial did not have malaria. The coverage rate with A+M is therefore the proportion of those who received A+M over those who received any non-chloroquine antimalarial, which in this case was three out of seven (43%) in the public health facilities (Table A9-17).

Likelihood of adherence to A+M

Adherence to A+M was estimated for the different providers but because the numbers were so small, an average was taken for all formal providers (public health facilities, VMV and outreach) and was estimated at 77%. In the private sector adherence to A+M was 59% (Table 7-13).

The model also required estimates of adherence to the monotherapy, drug A, which in this case was mefloquine. However, mefloquine was seldom prescribed or bought. Therefore for the purpose of the model it was assumed that adherence to the monotherapy would be same as that for the combination therapy in the formal sector. In the informal sector, because mefloquine is relatively expensive, it was assumed that adherence was an arbitrary 30%. The inputs are summarised in Table 7-19.

Table 7-19: Parameter inputs for "behaviour" sub-model derived from results of the survey

Input parameters for patients with symptomatic malaria	Scenario			
	No change	Change to ACT	Change to ACT + outreach	Change to ACT + VMV
Proportion receiving antimalarial treatment	95%	95%	95%	95%
Proportion seeking treatment in health centre	8%	8%	8%	8%
Proportion receiving ACT if seen in health centre	0%	43%	43%	43%
Proportion seeking treatment from outreach or VMV	0%	0%	24%	86%
Proportion receiving ACT if seen by outreach or VMV	NA	NA	100%	100%
Proportion seeking treatment in formal sector (health centre, outreach or VMV)	8%	8%	32%	94%
Proportion seeking treatment in informal sector	92%	92%	68%	6%
Proportion receiving ACT if seen in informal sector	0%	8%	8%	8%
Adherence rates:				
A+M (public sector)	80%	80%	80%	80%
Mefloquine (public sector)	80%	80%	80%	80%
A+M (informal sector)	59%	59%	59%	59%
Mefloquine (informal sector)	30%	30%	30%	30%

7.5 Discussion

In this section the findings of the research are discussed and suggestions for further research specific to Cambodia made. The study's strengths and weaknesses and more general recommendations for policy and research are discussed in the final discussion chapter.

This study documented for the first time the actual impact of the change in policy to ACTs in communities affected by malaria, and the impact of different delivery strategies in Cambodia. It was also unique for a study on treatment seeking for malaria, in attempting to explore the proportion of fever patients who actually had evidence of recent *P. falciparum* malaria, by carrying out a rapid diagnostic test at the time of the study. Although in practice there were problems with interpreting the results, as discussed below, the experience showed that with adaptation this approach may prove useful in future studies of treatment seeking for "malaria".

The key findings in this study were that the coverage with both arms of the "Early Diagnosis and Appropriate Therapy" approach was low, but that significant improvements could be made with specific interventions to improve access to reliable diagnosis and free drugs. The other important finding was the widespread use of artemisinin derivatives without mefloquine - over 78% of treatments containing artemisinins in non-intervention areas.

In the absence of any intervention, only 17% of respondents received a biological diagnosis for the most recent episode of fever and only 11% received artesunate and mefloquine for malaria-like illnesses in the last two months. The results came as a surprise and disappointment as much work had gone into the changing of the policy and Cambodia was seen as an example of a country with an innovative policy (WHO 2002). In particular, there had been much optimism for the attempts to socially market Malarine®. However the finding in this study were later confirmed in a larger national antimalarial drug usage survey the following year in nine districts in which 1277 household respondents in 36 villages participated. The survey differed from this study in that districts did not have any special interventions to increase coverage⁶⁰. In this national survey, only 11% of adults, 10% of children (five to 14 years) and only 2% of the 116 children under five years received the recommended treatment (Duzey, Kim et al. 2003)⁶¹. An even higher proportion (92%) of treatments containing an artemisinin derivative were taken without mefloquine if they were not blister-packaged with mefloquine (Duzey, Kim et al. 2003).

⁶⁰ However half had purposively been selected as they were districts in which there were sentinel sites for the monitoring of drug resistance and therefore by implication had relatively well functioning health centres.

⁶¹ Only two children received an artemisinin derivative as a suppository and only five received oral artesunate and mefloquine.

One of the reasons for the low coverage rate with A+M in Cambodia is that few treatments were obtained in public health facilities. In the thesis, in the absence of any interventions, only 8% of respondents sought treatment from a public health facility for the most recent episode of a malaria-like illness, with the most popular first source of treatment (56%) being untrained village providers. These findings are similar to rates found in other settings with poorly functioning health systems (Slutsker, Chitsulo et al. 1994; Ruebush, Kern et al. 1995; McCombie 2002; Williams and Jones 2004) and confirms previous reports in Cambodia. In other studies in Ko Kong, only 2 to 4% (Denis, Macdonald et al. 1994; Sedano 2002) of patients first sought treatment for malaria in the formal sector. In other areas rates of 7 and 26% have been described with the variation between villages being explained by proximity to roads and the nearest health centre (Bury 1999). In the national antimalarial drug usage survey in 2002, 18% of first treatments were received from public or NGO facilities⁶² (Duzey, Kim et al. 2003).

However, even in public health facilities, the treatment guidelines were often not followed. In 2001, from the official statistics, 169,215 patients were treated for malaria in public health facilities of whom 32% received a biological diagnosis. Of those having a biological diagnosis, only 7% were by an RDT with an average positivity rate of 48%⁶³ (range of 18-70% depending of the province) (Soley L, personal communication). Unfortunately, information about what treatments patients diagnosed with malaria actually received was not available and there was no accurate information on the distribution of drugs and RDTs in that year. However less than 60,000 doses of pre-packaged A+M were produced (CNM 2001) and in the preceding year only 21,850 doses of drug and 13,725 rapid diagnostic tests were distributed (CNM 2000). Therefore the low rates of biological diagnosis (52%) and use of the combination therapy in public health facilities found in this study are not surprising. From interviews with health centre staff it became apparent that they continued to stock and use the old drugs (quinine and tetracycline) for the first-line treatment of *P. falciparum* malaria.

The low uptake of Malarine® in the informal sector was less surprising, but still disappointing, particularly in Sampalouen district where the pilot project had been ongoing for over a year. There are a possible number of explanations for this: low awareness of the policy by both patients and/or providers; low availability of the RDTs and A+M; unaffordability; or preference, based on some other factor such as familiarity of older drugs or fear of side effects⁶⁴.

⁶² It was also noted that the likelihood of going to the public/NGO sector increased as more treatments were sought.

⁶³ The overall slide positive rate was 35%, of which 90% were *P. falciparum*, the remainder being mainly *P. vivax*.

⁶⁴ Although the experience or fear of side effects with mefloquine was widely reported anecdotally, this was not confirmed in this study. Unlike foreigners taking mefloquine for chemoprophylaxis who mainly associate mefloquine with its much rarer neuropsychiatric side-effects, the main side-effects experienced in the local communities are nausea, vomiting and dizziness. However from the national survey the

The policy had been accompanied by an advertising campaign on the television and local radio, largely promoting the availability of Malarine® and dipsticks from private providers. At the end of the advertisements brief mention was made to the fact that both could be obtained free at health centres. It had been hoped that there would be sufficient financial incentive to encourage more patients to use the public health facilities rather than the private sector for their treatment and that patient demand would result in the provision of Malarine® in the informal sector. The poor uptake was due mainly to the one-year delay between the publicity campaign and the launching of the nationwide implementation. During this extended “pilot” phase, even interest from the 10 pilot market retailers waned and the product did not penetrate into the villages in the catchment area. It was during this period that this study was conducted and therefore the findings do not reflect the results of the full-scale implementation. However, the national antimalarial drug usage survey was carried out six months after the nationwide launch of the social marketing project. This confirmed that Malarine® was not penetrating into rural areas – none of the village providers stocked Malarine® compared to 40% of market providers⁶⁵. It also showed low levels of awareness of the product and of the national antimalarial guidelines (Duzey, Kim et al. 2003).

However, there was evidence of widespread leakage of blister-packaged A+M from the public sector into the private sector in both this study and the nationwide antimalarial survey. In the latter, blister-packaged A+M was found in over 30% of market providers and over 15% of village providers. The problems of low motivation and low pay amongst health staff in the periphery are well known and there are a number of initiatives aimed at addressing this. However, this will take some time and although the leakage is seen as a very serious problem, there is also a pragmatism, amongst certain donors and senior health officials, that recognises that it is preferable for patients with malaria to receive effective treatment and for some public money to go into the pockets of a few private individuals, than for patients to risk death from receiving inappropriate drugs in the informal sector.

Previous studies (Rose, Dixon et al. 2002) have documented the severity of the problem of inappropriate drug usage in Phnom Penh in Cambodia. The problem of unnecessary infusions and injections is particularly worrying. Unfortunately in rural areas, where malaria is often perceived as a potentially life-threatening disease, some patients are willing to pay for more expensive treatment often including injections or infusions. Therefore a financial incentive exists for private health workers to make a diagnosis of malaria. There was evidence for this in

following year, these side-effects did not occur more often with mefloquine than with other drugs and neither patients nor providers reported this as a common reason for not taking A+M.

⁶⁵ The provider arm of the study included 49 market-level facilities, 107 village-level facilities and 12 public health facilities.

Malai district which recorded the highest rate of biological blood tests and the highest rate of positive tests and yet the lowest rate of positive study RDT tests. Interestingly we were told that a diagnosis of "Falciparum" would inevitably result in the prescription of parenteral drugs because the word sounds like "Svar" (monkey) "psi" (eat) "serum" (serum or intravenous fluids) in the Khmer language!

The challenges in changing prescribing practice in the informal sector are considerable and make the alternative, of community based interventions, very attractive. It was clear from this study that the interventions to improve coverage were effective, in particular the VMV scheme. The likelihood of receiving a biological diagnosis was increased 11-fold and the likelihood of receiving A+M was increased eight-fold. The use of artemisinin derivative monotherapy was also much lower than in non-intervention areas. However there were some surprising results. In the VMV area a higher proportion of patients reported remaining untreated despite having had malaria-like symptoms and waited for longer before seeking treatment. This could be for a number of reasons. The presence of a VMV may have allowed them to risk waiting for longer to see how symptoms evolved before seeking treatment, assured that if they did have malaria they would receive the right treatment immediately, or patients may not have been able to find the VMV if they were in the field or elsewhere.

Coverage was lower than anticipated with the outreach programme. From discussion with the villagers it was apparent that this was mainly an issue of time and convenience. For those that were close to roads, if they could afford the transport and drug costs, they preferred to go to buy drugs rather than wait for the outreach service to come to them, unless they knew that they were arriving in the next day or two. For the more remote and poor villages, they seemed to be more willing to wait. Unfortunately numbers were not big enough to test this hypothesis statistically.

The two interventions cannot really be compared, as the contexts were very different. In Ko Kong, the communities had generally been in place for longer and there was a strong sense of community, which meant that there were willing volunteers. In Anlong Veng, much of the population had arrived recently from disparate locations and there was little connection between them. Individual households were struggling to survive, building themselves crude shelters and clearing land. It was therefore felt that there was little capacity or inclination for community volunteers. It may also be that there was a bias in the philosophy of the organisations involved that meant different systems were favoured.

The rates of receiving any kind of modern treatment were generally lower than expected. However in non-intervention areas for those who did receive modern treatment, over 60% received treatment within two days of the onset of treatment. Reassuringly there appeared to be

some recognition that young children were particularly at risk of malaria, as they were significantly more likely to receive modern treatment within two days of symptoms and were three times more likely to be seen in the formal sector than older children and adults. They were also three times more likely to receive a biological diagnosis, but were no more likely to receive the recommended A+M than older age groups.

Interestingly, data on drug costs suggested that households pay \$0.5 to \$2.60 with a median of \$0.77 for antimalarial drugs and this was in fact the median costs paid for blister-packaged A+M. In general, there was a great deal of variation in the price paid for treatments with people paying up to \$41 for a single course of treatment from a private provider. The median cost of a course of an artemisinin drug *without* another antimalarial appeared to be more than that if provided with another (non-mefloquine) antimalarial but with less variation (range \$0.90-2.69) compared to \$1.67 (range \$0.77-5.13) respectively. This was because artesunate tablets, the most popular form of artemisinin derivative, were generally sold either in whole blister packets containing 12 artesunate tablets at a usual cost of around \$2 per packet, or as a single tablet packaged with a number of other cheaper drugs such as paracetamol and chloroquine to constitute a single dose of treatment at a cost of about \$0.25-0.50 per packet. For the latter, the number of doses of treatment bought would depend on a number of factors including how much the patient could afford and how ill they were.

Of note the only variable with a significant correlation to the amount of money paid for treatment was poverty rank. This confirms previous findings of the relationship between poverty and treatment expenditure (Filmer, Giao et al. 2005) and adds weight to the argument that ACTs will need to be provided almost free if the biologically vulnerable (who are usually the most economically vulnerable) are to be reached (Arrow, Panosian et al. 2004).

Reassuringly, the cost of treatments was cheaper in the formal sector compared to the informal sector⁶⁶. Treatment from the VMVs was supposed to be provided free and the study suggested that usually this was the case, although there was evidence that occasionally small payments were made (maximum \$0.54). In outreach areas the median cost of treatment from an outreach worker was reported to be \$0.64 but ranged up to \$5.1. This is concerning as the patients were only supposed to be charged up to a maximum of \$0.75 depending on their means (as assessed informally by the outreach worker) and it was said that the majority of patients received their treatment for free. In contrast, treatment from a simple seller cost a median of \$0.77 and from a private health worker \$2.95 if the patient went to the health worker and \$6.44 if the health worker came to the patient's house.

⁶⁶ This is similar to the findings in the national drug usage survey where the median cost was 8000 riel in the private sector (n=554) which was almost double the cost of public sources (4550 riel) (n=132).

The study revealed encouraging results with regard to adherence to the ACT. Of patients who did receive the blister-packaged artesunate and mefloquine, 77% reported to taking the whole package over 3 days and were therefore considered adherent. Although an attempt was made to differentiate between A+M that was blister-packaged and artesunate and mefloquine provided separately, there was no apparent difference in adherence. This is most likely due to the small sample size or failure to differentiate between the two. It may also be because there was no real difference or because when A+M was provided “separately” it was actually the blister-packaged A+M which had been re-packaged so that it was not recognizable as A+M⁶⁷. In the national drug usage survey using similar criteria, adherence rates were between 73% for Malarine and 97% for A+M, possibly reflecting that A+M was more likely to be obtained in the formal sector where it was provided free and by a trained provider (Duzey, Kim et al. 2003). The results compare favourably with clinic-based studies of adherence to artesunate and SP (Depoortere, Guthmann et al. 2004) and artemether-lumefantrine (Fogg, Bajunirwe et al. 2004) where rates of 78% and 90-93% were reported respectively. The latter is co-formulated which ensures that both drugs are taken, but requires twice daily dosing, which is likely to decrease adherence in terms of frequency and overall dosing, making direct comparison difficult.

7.5.1 Further research

This study aimed at answering a number of questions: 1) What proportion of patients with malaria received a reliable diagnostic test and A+M? 2) How adherent were patients to A+M? and 3) How effective were outreach and VMVs in improving access to early diagnosis and appropriate treatment? Although all of these questions were answered to a certain extent, the process of undertaking this study and the finding themselves exposed areas where further research would be helpful. Further research specific to Cambodia are discussed here. More general recommendations for studies of antimalarial drug usage and treatment seeking behaviour are made in Chapter 5 and in Chapter 10.

Given the size of the study, one of the main priorities was to validate the findings and attempt to quantify the extent of the problem nationally. In addition there was a lack of information on high-risk groups in particular pregnant women and children. As discussed earlier this in fact was achieved the following year (Duzey, Kim et al. 2003) using a simplified survey in nine districts across the country.

⁶⁷ There was evidence that this was done from inspecting some drug packages obtained from the private providers. This was also practised by one of the outreach workers who cut up the blisters and put each dose into a separate plastic bag, believing that it would easier to take.

As the study in this thesis purposefully focused on the behaviour of patients, only limited information was gathered from providers themselves. However providers in each village and town were visited and although the information has not been presented, it seems that there was a low level of awareness of the national antimalarial guidelines, and low availability of the ACT and RDTs. There was also widespread evidence of leakage of A+M and availability of fake artesunate. It was clear therefore that much more systematic information was required from the supply side of the antimalarial drug market, focusing on these issues. It would also be useful to explore attitudes and knowledge about the current policy and the willingness to participate in training and provision of malaria curative services. Fortunately, following this study, a number of other studies has been undertaken addressing some of these concerns.

Finally, this was a quantitative survey, aimed at answering questions of the “How much” or “When” type rather than the “Whys?” and “Hows?”. It revealed substantial gaps in our understanding about why uptake of A+M and RDTs has been so low. More qualitative work will be essential in order to understand the perceptions, attitudes and reasons underlying patients’ and providers’ behaviour, if implementation strategies are to succeed. One particular area where there is little understanding is the acceptability of using rectal medication in children. The policy was introduced with limited consultation with health care workers and patients themselves and it would appear that there may be problems with acceptability.

7.6 Conclusion

This study has shown that the main challenge in changing to ACTs is ensuring adequate access to accurate diagnosis and ACTs in the poor rural areas where the community have limited access to any kind of health care. Adherence to the ACTs once received appears to be good if provided in blister-packaged doses. In order to improve access, the training of volunteers at the village level and provision of free RDTs and drugs certainly seems to be effective but may not be appropriate in all circumstances, and there may be a role for outreach teams in new settlements where there is much fluidity in the population movement and a lack of social cohesion. Visits may well need to be more frequent than once weekly, and even so patients are still likely to seek treatment from the private sector. However, low uptake of the socially marketed Malarine® was disappointing and much more effort needs to be made in ensuring a higher level of awareness and availability of drugs. This will require both a greater understanding of how the market currently works and the costs patients are willing to pay. Successful implementation will probably require more direct communication with providers who, on the whole, did appear very willing to improve the quality of the service they provided to their clients. This has been successfully done in other countries both focusing on malaria (Marsh, Mutemi et al. 1999; Marsh, Mutemi et al. 2004) and other diseases (Luby, Zaidi et al.

2002). The latter is relevant in view of the limitations of focusing only on malaria diagnosis and treatment rather than the provision of a more holistic service.

CHAPTER 8

MODELLING ANTIMALARIAL DRUG RESISTANCE AND ARTEMISININ-BASED COMBINATION THERAPY: RESULTS

In Chapter 4, the model development and structure was described. In this chapter, the model is run to illustrate how it functions and is applied to explore the spread of drug resistance and the effect of combination therapy in a low transmission setting.

8.1. Overview of the chapter

The chapter starts with the presentation of results when the biological model is run to simulate a base-case scenario in which use of monotherapy is continued in a low transmission setting. This enables the detailed exploration of the outputs of the biological model in terms of the spread of drug resistance, number of infections and recrudescence infections in a “no change” situation. These outputs are then fed into the sub-models to illustrate how these component models link together to produce outcomes in terms of severe malaria, deaths, disability-adjusted life years (DALYs) and costs.

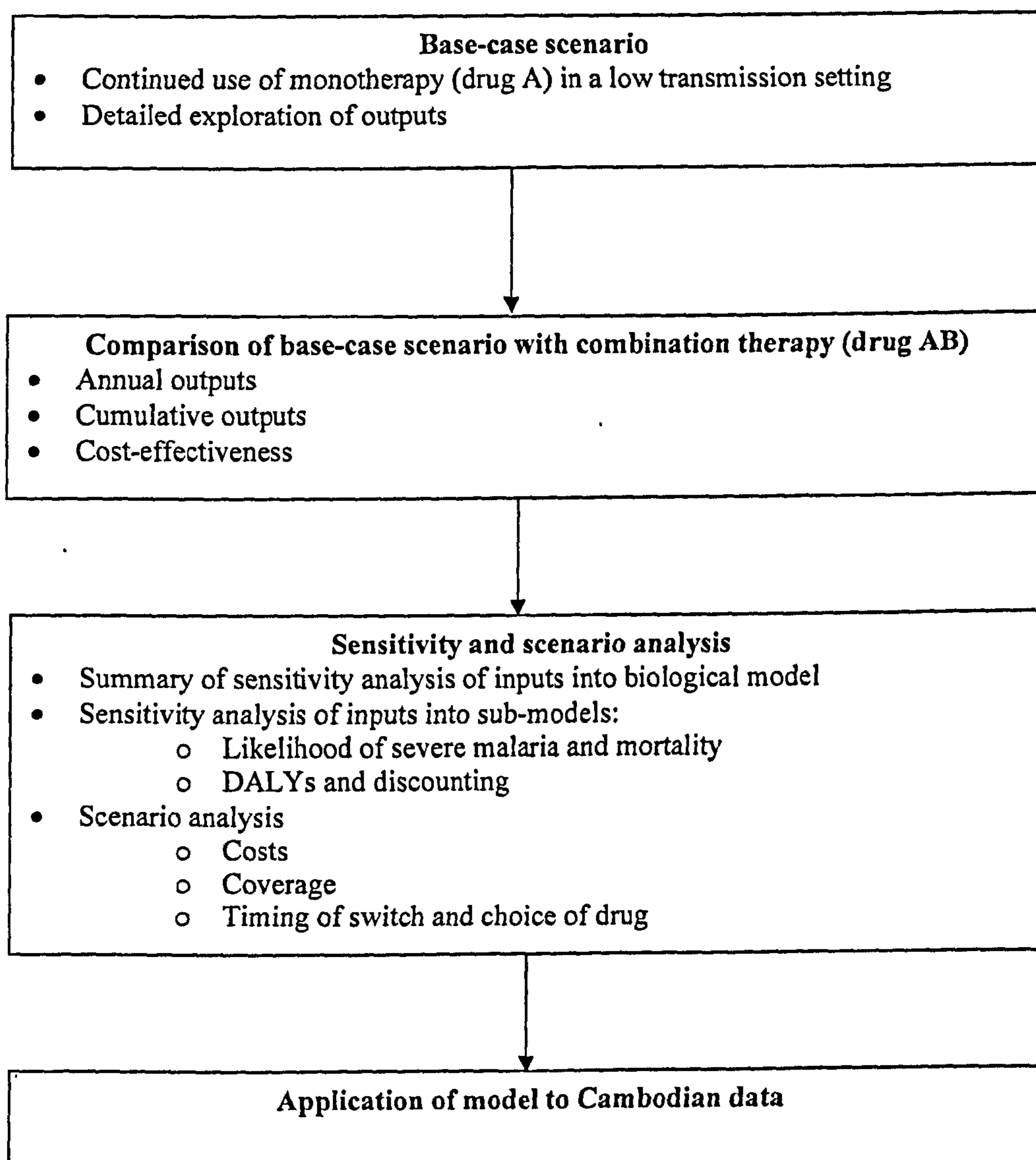
The model is then run to simulate the introduction of an artemisinin-based combination therapy (ACT) in presumably ideal conditions, where the switch from monotherapy is made early and the coverage rate with ACT is high. The results of comparing these first two scenarios are then presented and form the basis of the cost-effectiveness analysis of combination therapy. In the next section, the results of the sensitivity analysis are shown. Firstly, a brief summary of the extensive sensitivity analysis of the biological model undertaken by WP is presented, followed by sensitivity analysis of some of the parameters and assumptions used in the sub-models. Scenario analyses are then presented, of the cost, effect and cost-effectiveness of combination therapy compared to monotherapy in different circumstances. Finally, the chapter illustrates how the model might be applied to a real-life scenario to predict the cost-effectiveness of different interventions by using the data collected in Cambodia. This sequence of presentation of results is illustrated in Figure 8-1.

Because the inter-relationships between the factors that influence transmission and drug resistance are complex, and this complexity is reflected in this model, the outcomes for a given set of inputs were not predictable and were often surprising. When such results were produced during the development of the model, they were occasionally due to errors in the model script

that had to be corrected. However once such errors had been ironed out, it was often in the investigation of these initially unexpected results, that the importance of certain factors and relationships emerged or assumptions that had been made in the modelling were uncovered. These discoveries would lead to refinements in the model, the gathering of more data or a note of the importance of specific assumptions made.

Although not the focus in this thesis, the preliminary application of the model to a high transmission setting has also been undertaken and results provided in Annex 10. Specific comments are provided in the chapter text where the results are of interest.

Figure 8-1: Sequence of presentation of results in this chapter



8.2. Presentation of results

For each simulation of the biological model, a large amount of outputs are produced. The choice of which outputs to present, and how to present them, needs to reflect the requirements of the audience for whom the analysis is intended. Many of the outputs of the biological model are useful for problem shooting and in refining the model, and will be useful for further exploration of particular aspects of malaria transmission and resistance. However they are not of direct relevance to the economic analysis and are therefore not presented here.

The purpose of this chapter is to focus on the outcomes most relevant to policy and to present them in a way that is accessible and potentially useful. Therefore, the choice of results included reflects an attempt to balance parsimony with sufficient information. The eventual choice is discussed and justified below:

- *Annual versus cumulative results.* Annual and cumulative results are both presented, as annual results show the change in outcomes over time, and the results cumulated over time capture the long-term costs and consequences. The latter can illustrate the importance of using a sufficiently long time-scale when the externality benefits of reducing resistance and transmission are to be considered.
- *Incidence in terms of patent versus symptomatic or treated infections.* Although the number of patent infections is important in terms of transmission, it is the numbers of symptomatic or treated infections that are more tangible, are routinely measured in studies and are directly associated with clinical outcomes and costs. In low transmission settings they are similar but there is considerable divergence in high transmission settings where immunity is high. The incidence of patent infections is therefore not presented.
- *Symptomatic infections versus treated infections.* Both could have been presented but this was unnecessary as the model assumes that a fixed proportion of symptomatic infections are treated. In the base-case scenario, this proportion is fixed at 95% and only results of treated infections are presented as these are the ones for which costs of treatment are incurred.
- *Direct costs alone versus total costs inclusive of indirect costs.* Direct costs are tangible and hold meaning for policy makers in terms of actual monetary value and are therefore shown throughout. Indirect costs are difficult to measure and value estimates vary widely depending on the setting and the methodology used. However they do attempt to capture the total cost of malaria and are therefore shown intermittently to emphasise the societal cost of drug resistance.

- *Ideal versus realistic coverage rate with combination therapy.* In basic comparison between monotherapy with combination therapy, an “ideal” coverage rate of 100% and a realistically more achievable rate of 80% are both shown. This is to make clear what is the maximum possible effect of combination therapy from a theoretical point of view as well as the effect that is practically more likely. Having illustrated the potential difference in outcomes, for clarity, the model was run with 100% ACT coverage thereafter except when coverage rates were varied from 10% to 100% in the scenario analysis.
- *Discounted versus undiscounted future costs and benefits.* As discussed in Chapter 3, costs and DALYs are discounted at a rate of 3% for comparability with other studies. Undiscounted costs and DALYs are tested in the sensitivity analysis. All costs are expressed in terms of US\$ 2002.

8.3. Base-case scenario – The continued use of monotherapy

8.3.1. Results of the biological model

The model was run with inputs for a “base-case scenario” in order to explore in detail the outcomes of the model and the relationships between different inputs, and as a reference case with which other scenarios could be compared. This base-case scenario is the continued use of monotherapy at a treatment rate of 95% in an area of relatively low transmission intensity with an entomological inoculation rate (EIR) of one or less⁶⁸. Although, for this example it is assumed that the monotherapy (Drug A) is mefloquine, the values of the inputs would in fact be the same for SP. Later, this base-case scenario is compared with a switch to a combination of artesunate with mefloquine⁶⁹ (Drug AB). The characteristics assigned to both the monotherapy and combination therapy are shown in Table 8-1.

The model was run for 12 years, with the first two years being the time to reach steady state without drug resistance. At this point resistance to drug A is introduced with a starting level of 1% of patent infections. All the fixed model inputs are highlighted in the parameter tables in Annex 6. The values of the variable parameters used in the base-case scenario are shown in Table 8-2. A population size of 10,000 was used and the analysis was carried out using three age groups (<5 years, 5-12 years and >12 years). Although the analysis could have been undertaken with more age groups, it would have taken longer for the model to run, and would not have provided additional useful information for the purpose of this thesis.

⁶⁸ Although the WHO recommend the inclusion of a “null case” scenario, which in effect is the natural course of disease, we felt that it was more helpful to take as the base-case, the common scenario which is the continued use of monotherapy.

⁶⁹ The assumed dosages were: mefloquine at a single dose of 25mg/kg, and for combination therapy, artesunate at 4 mg/kg once daily for three days with mefloquine 25mg/kg in single dose on the first day.

Table 8-1: Characteristics of monotherapy (drug A) and ACT (drug AB)

Parameter	Value in base-case scenario
Failure rates in the non-immune host if:	
Sensitive to Drug A and treated with Drug A	10%
Resistant to Drug A and treated with Drug A	95%
Sensitive to Drug A and treated with Drug AB	3 %
Resistant to Drug A and treated with Drug AB	30%
Minimum parasite reduction ratio with Drug A if sensitive to Drug A	1,000
Minimum parasite reduction ratio with Drug A if resistant to Drug A	100
Minimum parasite reduction ratio with Drug AB if sensitive to Drug A	50,000
Minimum parasite reduction ratio with Drug AB if resistant to Drug A	50,000
Gametocyte switching rate with Drug A	0.003
Gametocyte switching rate with Drug AB	0.0009
Cost of adult course of drugs ⁷⁰ :	
Drug A	\$1.11
Drug AB	\$3.77

Table 8-2: Values of variable parameters used in base-case scenario

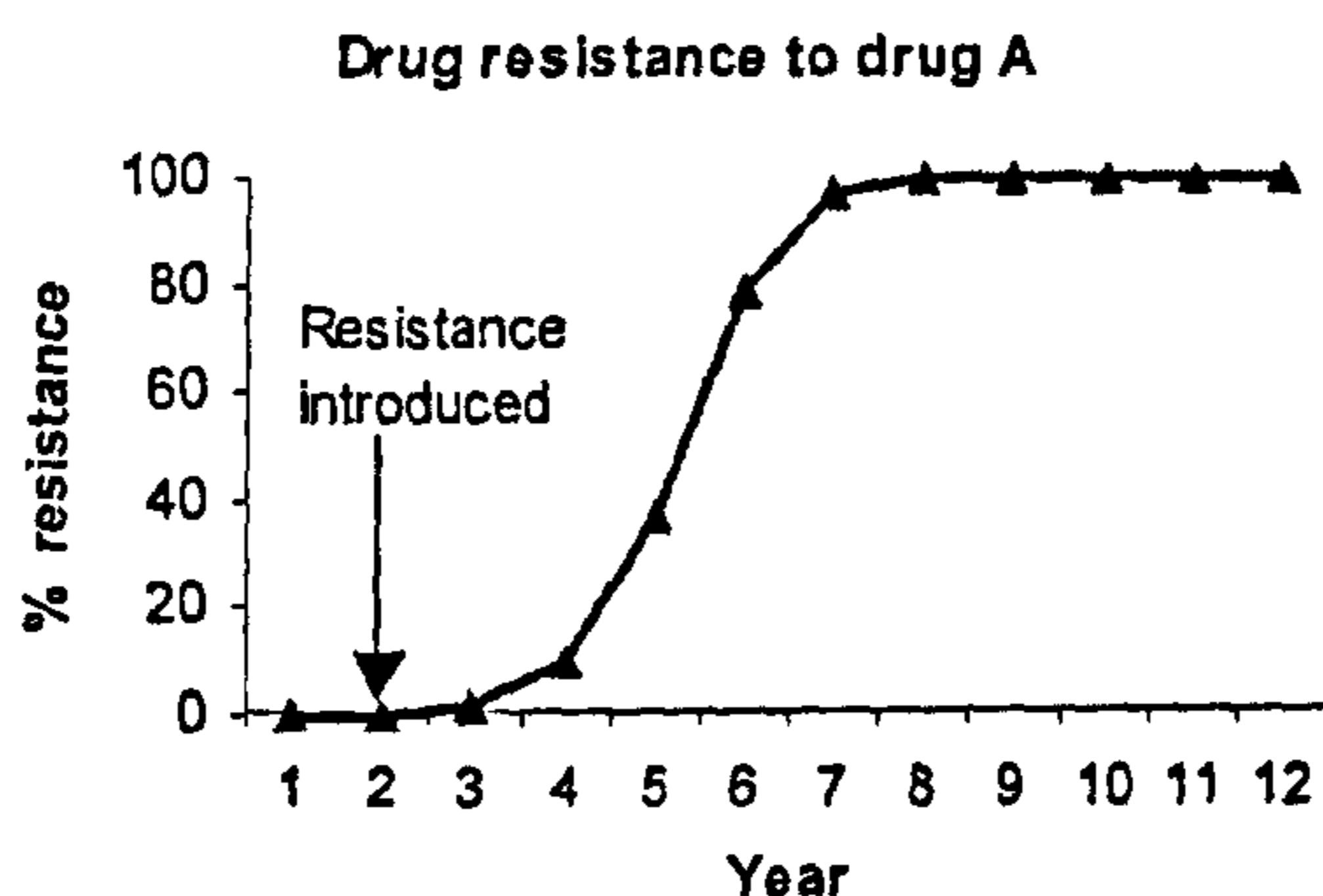
Parameter	Value in base-case scenario
Population size	10,000
Number of age-groups	3
Vectorial Capacity (giving an initial EIR of 1)	0.1
Seasonal variation in transmission	None
Likelihood that symptomatic patient receives antimalarial treatment	95%
Time delay before seeking treatment	1.2 days
Coverage rate with combination therapy	0%
Proportion of humans who have inhibitory concentrations of antimalarial drug in their blood	10%
New "migrant" infections as a proportion of the total human population	5%
Time of undetectable parasitaemia between initial infections and recrudescence	14 days
Starting level of resistance to drug A	1%

⁷⁰ The cost of most drugs for children aged 6 to 12 years and 1 to 5 years was assumed to be 50% and 25% of the cost of the adult course respectively. For artesunate and mefloquine the costs were based on the cost obtained for blister-packaged "A+M" in Cambodia with an adjustment for the difference in age grouping.

8.3.1.1. Drug resistance

As shown Figure 8-2, in this scenario, resistance rises exponentially from 1%, at the time of introduction of drug resistance, to almost 100% in around six years, and stays at this level thereafter. This rapid increase in resistance until saturation point occurs in this scenario because it represents a low transmission setting, where adults as well as children are not immune and therefore most patent infections result in clinical symptoms for which treatment is taken. In this example, the treatment rate is assumed to be 95%, all of whom receive monotherapy and are compliant. This means that nearly all parasites are subject to the drug pressure that discriminates against sensitive organisms and allows resistant organisms to persist, causing recrudescence infections and therefore the increase in their relative infectiousness and an expansion in their numbers relative to their drug-sensitive counterparts. In high transmission settings a much smaller proportion of parasites are exposed to drug pressure and resistance therefore rises more slowly (Figure A10-1).

Figure 8-2: Spread of drug resistance to drug A with continued use of drug A monotherapy



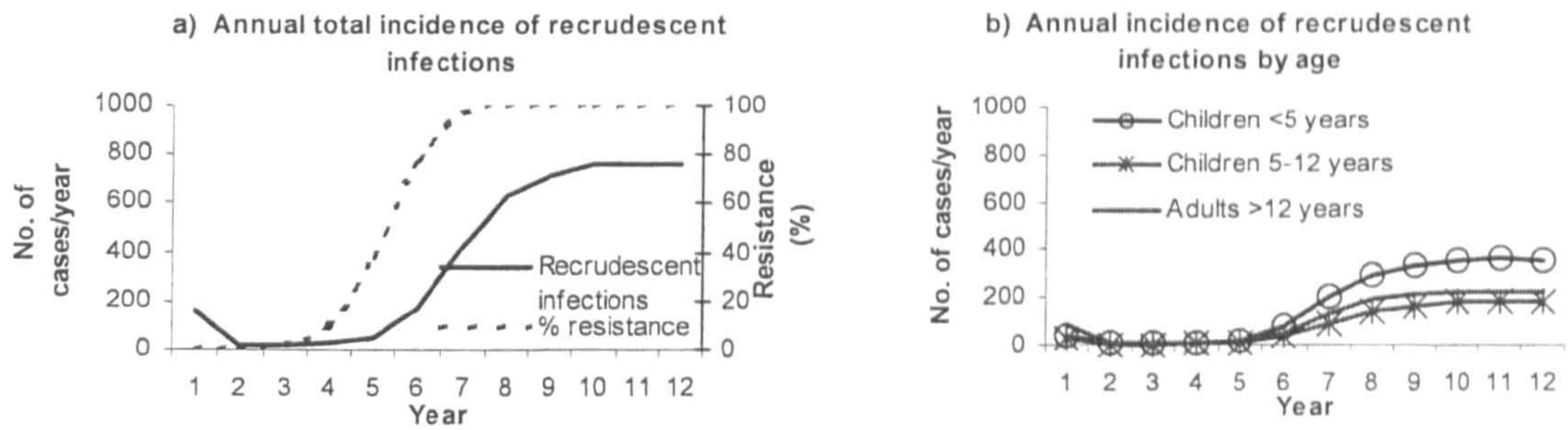
8.3.1.2. Recrudescence infections

Figure 8-3a shows the total number of recrudescence infections. As expected, once steady state is reached and drug resistance is still low, there are few recrudescence infections in the first few years – less than 30 cases per year. As resistance rises, so does the number of recrudescence infections. After drug resistance reaches 100%, recrudescence infections also start to plateau at around 760 cases per year representing a 25-fold increase in incidence of recrudescence infections.

The failure rates in the base-case scenario were chosen to reflect high levels of patient adherence to treatment. Therefore the maximum failure rate when a sensitive infection is treated is assumed to be 10% in the youngest age group. Older children and adults are assumed to acquire a degree of immunity that enables them to self-cure. Therefore, when we examine the age group in which the recrudescence infections are occurring, it can be seen that the youngest age group contribute the most to the total number of recrudescence infections (Figure 8-3b).

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Figure 8-3: Recrudescent infections - a) Total number of cases b) By age group

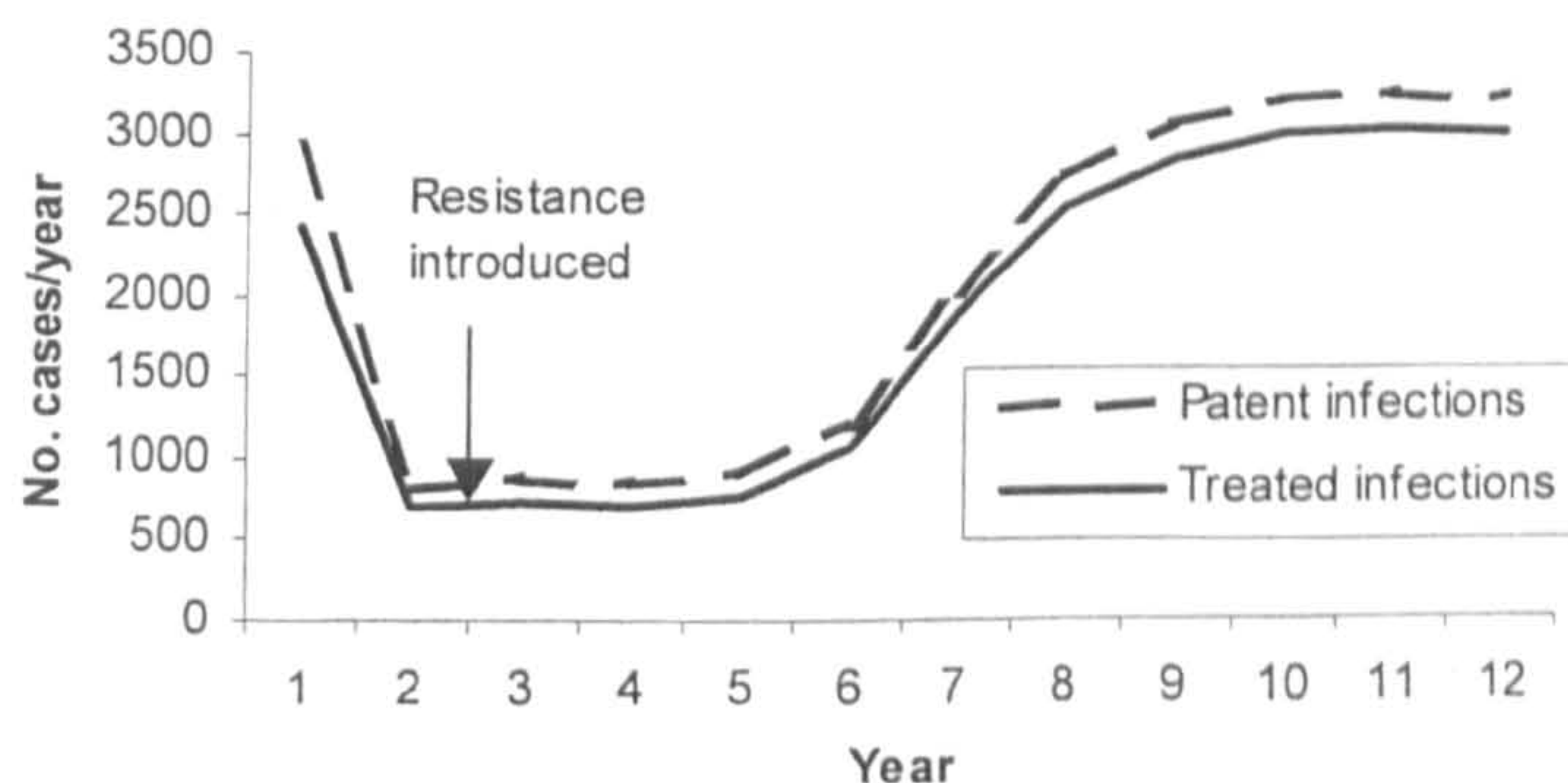


It may appear to be unrealistic to allow the model to continue running without a change in therapy and one would hope that a switch to an efficacious therapy would occur much earlier. However, in reality resistance to chloroquine is known to have reached extremely high levels and yet the drug continues to be used.

8.3.1.3. New infections

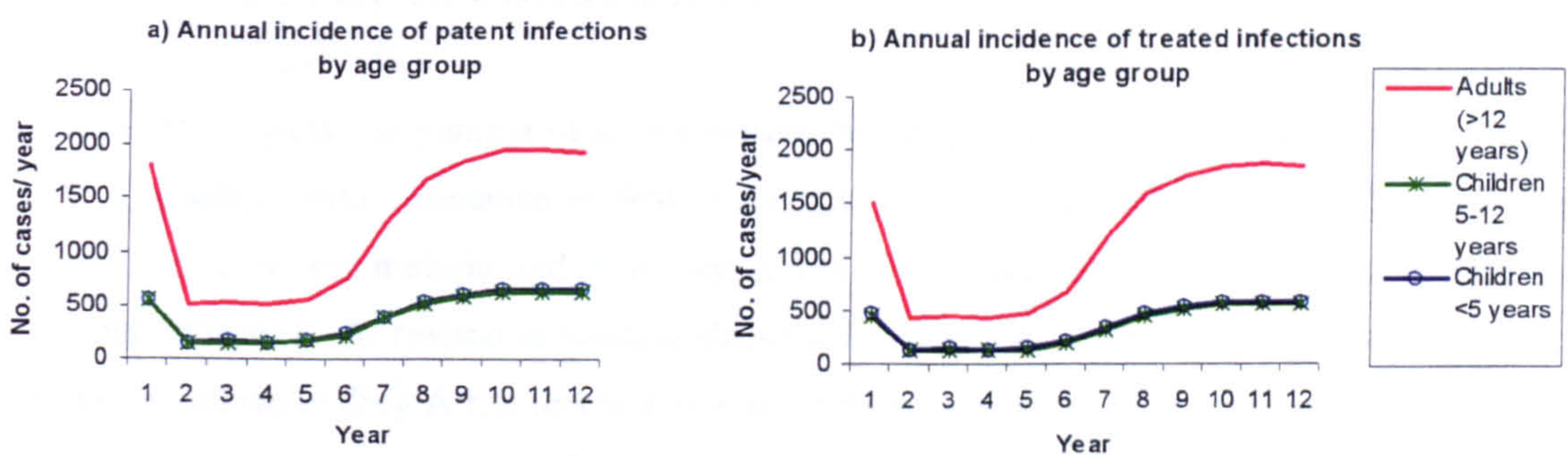
The annual incidence of new patent and treated infections is shown in Figure 8-4. It can be seen that under these conditions, after reaching steady state, the incidence of patent infections initially remains steady at around 700 infections per year. Then about four years after the introduction of drug resistance, there is an exponential rise in the incidence of new infections. This is because with the increasing number of recrudescent infections, the infectiousness of the population increases. This increase appears to stabilize at around 3000 after another three years as resistance reaches a maximum and there is no possible further increase in recrudescent infections and therefore in infectiousness. In a low transmission intensity setting such as this, all age groups have low immunity therefore most patent infections manifest symptomatically and are treated. In a high transmission setting most patent infections are asymptomatic and remain untreated (Figure A10-2).

Figure 8-4: Annual incidence of patent and treated infections (assuming that 95% of symptomatic infections are treated)



Breakdown of patent and treated infections by age groups is shown in the next figures. This shows that infections occur in all ages, including adults and is explained by the low level of acquired immunity and therefore susceptibility to infection throughout life. The absolute number of infections is greater in the adult age-group because this is numerically the largest group. There is an overlap in the two child age-groups because the size and immunity profiles result in a similar number of cases in these groups. In higher transmission intensities, only a small proportion of the patent infections are symptomatic and treated and the majority of infections would be expected to occur in the youngest age group (Figure A10-3).

Figure 8-5 Annual incidence of a) patent and b) treated infections by age group

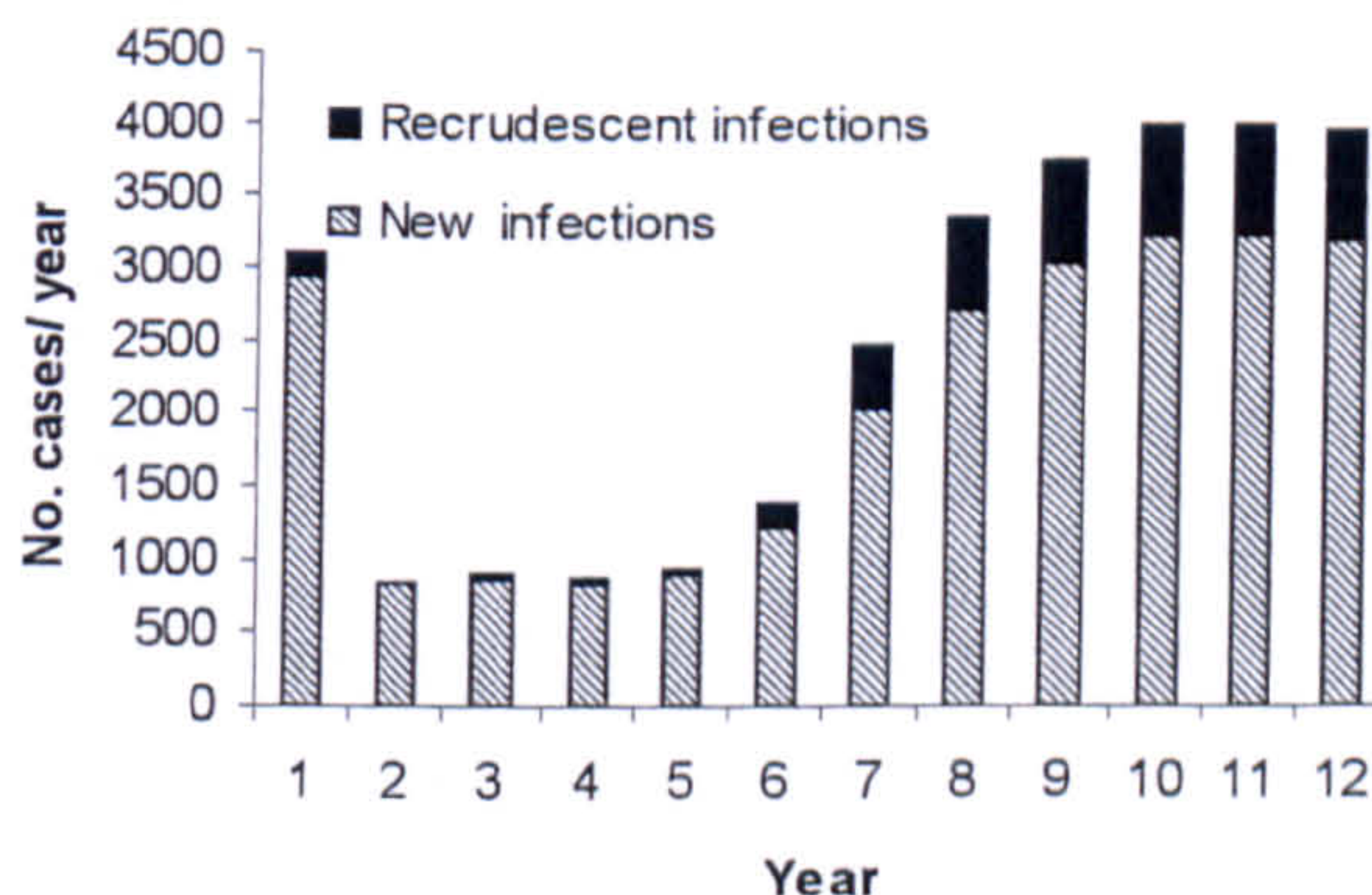


At an operational level, neither patients nor health workers routinely discriminate between “new” infections and recrudescence infections when patients present with a fever, unless little or no time has elapsed between a prior fever and the current presentation. Therefore, in the face of an increase in the number of clinical infections, it will not be apparent what proportion is due to recrudescence. Figure 8-6 illustrates how in this base-case scenario, although there is a dramatic rise in recrudescence infections, this is masked by the concurrent rise in new infections.

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Figure 8-6: Total number of patent infections showing the proportion due to recrudescence compared to new infections



8.3.2. Results of the sub-models

8.3.2.1. Severe infections, and deaths

In this section the outputs from the biological model are used in the clinical outcomes sub-model, to calculate the number of severe infections and deaths in each age group. In this base-case scenario, the inputs to make the calculations were as follows:

- Likelihood of severe malaria in a treated symptomatic infection in a non-immune host, in the absence of drug resistance, (0.05). 5%!
- Likelihood of severe malaria in an untreated symptomatic infection, in a non-immune host (0.15). This is the likelihood of severe malaria in symptomatic infections when drug resistance has reached 100% and the drug is considered completely ineffective.
- The mortality rate was fixed in relation to the severe rate at 20%.

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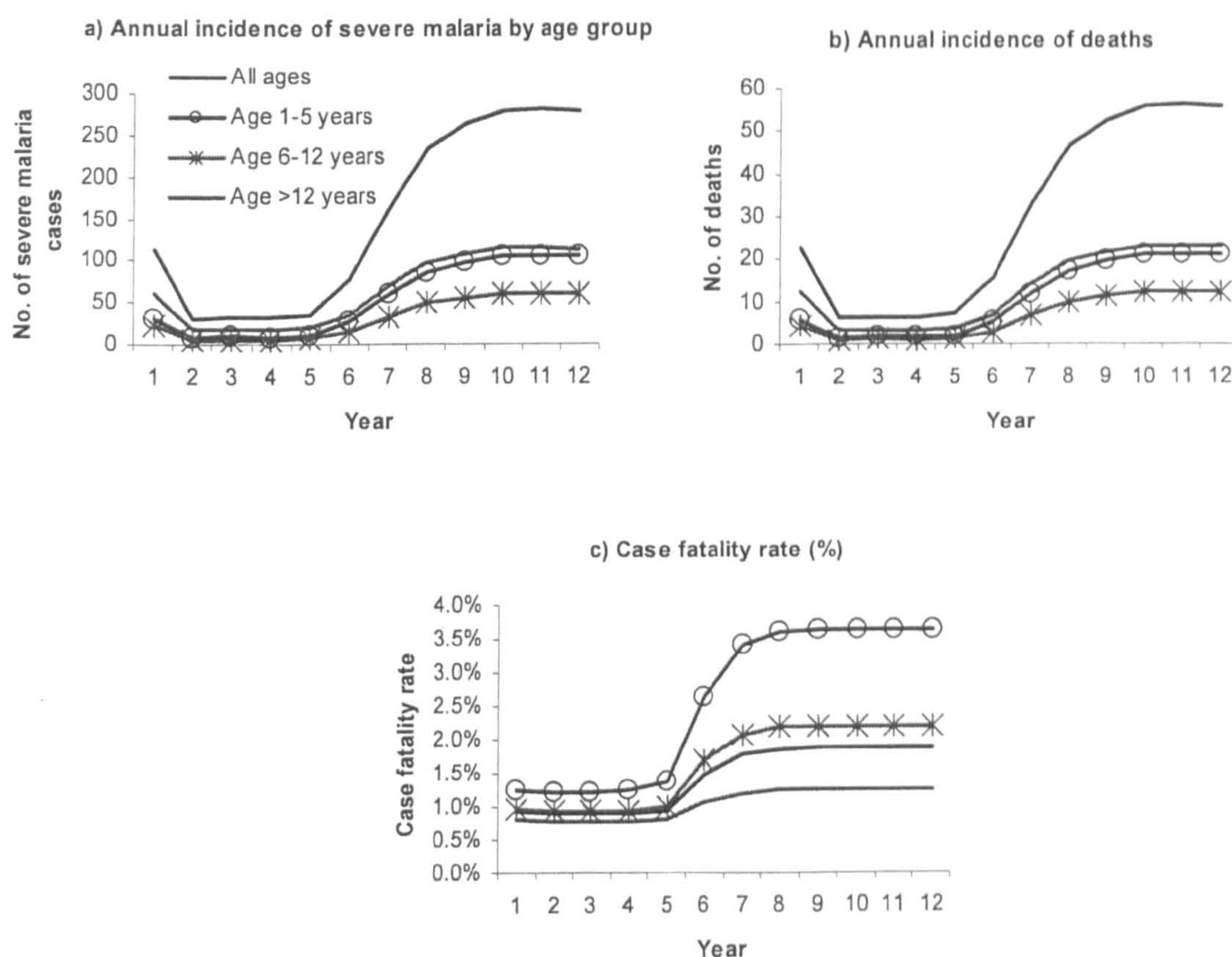
Given these inputs, the number of severe patients by age group is generated, as shown in Figure 8-7. Initially, when resistance is first introduced into the model at the end of year 2, the incidence of severe malaria and mortality is low, 33 severe cases and seven deaths, out of around 700 cases. As resistance rises, so does the likelihood of severe malaria and death so that when resistance to drug A has reached almost 100% six years later, the number of severe cases and deaths has gone up by seven-fold to 234 and 47 respectively.

The increase in severe infections is due not only to the increase in recrudescence but also to the increased likelihood of developing severe malaria as drug resistance rises and because of the absolute increase in the number of new cases.

In this setting adults contribute almost the same numbers of severe cases as the youngest age group. This is because although there are more infected adults than children, because adults are assumed to have a degree of clinical immunity, they are less likely to develop severe malaria.

This is reflected in the case fatality rate which shows that the rate in the youngest age group is almost double that in adults.

Figure 8-7: Annual incidence of a) severe cases by age group, b) deaths and c) case fatality rate by age group



8.3.2.1. Costs

In this section the costs in the base-case scenario are presented. As explained in the methodology section, costs are presented in a number of different ways to address the needs of different audiences. From the point of view of donors and malaria control programmes, it is mainly the incremental costs of combination therapy compared to monotherapy that are of interest. This includes the cost of drugs and any additional delivery costs. The cost of the monotherapy drug therefore forms the base cost with which the incremental cost of switching to combination therapy can be compared. It is this difference in drug costs that forms the numerator in the cost-effectiveness ratio in terms of the incremental cost per case, death or DALY averted.

In order to quantify the benefits in monetary terms, the total cost of malaria to patients and providers is also calculated. In this base-case scenario it is assumed that all patients go to the formal sector. The direct costs to the provider of the initial infection include the costs of consultation and of diagnosis. The direct costs of treatment failures, borne by the provider are those associated with recrudescence and severe infections, which include the cost of

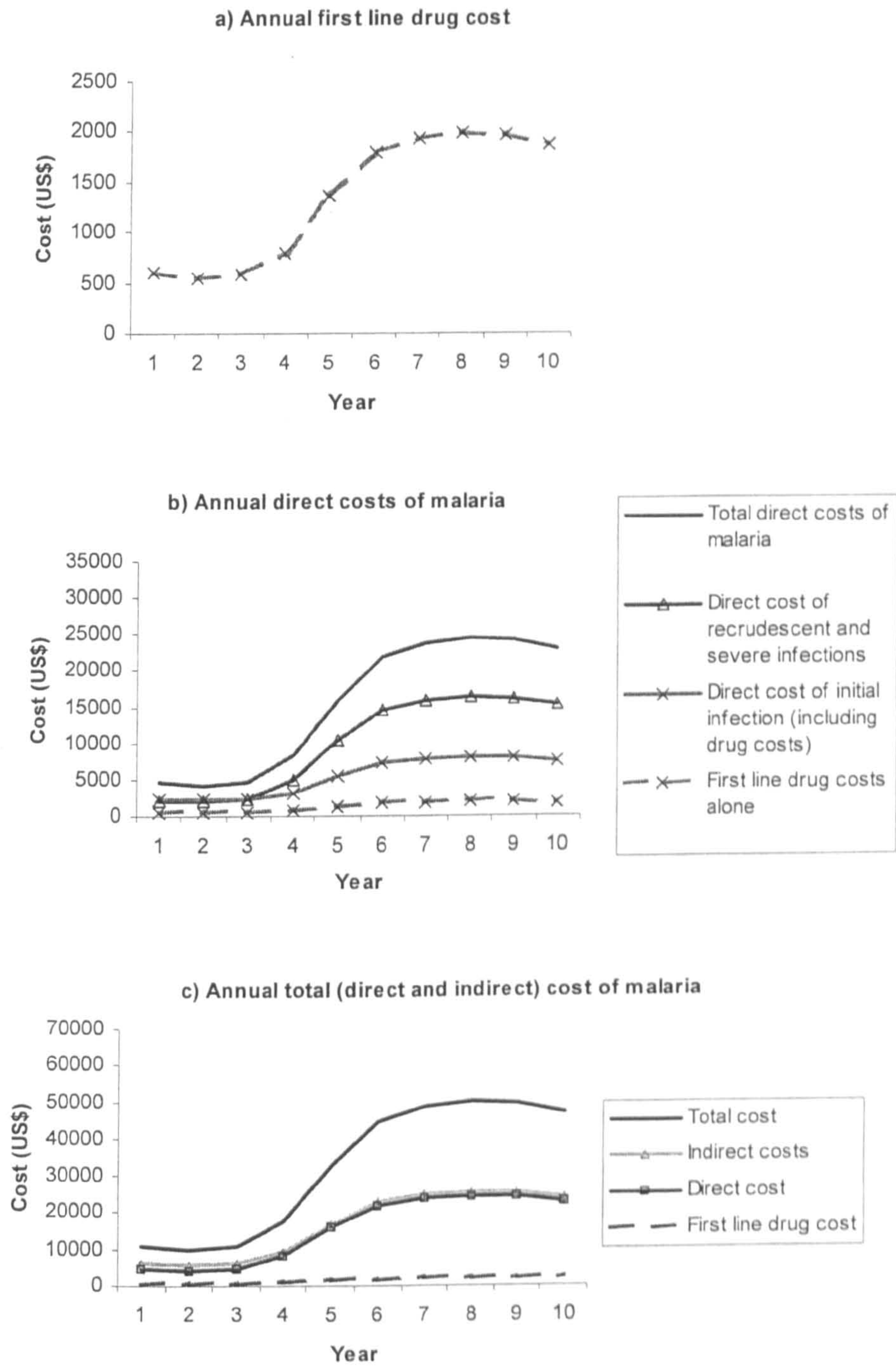
hospitalisation. The direct costs borne by households are therefore the cost of transport and food and other consumables. In addition they bear the indirect cost due to loss of productivity.

For clarity, from hereafter in the presentation of the results, the first 2 years of the biological model simulations are not shown in the figures. This is because, during this time, the model is reaching a steady state in the absence of drug resistance and is the same for all scenarios.

In the base-case scenario, the annual cost of drugs rises in line with the epidemic increase in new cases as shown in Figure 8-8a. After drug resistance reaches 100%, there is no further increase in the annual incidence of new cases and the cost of the first-line drug therefore also plateaus. On close inspection, the costs in fact appear to start to fall. This is because costs are discounted.

Figure 8-8b shows the overall direct cost of treatment. It can be seen that initially the cost of treating new infections is higher than the cost of severe and recrudescient infections. However, the latter rises steeply with increasing drug resistance so that by year 3, the cost of treating recrudescient infections and severe infections is the same as the cost of treating new infections and thereafter exceeds it. Once drug resistance has reached these high levels, the cost of the first-line drug represents only a very small proportion of the overall direct treatment costs. In Figure 8-8c the total costs, inclusive of indirect costs, are presented. Taking a societal perspective, the incremental cost of drugs is comparatively insignificant in comparison to the total cost of treatment failure.

Figure 8-8: Annual costs in the base-case scenario (continued use of monotherapy)



8.4. Monotherapy versus combination therapy

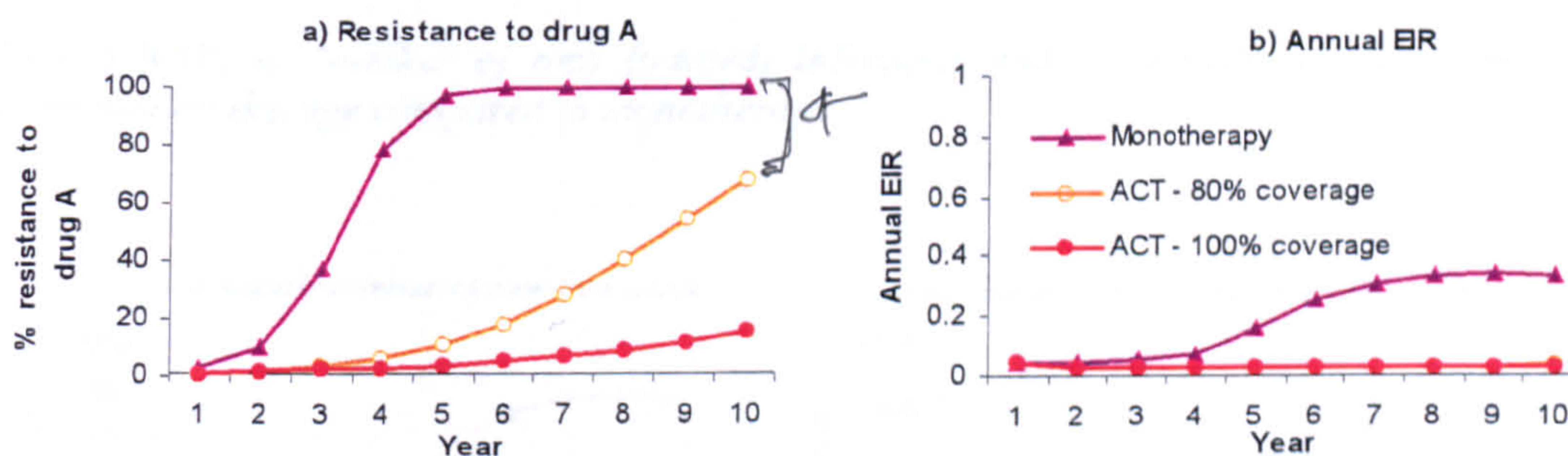
In this section, the base-case scenario of the continued use of mefloquine (drug A) is compared to a switch to the ACT of blister-packaged artesunate and mefloquine (drug AB). It is assumed that the switch to combination therapy occurs when resistance to drug A is introduced at a level of 1%. It is also assumed that the switch is made instantaneously and that drug resistance to artesunate (drug B) does not arise. The results from scenarios with coverage rates of 100% and 80% are both shown in order to compare an “ideal situation” with a more achievable coverage rate.

8.4.1. Outcomes

8.4.1.1. Drug resistance and number of infections

In the base-case scenario we saw that the model predicts that once drug resistance is introduced, it spreads rapidly with the continued use of that drug on its own. The impact that combination therapy has on this rate of spread is one of the key model outcomes and is shown in Figure 8-9a.

Figure 8-9: a) Resistance and b) Annual EIR with ACT compared to monotherapy



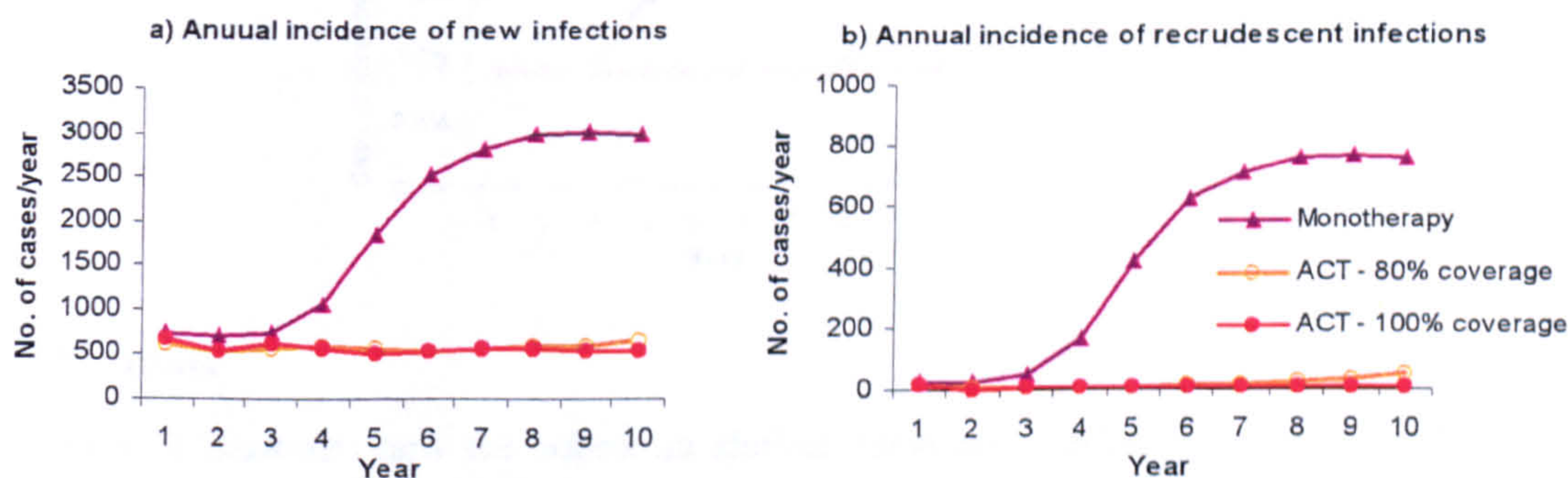
The results in this scenario suggest that when an ACT is deployed at 100% coverage, there is a dramatic slowing in the spread of resistance. Under the ideal conditions in this example, by year 10 drug resistance to drug A has only reached 15%. However, under slightly more realistic conditions, with 80% coverage, the use of combination therapy appears to have much less effect on the spread of drug resistance to the monotherapy, so that by year 6 it has already reached 20% and by year 10 it has reached 75%. The effect of different coverage rates is explored in more detail later in the scenario analysis.

In a relatively low transmission setting such as this, it might be expected that widespread use of an efficacious therapy would result in a decrease in transmission intensity and a decrease in the number of new infections. This is confirmed in this analysis that suggests that a switch to the ACT does effectively prevent the epidemic increase in the incidence of malaria seen with the

continued use of monotherapy. At 80% ACT coverage, despite the rise in drug resistance, annual incidence remains low with around 700-750 infections per year (compared to 650-700 with 100% coverage). This is because most resistant infections that are treated with the combination therapy are still cured, with a maximum failure rate of 30%, and because only 20% of resistant infections are exposed to monotherapy. Therefore, initially there is only a very small increase in recrudescence infections and infectiousness in the population (Figure 8-10b).

In these examples, the maintenance of infection in the population is largely due to the new “migrant” infections introduced from outside. This is allowed for because during the exploratory phase of running the model, it was found that in low transmission settings, a constant input of new infections was required in order to maintain transmission. The rate at which this was assumed to occur in these scenarios was varied stochastically between 3-7% of the total population per day. Although this may seem unrealistic, there is evidence that in areas of low transmission, migrants from high transmission settings or individuals travelling between areas of high transmission and low transmission are responsible for a significant proportion of infections (Gu, Killeen et al. 2003; Craig, Kleinschmidt et al. 2004; Zhou, Sirichaisinthop et al. 2005).

Figure 8-10: a) Number of new (treated) infections and b) recrudescence infections with combination therapy compared to monotherapy



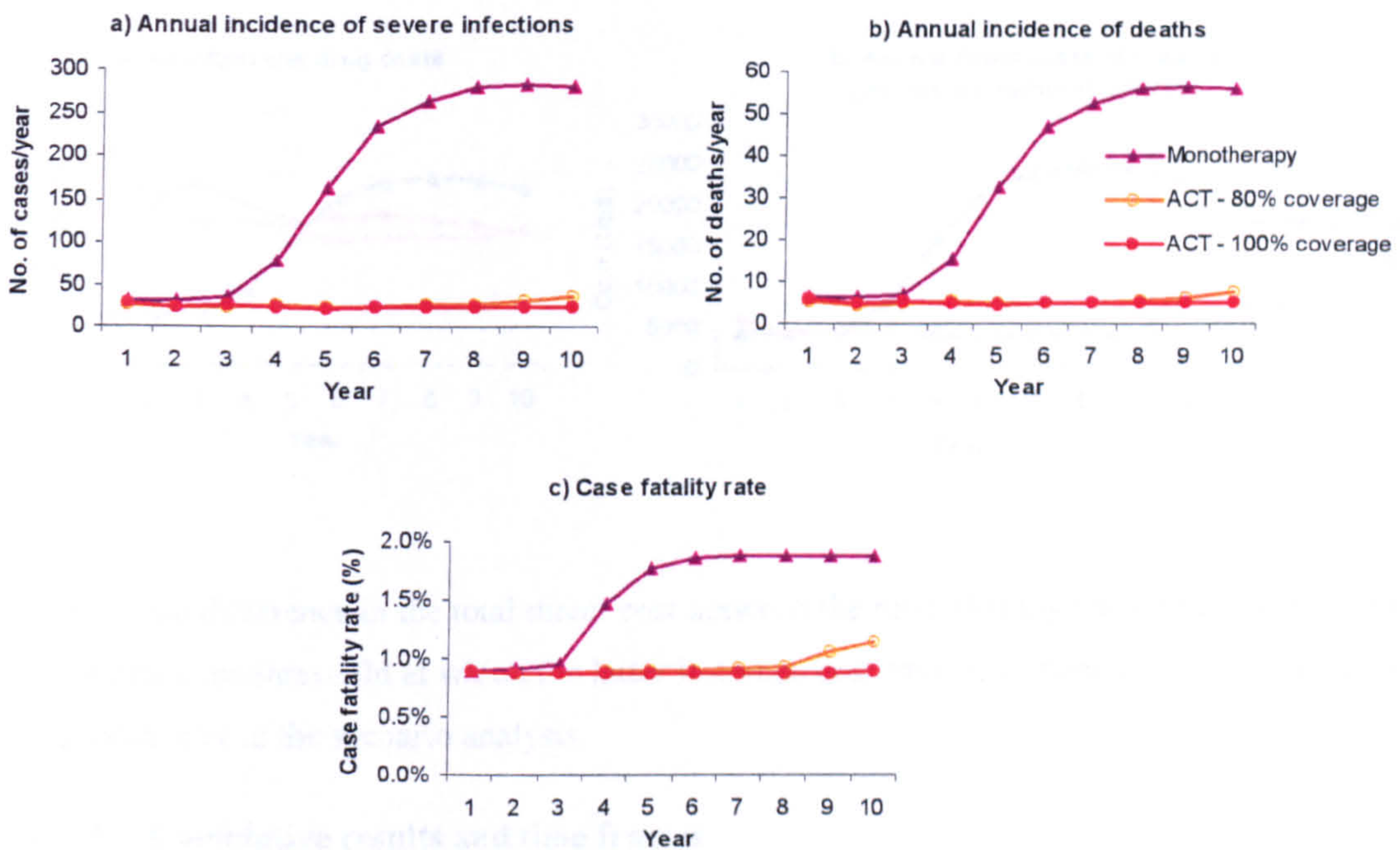
In a high transmission setting, only a small proportion of patent infections are symptomatic and treated and altering their transmissibility would therefore be expected to have little impact on the overall transmission intensity (Figure A10-2) and less impact of clinical outcomes (Figure A10-4). Depending on the proportion of the human population with drug A presumptively and with inhibitory levels of the drug in their blood stream, resistance to drug A may, the introduction of ACT for the treatment of symptomatic infections may have little impact on the increase in drug resistance to drug A.

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8.4.1.2. Severe malaria and deaths

The number of severe cases and deaths averted by the use of combination therapy compared to monotherapy directly reflects the reduction in the number of cases of recrudescence infections due to use of an increasingly failing drug. As shown in Figure 8-11, with 100% ACT, the number of severe cases and deaths remains at around 25 and five respectively with a case fatality rate of around 1%. With 80% coverage, the number of severe cases and deaths remains stable for the first eight years but then begins to rise, so that by the end of year 10 there are around 39 severe cases and eight deaths.

Figure 8-11: Number of a) severe cases and b) deaths with combination therapy compared to monotherapy



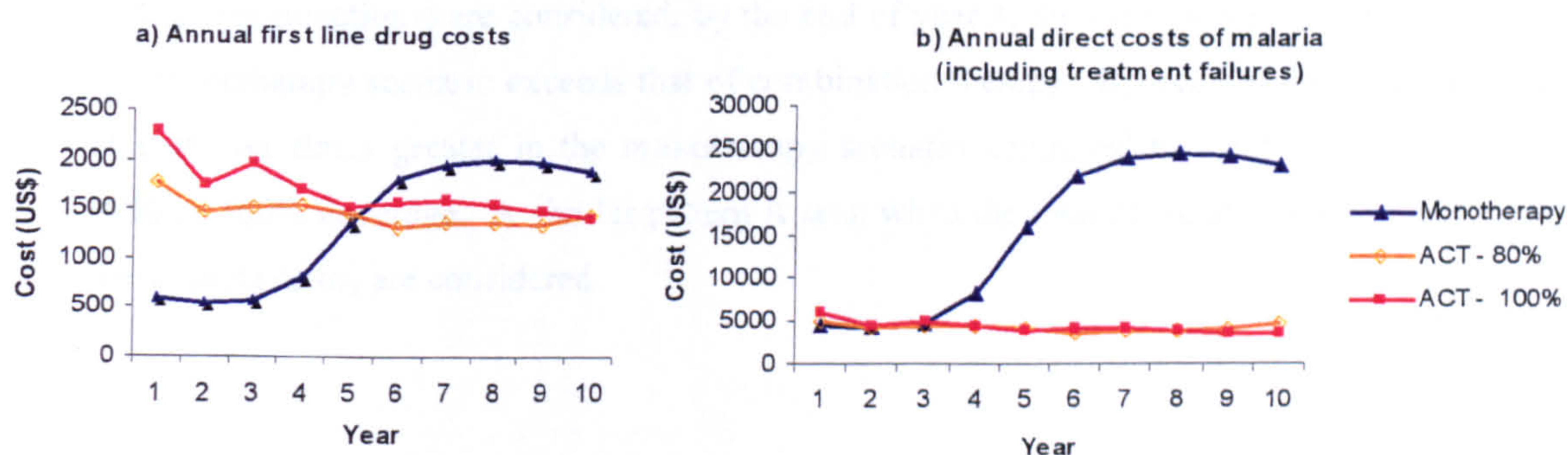
8.4.2. Costs

Figure 8-12 illustrates how the effects on clinical outcomes translate into costs. In the first figure, the annual cost of the first-line drugs is compared and shows that initially the annual drug costs of combination therapy exceed that of monotherapy. However, the use of ACT averts the epidemic increase in cases seen with the monotherapy and the associated increase in drug costs and therefore by year 5, the annual drug costs are lower in the ACT scenario.

The next figure compares the total annual direct cost of malaria, including the costs of treating treatment failures and severe infections. It is only for the first two years, that the overall annual direct costs in the combination therapy scenario are greater than in the monotherapy scenario. After this, the costs in the monotherapy scenario increase rapidly whilst the costs in the combination therapy scenarios remain static. Thus, by year 10 they differ by almost five-fold

(Figure 8-12). In this example, the direct cost of treating severe malaria in an adult is assumed to be \$61.19 and the cost of an adult course of combination therapy of artesunate and mefloquine is assumed to be \$3.77 compared to \$1.11 for mefloquine, i.e. an incremental cost of \$2.69 per treatment. The incremental cost of treating one severe infection is therefore equivalent to the incremental cost of 23 treatments ($61.19/2.69$). Even in the absence of any effect on the incidence of malaria, switching to combination therapy is cost saving if it averts at least one in 23 severe infections. When the effects of ACT also include a reduction in the number of cases, as in this example, the threshold is lower.

Figure 8-12: Annual direct costs of a) First-line drug alone⁷¹ b) All direct treatment costs for malaria



Clearly the difference in the total direct cost between the monotherapy and combination therapy determines the threshold at which the latter becomes cost saving, if indeed it does at all. This is explored later in the scenario analysis.

8.4.3. Cumulative results and time frames

So far, the outcomes and costs have been expressed in terms of annual rates. This allows us to compare easily the relative *changes over time* between the alternatives. However, the presentation of results in this way does not easily allow for a comparative summary measure of costs and outcomes, which can be used to compare cost-effectiveness over different time frames. The changes in costs and outcomes over time are non-linear and taking a single annual measure at any particular time does not give any information about outcomes and costs prior to, or after this snapshot in time. Therefore for a given time period, in order to provide a summary measure and to compare cost-effectiveness, the total (i.e. annual cumulative) outcomes and costs in that period are compared.

⁷¹ The small increase in drug costs at year 3 with 100% ACT coverage is because by chance there were more “migration” cases in that year. This is not apparent in the earlier figure because of the scale chosen.

The cumulative outcomes are shown in Figure 8-13 and in Table 8-3. Using a 10-year time frame, the cumulative number of new cases in the monotherapy scenario, is more than three times greater than in the combination therapy scenarios, and the cumulative number of severe infections, deaths and DALYs is almost seven times greater.

Table 8-3 shows the cumulative costs of the first-line drugs alone. Unlike the comparison of annual costs, the cumulative cost of combination therapy remains more than that of monotherapy. However, the difference gradually decreases over time because of the larger number of doses needed in the monotherapy scenario, so that by year 10 the cumulative drug cost of combination therapy is \$16,905 compared to \$13,500 with monotherapy.

When the cumulative overall direct costs of treating malaria (including the costs of recrudescence and severe infections) are considered, by the end of year 4, the cumulative cost of treatment in the monotherapy scenario exceeds that of combination therapy. By year 10 the direct costs are almost four times greater in the monotherapy scenario compared to combination therapy, at 80% or 100% coverage. A similar pattern is seen when the total cumulative costs, inclusive of the indirect costs, are considered.

Figure 8-13: Cumulative results comparing outcomes with monotherapy compared to combination therapy

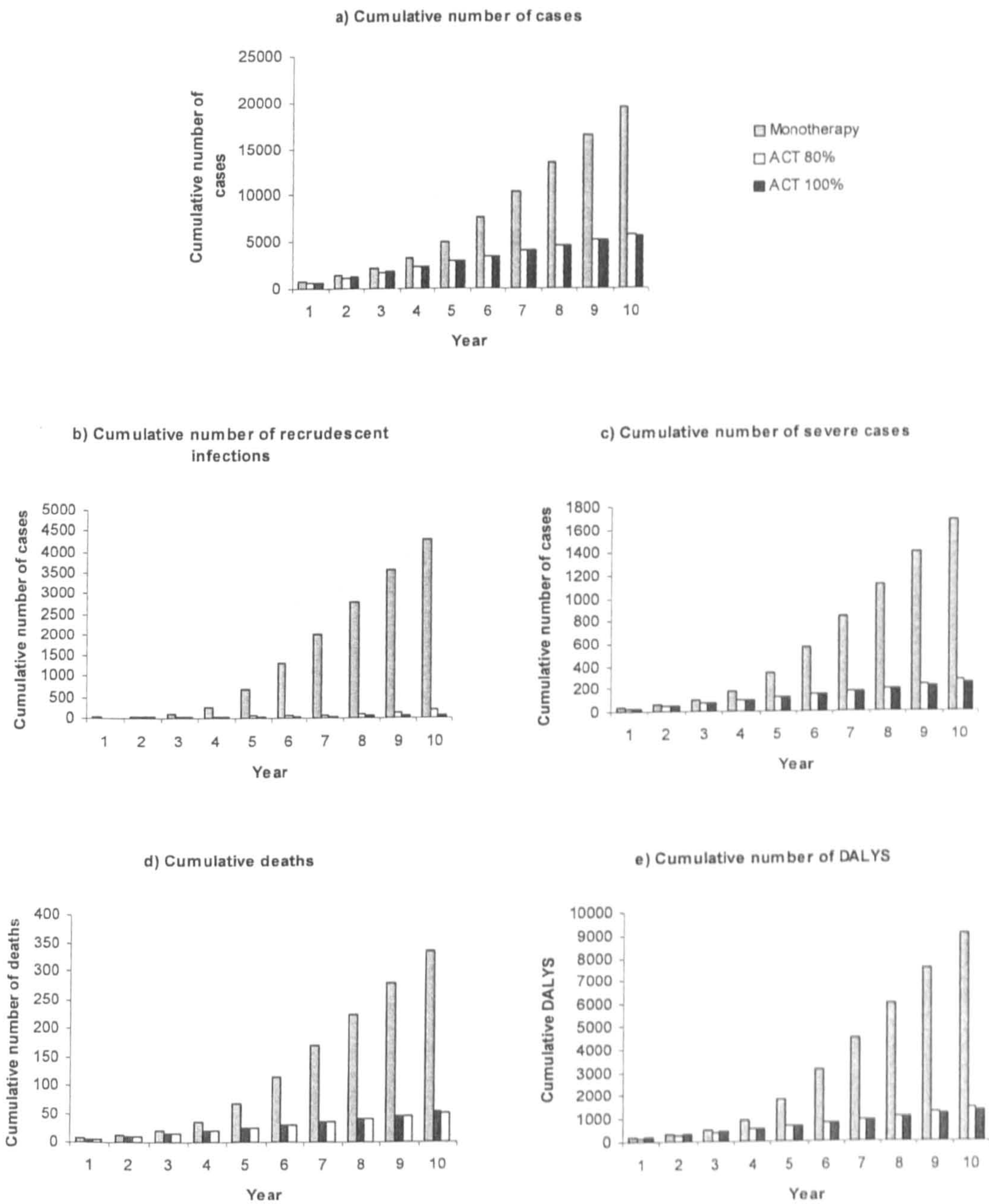
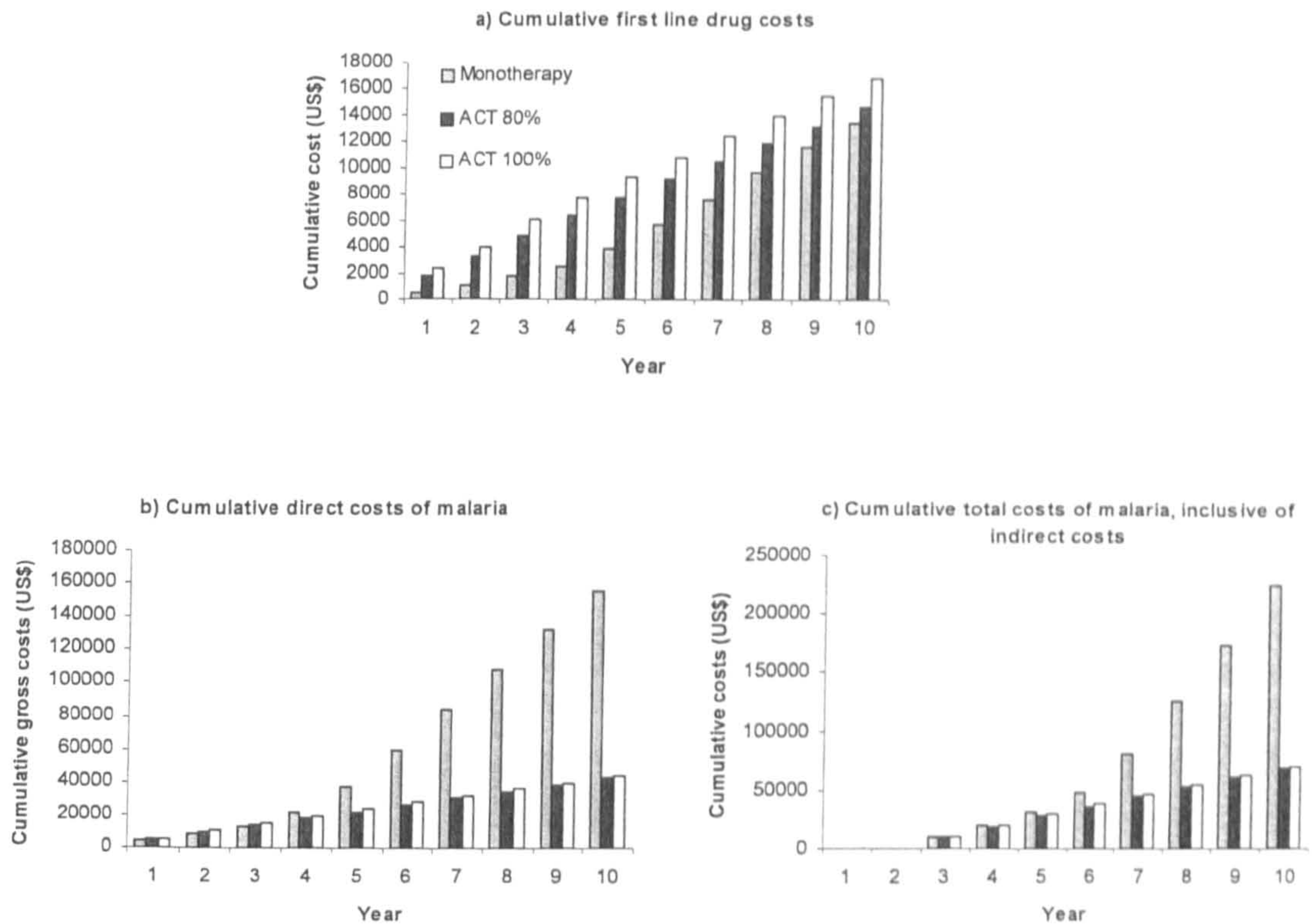


Figure 8-14: Cumulative cost of first-line treatment



8.4.4. Cost-effectiveness

So far, the benefit of using combination therapy has been expressed in monetary terms by attaching costs to the treatment of malaria including recrudescence and severe infections, so that the total costs of the alternatives could be compared. In this section, the cost-effectiveness of combination therapy is explored by comparing the incremental cost of ACT to monotherapy, and the incremental effect in health outcomes in terms of cases, failures, deaths or DALYs averted, using the cumulative results as explained above. The cumulative incremental cost-effectiveness at the end of one, five and 10 years is presented in the next set of tables and figures, in order to explore the effect of the time frame of the analysis on the cost-effectiveness of 100% combination therapy.

In each example, the numerator is the incremental cost of combination therapy compared to monotherapy and the denominators are the different outcomes of interest. As discussed in the background, the perspective taken determines the choice of the outcome and time frame of the analysis. From the perspective of the patient or their carer and the health-care worker, the interest is in the immediate outcome, and therefore the cost per cure or the cost per severe outcome averted is appropriate. From the perspective of the Ministry of Health and donors, the cost-effectiveness compared to other health interventions will be relevant, in terms of the cost

per death or DALY averted. By taking a more long-term perspective, all these outcomes capture the externality benefits due to delayed drug resistance and reduced transmission.

Figure 8-15 and Table 8-3 show the change in cumulative incremental cost-effectiveness over time. It can be seen that the longer the time frame used, the more cost-effective ACT becomes. It can also be seen that most of the gain is seen in the first five years. This is because it is within this period that resistance to drug A rises rapidly when it continues to be used on its own, a rise that is avoided by the use of combination therapy. The use of ACT therefore averts the year-on-year increase in the consequences of drug resistance. By year 6, resistance saturates and there is no further increase in cases or failures. In this example, the cumulative incremental cost per DALY averted at one year is \$129, at 5 years \$4.7 and at 10 years \$0.4.

If the incremental cost of drugs is replaced by the incremental total costs as the numerator for the cost-effectiveness ratio, then ACT are clearly much more cost-effective than monotherapy even with a short time frame. After one year the total direct cost per DALY averted is \$105.7 (-1383.5/129.0) and the total cost inclusive of indirect cost, per DALY averted is \$70.7 (925/129.1). By year 5, because the total costs are less in the ACT scenario compared to the monotherapy scenarios, ACTs are clearly dominant because they are both more effective and cost saving.

Figure 8-15: Cumulative cost-effectiveness of combination therapy (at 100% coverage) compared to monotherapy over time

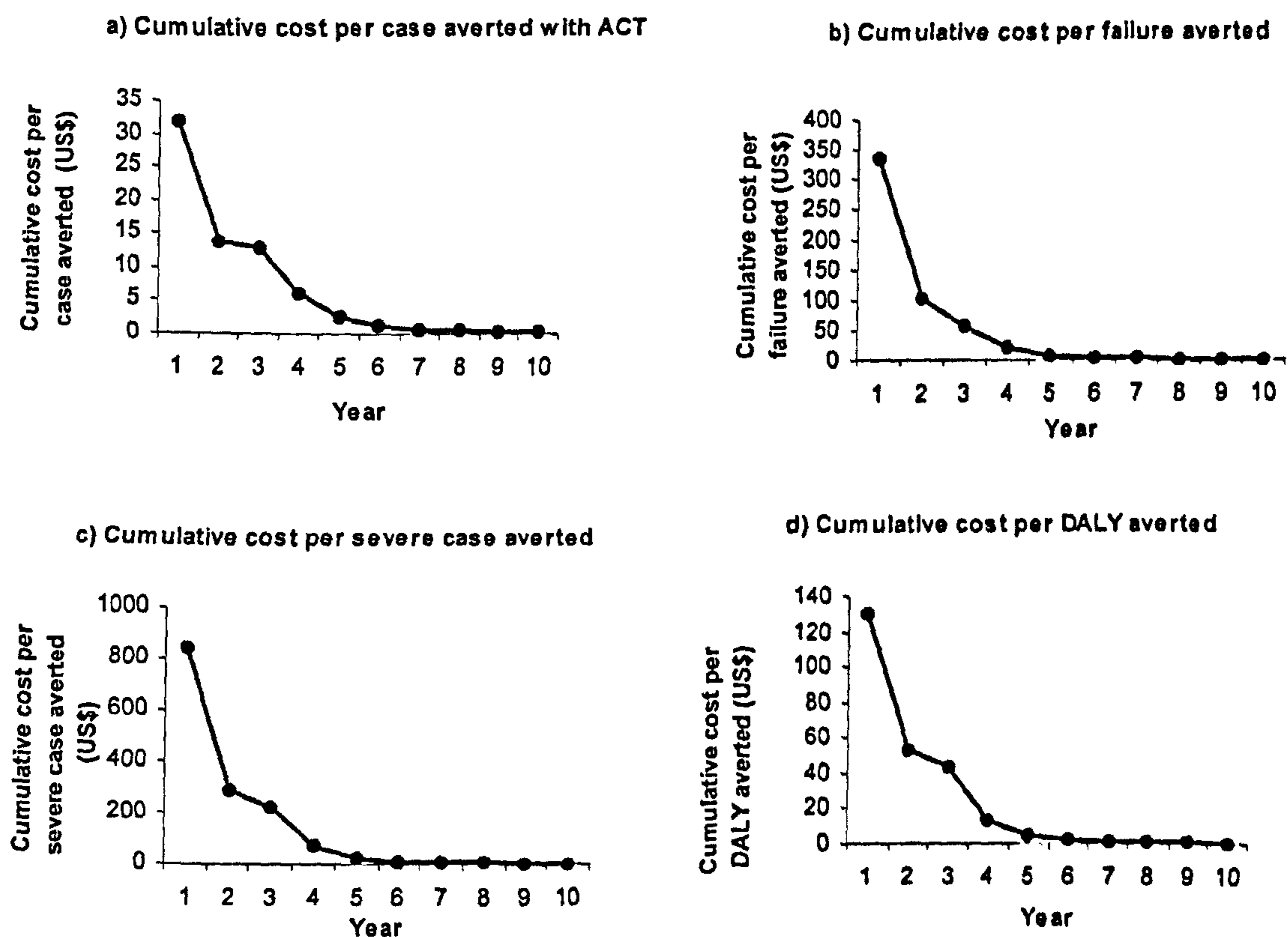


Table 8-3: Cumulative effects, costs and cost-effectiveness of combination therapy (100%) compared to monotherapy at 1, 5 and 10 years
Cumulative costs and effects

	After 1 year			After 5 years			After 10 years		
	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)
Number of treated cases	739	686	-53	5,107	2,931	-2,176	19,438	5,729	-13,709
Number of recrudescences	21	16	-5	688	38	-650	4,316	77	-4,239
Number of severe cases	33	31	-2	342	129	-213	1,682	252	-1,430
Number of deaths	7	6	-1	68	26	42	337	50	-287
Number of DALYs	175	162	13	1,828	683	-1,145	9,026	1,337	-7,689
Cost of drug (US\$)	607	2,296	1,689	3,916	9,275	5,359	13,500	16,905	3,405
Direct cost of malaria (US\$)	4,622	6,005	1,383	37,793	24,104	-13,689	155,267	43,949	-111,318
Total cost (US\$) (indirect and direct)	10,636	11,561	925	81,485	46,345	-35140	321,291	84,508	-236,783
Incremental cost of drug per consequence averted									
Cost of drug (US\$) per	After 1 year			After 5 years			After 10 years		
- case averted		31.9			2.5			0.2	
- recrudescence averted		337.9			8.2			0.8	
- severe infection averted		664.1			25.1			2.4	
- death averted		1,859.0			125.5			11.9	
- DALY averted		129.1			4.7			0.4	

8.5. Sensitivity analysis

Sensitivity and scenario analysis were carried out to examine the effect of uncertainty of parameter inputs and the effects of varying inputs on the model outputs. The terms sensitivity analysis and scenario analysis are used to describe analyses that are undertaken with different objectives. The term “sensitivity analysis” is used to test the robustness of the model to uncertainties in the model inputs and assumptions within a range of possible values. The sensitivity analysis of the biological model was undertaken by WP, and a summary of the results is provided in Annex 11 and briefly discussed in the section below. In this thesis the focus of the sensitivity analysis is limited to uncertainties in the parameters and assumptions made in the sub-models. Scenario analysis, on the other hand, is used to describe the outcomes when the changes in the value of the inputs represent different settings or policy choices, for example a different choice of drug. The scenarios explored in the next section are:

- Different costs
- Different coverage rates with ACT
- Switching from drug A to drug BC (instead of drug AB) at different levels of resistance to drug A
- Cambodian scenarios with different delivery interventions

8.5.1. Sensitivity analysis of the biological model

The sensitivity analysis undertaken by WP involved 5000 simulations each for four scenarios, where the ACT was assumed to be drug AB:

- Low transmission (mean vectorial capacity of 0.1) - Low ACT coverage (10%)
- Low transmission (mean vectorial capacity of 0.1) - High ACT coverage (85%)
- High transmission (mean vectorial capacity of 15) - Low ACT coverage (10%)
- High transmission (mean vectorial capacity of 15) - High ACT coverage (85%)

As one simulation of the model for 12 years takes 2½ hours to run, the sensitivity analysis required a large amount of time and computational resources. At the beginning of each simulation, values for all input parameters were randomly selected from a range of values with the probability of selection dependant on a defined distribution (e.g. uniform, normal or log normal). The results of the 5,000 simulations for each scenario were then analysed by partial rank correlation co-efficient analysis, which ranks the parameters in order of influence on different outcomes for the model at different time points. The model outcomes included were

the level of drug resistance, the prevalence of patent infections, the percentage of infections that recrudescence and the percentage of patent infections that are treated. For each outcome the average result in terms of mean and median and the degree of variability in terms of standard deviation were also output. The detailed table of results are in Annex 11. The results for a low transmission setting are summarised in Table 8-4 and discussed briefly here.

For all model outcomes, the transmission intensity as measured by the vectorial capacity (VC) was the single most important parameter in determining the values at five and 10 years. For the level of drug resistance with the continued use of monotherapy, at 10 years, VC was the only parameter to which the model was sensitive. At five years the gametocyte switching rate, the proportion of the population with residual drug levels (i.e. chemoprophylaxis), and treatment rate were also important. With combination therapy, the coverage rate, the failure rate in infections resistant to drug A and treated with combination therapy relative to the failure rate with monotherapy, and the duration of untreated infections, were also important in determining the level of drug resistance reached.

The prevalence of patent parasitaemia was sensitive mainly to the gametocyte-switching rate, the level of susceptibility to infection in a non-immune host and the proportion of the population with residual drug levels. The treatment rate and duration of untreated infection were also important in the combination therapy scenario.

For the rate of recrudescence infections, unsurprisingly the failure rates in drug resistant infections treated with monotherapy and with combination therapy emerge as important parameters, as does the ACT coverage rate.

This sensitivity analysis helps us to understand the relative influence of the values of different parameters on model outcomes, and may therefore indicate in reality what factors are most likely to influence the spread of drug resistance, clinical outcomes and the transmission of malaria. It also indicates the sensitivity of the model to parameters for which there is much uncertainty, and for which more accurate data are required before conclusions from the model can be made with more confidence. However, this sensitivity analysis does not tell us about the absolute relationships. Therefore it is not possible to say, for example, that an increase in a certain input by $x\%$ results in an increase in the rate of resistance by $y\%$. This would be useful for specific parameters that represent factors that can be altered by interventions or for examining specific scenarios. This is done in the scenario analysis by taking the most policy relevant of these parameters, the ACT coverage rate, and varying it on its own to examine the effect on model outcomes.

Table 8-4: Summary of sensitivity analysis of biological model undertaken by WVP for a low transmission setting. The table shows parameters with the highest partial rank correlation coefficients of input parameters with actual values in brackets

Output	Monotherapy	Combination therapy
Drug resistance at 5 years	<ul style="list-style-type: none"> • Vectorial capacity (0.7) • Treatment rate (0.2) • GSR for monotherapy (0.2) • Proportion with residual drug (0.2) 	<ul style="list-style-type: none"> • Vectorial capacity (0.6) • GSR for monotherapy (0.2) • Relative failure rate in drug resistant infection treated with ACT (0.2) • Proportion with residual drug (0.2) • ACT coverage (-0.2) • Duration of untreated infections (-0.2)
Drug resistance at 10 years	<ul style="list-style-type: none"> • Vectorial capacity (0.3) 	<ul style="list-style-type: none"> • Vectorial capacity (0.6) • Proportion with residual drug (0.3) • GSR for monotherapy (0.2) • Relative failure rate in drug resistant infection treated with ACT (0.2) • ACT coverage (-0.2) • Duration of untreated infections (-0.2)
Prevalence of patent infections at 5 years	<ul style="list-style-type: none"> • Vectorial capacity (0.7) • Host susceptibility (0.2) • GSR for monotherapy (0.2) • Proportion with residual drug (0.2) 	<ul style="list-style-type: none"> • Vectorial capacity (0.7) • Host susceptibility (0.2) • GSR for monotherapy (0.2) • Duration of untreated infections (-0.2) • Treatment rate (-0.2)
Prevalence of patent infections at 10 years	<ul style="list-style-type: none"> • Vectorial capacity (0.7) • Host susceptibility (0.2) • GSR for monotherapy (0.2) • Relative parasite density in untreated infections (0.2) • Relative parasite density in recrudescence infections (0.2) 	<ul style="list-style-type: none"> • Vectorial capacity (0.7) • Host susceptibility (0.2) • GSR for monotherapy (0.2) • ACT coverage (-0.2)
% recrudescence at 5 years	<ul style="list-style-type: none"> • Vectorial capacity (0.7) • Host susceptibility (0.2) • GSR for monotherapy (0.2) 	<ul style="list-style-type: none"> • Vectorial capacity (0.4) • Relative failure rate in drug-resistant infection treated with ACT (0.4) • ACT coverage (-0.3) • Proportion of population with residual drug (0.2)
% recrudescence at 10 years	<ul style="list-style-type: none"> • ACT coverage rate (-0.5) • Vectorial capacity (0.4) • Failure rate in drug-resistant infection treated with monotherapy (0.4) 	<ul style="list-style-type: none"> • Relative failure rate in drug-resistant infection treated with ACT (0.6) • Vectorial capacity (0.4) • ACT coverage rate (-0.3)
% treated infections at 5 years	<ul style="list-style-type: none"> • Vectorial capacity (0.4) • Treatment rate (0.4) 	<ul style="list-style-type: none"> • Vectorial capacity (0.5) • Treatment rate (0.5) • GSR for monotherapy (0.2)
% treated infections at 10 years	<ul style="list-style-type: none"> • Treatment rate (0.4) • Vectorial capacity (0.3) 	<ul style="list-style-type: none"> • Vectorial capacity (0.6) • Treatment rate (0.4) • GSR for monotherapy (0.2)

GSR = Gametocyte Switching Rate

8.5.2. Sensitivity analysis of inputs for the sub-models

The sensitivity analysis of the sub-models was undertaken to explore the effect of uncertainties in the parameters used to calculate severe malaria and mortality, and the effect of different assumptions about discounting and disability-adjusted life years (DALYs). A simple approach was taken, in which only the parameter under question was varied, keeping all other parameters unchanged.

8.5.2.1. Severe malaria and mortality rates

As discussed in the previous chapter, there was considerable uncertainty about the maximum likelihood of severe malaria in a non-immune host, with and without drug resistance, as well as the mortality rate of severe malaria. The minimum and maximum estimates obtained from literature were tested in the sensitivity analysis. The results suggest that the cost-effectiveness of combination therapy compared to monotherapy is not very sensitive to this uncertainty. The cost per DALY averted varies from \$3.1 to \$6.7 at five years and from \$0.3 to \$0.6 at 10 years (Table 8-5).

8.5.2.2. DALYs and discounting

In the base-case scenarios, costs and DALYs were discounted at 3%, and DALYs were not weighted for age. The effects of *not* discounting DALYs and of adding age weighting were therefore both explored (Table 8-6). Both changes result in a slight decrease in the cost per outcome averted making ACT more cost-effective. The effect of not discounting reflects the importance of the greater difference in outcomes between the two scenarios in later years.

There is little effect of the discounting of costs on the cost-effectiveness of combination therapy so that at five years, the use of undiscounted cost results in a cost per DALY averted of \$5.0 compared to \$4.7 and at 10 years, the cost per DALY averted remains at \$0.4 whether or not costs are discounted.

Table 8-5: Sensitivity analysis of input values of likelihood of severe malaria and death with 5 and 10-year time frames

Input parameters				Outcomes at 5 years						
Likelihood of severe malaria in non-immune host	Likelihood of mortality if severe malaria	Case fatality rate in non-immune host		Severe cases		Deaths		DALYs		Incremental cost of drug averted per DALY (US\$)
		Minimum (no resistance)	Maximum (100% resistance)	Mono-therapy	ACT	Mono-therapy	ACT	Mono-therapy	ACT	
Baseline (0.05)	Baseline (0.2)	0.01	0.03	342	129	68	26	1,828	683	4.7
0.02	Baseline	0.004	0.03	214	65	43	13	1,149	349	6.7
0.1	Baseline	0.02	0.03	556	234	111	47	2,959	1,240	3.1
Baseline	Baseline	0.01	0.02	300	121	60	24	1,599	643	5.6
Baseline	Baseline	0.01	0.04	256	73	51	15	1,788	513	4.2
Baseline	0.1	0.005	0.015	342	129	34	13	936	351	9.2
Baseline	0.3	0.015	0.045	342	129	103	39	2,719	1,016	3.1
Outcomes at 10 years										
Baseline (0.05)	Baseline (0.2)	0.01	0.03	1,682	252	337	50	9,026	1,337	0.4
0.02	Baseline	0.004	0.03	1,143	128	229	26	6,167	683	0.6
0.1	Baseline	0.02	0.03	2,581	459	516	92	13,791	2,426	0.3
Baseline	Baseline	0.01	0.02	1,421	237	284	47	7,622	1,258	0.5
Baseline	Baseline	0.01	0.04	1,404	143	281	29	9,776	1,003	0.4
Baseline	0.1	0.005	0.15	1,682	252	168	25	4,618	686	0.9
Baseline	0.3	0.015	0.45	1,682	252	505	76	13,434	1,987	0.3

Table 8-6: Sensitivity of the incremental cost-effectiveness of ACT compared to monotherapy to assumptions about DALYs

Handling of DALYs	Cost and cost-effectiveness of ACT at 5 years			Cost and cost-effectiveness of ACT at 10 years		
	DALYs		Cost of drug per DALY averted (US\$)	DALYs		Cost of drug per DALY averted (US\$)
	Monotherapy	ACT		Monotherapy	ACT	
Discounted and <i>not</i> age-weighted (baseline)	1,828	683	4.7	9,026	1,337	0.4
Discounted and age-weighted	2,381	898	3.6	11,702	1,757	0.3
Undiscounted and <i>not</i> age-weighted	3,604	1313	2.5	18,249	2,569	0.2

8.6. Scenario analysis

8.6.1. Different drug and treatment costs

Estimates for costs vary widely from country to country and between different settings and institutions. In the baseline comparison, the drug costs were based on those in Cambodia, where the monotherapy was mefloquine and the combination therapy was blister-packaged artesunate and mefloquine. Mefloquine however, is relatively expensive compared to other drugs currently being used as a monotherapy and therefore the cost of the combination therapy was only 3.4 times greater than the monotherapy. In most other settings, the monotherapy is chloroquine or sulfadoxine-pyrimethamine (SP), which cost around \$0.10 for an adult dose. Therefore, the difference in the cost of drugs was maximised, firstly, by using the highest estimated cost for the ACT of artesunate and mefloquine and the lowest estimated cost of mefloquine alone and secondly, by substituting the cost of SP and the combination of artesunate and SP, assuming that the outcomes are similar to the mefloquine and artesunate and mefloquine scenarios. The artesunate with SP combination was assumed to be the commercially available product and therefore the packaging costs were considerably lower, resulting in a lower incremental cost in switching from the monotherapy to the combination therapy. The cost of the artesunate with SP combination was assumed to be \$1.39 for an adult course, which is 14.5 times greater than the monotherapy. The cost of switching from SP to artemether-lumefantrine is explored later because this combination involves not only a difference in costs but in outcomes as well.

In addition, the impact on total annual direct costs of different patient and provider costs of treatment was also explored, using minimum and maximum estimates.

The results at 10 years are shown in Table 8-7. It can be seen, perhaps unexpectedly, that the cost-effectiveness of switching from the monotherapy to a combination therapy is not greatly affected by changing to the cost of SP and artesunate plus SP. This is because it is the absolute difference in cost between the monotherapy and combination that determines the incremental cost of the combination therapy and not the relative difference. In this case the absolute difference between the monotherapy and combination in the two scenarios is \$2.69 for mefloquine versus artesunate plus mefloquine and \$1.29 for SP versus artesunate plus SP.

When this cost difference between the monotherapy and combination therapy is maximised to \$5.55, that is 3.3 fold greater than in the base-case scenario, the cost-effectiveness falls⁷² by the same factor from \$0.4 per DALY averted to \$1.3 per DALY averted.

⁷² For clarification an "increase" in cost-effectiveness implies that something becomes more cost-effective i.e. more favourable, and a "fall" in cost-effectiveness implies the reverse.

Table 8-7: Scenario analysis of different total direct costs at 10 years

Scenario		Drug cost			Total direct cost of treating malaria			Incremental cost of drug per case averted	Incremental cost of drug per DALY averted
		Mono-therapy	ACT	Difference (ACT-mono)	Mono-therapy	ACT	Difference (ACT-mono)		
Drug costs	Non-drug costs								
Base-case (M \$1.11, Art+Mef \$3.77)	Base-case (OPD \$2.60, IPD \$64.2)	13,500	16,905	3,405	155,267	43,949	-111,318	0.2	0.4
Maximum difference (M \$1.05, Art+Mef \$6.60)	Base-case	12,784	22,570	9,786	154,551	49,614	-104,937	0.7	1.3
SP versus Art +SP (SP\$0.10, Art+SP \$1.39)	Base-case	1,169	5,416	4,247	142,936	32,461	-110,475	0.3	0.6
Base-case	Minimum (OPD \$0.78, IPD \$12.1)	13,500	16,905	3,405	3,213,153	567,767	-2,645,386		
Base-case	Maximum (OPD \$15, IPD \$2,192.2)	13,500	16,905	3,405	4,4232	22,050	-22,182		

OPD = Outpatients

IPD=Inpatients

Art = Artesunate

Mef=mefloquine

Mono = Monotherapy

Varying the direct costs of malaria between minimum and maximum values results in the cumulative direct costs saved by using combination therapy varying from \$22,182 to \$264,586 or \$2.2 versus \$264.6 per capita. This compares to cost-savings of \$11.1 per capita using the baseline values.

8.6.2. Coverage rates

In the initial comparison between monotherapy and combination therapy, it was assumed that coverage with combination therapy was either 100% or 80%. In reality, the coverage rate is likely to be much lower but the impact that this will have on the effectiveness and cost-effectiveness of combination therapy is not known and difficult to predict intuitively. For example, it is not clear whether there are threshold coverage rates at which there are abrupt changes in effects. Therefore, in this section the results of a scenario analysis are presented in which the level of coverage with ACT (drug AB) is varied from 0 to 100% in 10% increments.

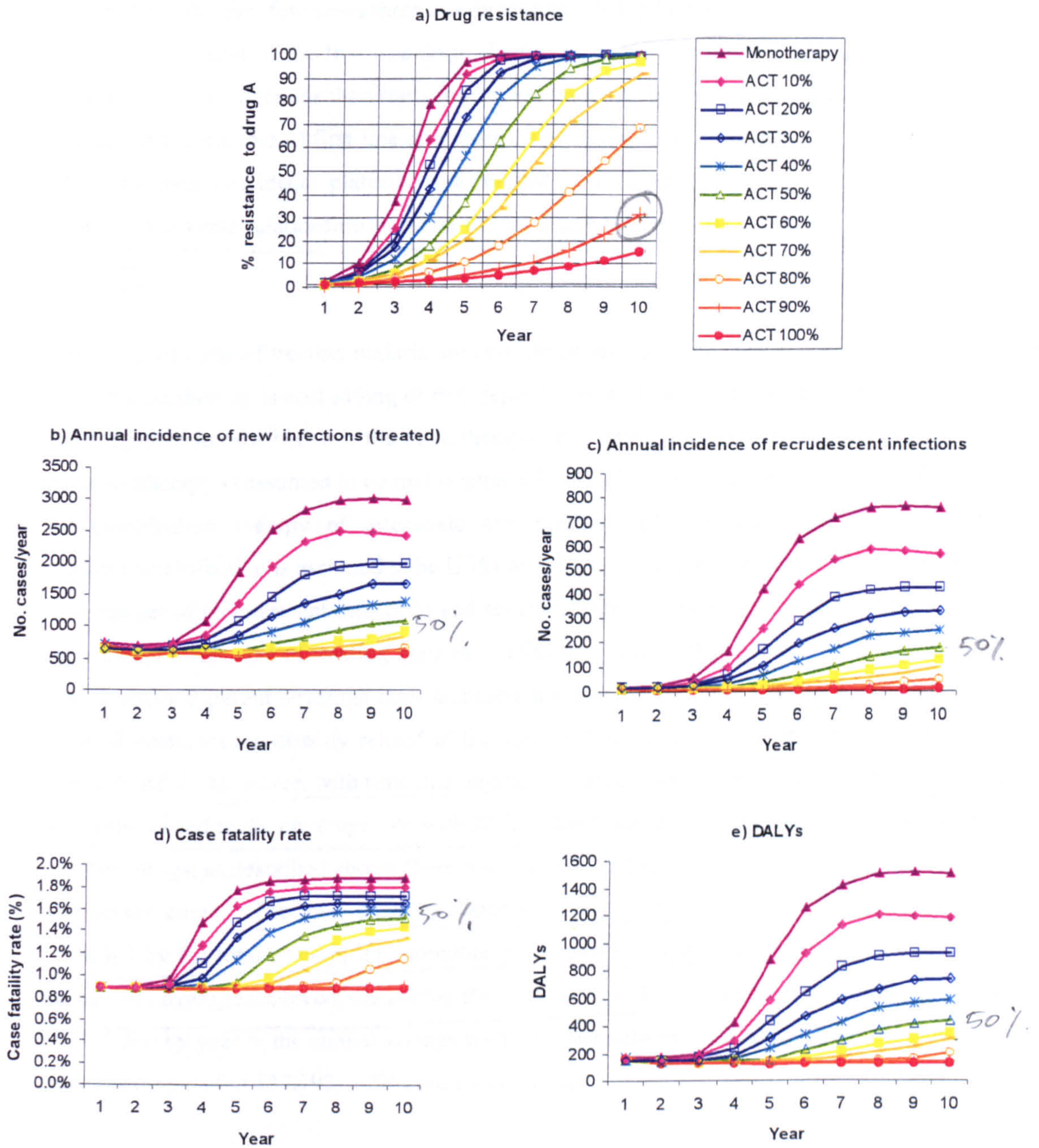
8.6.2.1. Effects

Figure 8-16 shows the change in outcomes in relation to the level of coverage with ACT. The graph of drug resistance suggests that when only low levels of coverage can be achieved, the introduction of combination therapy has little effect on the spread of resistance to drug A, and that it is not unless levels of over 80% are reached that there is any noticeable effect. However at these higher levels of coverage, small increments in the coverage with ACT has a significant effect on the rate of spread of resistance to drug A. Thus with a coverage rate of 90%, resistance reaches 50% at year 10 compared to 15% at 100% coverage.

However, when the effects on clinical outcomes are examined, a different pattern emerges. Even at low levels of coverage with combination therapy, there appears to be a noticeable impact on the incidence of malaria, recrudescence and severe infections and therefore deaths and DALYs. With a coverage rate of only 10%, there are 17% fewer new cases and 23% fewer recrudescence infections by year 10.

The graphs indicate that the higher the level of ACT coverage achieved, the slower the rate of rise of these outcomes, and the lower the level at which they plateau when 100% resistance to drug A is reached. This is because once resistance saturates, there is no further increase in the failure rate for a given coverage rate and therefore the proportion of infections which fail remains fixed.

Figure 8-16: Effect of different coverage rates with ACT (drug AB) on resistance (to drug A) and outcomes

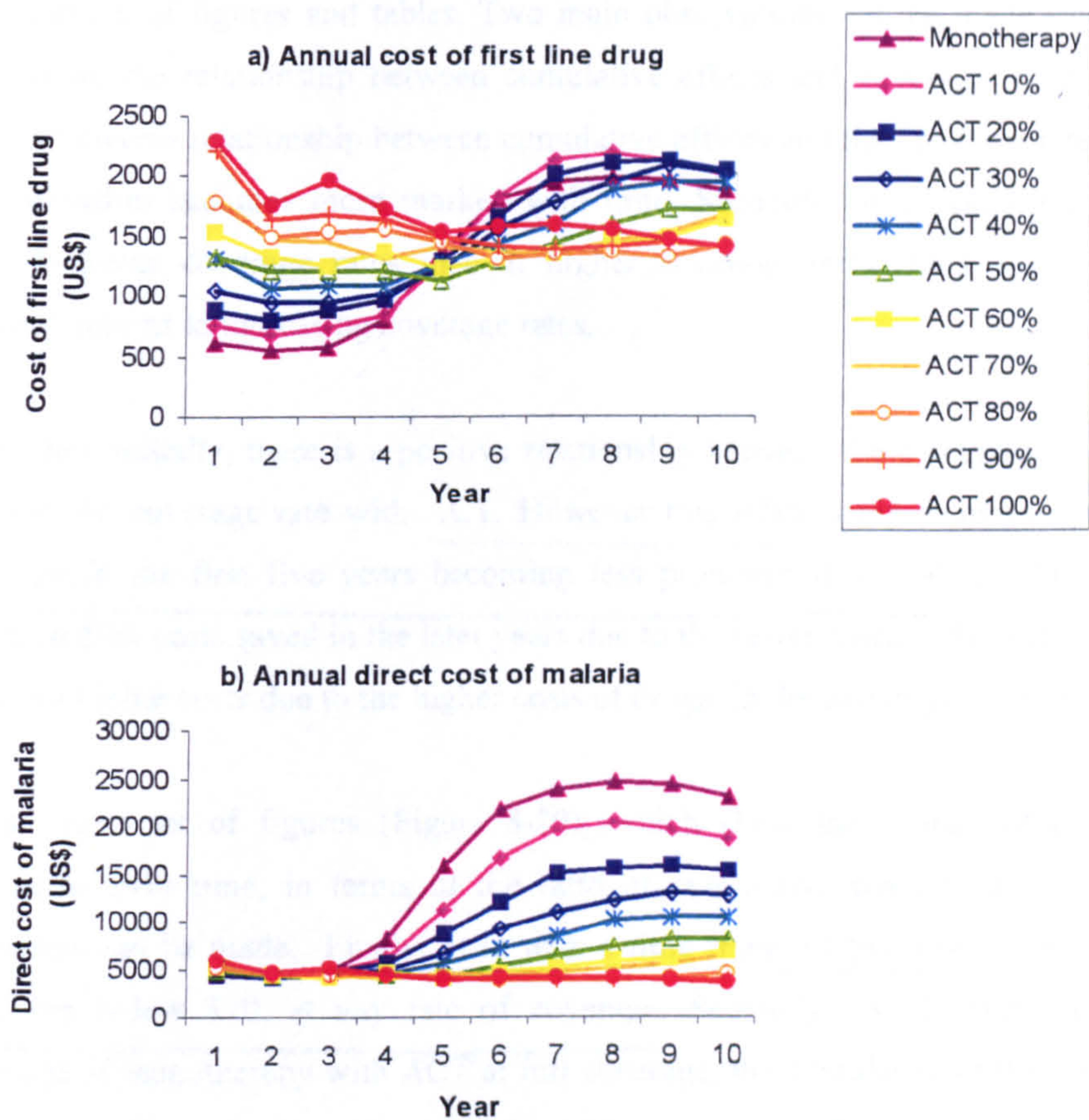


8.6.2.2. Costs

In the comparison between monotherapy and ACT at 100% coverage, the annual drug costs of ACT were initially higher than with monotherapy, but by the end of year 5, ACT became cost saving when considering first-line drug costs alone. It can be seen from Figure 8-17, that as expected, for the first few years there is a direct relationship between the coverage rate achieved and the annual cost of the first-line drug. However, at lower coverage rates (below 60%) the incidence of new infections then starts to increase with the rise in drug resistance, resulting in an increase in the number of first-line drug doses. The rate which this occurs and the final level at which the annual incidence plateaus, is dependent on the coverage rate. As a result, by year 10, there is an inverse relationship between the coverage rate with ACT and the annual first-line drug cost.

If the overall costs of treating malaria are considered instead, then clearly whether switching to combination therapy is cost saving or not, depends on the cost of treatment failure compared to the difference in cost between the monotherapy and combination therapy. In these scenarios, the monotherapy is assumed to be mefloquine at US\$1.11 per adult dose, compared to \$3.77 for the combination therapy of artesunate and mefloquine. The cost of an uncomplicated recrudescence infection is assumed to be US\$4.80, and for a severe infection US\$61.19 per adult. The number of recrudescence infections and severe infections therefore has a large impact on the total annual direct cost of treating malaria. In the first couple of years when drug resistance is similar under different coverage rates and there are few recrudescence infections, the total direct costs of treatment are directly related to the cost of first-line drugs and therefore the coverage rate with ACT. However, with time, the number of cases of treatment failure increases at a rate inversely related to the coverage rate with ACT. Therefore, in addition to the increased costs of first-line drugs, as described above, there is an increase in the total costs of treating recrudescence and severe cases. The total costs of continuing treatment with ACT are therefore rapidly exceeded by the total costs in the monotherapy scenarios at any rate of coverage. The higher the rate of coverage achieved, the greater the cost savings. Even with a coverage rate with ACT of 10% and by year 5, the annual savings with ACT are substantial - \$30,852 with combination therapy compared to \$37,793, a 22% reduction in cost.

Figure 8-17: Cost of first-line drugs and of total (direct) cost of malaria including recrudescence and severe infections by level of coverage with combination therapy



8.6.2.3. Cumulative costs, effects and cost-effectiveness

The incremental cost-effectiveness of moving from one coverage rate to another are presented in the next set of figures and tables. Two main observations can be made from Figure 8-18, which shows the relationship between cumulative effects and coverage. Firstly, as expected, there is an inverse relationship between cumulative effects and the coverage rate with ACT and this relationship becomes more marked with time. Secondly, at 10 years the relationship is steeper at lower coverage rates than at higher coverage rates. This means that there are decreasing returns to increasing coverage rates.

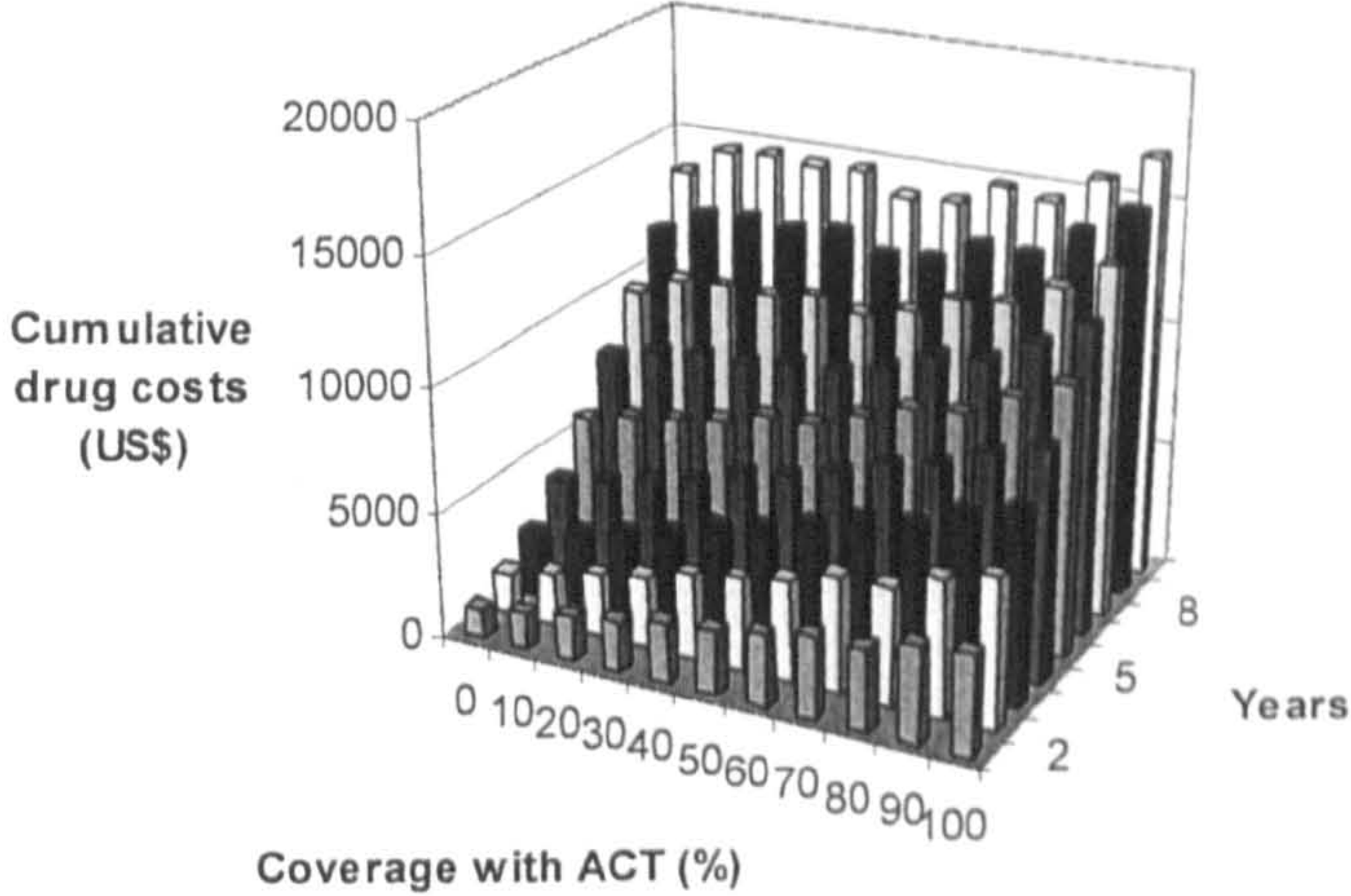
As expected, initially, there is a positive relationship between the cumulative cost of first-line drugs and the coverage rate with ACT. However this relationship changes over time, and is most acute in the first five years becoming less pronounced thereafter. This is because the cumulative drug costs saved in the later years due to the fewer cases with ACT, make up for the cumulative higher costs due to the higher costs of drugs, in the earlier years (Figure 8-19).

From the next set of figures (Figure 8-20), which show the change of cumulative cost-effectiveness over time, in terms of the ratio of cumulative costs to effects, a number of observations can be made. Firstly, even with a time frame of two years, the cost per DALY averted lies below \$70, at any rate of coverage. Secondly, as observed in the base line comparison of monotherapy with ACT at full coverage, the cumulative cost-effectiveness at all coverage rates increases over time. Finally, using a two and five-year time frame, there is a positive relationship between coverage rate and the cumulative cost per effect, implying that there are *decreasing* returns in terms of cost-effectiveness, to increasing coverage rates. By 10 years, coverage makes little difference to cumulative cost-effectiveness so that cost per DALY averted ranges from \$0.1 to \$0.4, although there is a suggestion that optimal cost-effectiveness is achieved at a coverage rate of 50 to 60%.

In order to show more clearly the change in cost-effectiveness in moving from one coverage rate to another, the relationship can also be compared using incremental cost-effectiveness (CE) planes. Figure 8-21 shows the cumulative incremental costs and DALYs averted, of ACT compared monotherapy at different coverage rates. These suggest that there are rapidly decreasing returns to achieving higher coverage rates above 50%, at both 5 and 10 years.

Figure 8-18: *Graphs showing cumulative effects by coverage rate and time frame*

a) Cumulative cost of firstline drugs by coverage rate and time frame



b) Cumulative direct costs of malaria by coverage rate and time frame

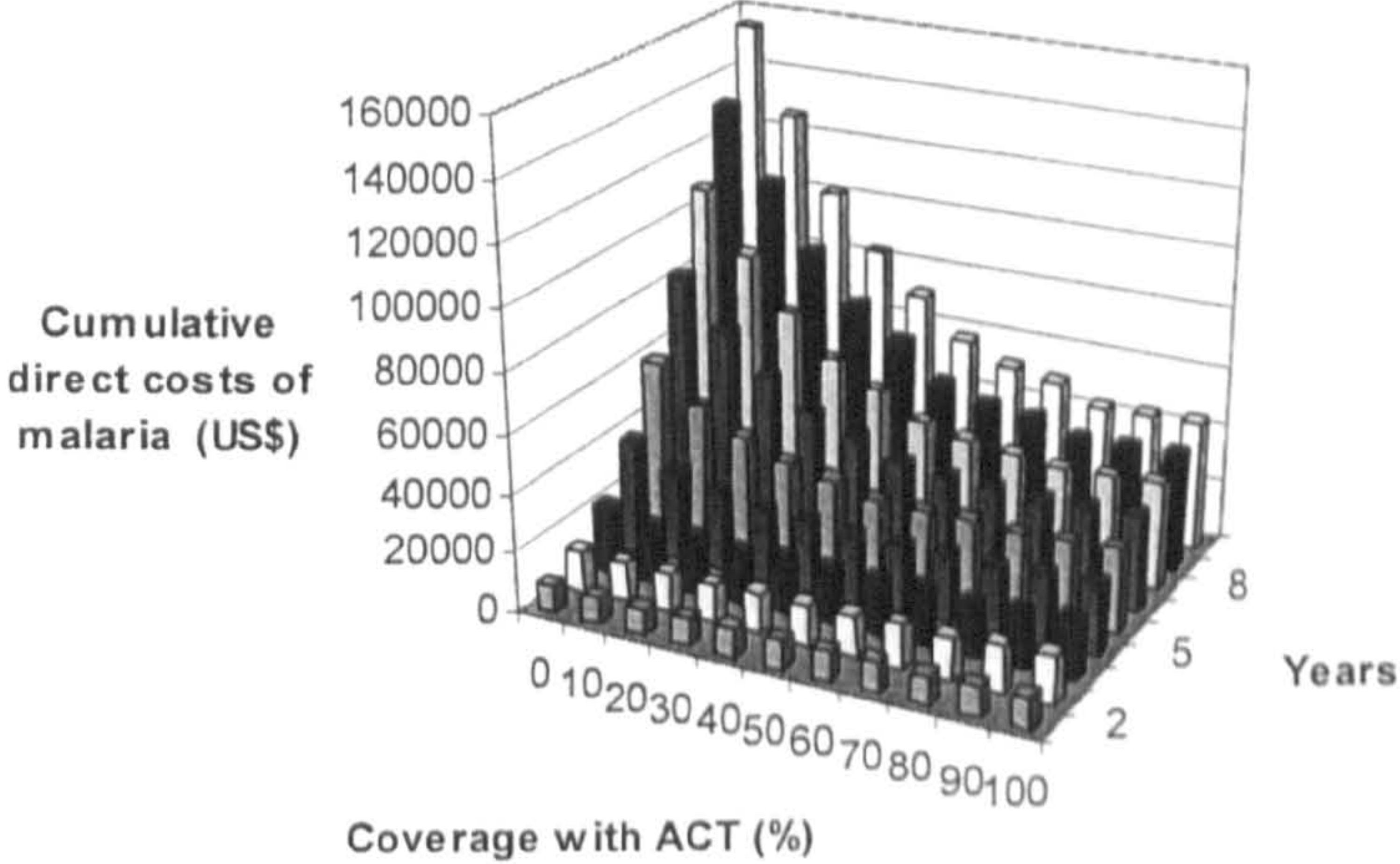
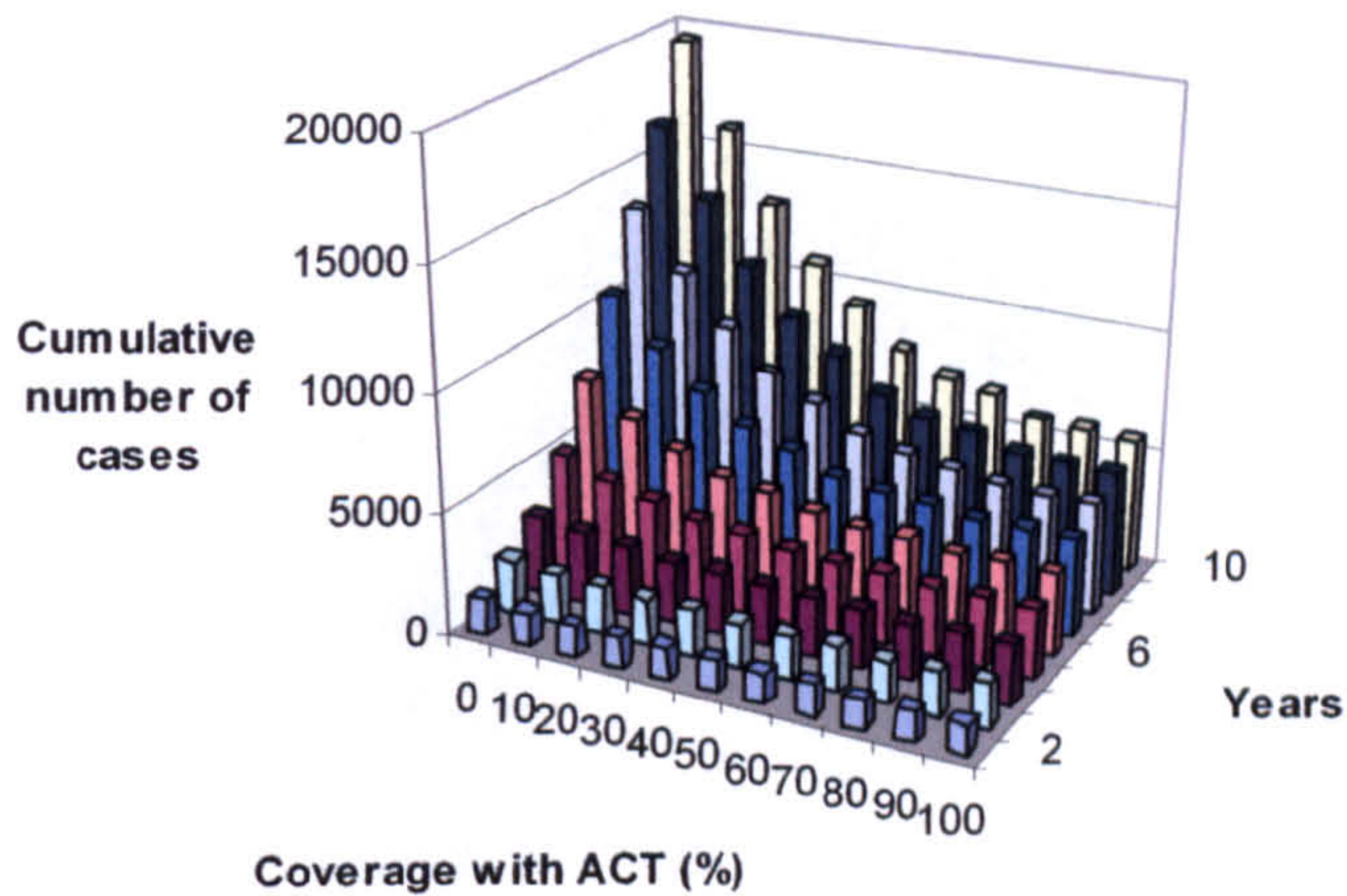
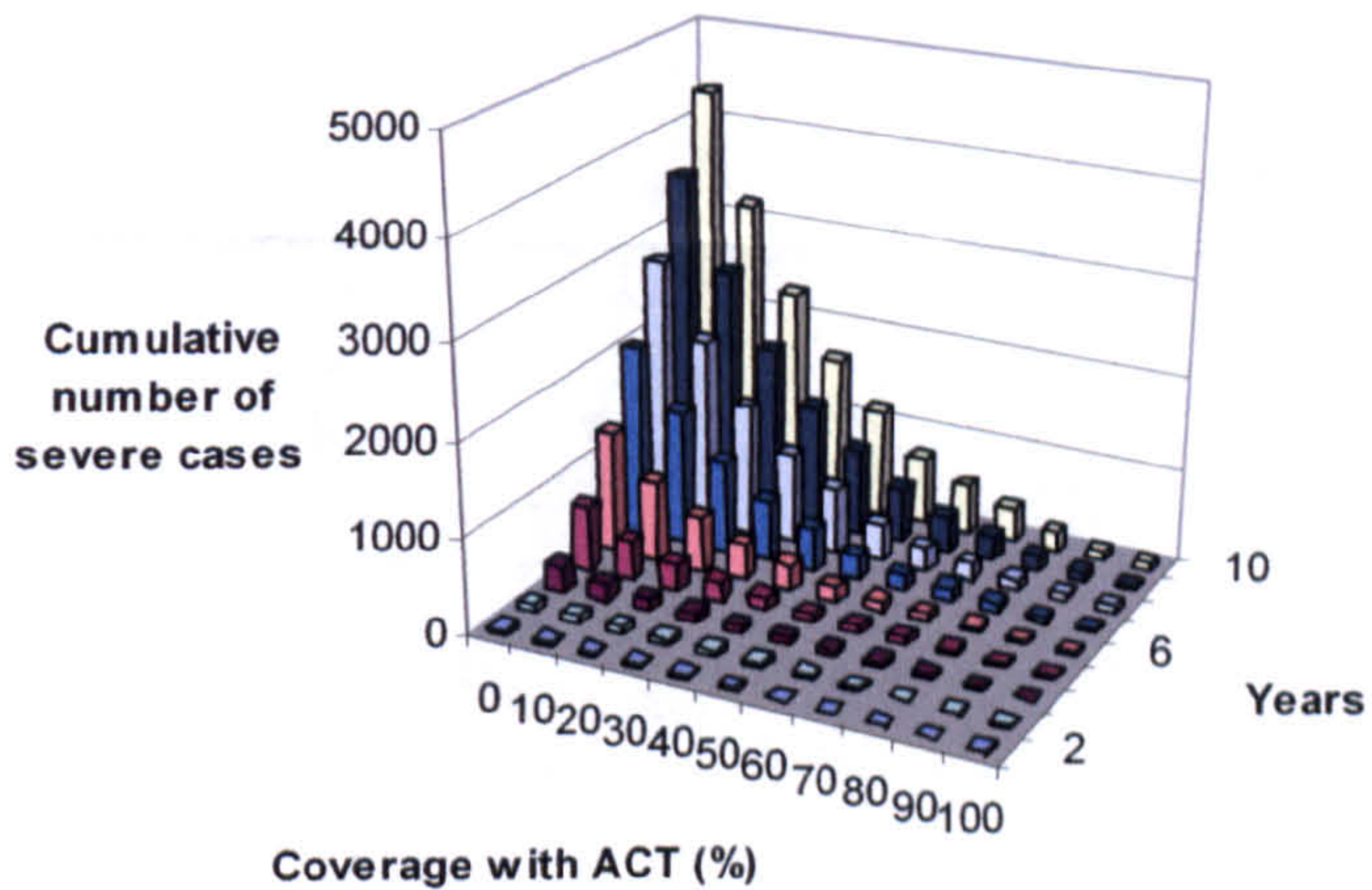


Figure 8-18: Graphs showing cumulative effects by coverage rate and time frame

a) Cumulative cases by coverage rate and time frame



b) Cumulative number of severe cases by coverage rate and time frame



c) Cumulative DALYS by coverage rate and time frame

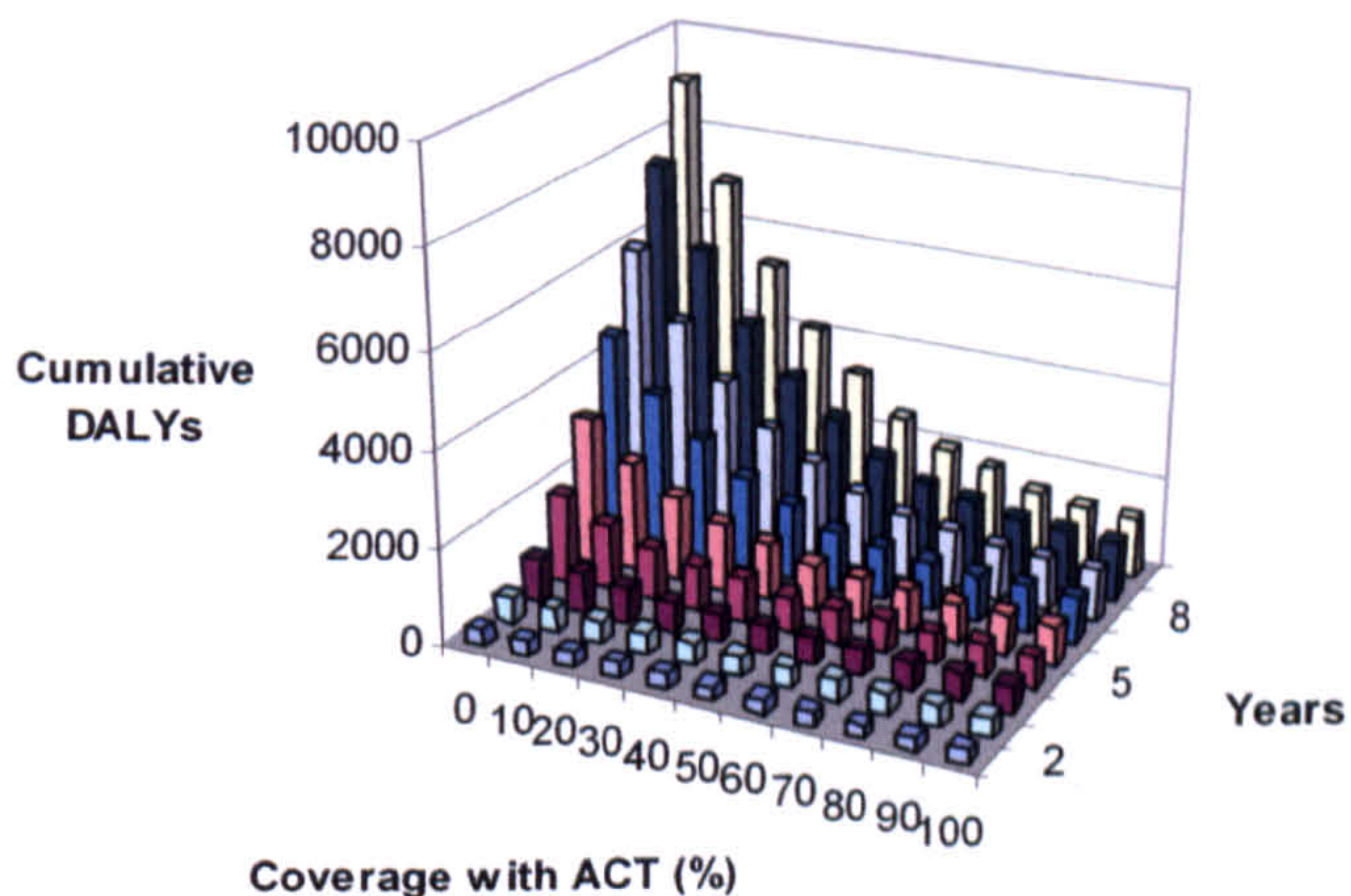


Figure 8-19: Graphs showing cumulative costs by coverage rate and time

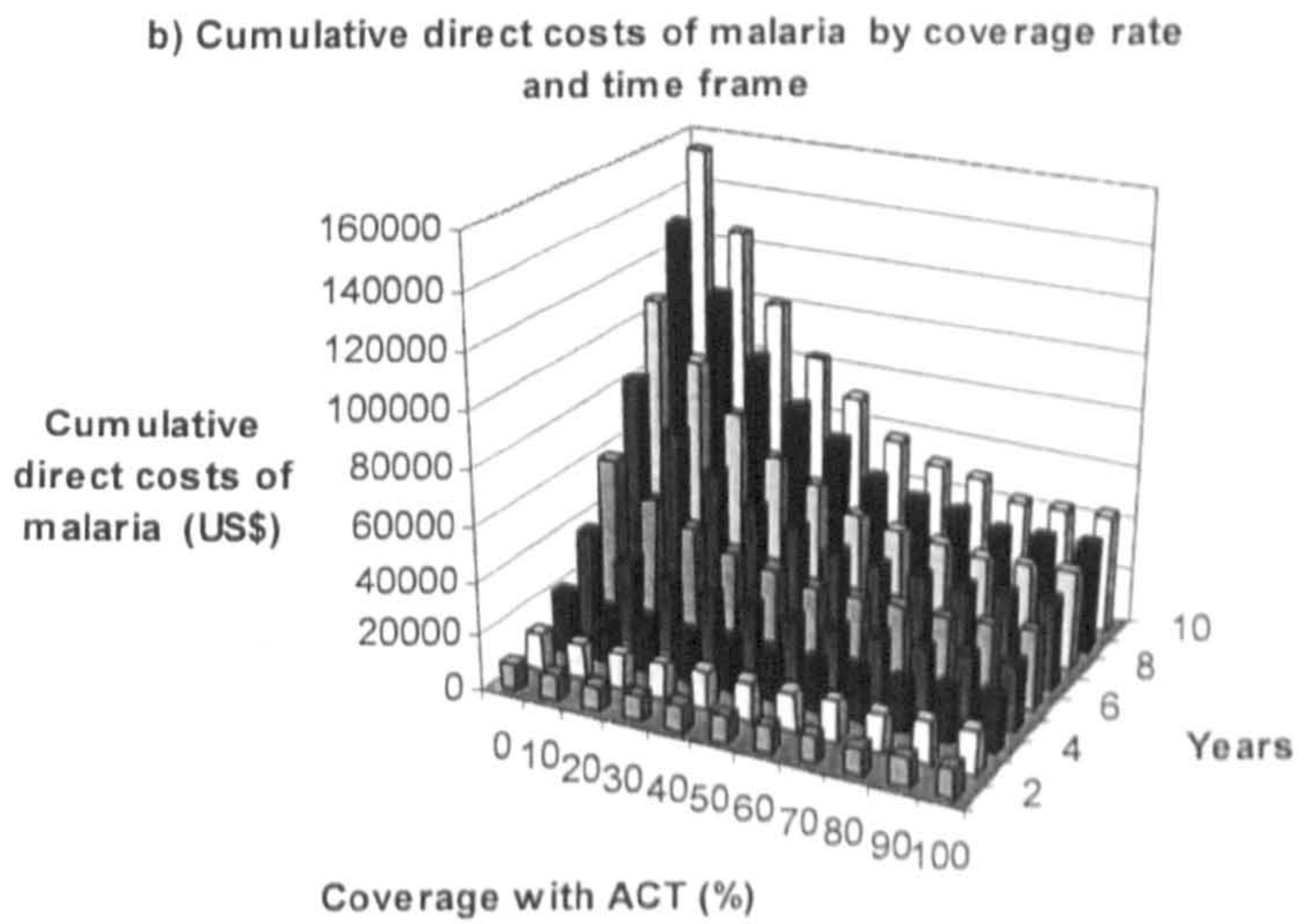
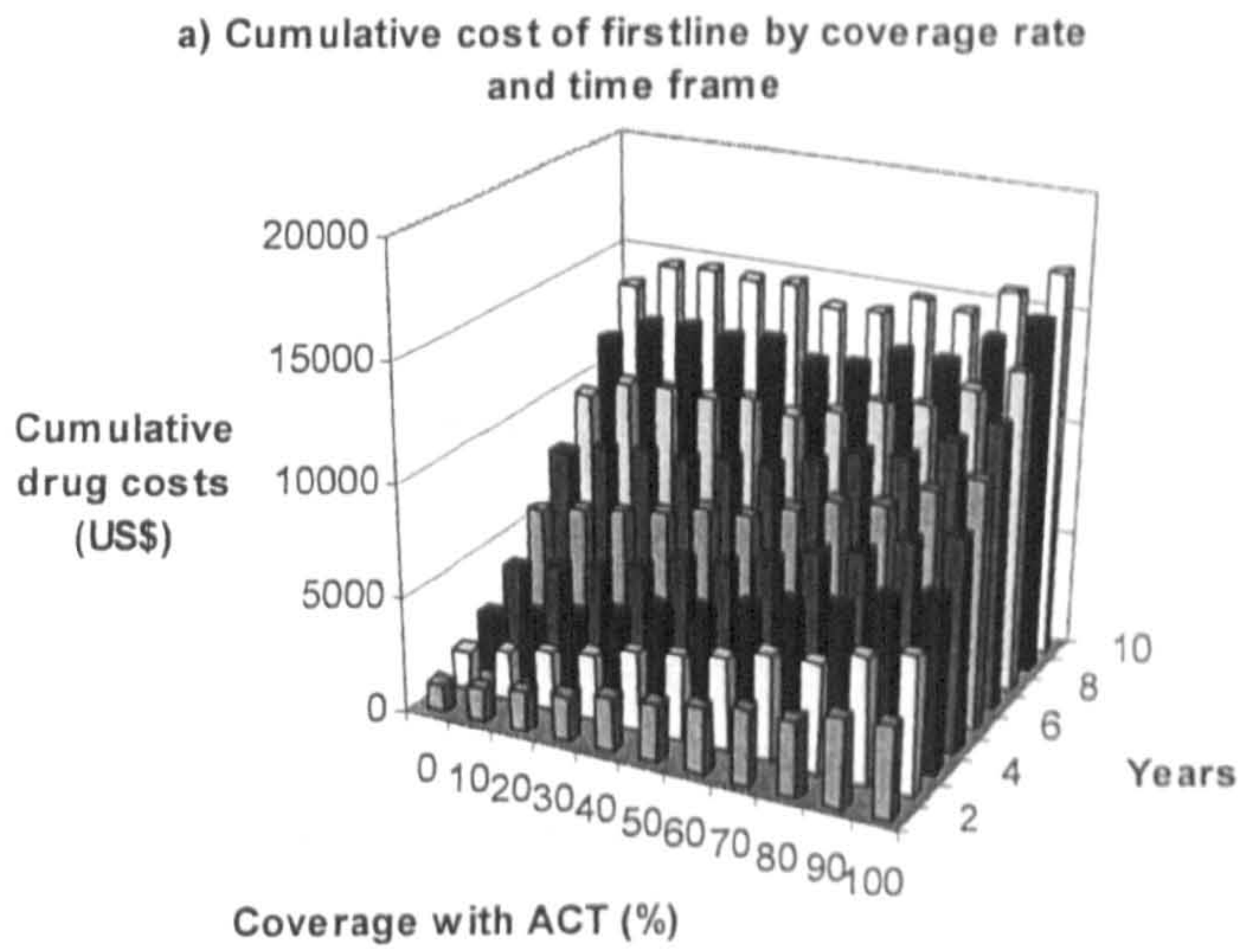


Figure 8-20: Cumulative incremental cost-effectiveness in terms of cost of drugs per case averted and cost of drugs per DALY averted by coverage rate at years 2,5 and 10.

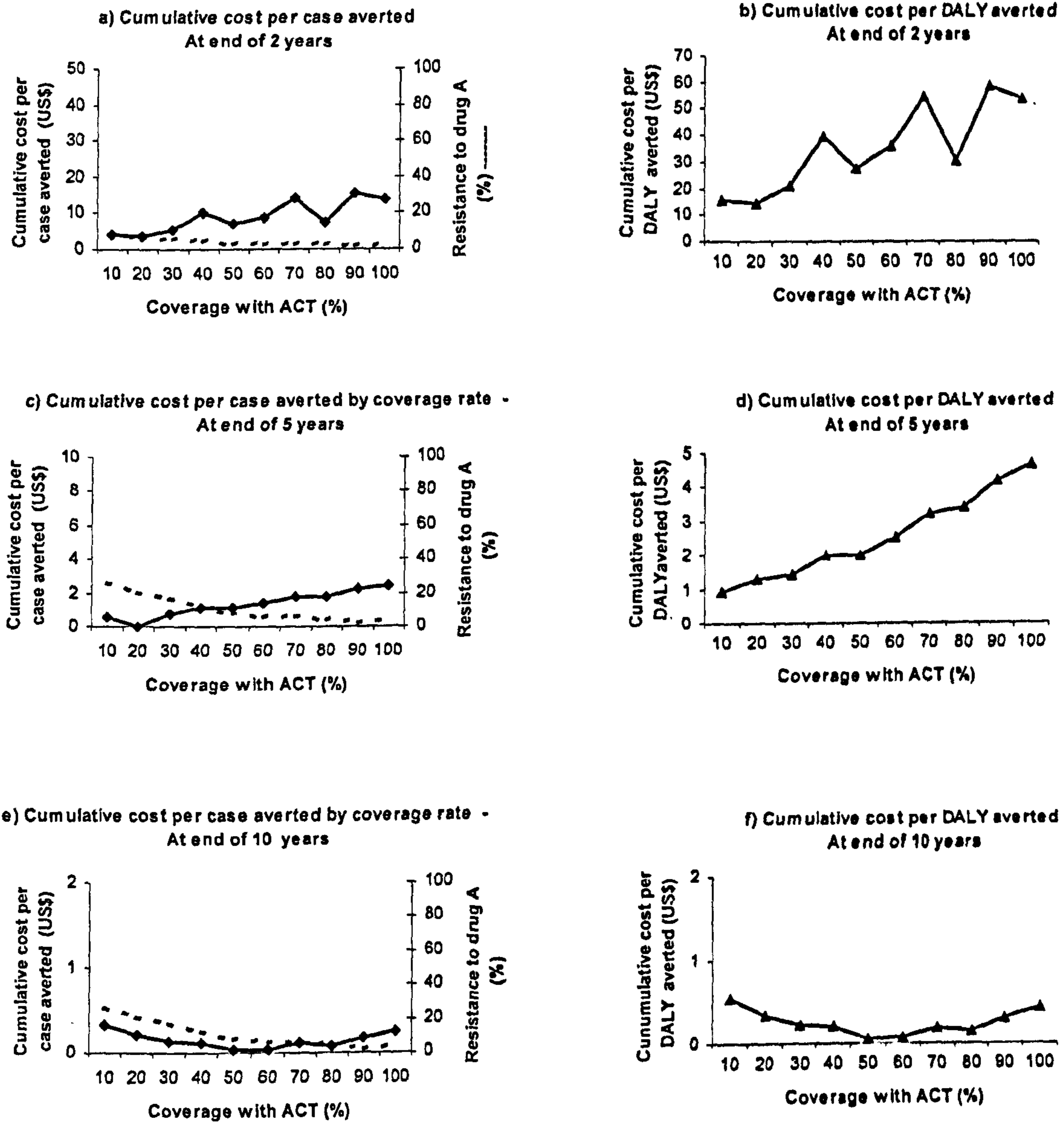
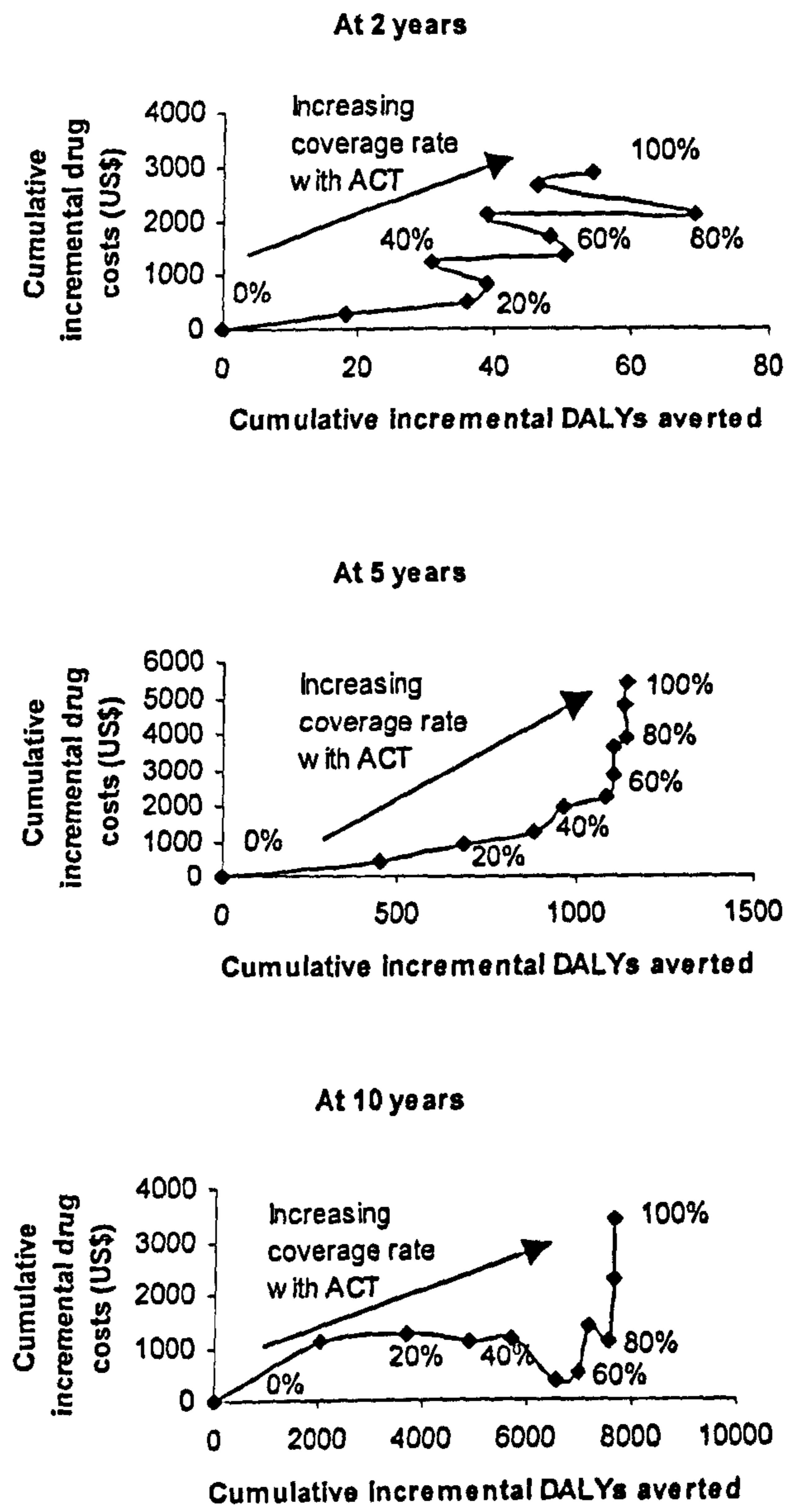


Figure 8-21: Cumulative cost-effectiveness planes showing effect of coverage rate with ACT compared to monotherapy on cumulative incremental cost of drugs compared to cumulative incremental DALYs averted



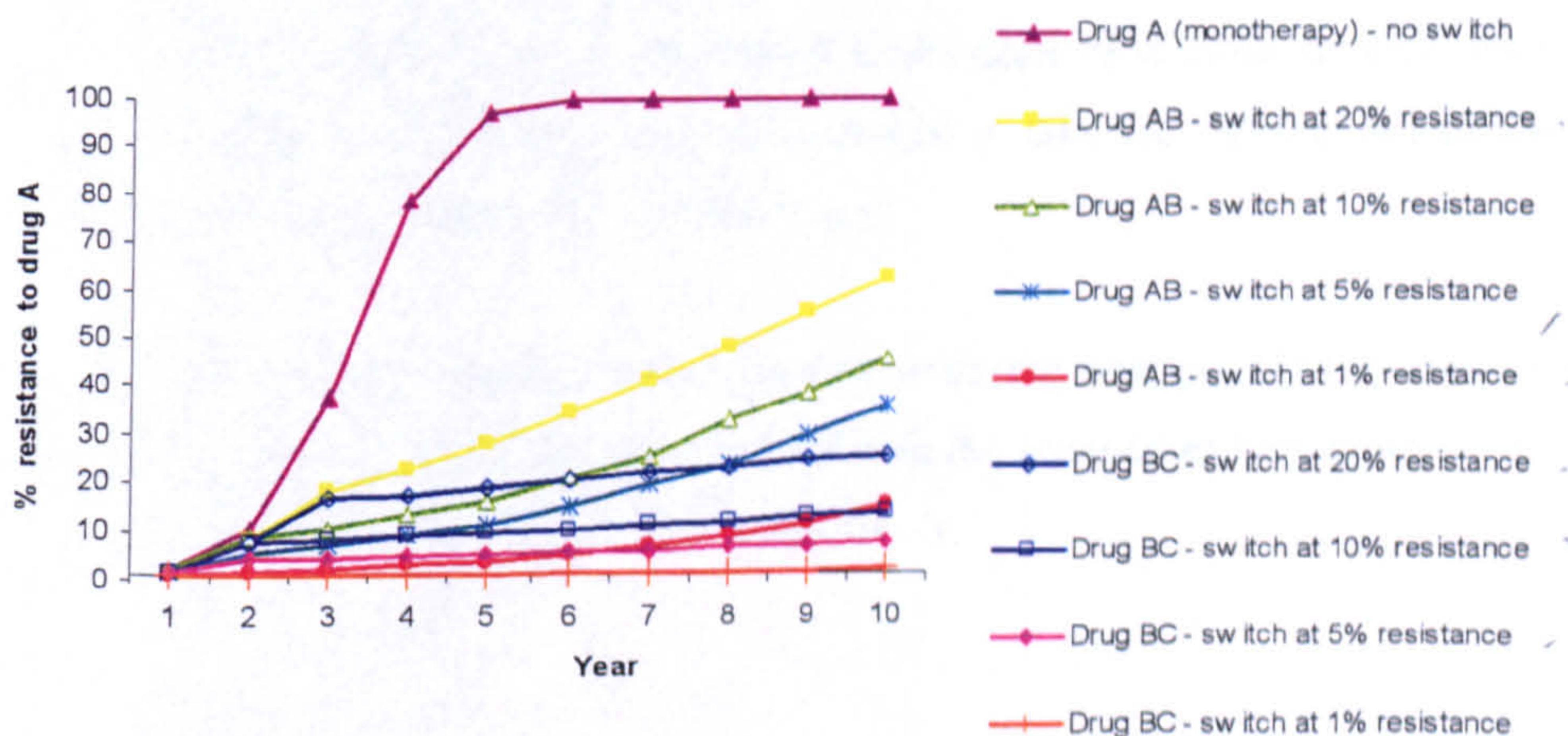
8.6.3. Choice of drug and timing of switch

Decisions regarding which particular artemisinin-based combination therapy to switch to, and when to switch, are important in the process of making antimalarial drug policy. So far in this analysis, the comparison has been between the continued use of drug A, mefloquine, and a switch to drug AB, which involves the addition of artesunate to mefloquine. However, the ideal choice of combination therapy is one in which there is no resistance to either drug in the combination, such as artemether-lumefantrine, that is a switch from drug A to drug BC. The choice of drug also influences the timing of the switch. If a switch is being made to drug BC, abandoning drug A, there may be a preference for continuing to use the cheaper drug A on its own for as long as possible. On the other hand if the switch is being made to drug AB, then the incentive may be to prolong the life of drug A, for as much as possible, by using it in combination. In order to explore these options, the model was run with inputs to compare a switch from drug A to either drug AB or to drug BC, at 100% coverage. This entailed changing the drug characteristics for drug BC, so that unlike drug AB, if infections resistant to drug A are treated with drug BC, they behave in the same way as infections that are sensitive to drug A. It is assumed that resistance does not develop to drugs B or C during the course of the analysis. In addition, to explore the effect of delaying a switch to combination therapy, the level of resistance to drug A, at which the switch was made, was varied from one to 20%.

8.6.3.1. Effects

The impact of different policies on drug resistance is shown in Figure 8-22. Once a switch is made to drug BC, the level of resistance to drug A remains almost static⁷³, unlike the switch to drug AB which is associated with a continued increase in resistance to drug A.

Figure 8-22: Drug resistance to drug A comparing the effect of switching to drug AB versus drug BC at different levels of resistance to drug A



⁷³ There is very small increase in resistance to drug A even after the switch to drug BC because the model assumes that there is still some presumptive use of drug A and therefore some drug pressure.

The next set of graphs (Figure 8-23) compare the incidence of new infections, recrudescence infections and severe infections. The most noticeable difference between the two combinations is in the incidence of recrudescence infections, a difference that increases over time. This is because although treatment with the addition of drug B to drug A is still very effective despite resistance to the latter, the drug resistance to drug A does compromise the efficacy of the combination and therefore the failure rate is slightly higher than with drug BC. Within the time frame of the analysis, however, there are only slightly more severe cases with drug AB than with drug BC and no difference in transmission intensity. If the analysis were continued for longer, as resistance continued to rise in the drug AB scenario, we would expect a larger difference to emerge between the two drug choices.

8.6.3.2. Costs and cost-effectiveness

In many settings, the monotherapy in question is often SP, and the actual choice is between switching from SP (drug A) to SP and artesunate (drug AB) or to artemether-lumefantrine (drug BC). There is a substantial difference in the cost of these combinations. The cost per adult course of these drugs is approximately \$0.10, \$1.39 and \$2.40 respectively⁷⁴. Therefore if only the short term, first-line drug costs are considered, the artesunate and SP choice is more attractive than artemether-lumefantrine Figure 8-24. In order to compare the cost-effectiveness of artesunate and SP with artemether-lumefantrine, the appropriate costs of drugs were substituted into the model. The results in terms of cumulative costs and cost-effectiveness are shown in Table 8-8 and Table 8-9. For clarity, only the costs of switching at 1% resistance to drug A are shown, but the results, when the switch is made at 20% resistance are also discussed with the tables of results shown in Annex 12.

? Because neither combinations impact on the incidence of malaria, the total annual drug costs of the combinations remain an order of magnitude greater than the continued use of SP and the annual drug costs of artemether-lumefantrine remain twice as high as the drug costs of artesunate with SP. However when the overall direct costs of malaria are examined, it can be seen that any difference *between* the ACT options is dwarfed by the annual cost savings compared to monotherapy, after the first few years.

In terms of cumulative cost-effectiveness, at five years the cost per DALY averted under the artesunate-SP scenario is \$2.3, compared to \$4.2 with the artemether-lumefantrine. At 10 years, the cost per DALY falls to \$0.6 and \$1.0 respectively.

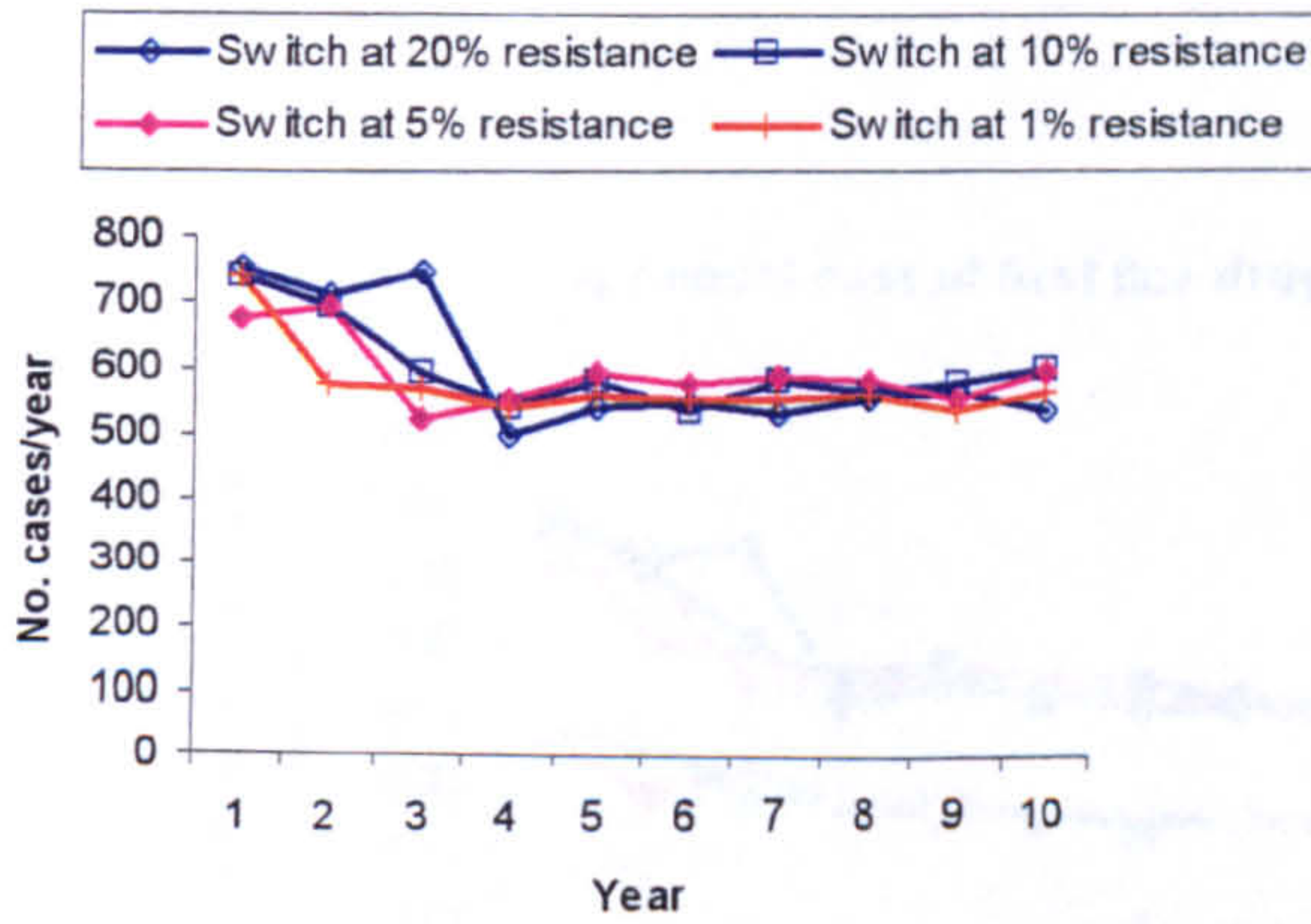
⁷⁴ Cost of packaging at \$0.21 per packet, cost of drugs for children aged 6-12 years and <6 years were estimated at 50% and 25% of adult course. The cost of drugs for treating recrudescence cases was assumed to be the same as the cost of the combination therapy.

Comparison of the effect of the timing of switch on cost-effectiveness suggests that the higher the level of resistance to drug A at which the switch is made, the less cost effective the switch, although the difference is very small. Thus, if the switch is made at 20% resistance to drug A rather than 1% resistance, there is slight decrease in the cumulative cost-effectiveness, so that the cost per DALY averted at five years is \$3.0 and \$5.0 for the artesunate-SP and artemether-lumefantrine scenarios, and \$0.6 and \$1.1 at 10 years, respectively. This is because, in the time it takes for resistance to increase from 1% to 20% resistance, the costs saved due to continuing to use a cheaper drug is proportionally less than the increase in recrudescence infections and severe infections.

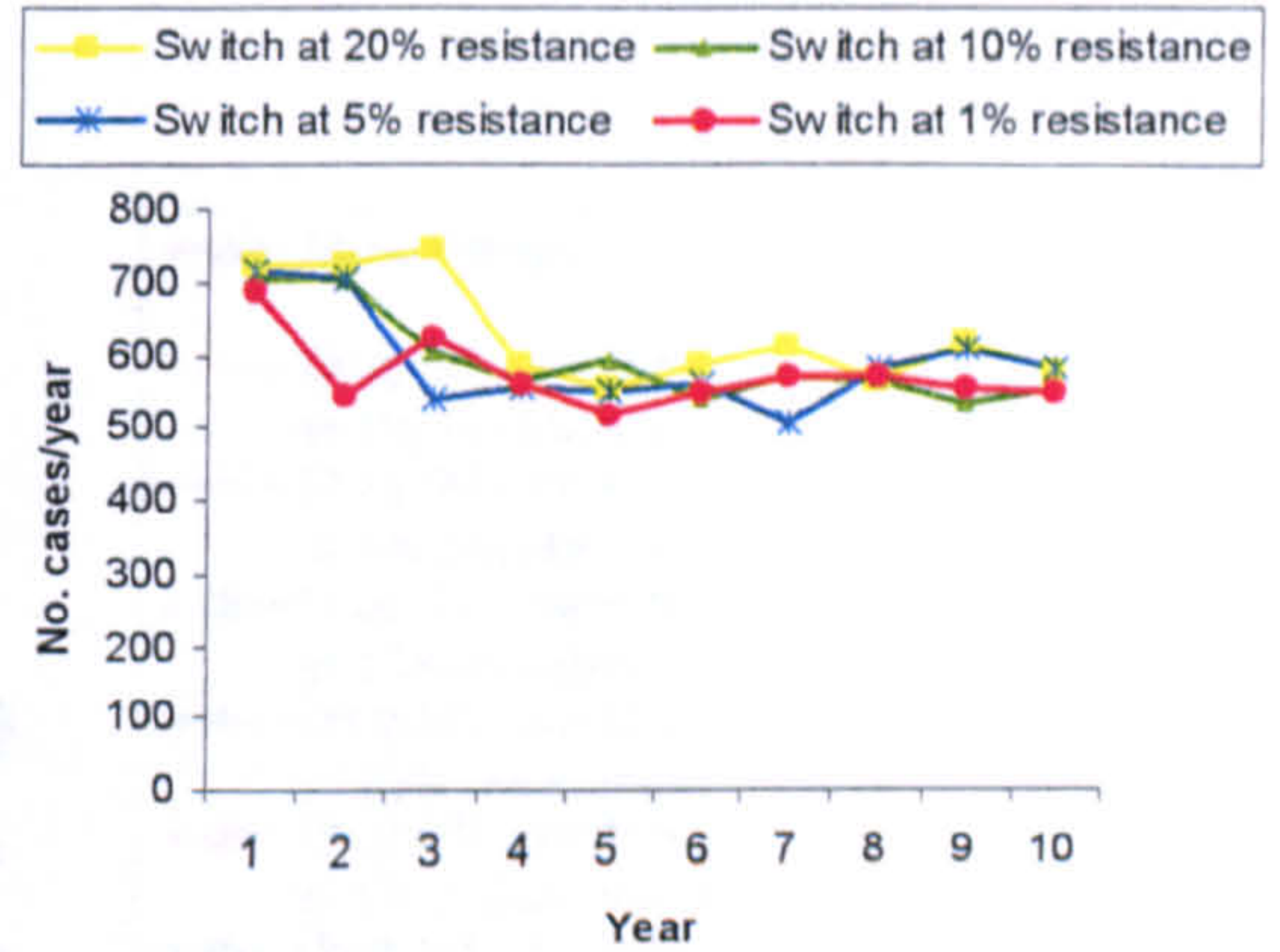
As resistance increases so does the incidence of recrudescence infections, severe infections and DALYs, so that at the higher the rate of resistance at which the switch is made, the greater the difference in these outcomes, before and after the switch.

Figure 8-23: Graphs comparing outcomes between switching from drug A to drug BC (on the left) and to drug AB on (the right) at different levels of resistance to drug A

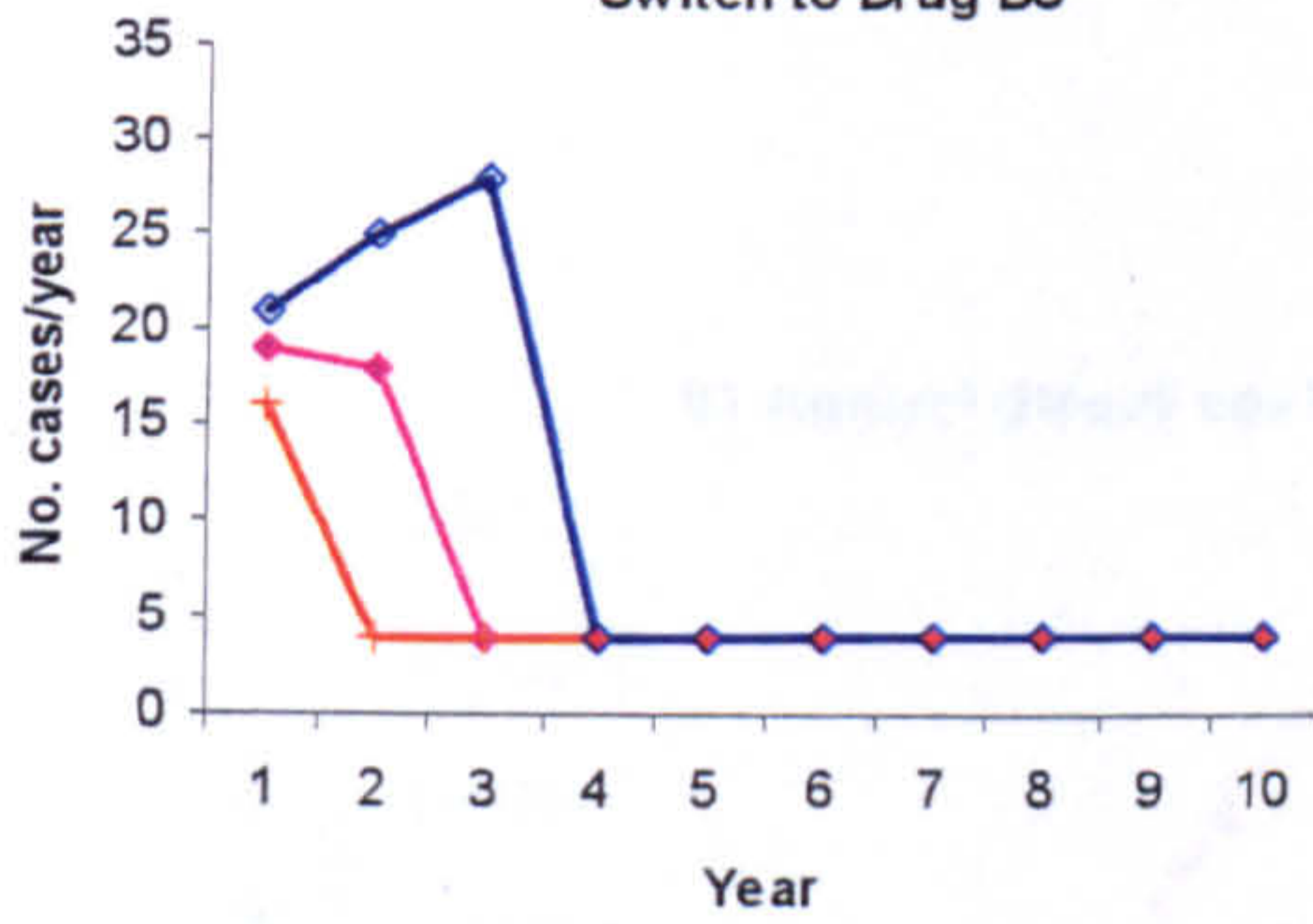
a) Annual incidence of new infections (treated)
Switch to Drug BC



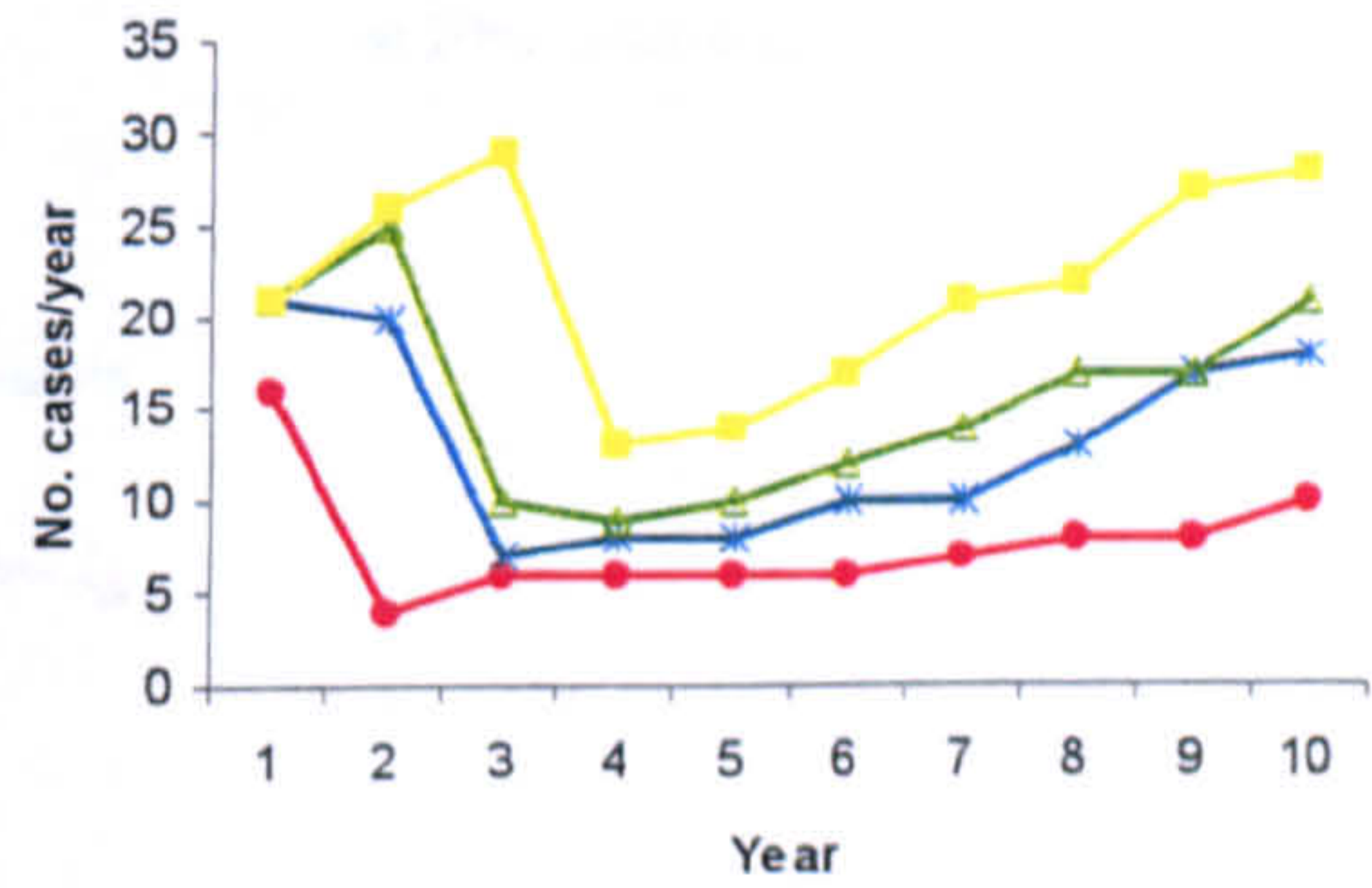
b) Annual incidence of new infections (treated)
Switch to Drug AB



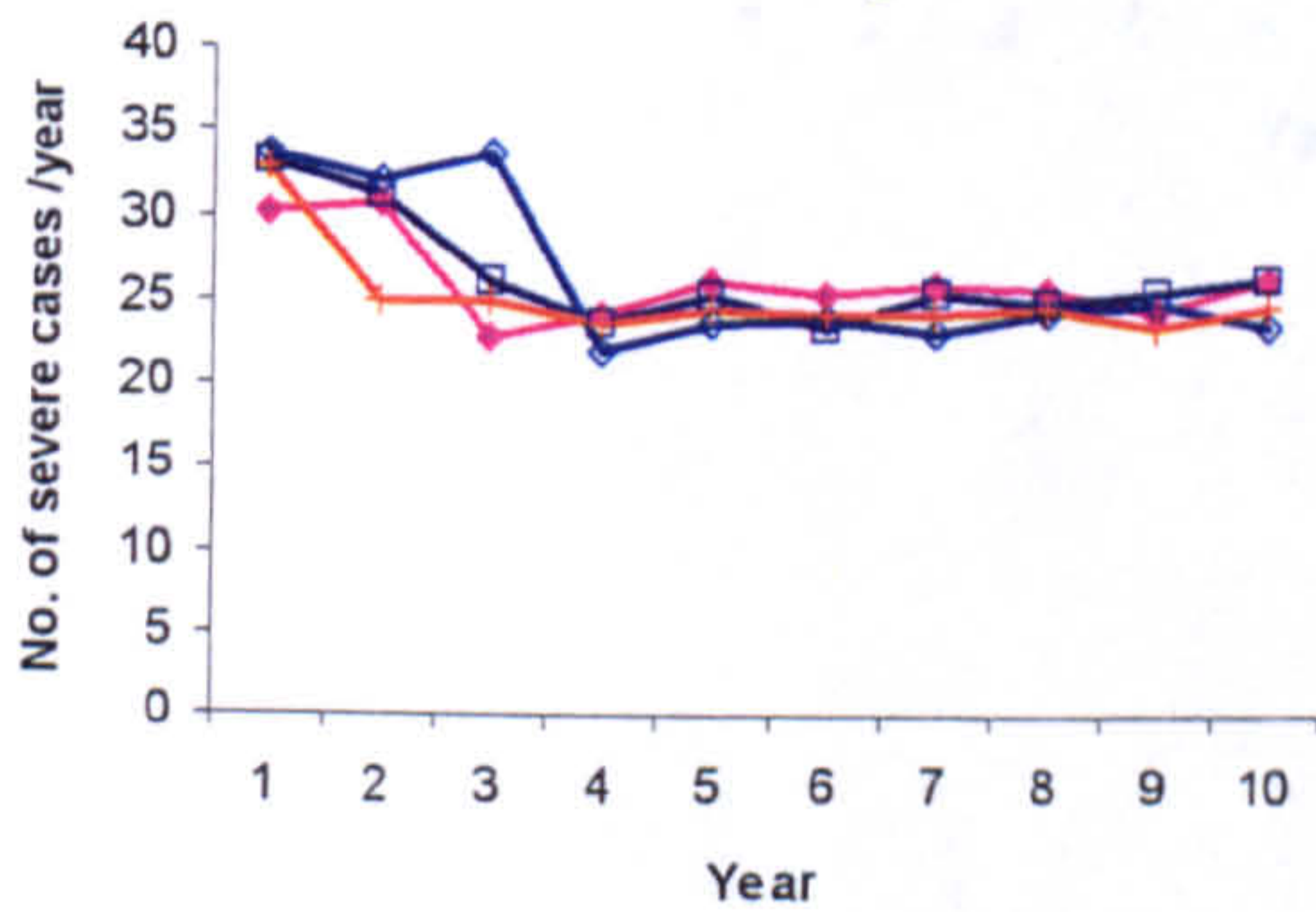
c) Annual incidence of recrudescence infections
Switch to Drug BC



d) Annual incidence of recrudescence infections
Switch to Drug AB



e) Annual incidence of severe malaria
Switch to Drug BC



f) Annual incidence of severe malaria
Switch to Drug AB

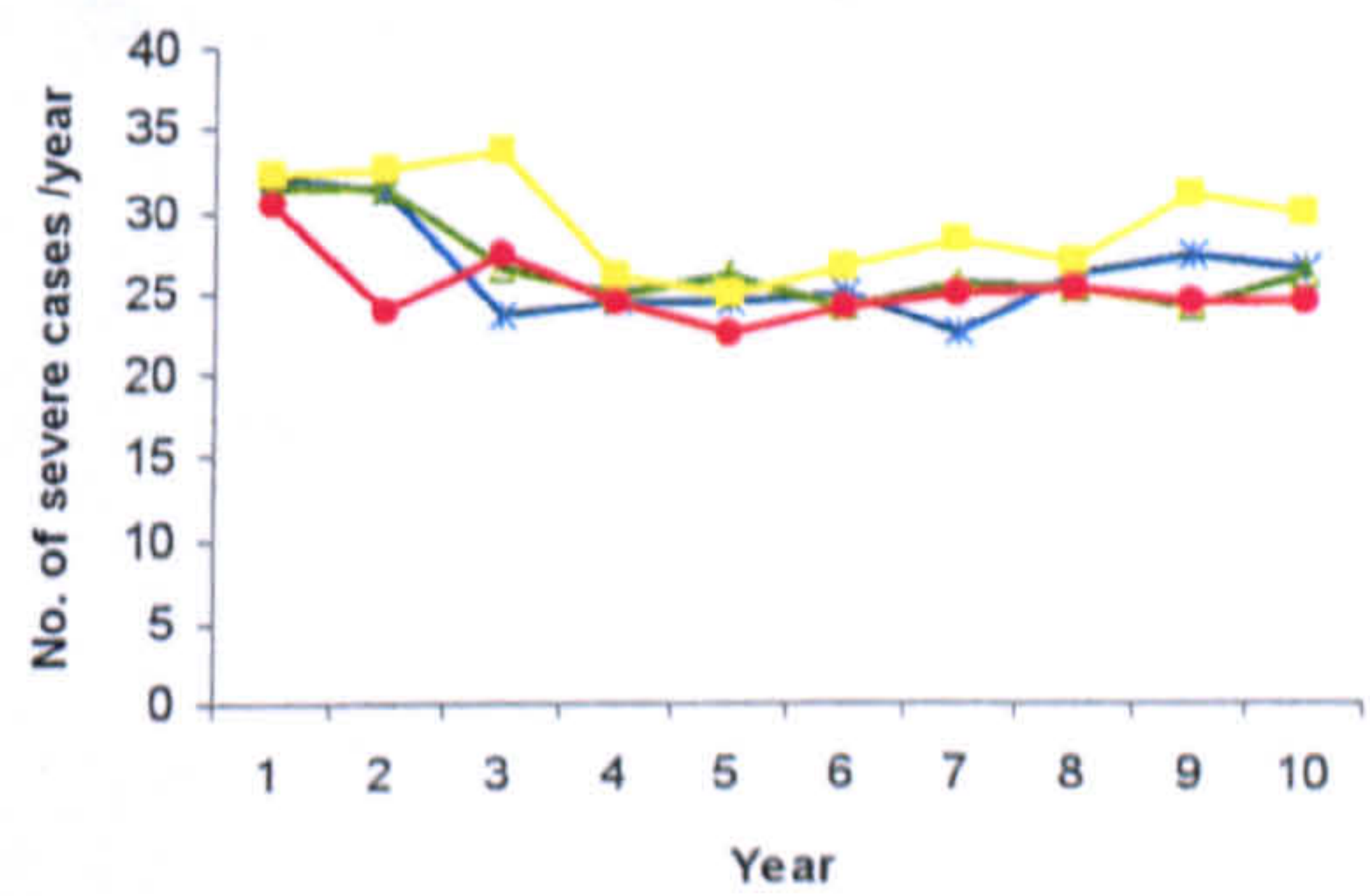


Figure 8-24: Annual cost of first-line drug and annual direct cost of treating malaria comparing monotherapy (drug A) to switching to drug AB or drug BC at different levels of drug resistance to drug A

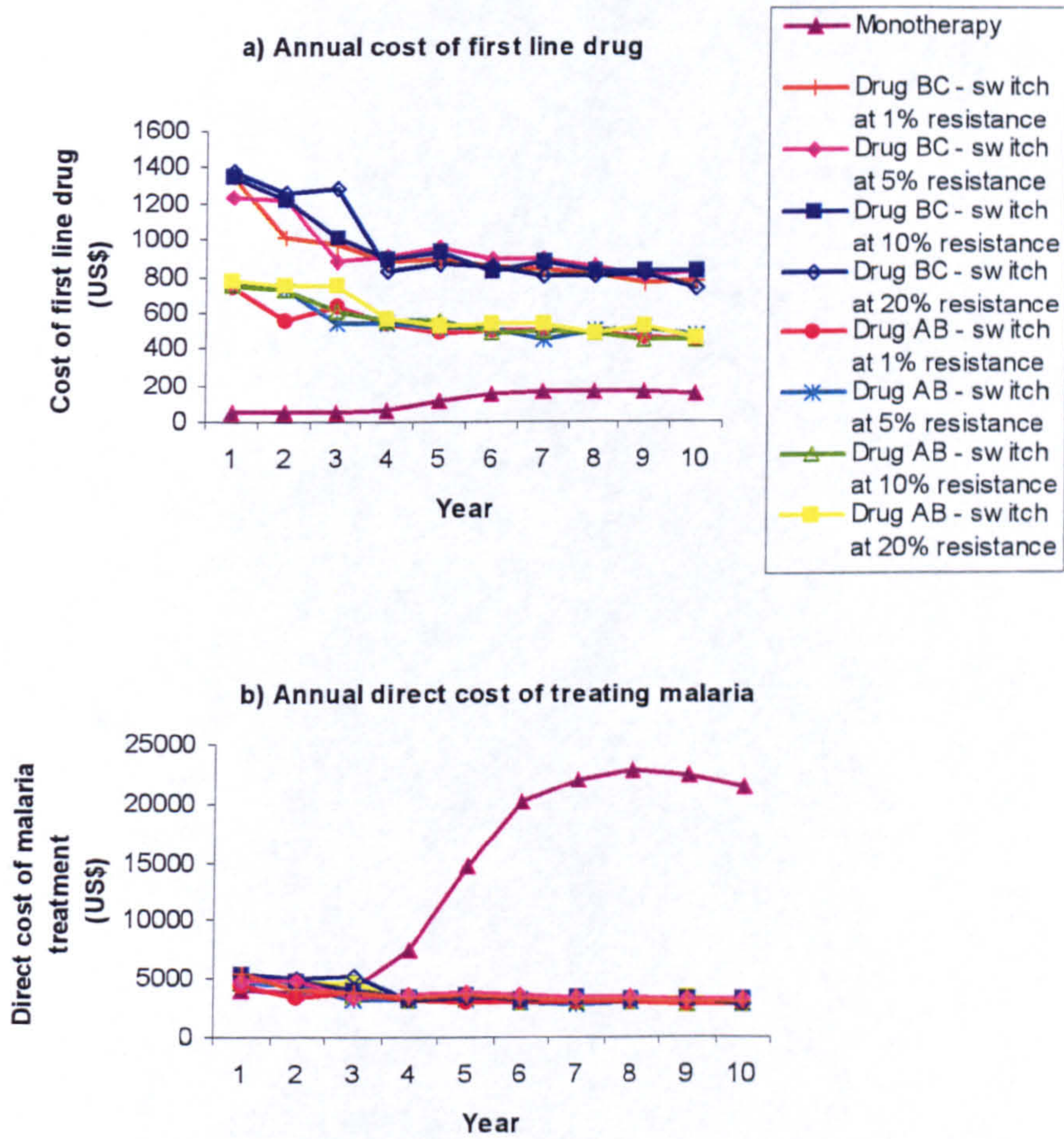


Table 8-8: Cumulative costs, effects and cost-effectiveness of switching to drug AB (artesunate + SP) from SP at 1% resistance to drug A (SP)

	Cumulative costs and effects											
	After 1 year			After 5 years			After 10 years					
	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)
Number of treated cases	739	686	-53	5,107	2,931	-2,176	19,438	5,729	-13,709			
Number of recrudescences	21	16	-5	688	38	-650	4,316	77	-4,239			
Number of severe cases	33	30	-3	342	129	-213	1,682	252	-1,430			
Number of deaths	7	6	-1	68	26	-43	336	50	-286			
Number of DALYs	175	161	-13	1,828	683	-1,145	9,026	1,336	-7,689			
Cost of drug	53	737	685	339	2,972	2,633	1,169	5,416	4,247			
Direct cost of malaria	4,068	4,447	379	34,213	17,801	-16,412	142,927	32,461	-110,467			
Total cost (indirect and direct)	10,081	10,002	-80	77,905	40,043	-37,863	308,952	73,019	-235,933			
	Incremental cost of drug per consequence averted											
Cost of drug (US\$) per case averted	After 1 year			After 5 years			After 10 years					
- recrudescence averted		12.9			1.2			0.3				
- severe infection averted		136.9			4.1			1.0				
- death averted		269.1			12.3			3.0				
- DALY averted		753.4			61.7			14.8				
		52.3			2.3			0.6				

Table 8-9: Cumulative costs, effects and cost-effectiveness of switching to drug BC (artemether-lumefantrine) from SP at 1% resistance to drug A (SP)

	Cumulative costs and effects											
	After 1 year			After 5 years			After 10 years					
	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)
Number of treated cases	739	741	2	5,107	2,980	-2,127	19,438	5,734	-13,704			
Number of recrudescences	21	16	-5	688	32	-656	4,316	52	-4,264			
Number of severe cases	33	33	0	342	131	-212	1,682	251	-1,431			
Number of deaths	7	7	0	68	26	-42	336	50	-286			
Number of DALYs	175	174	0	1,828	693	-1,135	9,026	1,331	-7,694			
Cost of drug	53	1,349	1,297	339	5,124	4,785	1,169	9,197	8,028			
Direct cost of malaria	4,068	5,345	1,277	34,213	20,170	-14,043	142,927	36,165	-106,762			
Total cost (indirect and direct)	10,081	11,328	1,247	77,905	42,738	-35,168	308,952	76,628	-232,324			
Incremental cost of drug per consequence averted												
Cost of drug (US\$) per	After 1 year*			After 5 years			After 10 years					
-case averted		-648.3			2.2			0.6				
- recrudescence averted		259.3			7.3			1.9				
- severe infection averted		-			22.6			5.6				
- death averted		-			113.1			28.0				
- DALY averted		-			4.2			1.0				

*Note: At one year the incidence of new infections is slightly *higher* in the ACT compared to the monotherapy scenario due to stochastic variation in migrant cases. There is no difference in the number of severe cases. Therefore ACT appears to be more costly and less effective at this time point.

8.7. Application of the model to Cambodian data

8.7.1. Introduction

For the purpose of illustration, the results up until now have been from an idealised setting in which the coverage rate to combination therapy has been assumed to be high, and the failure rates reflective of complete adherence to the antimalarial drugs taken.

In this section, in order to evaluate how the model performs with realistic scenarios, it was run with data from Cambodia to assess the cost-effectiveness of switching to combination therapy with and without interventions aimed at increasing coverage.

As described previously, use of the public sector has been very low in Cambodia, with the public sector delivering less than 10% of first-line treatments for malaria. In the informal sector, patients receive a wide variety of treatments for malaria, which rarely follow the national guidelines. In order to address this problem, a number of local interventions were introduced, to increase access to reliable diagnosis using rapid diagnostic tests (RDTs) and treatment with artesunate and mefloquine. The two main initiatives were an “outreach” service and village malaria volunteers (VMVs).

The model was therefore run using the primary data collected in Cambodia presented in Chapters 6 and 7. The aim was to explore the effects, cost and cost-effectiveness of the change in policy to ACT in Cambodia and to predict the incremental cost and impact of adding the interventions to increase coverage.

8.7.2. Inputs and parameterization

In the methods chapter, the use of sub-models to calculate the coverage rate with ACT and failure rates based on actual real-life conditions was described. However, up until now, these have not been used, as it has been assumed that all patients received free and appropriate treatment in a public health facility following biological confirmation and that patients were all adherent to therapy. In reality, this is seldom the case, and the proportion of patients with malaria who receive the recommended drug and take the full course is far from optimal. There are a large number of steps required to reach the ideal state. For simplicity, these individual steps have been reduced to the choice of provider (formal or informal) and the impact that this choice has on coverage rates, adherence rates and costs. Attempting to increase the coverage rate with ACT by delivery strategies such as outreach clinics and VMVs increases the incremental cost of switching to ACT. In order to assess the impact this has on cost-effectiveness, this incremental cost is compared to the increase in effects. Because both of these delivery interventions involved the introduction of biological diagnosis with RDTs, this cost is also included in the analysis. Although the cost-effectiveness of diagnosis with RDTs is an

important issue, it is not dealt with specifically here as it lies outside the focus of this thesis and is being dealt with in detail by others (Goodman C, personal communication).

The inputs derived from the drug usage survey were summarised in Section 6.4.4 and in Table 7-19 in the previous chapters. The values used to calculate the maximum failure rates in the model in relation to the overall adherence rates are shown in Table 8-10 and the resulting inputs into the model are shown in Table 8-11 and are discussed below.

8.7.2.1. Type of provider

Where patients with malaria go for treatment determines the likelihood of them receiving combination therapy and therefore the “coverage rate” input into the biological model. All malaria patients seen by outreach workers and VMVs receive artesunate and mefloquine, but only 43% of those seen in a public health facility and 8% of those seen in the informal sector. The likelihood of adherence, and therefore cure, also depends on where treatment is obtained. Patients receiving treatment from VMVs or outreach workers are assumed to have the same likelihood of adherence as if they went to the public health facility. Therefore the value for the maximum failure rates that are input into the biological model vary according to the proportion of treatments sought in the formal sector compared to the informal sector and the associated adherence rates. The introduction of VMVs and outreach clinics is assumed to attract patients who would have otherwise sought treatment from the informal sector, and therefore leads to a marginal increase in treatments sought in the formal sector. In other words, the interventions do not substitute for the public health facilities.

Second-line treatment for recrudescence and treatment of severe infections are more likely to be obtained in public health facilities than are first-line treatments for new infections. The actual proportion and the type of treatment received in different facilities depends on a number of different factors. However, for simplicity, in these scenarios, as in previous scenarios, it is assumed that all recrudescence and severe infections are treated in the public sector. Although this results in an underestimate of the cost of malaria to the patient and an overestimate in the cost of malaria to the provider, accurate data were not available.

8.7.2.2. Costs

If patients seek treatment in a public health facility, then the costs of consultation, diagnosis and treatment are assumed to be borne by the provider, whilst the patient bears the cost of transport, food and other consumables. If they seek treatment in the informal sector, then the patient bears all the costs.

In the “intervention” scenarios, in addition to the variable costs associated with the number and age of patients treated, there is an annual fixed cost of each intervention. All these costs are borne by the provider. The variable costs are the cost of the drugs and the cost of the RDTs, including the cost of the negative tests performed on patients who did not have malaria. To calculate the latter, based on the experience in Cambodia, it was assumed that the likelihood of a positive test was 25%, and therefore for every positive test, there were three “wasted” tests. This value is dependent on the prevalence of malaria and the treatment seeking behaviour of the population and can be varied depending on the setting.

8.7.2.3. Level of drug resistance

In Cambodia, the decision to switch to artesunate and mefloquine occurred when resistance to mefloquine was already well established in some parts of the country. However, it is of interest to explore the cost-effectiveness of ACTs in other similar settings where the level of resistance to the monotherapy is still low. Therefore the scenarios have been run with the switch being made at both 1% and 20% resistance to the monotherapy.

8.7.2.4. Treatment rate and time to receiving treatment

Although, treatment rates were around 85% in the primary data collection in Cambodia, a value of 95% is used in running the model for a number of reasons. Firstly, the model is structured with the assumption that malaria patients who are treated are relatively non-immune, and that those who are untreated are relatively immune. Therefore assigning non-immune symptomatic patients to the “untreated” group artificially increases the level of immunity of the population, with a potentially significant impact on the model outcomes. Secondly, as discussed previously, the result from the study in Cambodia does appear to be unusually low and the literature generally suggests higher treatment rates.

It was also assumed that the time interval between the development of symptoms and receiving treatment was not affected by the interventions. This assumption was made in order to simplify comparison across different scenarios, and because the findings from the study did not suggest a consistent relationship. The sensitivity analysis of the biological model suggests that varying the length of this time interval would not have made a significant difference to the outcome.

Table 8-10: Maximum failure rates input into sub-model to calculate overall failure rates

Maximum failure rates in non-immune host	If adherent	If non-adherent
Sensitive to mefloquine, treated with artesunate and mefloquine	2%	2%
Resistant to mefloquine, treated with artesunate and mefloquine	20%	40%
Sensitive to mefloquine, treated with mefloquine	5%	40%
Resistant to mefloquine, treated with mefloquine	85%	85%

Table 8-11: Calculated coverage rate and failure rates to monotherapy mefloquine (drug A) and the ACT, artesunate and mefloquine (drug AB) in non-immune host, as biological model inputs

Calculated inputs into biological model	Scenarios			
	No change	Change to ACT	Change to ACT + outreach	Change to ACT + VMV
Coverage rate with drug AB	0%	10%	32%	90%
Overall maximum failure rates				
Sensitive to drug A, treated with drug A	28%	28%	24%	13%
Resistant to drug A, treated with drug A	85%	85%	85%	85%
Sensitive to drug A, treated with drug AB	-	9%	7%	5%
Resistant to drug A, treated with drug AB	-	28%	26%	24%
Ratio of maximum failure rate with drug AB compared to drug A for infections <i>sensitive</i> to drug A	-	0.32	0.29	0.38
Ratio of maximum failure rate with drug AB compared to drug A for infections <i>resistant</i> to drug A	-	0.33	0.30	0.28

Why similar?

8.7.3. Results

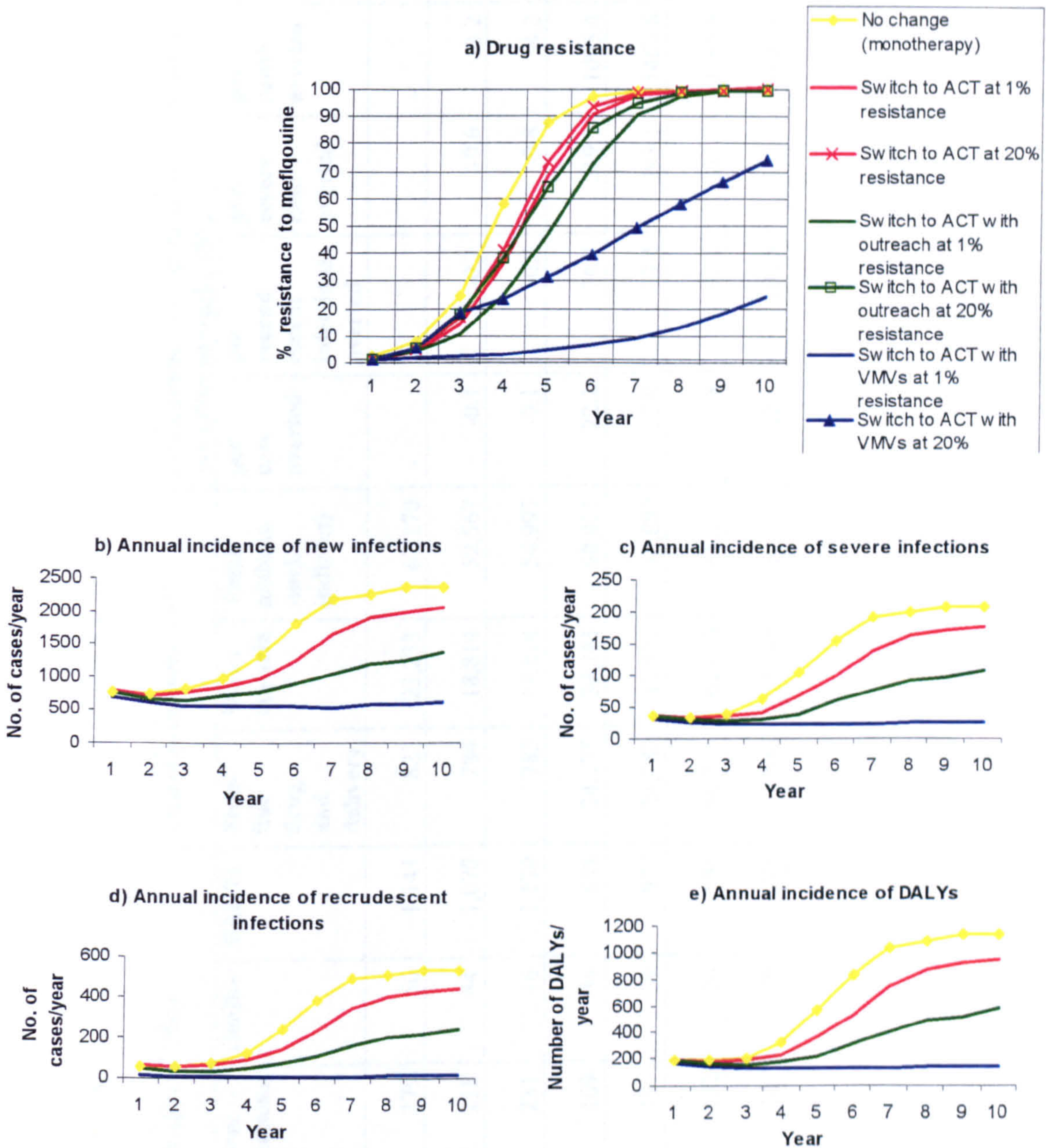
8.7.3.1. Effects

In Cambodia, the introduction of ACT, without any delivery interventions to improve access, resulted in a coverage rate with ACT of only 10%. Unsurprisingly, the model suggests that this would have little effect on the spread of resistance over time (Figure 8-25). However, because treatment with the combination results in cure of infections, which would have failed with monotherapy, there is still an impact on the number of recrudescence infections and transmission, whether the switch is made at 1% or 20% resistance to mefloquine (Figure 8-25). With a five-year time frame, if the switch to ACT is made at 1% drug resistance, then compared to monotherapy there are 12% fewer cases, 26% fewer recrudescence infections and 22% fewer severe cases and deaths. If the switch is made at 20% resistance the impact is slightly less marked (8%, 19% and 17% respectively) but by 10 years there is little difference between the cumulative results of the two scenarios. For clarity only the results from a switch made at 1% resistance are described in detail hereafter.

In Anlong Veng, the introduction of outreach increased the coverage rate with ACT to 32%. The model suggests that this incremental increase would have little effect on the spread of resistance but a significant effect on recrudescence infections, severe outcomes and transmission. Therefore, with a five-year time frame, if the switch to ACT is made at 1% resistance to mefloquine, the model predicts that compared to monotherapy there would be cumulatively 23% fewer new cases, 57% fewer recrudescence cases and 39% fewer severe cases and deaths compared to the monotherapy scenario (Table 8-12). At 10 years, the difference is expected to have increased, so that there would be 40% fewer new cases, 61% fewer recrudescence infections and 51% fewer severe cases and deaths (Table 8-13).

The introduction of VMVs increased the coverage rate with ACT up to 90% and as expected, the model predicts that this would result in a substantial impact not only on recrudescence, severe infections and transmission, but also on the spread of resistance to mefloquine as well. Because of this, the increase in the number of cases that is seen in the other scenarios is not seen with the introduction of VMVs and the incidence rates remain stable for the 10 years of the analysis.

Figure 8-25: Annual outcomes predicted by model for Cambodian scenarios⁷⁵



⁷⁵ For clinical outcomes and DALYs, only the results for the scenarios at which a switch is made at 1% resistance to drug A are shown. The results for a switch at 20% are very similar and if included make the figures difficult to read.

Table 8-12: Cumulative effects, costs and incremental cost-effectiveness of switching policy to ACT with and without interventions to improve coverage, with a 5-year time frame

Scenario (% level of resistance at time of switch)	Cumulative effects (No.)							Cumulative costs (US\$)				Incremental cost of drug and delivery intervention per effect averted (US\$)				
	New cases	Recrud- escent infections	Severe infections	Deaths	DALYs	First- line drug and delivery	Direct malaria	Total malaria (incl. indirect)	per case averted	per recrud- escent infections averted	per severe case averted	per death averted	per DALY averted			
Monotherapy (base-case)	4,624	564	279	56	1,343	823	23,233	62,270	-	-	-	-	-			
ACT only (1%)	4,083	420	218	44	1,070	784	18,814	52,567	-0.1	-0.3	-0.6	-3.2	-0.1			
ACT only (20%)	4,231	459	231	46	1,130	783	19,814	54,997	-0.1	-0.4	-0.8	-4.2	-0.2			
ACT with outreach (1%)	3,544	241	169	34	848	24,775	39,743	68,021	22.2	74.2	219.1	1095.4	48.4			
ACT with outreach (20%)	3,875	323	197	39	975	24,782	41,575	73,092	32.0	99.4	293.1	1465.6	65.2			
ACT with VMVs (1%)	2,967	64	132	26	666	46,811	62,416	85,123	27.8	92.0	313.1	1565.6	68.0			
ACT with VMVs (20%)	3,255	128	147	29	745	45,082	59,340	84,691	32.3	101.5	337.1	1685.6	74.0			

Table 8-13: Cumulative effects, costs and incremental cost-effectiveness of switching policy to ACT with and without interventions to improve coverage, with a 10-year time frame

Scenario (% level of resistance at time of switch)	Cumulative effects (No.)						Cumulative costs (US\$)				Incremental cost of drug and delivery intervention per effect averted				
	New cases	Recrud- escent infections	Severe infections	Deaths	DALYs	First- line drug and deliver	Direct malaria	Total malaria (incl. indirect)	per case averted	per recrud- escent infections averted	per severe case averted	per death averted	per DALY averted		
Monotherapy (base-case)	15630	3020	1241	248	5729	2527	89983	220096	-	-	-	-	-		
ACT only (1%)	12961	2258	965	193	4510	2272	70774	176591	-0.1	-0.3	-0.9	-4.6	-0.2		
ACT only (20%)	13296	2349	997	199	4653	2305	73099	182072	-0.1	-0.3	-0.9	-4.5	-0.2		
ACT with outreach (1%)	9305	1177	603	121	2871	48870	94547	167469	7.3	25.1	72.6	363.1	16.2		
ACT with outreach (20%)	10100	1374	674	135	3195	49420	99981	180122	8.5	28.5	82.7	413.3	18.5		
ACT with VMVs (1%)	5845	132	260	52	1313	87624	117079	158773	8.7	29.5	86.7	433.5	19.3		
ACT with VMVs (20%)	6256	282	301	60	1499	86486	116435	162329	9.0	30.7	89.3	446.6	19.8		

8.7.3.2. Costs

In terms of the annual drug cost to the provider over the 10-year period, the costs of switching to ACT without any delivery interventions is almost the same, or marginally lower, than the continued use of monotherapy (Figure 8-26 and Table 8-14). This is because although there is an incremental increase in the cost of drug per patient treated with ACT, there are fewer new cases overall than with monotherapy, and therefore the overall effect is that the drug costs remain almost the same. However, there is still a rise in the number of cases over time and therefore there is an increase in the cost of first-line drug. Most of this increase in cost is borne by patients, with the annual drug costs to patients doubling from around \$800 per year in the first year, to \$1,600 in year 10.

The introduction of the two delivery interventions increases the provider cost of first-line treatment substantially. For outreach, the annual cost remains constant over the 10-year period at approximately \$4,800 per year, and for VMVs, the annual costs falls, from approximately \$10,000 to \$7,800, if the switch is made at 1% resistance (Table 8-14). This compares to the annual costs of monotherapy or combination therapy, without any delivery intervention, which do rise over time but at year 10, only reach \$345 and \$326 per year respectively.

However, as expected, substantial cost-savings are experienced by patients as a result of the introduction of outreach or VMVs. This is both because the cost per case is less, since patients do not have to pay for drugs or transport, but also because overall, there are fewer cases than in the non-intervention scenarios. This is especially the case with the high coverage rates reached with VMVs where costs remain constant so that by year 10 the annual direct cost to patients for first-line treatment (inclusive of transport and other costs of consultation) is still only \$65. This represents only 1% of the total direct cost of first-line treatment. With the lower coverage rates achieved with outreach, on average, patients bear more of the treatment costs per case and there is a rise in the number of cases over time, so that by year 10, the total annual cost to patients is \$824 per year or 15% of the total direct costs. This compares to \$1,616 (84% of total costs) for introduction of ACT without any delivery intervention and \$1,849 (83% of total costs) for the continued use of monotherapy.

If the direct costs of malaria including the cost of severe and recrudescant infections are considered, then the broader economic impact of the different strategies can be appreciated. From Figure 8-26 it can be seen that initially, the annual direct costs of malaria directly reflect the provider and patient cost of first-line treatment. At the end of the first year, the costs are approximately \$12,800 in the VMV scenario, \$8,500 in the outreach scenario and \$3,400 in the non-intervention scenarios, with either monotherapy or with ACT. The direct costs in the VMV scenario gradually fall over the years, whereas after a few years, the costs in the other scenarios

rise, mainly due to the rise in severe cases. These costs plateau after drug resistance to mefloquine reaches 100% at around year 8. In this analysis, the level at which they plateau results in the direct costs of all scenarios falling between \$10,500 and 13,500, with the highest level being in the monotherapy scenario and the lowest level being in the combination therapy with VMV scenario.

By considering the total costs, inclusive of the indirect cost of lost productivity borne by households, we can get some indication of the societal costs of malaria with the different strategies. From this perspective, it can be seen that, although the addition of delivery strategies results in the initial total costs being higher, this difference is relatively small compared to the initial difference in direct costs. Thus, initially in the absence of any delivery interventions, the total annual cost is approximately \$10,000 (with or without a switch to ACT) and the addition of outreach and VMV brings these costs up to approximately \$15,000 and \$17,000 respectively. When annual indirect costs are taken into account, by the end of year 5, the VMV intervention becomes cost-saving relative to the outreach intervention, and the outreach intervention becomes cost-saving relative to the introduction of ACT without any delivery intervention.

8.7.3.3. Cost-effectiveness

In order to compare the cost-effectiveness of the different scenarios, the cumulative costs, effects and cost-effectiveness at five and 10 years are shown in Table 8-12 and Table 8-13 respectively, and the cost-effectiveness (CE) planes are shown in Figure 8-27. The latter compares the incremental cost of the first-line drug including the cost of delivery intervention, with the incremental effect in terms of DALYs averted.

Firstly, compared to the continued use of monotherapy, the introduction of ACT without delivery interventions is more effective and almost cost neutral and ~~therefore~~ is therefore definitely cost-effective. Secondly, as observed previously, the cumulative cost-effectiveness of all interventions increases the longer the time frame used. Thirdly, the cost-effectiveness of outreach and VMVs is very similar so that at 10 years the cost per DALY averted is \$16.2 with the outreach intervention and \$19.3 with the VMV intervention. This results in the appearance of the CE plane, which shows a linear relationship in moving from the introduction of ACT without interventions, to the introduction of ACT with outreach, and then to the introduction of ACT with VMVs.

Whether the policy is switched at 1% or 20% resistance to mefloquine has little effect on the costs, effects and cost-effectiveness because in this example, resistance rises to 20% by the end of year 3 and the avoidance of negative outcomes in the first couple of years is dwarfed by the magnitude of effects in later years.

Figure 8-26: Annual costs predicted by model for Cambodian scenarios (switching at 1% resistance)

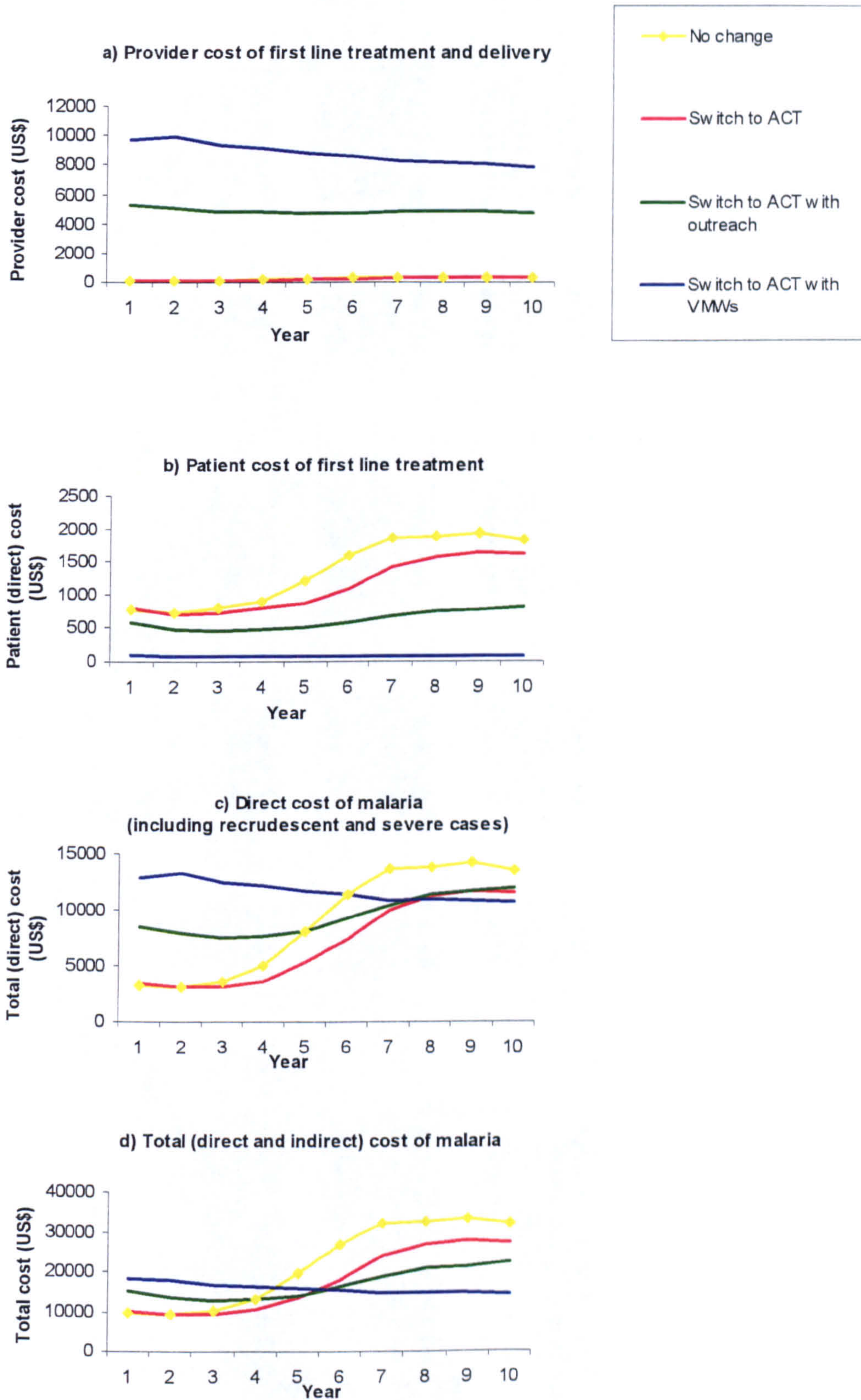
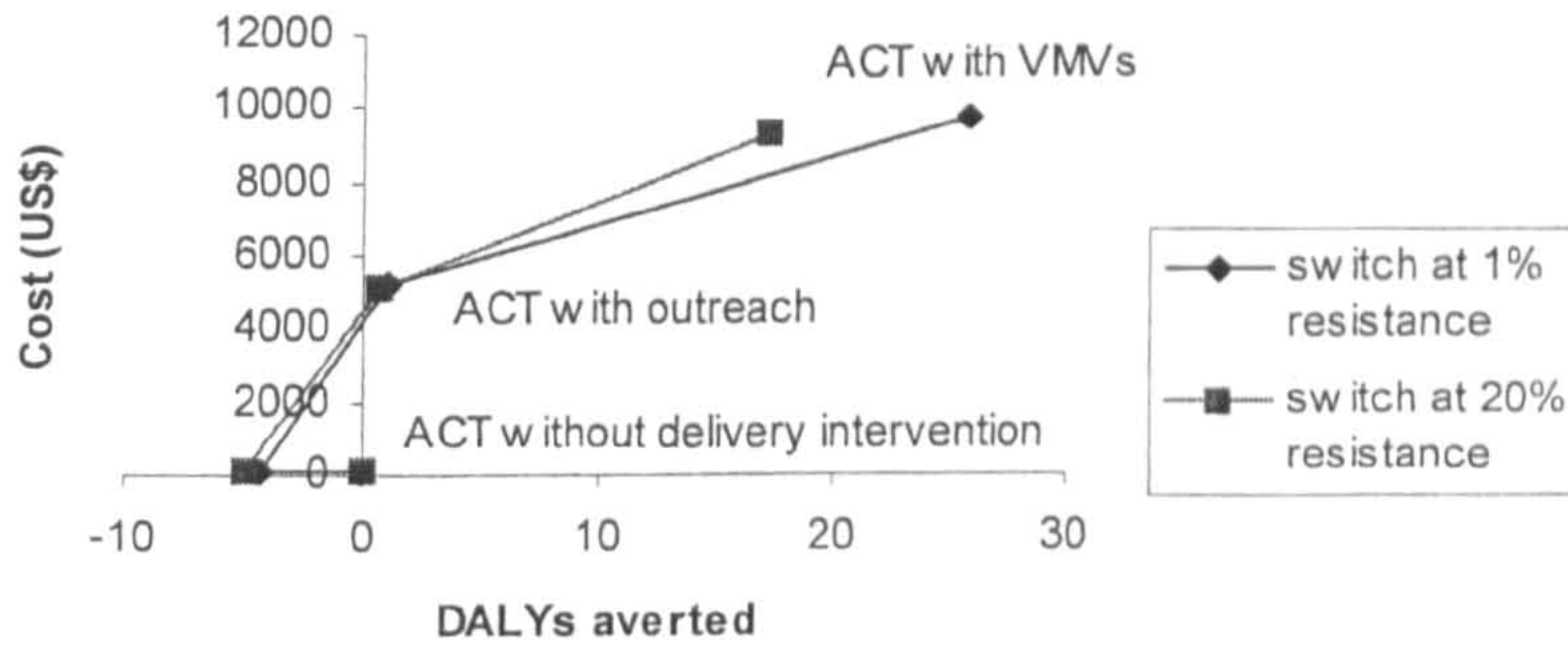


Table 8-14: Annual cost of first-line treatment and total (direct and indirect) costs showing distribution of costs between provider and patient (Switching at 1% resistance)

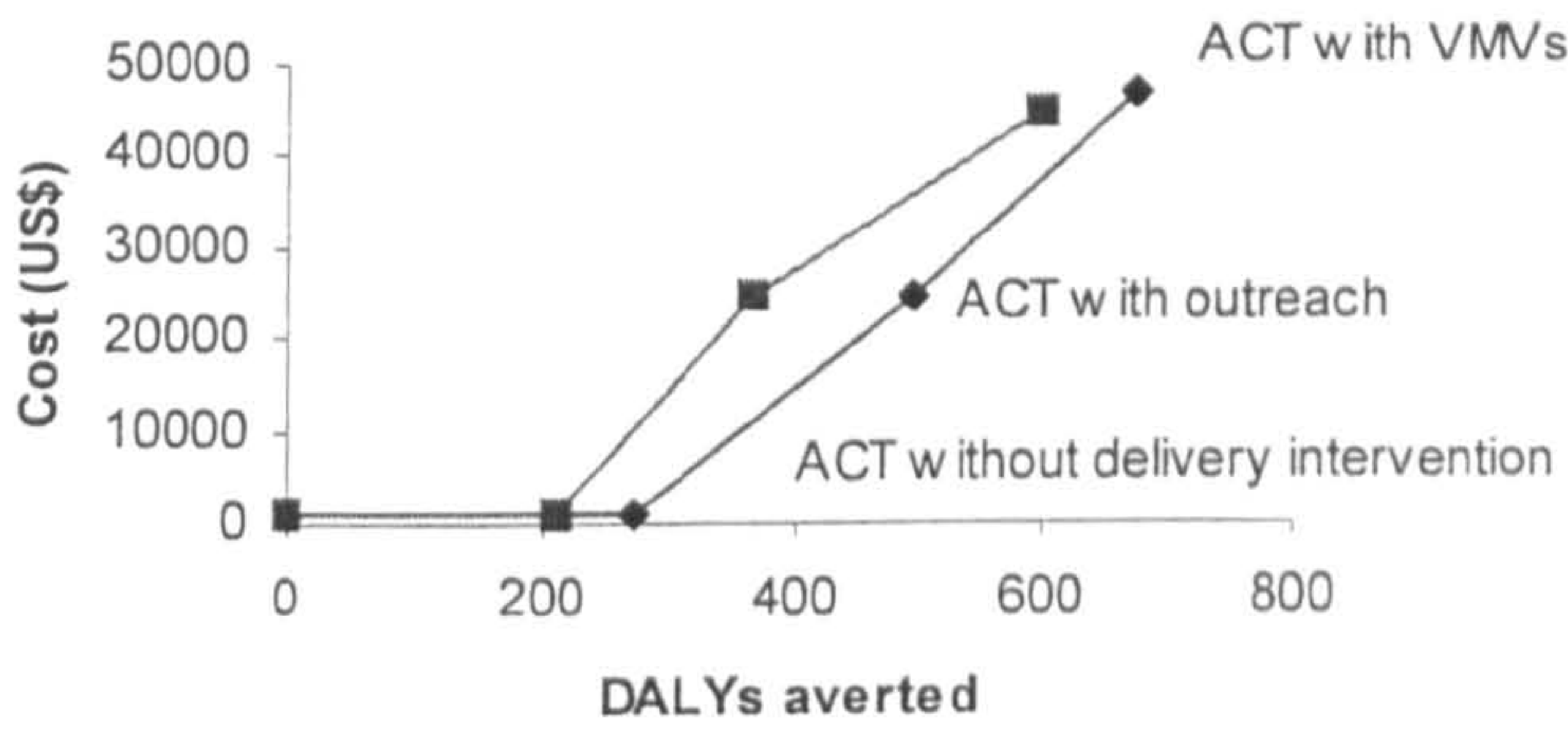
Scenario	Annual direct cost of first-line treatment including consultation, diagnosis, transport (US\$)			Annual total (direct and indirect costs) of malaria (US\$)			
	Total	Provider (% of total)	Patient (% of total)	Total	Provider (% of total)	Patient (% of total)	
At 1 year	No change	925	146 (16%)	779 (84%)	9,908	2,393 (24%)	7,515 (76%)
	Switch to ACT	946	153 (16%)	793 (84%)	10,163	2,465 (24%)	7,697 (76%)
	Switch to ACT with outreach	5,823	5,230 (90%)	594 (10%)	14,705	7,434 (51%)	7,271 (49%)
	Switch to ACT with VMV	9,794	9,699 (99%)	95 (1%)	17,375	11,547 (66%)	5,828 (34%)
At 5 years	No change	1,426	224 (16%)	1,202 (84%)	19,572	6,233 (32%)	13,339 (68%)
	Switch to ACT	1,053	177 (17%)	875 (83%)	13,340	4,027 (30%)	9,313 (70%)
	Switch to ACT with outreach	5,283	4,762 (90%)	521 (10%)	13,689	7,028 (51%)	6,661 (49%)
	Switch to ACT with VMV	8,870	8,802 (99%)	69 (1%)	14,291	10,116 (71%)	4,175 (29%)
At 10 years	No change	2,194	345 (16%)	1,849 (84%)	32,088	10,646 (33%)	21,442 (67%)
	Switch to ACT	1,942	326 (17%)	1,616 (83%)	27,435	9,014 (33%)	18,421 (67%)
	Switch to ACT with outreach	5,612	4,788 (85%)	824 (15%)	21,733	10,081 (46%)	11,652 (54%)
	Switch to ACT with VMV	7,897	7,832 (99%)	65 (1%)	13,078	9,098 (70%)	3,980 (30%)

Figure 8-27: CE planes comparing the incremental cost of first-line drug and delivery interventions with DALYs averted for the different Cambodian scenarios. The origin (or comparator) is the continued use of monotherapy

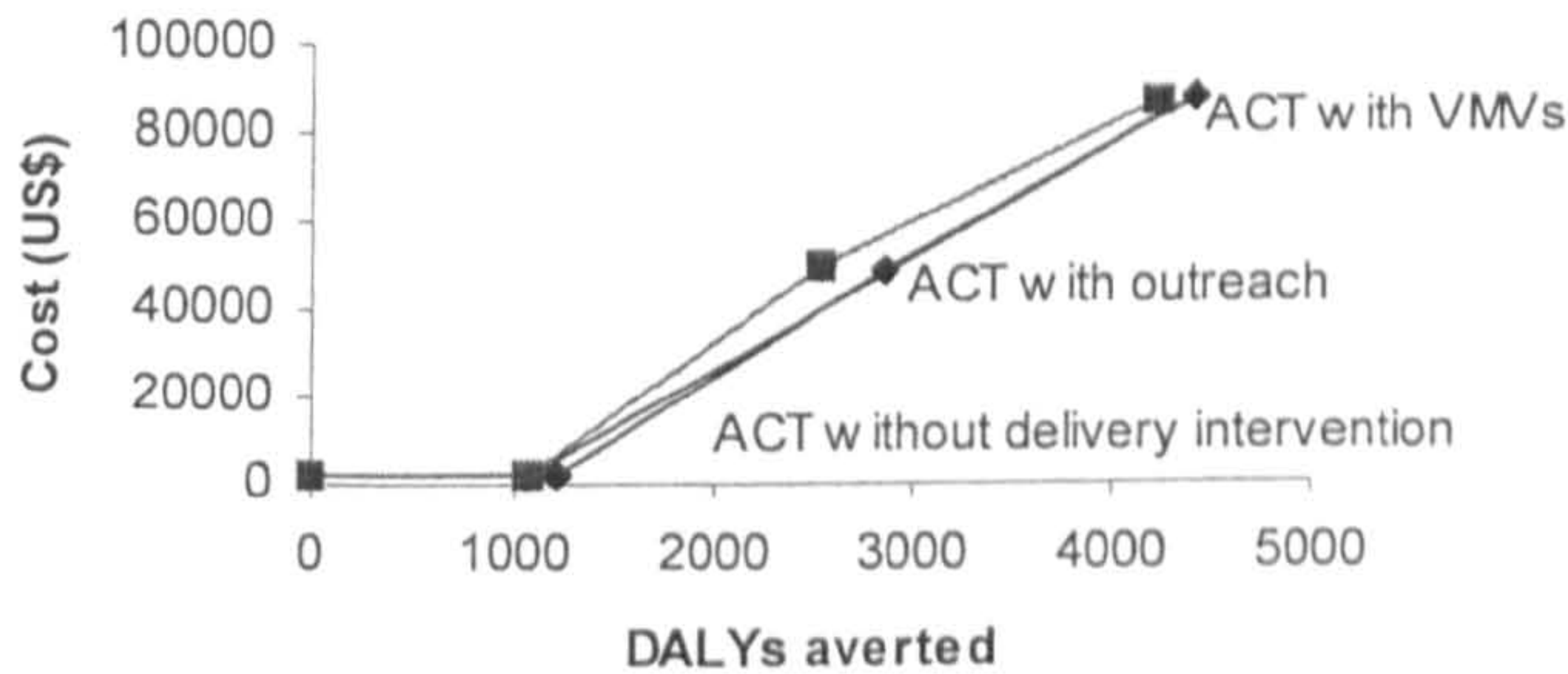
a) Incremental cost and effects of switching to ACT from monotherapy (1 year time frame)



b) Incremental cost and effects of switching to ACT from monotherapy (5 year time frame)



Incremental cost and effects of switching to ACT from monotherapy (10 year time frame)



8.8. Summary

In this chapter, the results from running the combined biological model and sub-models have been presented. The process of running the model showed that it was reasonably easy to apply and as hoped, could be adapted to explore the spread of drug resistance, malaria transmission and clinical outcomes in a wide range of scenarios. However it was also found that, because of the complexity of the model, it took a long time to run, with one scenario taking almost three hours. For the purpose of this thesis, the application of the model was focused on a low transmission setting, although a preliminary run of the model for a high transmission setting indicate that it will generate meaningful results.

In the base-case scenario, with the continued use of monotherapy, the model predicts that resistance spreads very quickly, going from 1% to 100% in six years, and this is associated with a 25-fold increase in recrudescence infections. This results in a 4-fold increase in the annual incidence of new infections and seven-fold increase in the number of severe infections and deaths. Because of the lack of immunity in all of the population, nearly all patent infections are symptomatic and treated and adults account for a large proportion of new infections. However, adults are assumed to have slightly more clinical immunity against severe malaria, which results in children making up a larger proportion of the cases of severe malaria and deaths.

The introduction of combination therapy with drug AB under ideal coverage (100%) or near ideal (80%) coverage results in a dramatic slowing in the spread of drug resistance and averts the rise in incidence of malaria and the consequences of treatment failure that are seen with the continued use of monotherapy. As a result, in these circumstances the introduction of ACT becomes cost saving within two years if the total annual direct costs of treating malaria are considered and within five years if the cost of the first-line drug alone is considered. The introduction of ACT is therefore clearly cost-effective with a cumulative cost per DALY averted of \$4.7 using a five-year time frame and \$0.4 with a 10-year time frame.

The results of the biological model were subjected to a sensitivity analysis conducted by WP. This indicated that the outputs of the biological model are particularly sensitive to the vectorial capacity. In addition, in a low transmission setting, other important biological parameters to which the model is sensitive include host susceptibility, the gametocyte switching rate and the duration of untreated infections. The drug and behavioural related characteristics that are important are mainly the treatment rate, coverage rate with ACT, the failure rate of drug resistant infections and the proportion of the population with residual levels of antimalarial drugs in their blood.

The cost-effectiveness of combination therapy compared to monotherapy was also subjected to a sensitivity analysis of the clinical outcomes parameters used outside of the biological model and to the assumptions made about discounting and DALYs. This suggested that the cost-effectiveness ratio was not substantially altered by changes in the rates of severe malaria and mortality, the use of discounting or the handling of DALYs.

In examining the effect of different drug costs on cost-effectiveness, the analysis clarified that it is the absolute difference in the cost between the monotherapy and the combination therapy that affects the incremental cost-effectiveness of combination therapy. Thus a switch from SP monotherapy to a combination of artesunate and SP is likely to be almost as cost-effective as a switch from mefloquine to artesunate and mefloquine. In order to compare this combination with artemether-lumefantrine, the model was run with changes in both the cost of drug and the characteristics assigned to the artemether-lumefantrine. The results suggest that at 100% coverage, and within the time frame of this analysis, the artesunate-SP combination remains both more cost-effective and more cost-saving than the artemether-lumefantrine combination, although they are both very cost-effective, costing \$2.3 per DALY averted and \$4.2 per DALY averted respectively at five years, and \$0.6 and \$1.0 respectively at 10 years. If the scenarios were run for a longer period or at a lower coverage rate, we would expect artemether-lumefantrine to become more cost-effective relative to artesunate-SP. This is because SP resistance would continue to spread in the artesunate-SP scenario, resulting in an increasing number of negative outcomes, and an increase in incidence of new infections and therefore first-line drug costs.

Achieving a high coverage rate with ACT (greater than 80%) was shown to be important in slowing down the spread of drug resistance to drug A, but is less important in terms of clinical outcomes and cost-effectiveness. Switching to ACT appears to be cost-effective at any level of ACT coverage, with the cumulative cost-effectiveness increasing with the length of time frame used. Therefore, even using a relatively short time frame of two years, the cumulative cost per DALY averted, at any rate of coverage, is less than \$60. This, is because, in addition to ACT being more efficacious, it has the externality benefit of reduced transmission resulting in fewer new cases. This in turn, leads to less potential for recrudescence infections, but in addition, leads to lower first-line drug costs thereby reducing the cost component of the cost-effectiveness ratio. Because the use of ACT is associated with a decrease in the first-line drug costs, ACT is actually cost saving relative to monotherapy after five years, even when the costs of severe and recrudescence infections are excluded. If these costs are included, then ACT becomes cost-saving within a shorter time frame.

The effect of the ACT coverage rate on the cost-effectiveness of combination therapy was explored further when the model was applied to the data collected in Cambodia, where the coverage rate was around 10%. Interventions to improve coverage add a considerable amount to the incremental cost of introducing ACT. Thus the implementation of an outreach service raised coverage to 32%, and resulted in increasing the cost of the first-line drug, inclusive of delivery costs, to \$4,800 per annum. The implementation of village malaria volunteers initially costs \$10,000 per annum, to raise coverage to 90%. This resulted in a cumulative cost per DALY at five years of between \$48 for outreach and \$68 for village malaria workers, if the switch is made when drug resistance to mefloquine is only 1%. At 10 years the cumulative cost per DALY is \$16.2 and \$19.3 respectively. Delaying the timing of the switch until resistance has reached 20% results in a slight decrease in cumulative cost-effectiveness, because resistance rises to this level in a short space of time. Thus, even with the additional costs required to increase coverage, the switch to combination therapy in these circumstances is still very cost effective. The additional resources required compared to the ideal scenarios mean that cost savings are less likely to occur. However, in this example, both interventions become cost saving by year 7 if only direct costs of malaria are considered, and by year 5 if indirect costs are also considered.

As expected, very different results were obtained when the model was run to simulate a high transmission setting. Under the continued use of monotherapy, the model predicted that resistance to drug A spreads much more slowly than in a low transmission setting and that the use of combination therapy has much less effect. In fact, in the combination therapy scenarios, if it is assumed that the proportion of the population who have inhibitory levels of drug A is the same in both settings, then the model predicts that resistance to drug A will spread faster in the high transmission setting. The model therefore predicts that the switch to combination therapy has less impact on clinical outcomes than in low transmission settings and no impact on malaria transmission.

CHAPTER 9

DISCUSSION I: METHODOLOGICAL STRENGTHS AND WEAKNESSES AND DISCUSSION OF RESULTS

The aim of this thesis was to produce a bio-economic model of the spread of antimalarial drug resistance, which could be applied to assess the cost-effectiveness of implementing ACT under different conditions and to collect the necessary data both to construct the model and to apply it to realistic situations. In this chapter the methodological strengths and limitations of the study are assessed and the research findings are summarised and discussed. In the next chapter the policy implications arising from the study are discussed and recommendations for further research are made.

9.1 Methodological strengths and weaknesses

9.1.1 Conceptual framework

Strengths

At the core of this thesis is an economic analysis of combination therapy in which the spread of antimalarial drug resistance plays the central role. Because of this, many of the difficulties associated with incorporating drug resistance into economic evaluations have been dealt with explicitly. These difficulties in the past have generally led to drug resistance being ignored in economic evaluations comparing management strategies of infectious disease (Coast, Smith et al. 1996; Coast, Smith et al. 1998). The problems such as the diffuse nature of the impact of drug resistance and the intergenerational nature of the externalities are implicitly dealt with because the model is population-based and constructed to measure the spread of drug resistance over time. In addition the effect of drug resistance on clinical outcomes and the long-term effect of the pattern of antimalarial consumption on drug resistance are elucidated. This study therefore takes a microeconomic approach. Although this means that the full impact of antimalarial drug resistance on the economy as a whole is not assessed, such a micro approach is essential for contributing to the accuracy of any macroeconomic analyses of antimalarial drug resistance (Smith, Yago et al. 2005). We know from macroeconomic studies of the impact of malaria (Sachs and Malaney 2002) and of antimicrobial drug resistance (Smith, Yago et al. 2005), that the health-care related costs are dwarfed by the impact on national income and productivity.

Another strength of the approach taken in this study is that the resulting model can be generalised to different settings. As recommended by Gold in guidelines for maximising the generalisability of economic evaluations (Gold 1996), it assumes the inclusion of a reference case alternative where the option taken is of “doing nothing” (the continued use of monotherapy). In theory, the simulation of a hypothetical state of no interventions – the “null case” scenario - is also possible, as advocated in the WHO guidelines on generalised cost-effectiveness analysis (Murray, Evans et al. 2000), but was not done here.

The development of the model was a multidisciplinary effort between a mathematician and myself. This did mean that at times the progression of the model was delayed whilst awaiting the collection or interpretation of data and conversely that the running of the full bio-economic model was dependent on the completion and correctness of the underlying biological model. However this collaborative approach was essential to ensure that the model was biologically plausible, and policy relevant as well as being mathematically correct, and its completion would not have been possible without both elements.

Limitations

There are two main limitations with the overall approach taken. Firstly, as mentioned this is fundamentally a microeconomic analysis and therefore the results presented here represent an underestimate of the negative impact of antimalarial drug resistance and the potential positive impact of combination therapy. Secondly, only the spread of drug resistance is considered and not its emergence. This preference for studying the spread rather than the emergence of antimicrobial drug resistance has been previously noted and is largely to do with the degree of uncertainty in the latter (Coast, Smith et al. 2002). One of the main rationales for the introduction of ACT is that it will delay the emergence of drug resistance (White 1999; Hastings and D'Alessandro 2000). The results from this analysis therefore underestimate the overall potential benefit of introducing ACT. However a biological model of the emergence and survival of antimalarial drug resistance is currently underway. Ultimately this “emergence model” will be dovetailed into the “spread model” presented here, enabling a more complete economic evaluation of the cost-effectiveness of ACT.

A third issue that may be considered a limitation is that this analysis focuses on antimalarial drugs and does not deal explicitly with other important aspects of malaria control, in particular vector control. Other studies have compared the cost-effectiveness of different malaria control strategies (Goodman, Coleman et al. 2000; Morel, Lauer et al. 2005). This model can, if necessary, be used to explore the implication of changes in vector dynamics and synergistic interactions resulting from integrating different strategies.

9.1.2 Primary data collection in Cambodia

Strengths

The main contribution of this study was that it was the first study to attempt to evaluate the implementation of a change in national antimalarial drug policy to an ACT. It was particularly useful because it included areas with delivery interventions aimed at increasing access to early diagnosis and treatment with ACT. The cost-effectiveness of these interventions could therefore be assessed not only in terms of increasing coverage but also in terms of effect on drug resistance and clinical outcomes by feeding data into the bio-economic model. Methodological advances of the study included the use of a drug identification board to assist the respondents in their recall of the medicines and the use of rapid diagnostic tests to indicate recent infection with *P. falciparum*. Although there are problems in the interpretation of the results of the latter, this appears to be the first time that they have been applied in the study of treatment seeking for "malaria" and may pave the way for further research on the definition of "malaria" and non-malarial illness. This may provide greater confidence on defining whether the treatment received by patients is appropriate or not.

The questionnaire itself was comprehensive, generating a rich amount of data that included information on both treatment seeking and adherence as well as socio-economic status and household costs. The inclusion criteria was limited to those who had experienced a malaria-like illness in the last three weeks and the information was gathered about specific episodes rather than general behaviour. This helped to reduce recall bias and to aid in the accuracy of the data obtained, as recommended in McCombie's review of studies of malaria treatment seeking behaviour (McCombie 1996).

This project was fortunate in having a research team that consisted of experienced and highly motivated research assistants all of whom had a background in health care and who were therefore able to seek clarification and to make appropriate explanations during the process of the interviews. It could be argued that this could have led to a bias by influencing respondents to answer in a particular way, for example to try to give what they thought were "correct" answers. This would have most likely lead to an overestimation of adherence and to have resulted in the cost estimates either being too high (if respondents thought that there was a possibility of compensation for the costs paid for treatment) or too low (if they were charged fees for supposedly free services and did not want to implicate the provider). There is also a danger that the research assistants may unwittingly influence the answers given, based on their medical knowledge. However the trade-off was that the quality of data was good and that there was a high participation rate. The latter was probably due to a combination of factors including the fact that participation was perceived to be potentially beneficial, as it could result in a blood

test and if appropriate, anti-malarial treatment. This could have also led to some respondents to answer the screening questions positively in order to be included in the study. Although this would possibly reduce the reliability of the results, it is difficult to predict how this would have led to a systematic bias in individual responses. Reassuringly, the findings in this study were generally in keeping with other similar studies in Cambodia using lay people as research assistants and therefore substantial systematic bias is unlikely.

Limitations

The main limitations of the Cambodian survey are that the sample size was relatively small and that the sample selection was purposive up to the point of the health-centre catchment areas sampled. This was largely due to difficulties related to carrying out fieldwork in the remote areas in which malaria occurs. Many communities were located far from roads and reached only by motorcycle, ox-cart, canoe or by foot through dense forest. In order to capture malaria treatment seeking behaviour, the study was conducted during the wet season when road conditions were at their worst. In addition, in some areas there was a risk of unexploded landmines, which further limited access. The sample size from the VMV intervention area was particularly small, with only two villages included. For political reasons, the study had to be withdrawn early from the area.

The main consequence of the small sample size is that some of the apparent differences between intervention and non-intervention areas failed to reach statistical significance, after adjusting for study design. This was particularly the case for outreach areas because although the sample size was larger than from the VMV areas, the differences were much less marked and therefore less often reached significance. The small sample size also meant that relatively few children and pregnant women were included. Of note was low numbers of children aged five years or younger. This in part reflects a difference in exposure, as children often stay behind in the village, whilst adults go to work in the forest where malaria transmission occurs.

Although the sampling was purposive up to the health-centre catchment areas, the selection process should have ensured that the results were representative of those villages affected by malaria in those areas. Within each village, all households were seen. For a more widely representative sample, it may have been preferable to randomly select a proportion of households and to sample from more villages; however this was not possible within the time and resource available. Malaria transmission in Cambodia varies widely, and the sampling strategy chosen enabled us to collect useful data about treatment seeking behaviour for malaria in villages that were believed to have malaria transmission without wasting limited time and resources in villages with no malaria transmission. Although the results cannot therefore be extrapolated to the rest of the country, the areas were chosen by local experts to represent the

range of settings in which malaria is transmitted in Cambodia and the results were not dissimilar to the much larger, systematic survey that was carried out the following year (Duzey, Kim et al. 2003), suggesting that the results were reasonably representative.

A potential source of bias is that only the households in which an adult was present on the day of the interview were included. This could result in a bias towards villagers who tend to stay in the village and against those who worked and stayed in their “chamkars” - plots of farming land in the forest. The latter group are at the highest risk of being infected with malaria and may behave differently in relation to seeking and taking treatment. In order to avoid this problem, as far as possible, communities were forewarned of the day of the study. In addition, the timing of the study itself was at the beginning of the wet season, when planting had already taken place and harvesting was yet to happen, and therefore village occupancy was close to a maximum.

In terms of the actual data collection, the questionnaire itself was initially quite difficult to administer. This was because it had been designed with the intention of capturing information on preceding episodes of fever as an indication of chronic, untreated infections or re-infections. The team of research assistants was small and highly motivated and were soon able to undertake the interview without problem. In addition, there were potential disadvantages of the drug identification board. Many drugs look alike and respondents may have had a tendency to positively identify drugs as one thing when in fact they may have taken a completely different but similar looking drug.

The study had a number of other limitations which are general to studies of treatment seeking behaviour and adherence rather than specific to this particular one.

As in other studies of “treatment seeking behaviour” for malaria, it is not actually known whether or not patients who sought and took treatment for malaria actually had malaria. As a consequence the appropriateness of their management is difficult to judge with any certainty. If they did not really have symptoms of malaria, then they may not have warranted a diagnostic test and should not have received A+M, in which case their management would, in fact, have been “appropriate”.

In order to go some way to addressing this problem, RDTs were utilised based on the evidence that the HRP2-based tests, such as Paracheck®, remain positive for a few weeks following treatment (Mayxay, Pukrittayakamee et al. 2001). However the likelihood of a test being positive is not only related to whether or not a patient had *P. falciparum* malaria but also when they had it, the level of parasitaemia and the efficacy of the treatment taken. Therefore although the interpretation of a positive test was fairly straight-forward (i.e. the patient has or has had *P.*

falciparum malaria in the last few weeks), the interpretation of negative tests was more difficult. For example, a patient who had a low grade parasitaemia two weeks previously and had received a full course of A+M, could well be Paracheck® test negative by the time of the survey and would be impossible to differentiate from a patient who never had malaria. This difficulty in interpretation is highlighted by the finding that there were significant differences between intervention areas in the proportion of patients who had reportedly recently had a positive test and who were RDT test positive test on the day of the test.

Adding blood tests to the study also added a potential bias. For ethical reasons, patients who were symptomatic and who tested positive were treated with A+M. This may have resulted in respondents tending to answer the screening questions positively in order that themselves or their children would be included in the study. To overcome this potential bias, currently ill patients could have been excluded. However it was felt that it was important to document the lack of access to effective treatment, which would be reflected in malaria patients who had ongoing symptoms for several days. Reassuringly comparison of these results with those of the national drug usage survey, where inclusion criteria were similar but blood tests were not performed, showed similar inclusion rates.

However, as in all studies where data are based largely on self reporting, there still remains the problem of reporting bias. This was of particular concern for adherence as this was one of the main objects of the study. Attempts were therefore made to triangulate the self-reported data, firstly by asking respondents to produce the packaging and remaining medication and secondly by taking a small blood sample (200µl) on filter paper from patients who reported to having taken A+M, in order to establish the presence and quantity of mefloquine in their blood. The aim had been to compare the levels found with established population pharmacokinetic profiles in order to estimate the likelihood that an adequate dose had been taken. However because of the small number of respondents who reported to having taken mefloquine (n=44), it was not economically feasible to complete this part of the study. This reflects one of the other challenges inherent in attempting to capture both treatment seeking behaviour and adherence to specific antimalarial treatments in one study.

In order to specifically study adherence to A+M, other possible approaches would have been to identify patients who had been prescribed A+M and then to follow them up at home. However, if patients are informed that they will be followed-up at home, this may alter their behaviour so that they are more adherent than they would have been, had they not been aware of being observed (the "Hawthorne effect"). Providers may also behave differently, giving more information to patients to ensure that they understand how to take the drugs. Following-up patients without them having been informed is problematic both ethically and practically as

detailed descriptions of where they live are necessary in order to ensure successful follow-up. To validate the results in this study, the findings were compared to the results of the larger survey undertaken the following year.

Like most other studies of community-based interventions, this was an observational study of interventions that had already been implemented. We do not therefore know what the patterns of behaviour were preceding the interventions and do not know how much of the observed differences between the three intervention “groups” were due to the interventions. However as far as possible, non-intervention areas were chosen to be comparable to the intervention areas in terms of accessibility to health centres and markets, size of villages and estimated malaria prevalence.

9.1.3 Secondary data collection

The process of collecting secondary data resulted in the production of a comprehensive data base of parameter estimates, which revealed important gaps in data that will be important to address with future research, if more accurate predictions of the impact of ACTs on antimalarial drug resistance and malaria transmission are to be realised.

9.1.3.1. Review of antimalarial drug usage studies

Strengths

In Chapter 5, a review of antimalarial drug usage was presented, focusing on adherence to drugs, interventions to improve adherence and information linking clinical outcomes to the use of drugs outside of clinical trials. The main methodological strength of this part of the data collection was that the search of the literature and the inclusion and categorisation of the studies were performed systematically, resulting in a comprehensive review of the literature, allowing conclusions on the state of the available evidence to be made confidently.

Limitations

The limitations are mainly a result of the nature of the studies under review, in that the methodologies, settings and drug regimes varied greatly with studies being of poor quality, so that comparing and generalising from the studies was difficult.

9.1.3.2. Other parameter estimates

Strengths

The rest of the parameter estimates were collated and presented in table format. The main methodological strength of this part of the study is that it covers a broad range of parameters important in the biology and economics of malaria and antimalarial drug resistance. Modelling is often criticised for being opaque and there is often an underlying suspicion that specific

values are selected in order to produce desirable results. Obtaining estimates from several sources of data and presenting them in table format makes the process of parameterization more transparent. The process revealed important gaps in the data and by sharing the tables with other groups (Dean Jamison, Ric Price, Karen Barnes), further information and feedback was obtained. Moreover, the tables proved to be a useful resource, enabling others to bypass the time- and resource- consuming step of collecting all the necessary data for modelling the biology and economics of antimalarial drug resistance.

Limitations

The main limitation of the parameter tables is that they contain only the parameters that are used in the construction of this particular model, and models that are structured differently may require different data, for example disaggregated data for vectorial capacity or similar data but measured or expressed differently. Another inevitable limitation of any collection of secondary data is that new data are continuously being generated and therefore the information requires regular updating. However, since the production of the earlier versions of the parameter tables, it has been relatively easy to locate and update parameters as new data emerge.

9.1.4 Development of the bio-economic model

Strengths

This study has produced a new model of the spread of drug resistance designed to examine the effectiveness and cost-effectiveness of combination therapy in achieving better cure, delay in resistance and possible reduction in transmission in low transmission settings. It is a more comprehensive model than previous models, incorporating a wide number of factors including those related to the dynamics of malaria infection, host immunity, human behaviour, drug and vectorial characteristics. By integrating the costs of the drugs, delivery costs, cost of severe malaria and cost of interventions, the model can be used to compare the cost-effectiveness of different drug policies in different epidemiological settings. New approaches have been explored and an extensive amount of data incorporated resulting in a comprehensive model. Its application to a number of scenarios proved that it is usable and flexible enough to be adapted to answer a range of questions and to explore phenomena that could not previously have been explored using existing models. The interrelationships between factors are complex and the resulting outcomes are unpredictable. In creating the model a constant balance had to be struck between making the model realistic and avoiding it becoming overly cumbersome. The final product represents a compromise between reality and simplicity.

Most previous economic analysis of antimalarial drugs have focused on the immediate benefits of using a more efficacious drug in affecting clinical cure in the face of drug resistant malaria (Sudre, Breman et al. 1992; Phillips and Phillips-Howard 1996; Wilkins, Folb et al. 2002;

Gogtay, Kadam et al. 2003; Muheki, McIntyre et al. 2004) but have disregarded the effect of changing therapy on the course of drug resistance itself. Where drug resistance has been included, it has been assumed to rise at a fixed rate irrespective of drug treatment (Schapira, Beales et al. 1993; Coleman, Morel et al. 2004; Morel, Lauer et al. 2005). However, these models have not allowed any feedback so that, for example, different patterns of drug usage on transmission and spread of resistance could not be explored.

However, the potential for ACTs to delay the development of drug resistance has been one of the main rationales used in advocating the change in global drug policy from the use of single drugs. Therefore it is important that we have some indication of the size of this potential effect, and that an economic analysis of ACTs explicitly makes predictions of the effect on the evolution of drug resistance. For this a biological model of malaria drug resistance is required.

Most existing models of antimalarial drug resistance have come from the perspective of population biology, where the emergence, survival and spread of a single resistance clone is tracked (Curtis and Otoo 1986; Dye and Williams 1997; Hastings 1997; Mackinnon 1997; Hastings and D'Alessandro 2000). These models have elucidated the important factors in the emergence and spread of resistance within the parasite population but do not tell us about the distribution and spread of infections through the human population and the effect of immunity and human behaviour. In contrast, epidemiological models focus on the infections in the human host and mosquito host. However until recently epidemiological models had not been used to explore drug resistance (Koella and Antia 2003). Laxminarayan based an economic analysis of switching from monotherapy to an ACT on such a model (Laxminarayan 2004a). However, like other epidemiological models a number of important factors were either not treated realistically or explicitly, including: immunity, clinical outcomes, infectiousness, pharmacokinetics and pharmacodynamics.

Looking beyond the field of malaria did not prove fruitful in terms of models or approaches that could be adapted for use in this analysis. Most studies were based in hospitals, in developed country settings and dealt with anti-bacterial resistance (Wilton, Smith et al. 2002). There are many reasons why these are unsuitable for adaptation for an economic analysis of antimalarial drug resistance. These include basic biological differences between bacteria and *plasmodium*, including mode of transmission, the mechanism of how drug resistance evolves, the consequences of drug resistance, the long term carriage of infections and the role of host immunity. There are also differences in terms of the population and settings involved and the approaches to the control of drug resistance.

Therefore the development of this model represents a contribution to the field of malaria modelling and to the field of economic analysis of antimicrobial drug resistance.

One of the central aims of the model was that it could be used to explore the effect of transmission intensities on outcomes. This was in order to address concerns about the extent to which the successful implementation of ACTs in low transmission settings could be replicated in high transmission settings (Bloland, Ettlign et al. 2000). The transmission intensity is varied by setting the vectorial capacity at the beginning of a scenario to reflect a given transmission intensity. Feed-back is achieved by allowing the daily entomological inoculation rate (EIR) to vary during the running of the model according to the infectiousness of the population as expressed by gametocyte density in the human population.

Had the aim of this model been limited to the exploration of the spread of resistance in a high transmission setting, then it would have sufficed to use differences in clinical outcomes themselves to describe different transmission intensities (Goodman, Coleman et al. 2000). In high transmission settings, disease incidence is unlikely to be affected by ACTs and the main outcome of interest is the cure rate and the effect on the spread of drug resistance. However, in low transmission settings, transmission intensity may vary considerably depending on a number of factors including drug resistance, vector control and climatic changes (Craig, Kleinschmidt et al. 2004a; Craig, Kleinschmidt et al. 2004b). This would be expected to have an impact on the immunity of the population and to feed-back to the incidence of new infections. These changes are not captured in models that do not incorporate immunity.

The realistic modelling of immunity is therefore a unique and core part of this model. The effect of change of transmission intensity on different facets of immunity is manifest through "immunity functions" derived from EIR and age-stratified data on parasite density, symptomatic malaria and severe malaria. Moreover, using different clinical data to describe different "facets" of immunity adds an extra layer of sophistication to the model by simulating the differential rates of acquisition of different aspects of immunity.

The other advantage of incorporating immunity into the model in this way is that it leads to the population being stratified by age. This allows the change of inputs on the outcomes in different age groups to be explored and means that if necessary inputs can vary by age. An example where this might be useful is in the targeting of combination therapy at children only.

This model allows the introduction of new "migrant" or dormant infections. This is important in low transmission settings where infected migrants ~~for~~ ^{from} high transmission areas can be important in the maintenance of malaria infection in the population (Craig, Kleinschmidt et al.

2004a; Zhou, Sirichaisinthop et al. 2005). By allowing these “new infections” only to occur over a few months each year, the re-emergence of infections that have remained sub-patent over a dry season can also be simulated (Roper, Elhassan et al. 1996; Babiker 1998).

Another unique feature of the model is that it allows for a certain proportion of the human population to have inhibitory levels of antimalarial drugs in their blood. This proportion can be varied according to the rate of antimalarial drug usage in the population and the half-life of the drug in question. Although in the current model, this level does not vary by coverage, age group or resistance, the model could be modified if these were felt to be important.

Limitations

The model is a result of compromise between comprehensiveness and parsimony. The main “limitations” of the model therefore lie on either end of this axis. Thus, there are assumptions made which simplify reality but result in a loss of detail and there are details included which results in the model being more “realistic” but more complex. At each point the decision of which details to omit and which to include was made based on how important they were thought to be to the outcomes of the model, practically how easy they were to incorporate and whether the appropriate data were available. The model is complex because of the number of factors that it attempts to incorporate realistically. However it is also basically a deterministic population-based model in which homogeneity is assumed within each age group.

The differences between individuals or groups therefore cannot be explored and the inter-household risks of exposure to mosquitoes or differences in immunity between different racial groups are ignored. To explore the effect of this level of micro-heterogeneity within the population on model outcomes requires a model that tracks each individual in a population through time. Such an individual-based model would have added another layer of complexity and would have required far more computational power than was available. The current model as it stands is already fairly comprehensive and entails a long programme script with multiple arrays and loops. The programme in which it is written (Splus®) is not particularly user-friendly, making it difficult to understand, check and modify. It is also time-consuming to run, taking up to three hours for one scenario over 12 years, depending on the computer used. Although this is partly due to the choice of programming language, it is also because the model iterates on a daily basis. It could be argued that this level of sensitivity is unnecessary and that iterations every five, seven or 10 days would have sufficed, as the minimum period in any state in the malaria transmission cycle is around 10 days. However reducing the iterations to single days does allow for the exploration of factors such as the delay in obtaining treatment and the duration of treated infections for which the differences are counted in days.

One of the main reasons for the complexity of the model lies in the incorporation of immunity and there were a number of limitations with the construction and use of the immunity functions. In general, the functions were based on a few age-stratified datasets at different transmission settings. Whilst the resulting functions described a “best fit” to the data, it is possible that the data were not representative for that particular EIR or that definitions of methodologies in collecting the data resulted in differences which were falsely assumed to be due to differences in age or EIR. However for the immune function used most frequently in the model - the function describing the relationship between parasite density, age and EIR – individual-level data were used and checks were made with the authors to ensure that the methods of quantifying the parasite densities were comparable.

Another possible criticism of the model is that the effect of immunity is exaggerated by re-applying the same immune function in a number of places in the model. Thus the immune function based on parasite density is used to describe the relationship between age and parasite density and is then used to determine the relationship between age and duration of infections. However it is known that immunity does have important effects at several stages in the pathophysiology of malaria. It is not unreasonable to assume that the mechanism limiting the maximum parasite density reached in an individual, is the same mechanism that eliminates existing parasites from the bloodstream and therefore the duration of infection. To check for the robustness of the model to uncertainties in the immunity functions, it would be desirable to undertake a sensitivity analysis, varying the immune functions used.

Like previous models of antimalarial drug resistance (Hastings 1997; Koella and Antia 2003; Laxminarayan 2004a), it is assumed that infections are caused by single clones so that once humans are infected, they cannot acquire another infection until they have cleared the original infection. However, in reality, often humans and sometimes mosquitoes carry two or more infections at any one time, especially in high transmission areas. This assumption may have implications for the outcome of the model in terms of transmission intensity, host immunity, and the spread of drug resistance. Allowing superinfection would mean that both infected and non-infected humans would be equally likely to be inoculated at the beginning of each iteration and this may result in an alteration in the course of the pre-existing infection in terms of parasite density, gametocytogenesis, virulence and duration of infection and therefore the transmission of individual clones (Paul, Lafond et al. 2004). However these intra-host dynamics have not yet been fully described, with sometimes contradictory results and therefore these have not been incorporated into the model.

In relation to immunity, there is evidence that some aspects of immunity are clone-specific and therefore the acquisition of immunity depends on the clonal variation of infections as well as the

number of infections. In this model, there is no differentiation between different clones and it is assumed that all infections contribute equally to the infectious pool and have the same effect on host immunity. This was felt to be justifiable as there are insufficient data to describe this effect accurately. In addition although the model assumes a single clone, the data on which the immunity functions are based are derived from studies in which the number and types of clones in the individual infections are not known.

How clonal multiplicity affects the development of drug resistance is more important in this model. This is because during recombination, when genetic material is exchanged between different clones during the sexual stage in the mosquito, genetic mutants that confer resistance can either be broken down or produced. These recombinations are much more likely to result in the loss of resistance rather than a gain of drug resistance (Dye and Williams 1997) and therefore the more clones within each infection the less likely it is that resistance will be retained in the population (Hastings and D'Alessandro 2000). In addition, genetic mutations that confer resistance may also result in a survival disadvantage to the mutant in the absence of drugs. This is known as a "fitness cost" of drug resistance (Peters, Chen et al. 2002). Therefore in untreated infections, if a resistant clone co-exists with a sensitive clone, the latter is more likely to survive. This is supported by observational data which suggest that discontinuation of chloroquine and mefloquine has resulted in a decrease in resistance to those drugs (Brockman, Price et al. 2000; Kublin, Cortese et al. 2003). However, we also know that even before the use of a drug, resistance is present at low levels in many populations, in particular for quinine and proquanil (Peters 1987), suggesting that for some drugs the fitness cost is low enough to allow the mutant to survive in the absence of drug pressure. In this model we have assumed that ~~therefore assumed~~ that there is no fitness cost.

In high transmission settings, resistant mutants are therefore less likely to survive because infections are more likely to be multi-clonal and are less likely to be exposed to drugs than in low transmission settings. In reality the effect of multiple clones can both favour and disadvantage the spread of drug resistance and the balance of these effects are likely to vary depending on transmission intensity (Talisuna, Erhart et al. 2005).

Similar to most previous population genetic models of antimalarial drug resistance (Hastings 1997), (Curtis and Otoo 1986; Dye and Williams 1997; Koella and Antia 2003), this model assumes that there are only two gene classes in the population: fully sensitive and fully resistant. The main consequence is that the relationship between the half-life of a drug and the impact of chemoprophylaxis cannot be fully explored in the model. The duration of the "period of chemoprophylaxis" is important for the spread of drug resistance (Watkins and Mosobo 1993) and the implications have been extensively explored in a previous study by using an

intermediate level of susceptibility (Hastings, Watkins et al. 2002). To avoid the complexity that this would involve, the model incorporates this phenomenon simplistically as a variable proportion of the population with inhibitory levels of an antimalarial drug in their blood.

The other limitations of the model relate to some of the simplifying assumptions made and how certain relationships with age are handled. Thus treatment rates for symptomatic infections, coverage rates with ACT and adherence to therapy are assumed to be independent of age. In fact these may vary by age depending on a number of factors including the source and type of treatment. However it was felt that there were insufficient data on which to base the values and that varying them by age would make the findings more difficult to interpret.

In considering the consequences of malaria, only the direct consequences of malaria in terms of acute infections and neurological sequelae of severe malaria were considered. Therefore the role of malaria in causing anaemia and the effects of anaemia on growth and development were ignored. There is an increasing amount of data elucidating the link between malaria and anaemia (Brabin, Prinsen-Geerligs et al. 2003; Korenromp, Armstrong-Schellenberg et al. 2004) and demonstrating the effect of anaemia on cognitive and motor development and growth (Grantham-McGregor and Ani 2001). Similarly the effect of co-morbidity with acute bacterial infections (Berkley, Lowe et al. 2005) and with HIV were not considered (Francesconi, Fabiani et al. 2001; Grimwade, French et al. 2004). However there remain substantial gaps in our knowledge and it was felt to be clearer to omit these outcomes and to be aware that the estimated outcomes therefore represent an underestimate of the morbidity and cost of malaria.

The consequences of malaria in pregnancy were also not included. Pregnant women are relatively immune compromised compared to non-pregnant adults and are thus not only more susceptible to malaria but are also at a higher risk of going on to develop severe malaria and severe anaemia. The consequences to the foetus and newborn include miscarriage, stillbirth, intrauterine growth retardation and low birth-weight. The consequences of low birth-weight are multitude and include a higher risk of mortality and infection. Malaria in pregnancy is therefore a serious and often overlooked problem that requires a focused study. Incorporation into the model would have required creating a sub-population of women of child-bearing age and assigning to them a lower level of immunity and calculations of the likelihood of pregnancy and the likelihood of adverse outcomes. The effect on the overall model outcomes would be higher rates of morbidity, mortality, costs and DALYs. It would also be expected that the infectiousness of the population would be greater and therefore the transmission intensity may be marginally higher in low transmission settings.

9.2 Summary of results

In this section the findings of the thesis are summarised and discussed starting with a summary of the results from the collection of secondary and primary data. This is followed by a review of the key factors affecting transmission of malaria and the spread of drug resistance in the model and a summary of its application.

9.2.1 Primary data collection

The aim of the data collection in Cambodia was to assess the coverage of ACT and the adherence to therapy in non-clinic settings and to estimate the cost and effectiveness of interventions aimed at increasing access to diagnosis and appropriate treatment. As described in the background, Cambodia is not unlike many settings in sub-Saharan Africa in terms of poverty and poor healthcare infrastructure. It is also heavily dependent on foreign financial and technical assistance. Although care has to be taken in extrapolating the results to other settings, they do serve as an indication of the possible problems in implementing ACTs and of the range of costs and effectiveness of interventions in such settings.

9.2.1.1. Costing

The cost of an adult dose of artesunate and mefloquine (A+M) blister-packaged in Cambodia was around \$3.80. This compares to around \$2.40 for a course of artemether-lumefantrine or \$1.30 for non-fixed combinations of artesunate and SP or artesunate and amodiaquine. Although mefloquine is relatively costly compared to these other potential partner drugs, much of the difference in cost was due to the inefficiencies in production. The Cambodian cost could potentially be reduced to around \$2.60 if production was more efficient. Even at this cost, the difference between mefloquine monotherapy at \$1.11 for an adult course and blister-packaged A+M is substantially less than the difference between the ACTs and the current monotherapies in sub-Saharan Africa. This has obvious implications in terms of the cost-effectiveness of ACTs and also has implications in terms of the role of diagnostic tools in rationalising their use.

The annual fixed costs per capita of increasing access to diagnosis and treatment with the outreach and VMV interventions were \$0.44 and \$0.69 respectively. However the settings were not comparable, with a higher prevalence of malaria and poorer access to markets in the villages where VMVs were piloted compared to the area serviced by outreach. Therefore many more patients were screened and treated in villages with VMVs and when the costs per patient seen or per patient treated are considered, the estimated fixed costs were less for the VMV scheme at \$1.20 and \$2.66, compared to \$2.66 and \$12.75 in outreach areas, respectively.

9.2.1.2. Community-based study of treatment seeking behaviour and drug usage

The key findings in this arm of the study were that the coverage rate with ACTs and biological diagnosis was very low (8% and 17% respectively), the use of artemisinins as monotherapy was rife (78% of artemisinin use overall) and that both the VMV and outreach interventions significantly improved both of these outcomes. In addition, adherence to the blister-packaged artesunate and mefloquine appeared to be reasonably good.

The poor coverage in areas without delivery interventions was partly explained by the fact that the vast majority (92%) of patients never sought treatment for malaria-like illness from a public health facility. However even when treatment was received from a public health facility, A+M accounted for less than half of the prescriptions for presumed *P. falciparum* malaria and only half the respondents in the study reported to have had a biological diagnosis prior to antimalarial treatment.

VMVs appeared to be particularly effective in increasing the likelihood of biological diagnosis 11-fold (95% CI 4.7 – 24.3, $p < 0.001$) and the likelihood of A+M eight-fold (95% CI 1.84 – 28.2, $p = 0.007$). Outreach also increased the likelihood of biological diagnosis two-fold and A+M three-fold, but on adjustment for survey design and confounders, the differences just failed to reach significance. Use of artemisinins as monotherapy was substantially less in these areas with interventions.

Adherence to the blister-packaged A+M appeared to be reasonably good, with three-quarters of those who received it completing the whole package in three days. Adherence was particularly good if the treatment had been received from outreach workers or VMVs where treatment was usually free and always followed a confirmed RDT diagnosis.

The amount that people paid for treatment varied substantially, especially if the treatment was obtained in the private sector. The median cost of drugs alone when bought from a simple seller, the most popular source of treatment, was \$0.77 but with a range of up to \$13, and the median cost from private health workers was \$3 and up to \$41 for a single course of treatment. This compared to a median of \$0.95 (range 0 to \$9.23) from public health facilities, \$0 (range \$0-0.23) from VMVs and \$0.64 (\$1.28-5.1) from outreach respectively.

Other important findings were the poor uptake of the socially marketed Malarine® in the areas in which it was piloted, the evidence of leakage of A+M which was supposed to be restricted to use in the public sector and the suggestion of the misdiagnosis of *P. falciparum* malaria by microscopy in a certain area.

9.2.2 Parameter estimates

A wide range of data were reviewed and assessed for appropriateness for use in the model and tabulated for ease of reference. These included detailed information pertinent to the transmission of malaria, the spread of drug resistance, the human response to malaria infection, human behaviour and costs related to the treatment of malaria. Of particular note was the extensive amount of EIR and age-stratified data required for the construction of the immunity functions. There were plenty of data on certain parameters such as the age-stratified prevalence of malaria or estimates for the proportion of patients seeking treatment in public health facilities. However, there was a lack of information on other aspects of malaria, to some of which the outcomes of the model are particularly sensitive, such as the susceptibility of humans to infection. These gaps in data are discussed in more detail in the section on further research in the next chapter.

9.2.3 Review of antimalarial drug usage studies

One of the key concerns about ACTs is how effective they are likely to be in “real world settings”. It has been argued that coverage rates are likely to be low and that the indiscriminate use of the artemisinin monotherapy will become widespread leading to an increased risk of resistance to artemisinins, a potentially disastrous consequence. However the evidence base for these concerns was scanty and it was therefore felt that a formal review of the literature on adherence to antimalarial drugs would be useful.

The aim of the review was to collect information on three aspects of antimalarial drug usage: patient adherence to recommended treatment regimes; the effectiveness of interventions to increase adherence; and clinical effectiveness in relation to adherence or compared to supervised treatment. Overall, the review revealed that “adherence” was generally poorly defined, that methodologies varied widely and that there was a paucity of good quality data, although it was encouraging to see that this is rapidly changing. Adherence to chloroquine was generally very poor (Deming, Gayibor et al. 1989; Krause and Sauerborn 2000; Thera, D'Alessandro et al. 2000), however the available data did suggest better adherence to drugs when prescribed by trained providers and when efficacious regimes were used. Thus adherence rates of above 78% and 90% were reported in clinic-based studies using artesunate with SP and artemether-lumefantrine respectively (Depoortere, Guthmann et al. 2004; Fogg, Bajunirwe et al. 2004). There was also evidence that interventions such as pre-packaging of drugs (Qingjun, Jihui et al. 1998; Yeboah-Antwi, Gyapong et al. 2001), provision of instructions (Okonkwo, Akpala et al. 2001) and training of providers (Marsh, Mutemi et al. 1999; Marsh, Mutemi et al. 2004) could effectively improve adherence. However on the whole, there were large variations in study design and quality with a particular lack of information on ACTs, their actual usage and the link between adherence and actual effectiveness.

9.2.4 Modelling

The two main outcomes of the biological model are the incidence of new infections, which reflect transmission intensity, and the rate of spread of drug resistance. Both are influenced by a number of interacting factors. In order to understand the results of the model it is helpful to review which parameters are important and how they contribute to the final outcome. This is therefore summarised below.

9.2.4.1. Factors affecting transmission

The key factors driving transmission given a stable vector population are:

- Migrant infections
- The susceptibility of humans to infections which is determined by:
 - The maximum susceptibility in a non-immune host
 - The shape of the immunity function based on parasite density
 - The proportion of the population with chemoprophylactic levels of antimalarial
- The overall density of parasites in symptomatic and asymptomatic infections which is influenced by:
 - The maximum likelihood of symptomatic malaria
 - The shape of the immunity function based on likelihood of symptomatic malaria
 - The treatment rate
 - The coverage rate with combination therapy
 - The shape of the immune function based on parasite density
 - The parasite density in recrudescence compared to initial infections
- The duration of non-treated infections, treated and recrudescence infections which is influenced by:
 - The maximum duration of untreated infections
 - The minimum parasite reduction ratios in treated infections
 - The shape of the immunity function based on parasite density
- The probability of recrudescence which is influenced by:
 - The maximum failure rates in treated infections
 - The shape of the immunity function based on risk of severe malaria
- The gametocyte switching rates in initial and recrudescence infections
- The gametocyte half-life.

9.2.4.2. Factors affecting the spread of drug resistance

The key factors driving the spread of resistance to drug A are:

- The ratio of treated to untreated infections which is determined by:
 - The maximum likelihood of symptomatic malaria
 - The shape of the immunity function based on likelihood of symptomatic malaria
 - The treatment rate
- The proportion of the population with chemoprophylactic levels of antimalarial
- The relative characteristics of treated versus untreated infections i.e.:
 - The duration of infection
 - The parasite density
 - The gametocyte switching rate
- The coverage rate with combination therapy
- The relative characteristics of treated resistant versus sensitive infections i.e.:
 - The minimum parasite reduction ratios (and therefore maximum duration)
 - The failure rates
- The relative characteristics of recrudescence infections compared to initial infections i.e.:
 - The duration of infection
 - The parasite density
 - The gametocyte switching rate.

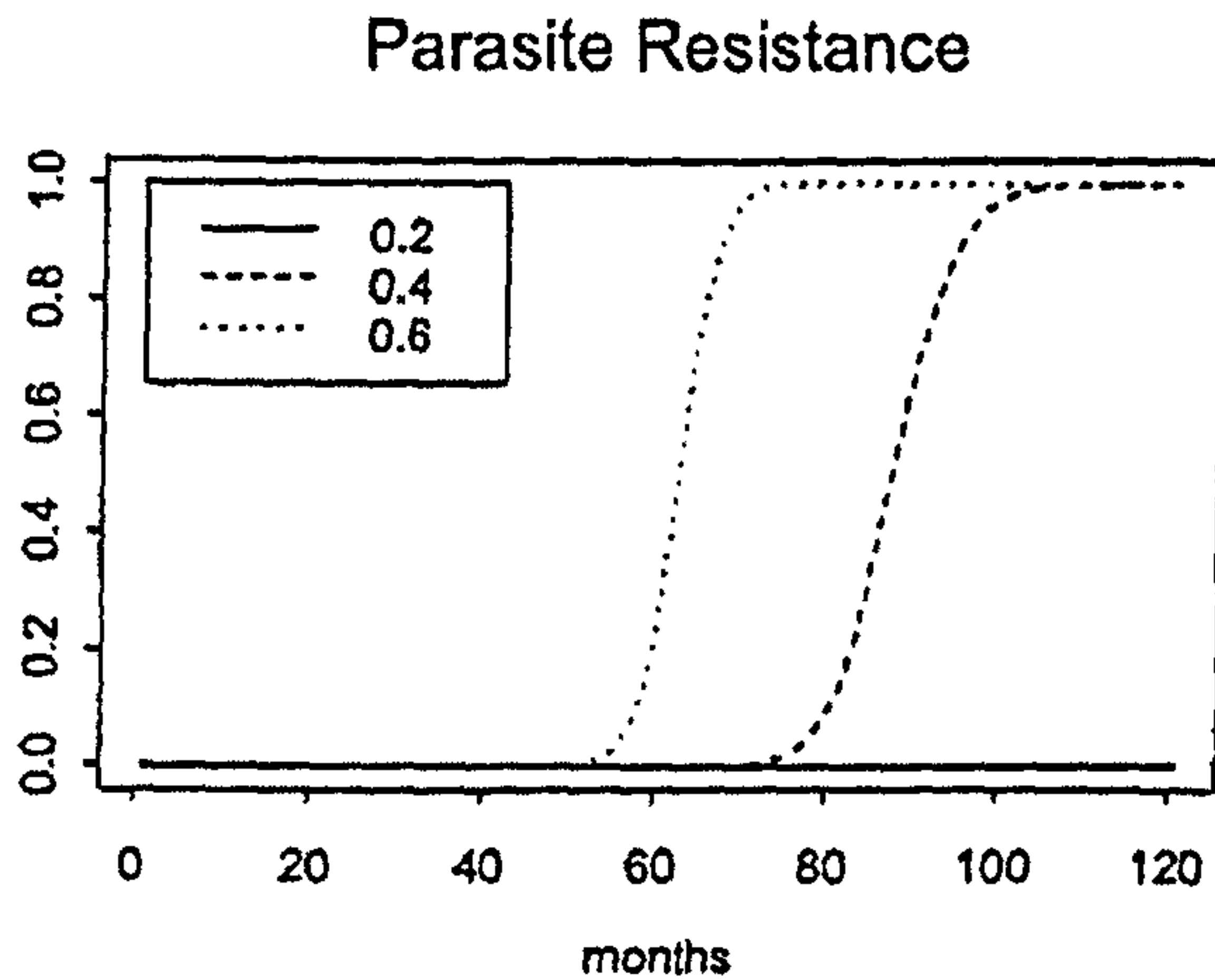
9.2.5 Modelling results

The model was run to assess how easy it was to apply and was used to explore the spread of drug resistance, clinical outcomes and costs with monotherapy and ACT in a low transmission setting. In this section the summary of the results are presented with comparisons to results from other models where available. The reason for some of the more surprising findings are discussed and where discrepancies exist between the outcomes predicted by the model and expected or actual findings the reasons are explored with suggestions for further investigation.

9.2.5.1. Drug resistance

One of the most striking model predictions is the speed at which resistance spreads going from 1% to 100% in six years. In the model described by Laxminarayan resistance was found to spread even more quickly once exponential growth started, reaching 100% within one to two years (Figure 9-1) (Laxminarayan 2004a). However it is important to note the difference between the two models. Laxminarayan's model is much simpler and does not deal explicitly with transmission. Also, in his model, resistance to the ACT is explored with the assumption that all those not covered by the ACT are treated with a drug that is *not* part of the combination, unlike the model presented in this study in which the resistance to a monotherapy (drug A) is explored and the combination therapy in the base-case scenario does contain this drug.

Figure 9-1: *The rate of spread of resistance to a combination therapy as predicted by Laxminarayan.*



The different lines refer to different coverage rates to the combination therapy. The x axis is the proportion of infections which are "resistant" (see text for definition of "coverage" in this paper)

Source: Laxminarayan R 2004a

There is a lack of real-life data with which to validate the rate of spread of resistance predicted in these models. The measurement of drug resistance as described in this model is the proportion of the parasite population that carry the mutation(s) required to confer complete resistance to a drug. Measurement of this information in reality requires the use of molecular technology to identify the responsible mutants (or reliable genetic markers) and to monitor change in their frequency in the parasite population over time. As this technology has only recently become available, there is a paucity of longitudinal molecular data which track the increase in resistance from the initial emergence of a resistant infection. Limited data from KwaZulu-Natal suggest that the frequency of the parasites carrying *dhfr* alleles which are linked to resistance to SP, increased from around 20% to 40% in four years although slower rates were seen for other mutants (Anderson and Roper 2005). As more data emerge, further validation of the model results will be possible and the investigation of discrepancies may reveal important factors affecting the spread of resistance not previously considered.

The rapid rate of spread predicted by the model may be partly explained by the choice of the values chosen for the parameters in the base-case scenario. As explained earlier, the spread of resistance is determined by the proportion of infections exposed to the drug to which the parasite is resistant and the selective advantage to the parasite of carrying the resistant gene. From the sensitivity analysis we know that in the monotherapy scenario, the parameters to which this outcome are particularly sensitive include: the treatment rate, the proportion of the population with chemoprophylaxis and the gametocyte switching rate (GSR). The data on which these estimates were based were scanty making it difficult to model with greater

accuracy. In addition we assumed that there is no fitness cost of resistance and this may have resulted in an overestimation of the rate at which resistance spreads.

The main factors affecting the spread of drug resistance in the model are listed below, with the values used in the base-case scenario in parenthesis.

- The maximum likelihood that a patent parasitaemia will be associated with symptoms in a non-immune host (0.8)
- The proportion of symptomatic infections which are treated (0.95)
- The duration of untreated infections (80 days)
- The duration of treated infection, which is dependent on the parasite reduction ratio of infections with resistant genotype (x100) compared to the parasite reduction ratio in sensitive infections (x1000) when they are treated with monotherapy (SP or mefloquine)
- The *maximum* failure rate for resistant infections (0.85) versus sensitive infections (0.06) for monotherapy
- The infectiousness of recrudescence infections (mainly drug resistant) compared to initial infections, which is dependent on:
 - The duration of infection (same as the initial infection)
 - The parasite density (0.5x that of the initial infection)
 - The gametocyte switching rate (x20 that of the initial infection)

Although data on the spread of drug resistance are lacking, data are available on the change of cure rates over time and although not directly comparable to mutation frequency, for the purpose of model validation, serve as a useful proxy of drug resistance. As can be seen in Figure 9-2, the model predicts that overall failure rates would rise from 3% to 16% in three years and to 24% the following year. This initial rate of rise compares reasonably well with data from low transmission settings in Thailand and South Africa. In the former, 28-day failure rates to mefloquine rose from under 10% in 1990, to 40% in 1994 in northwest Thailand (Figure 9-3) (Nosten, van Vugt et al. 2000). In KwaZulu-Natal the failure rates to chloroquine rose from 0% to 21% between 1983 and 1987 (Figure 9-4) (Hansford 1989; Craig, Kleinschmidt et al. 2004a). In both situations, the policy was switched at the end of these periods therefore it is not possible to compare beyond this point.

Figure 9-2: Age-stratified failure rates predicted by the model in the base-case scenario with monotherapy starting at 1% resistance at year 1

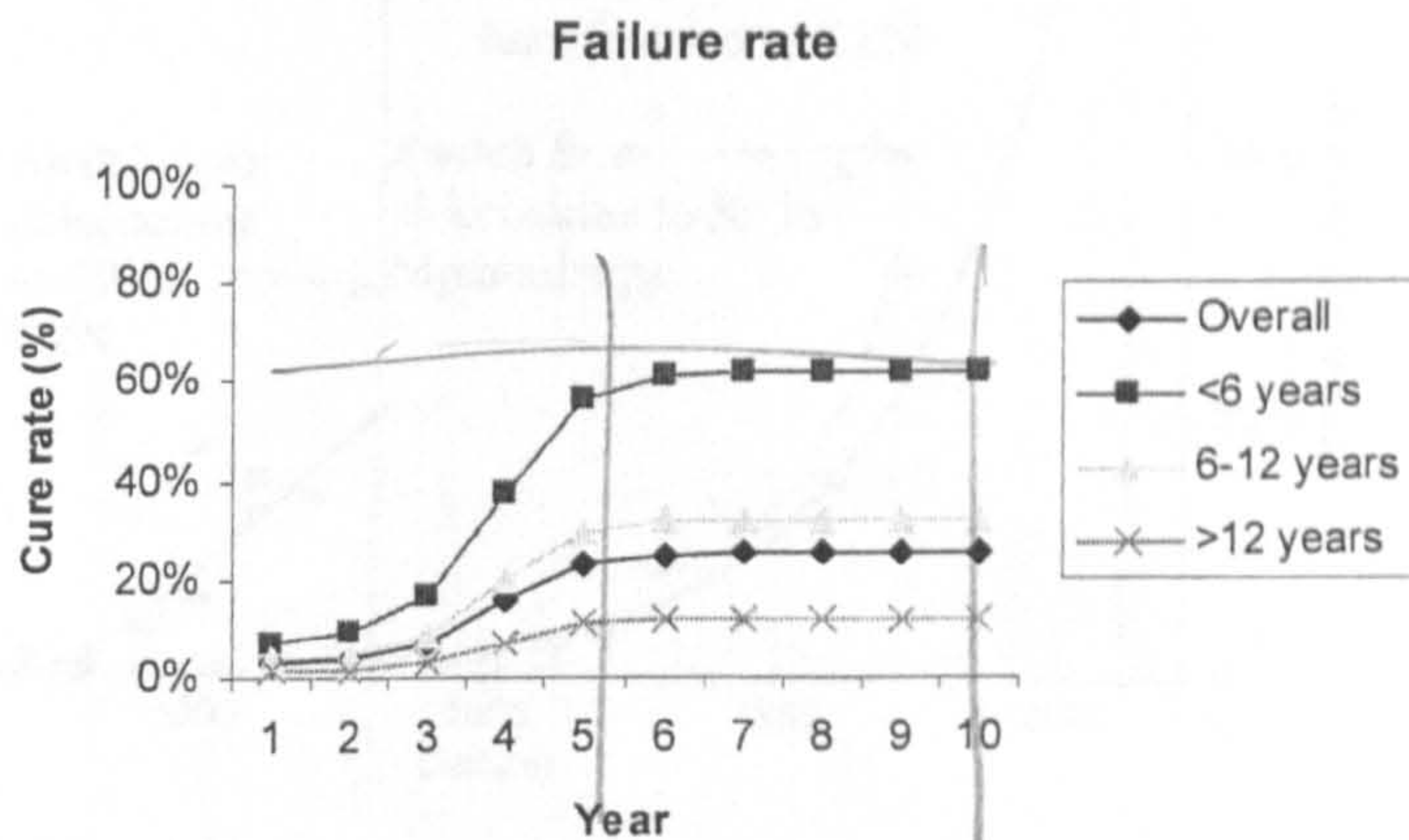
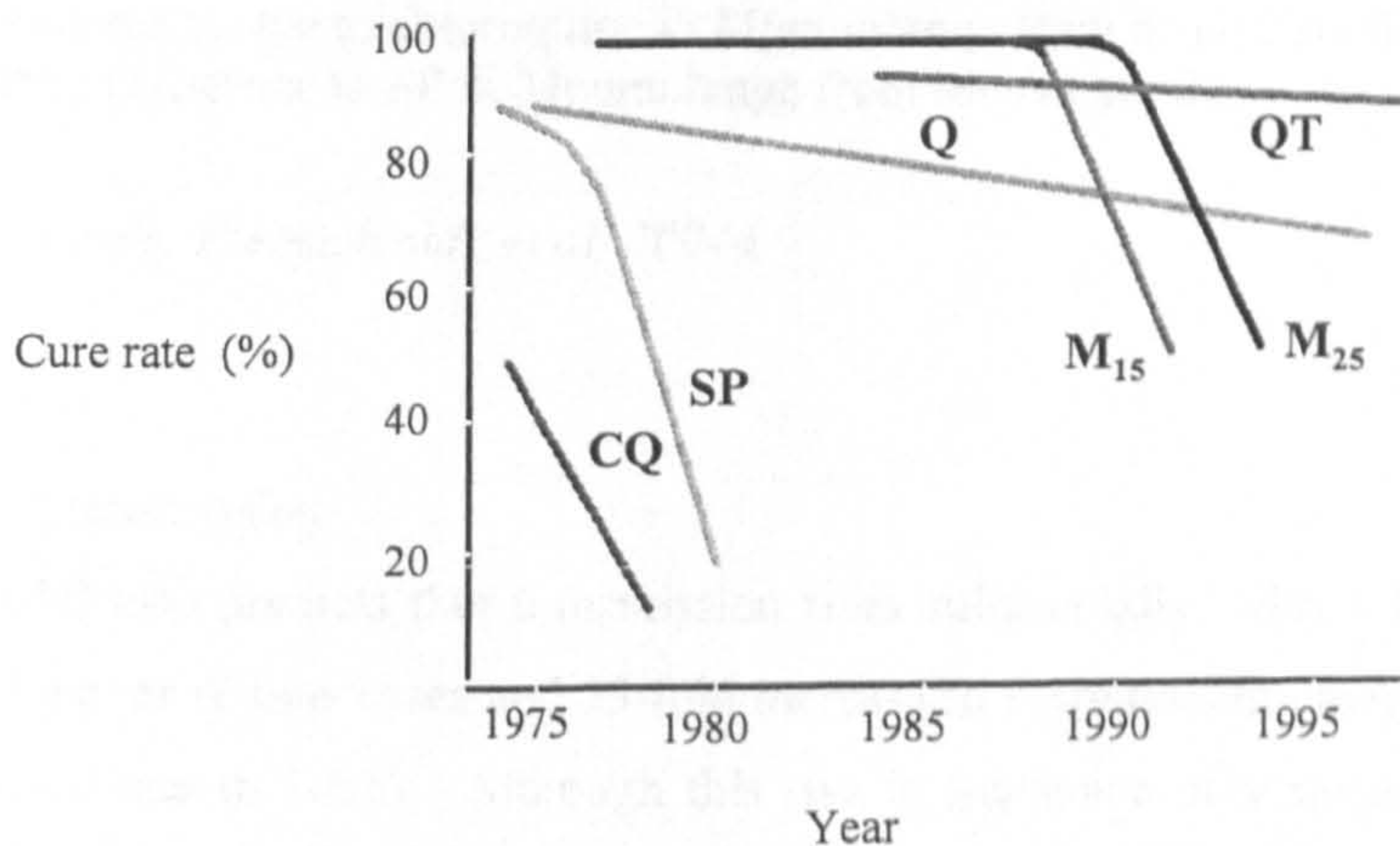
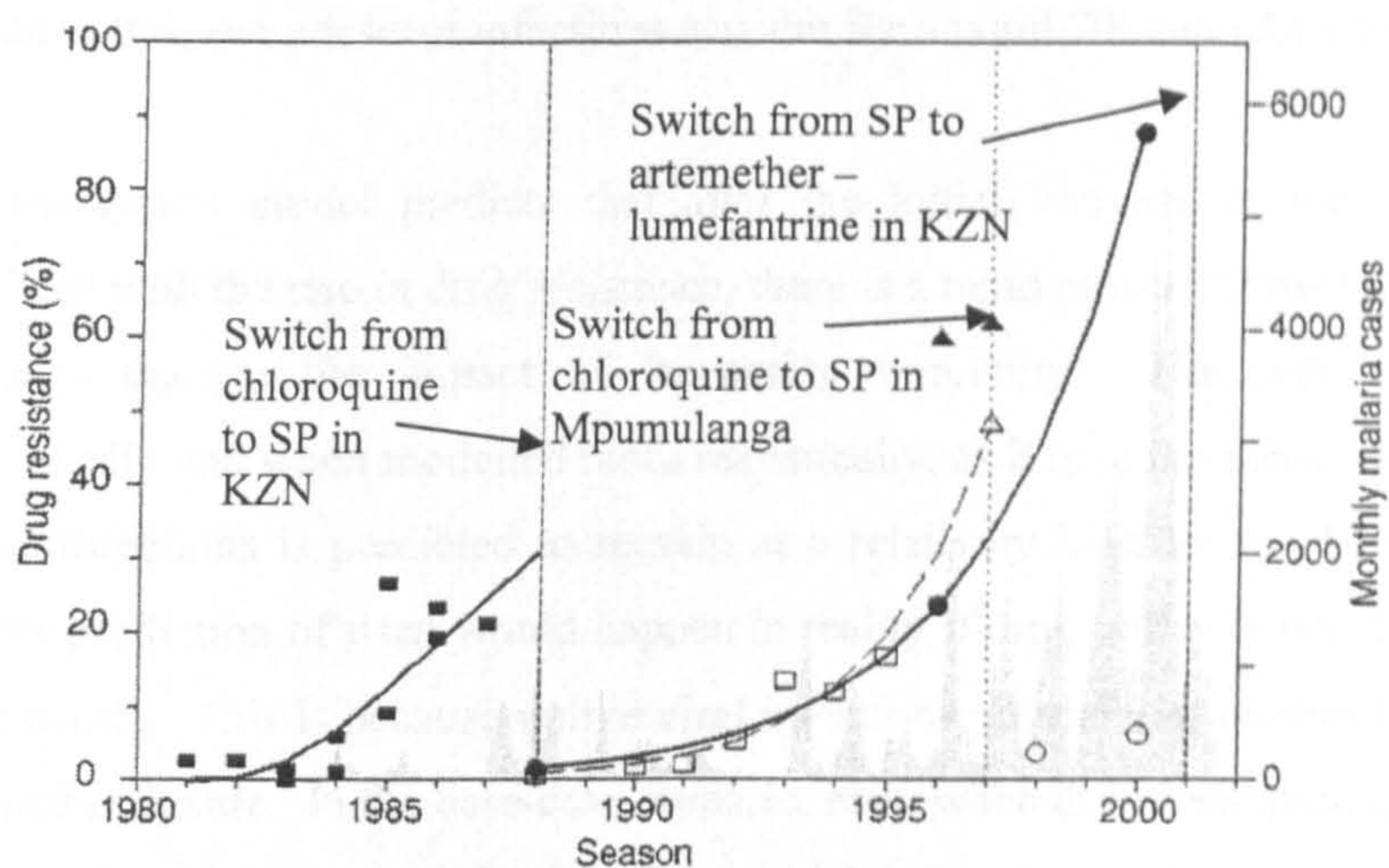


Figure 9-3: Cumulative cure rates assessed at day 28, for mefloquine 15mg/kg (M_{15}), mefloquine 25mg/kg (M_{25}) and mefloquine plus artesunate (MAS_3), on the Thai-Burmese border



Source: Adapted from Nosten, van Vugt et al. 2000

Figure 9-4: Drug resistance in KwaZulu-Natal (KZN) and Mpumulanga in South Africa



Key

The shaded area represents monthly malaria cases in KZN

- % drug resistance to chloroquine in KZN in terms of the reported treatment failure rate
- ▲ % drug resistance to chloroquine in KZN from *in-vivo* studies of drug resistance
- % drug resistance to SP in KZN from *in-vivo* studies
- % drug resistance to chloroquine in Mpumulanga in terms of the reported treatment failure rate
- △ % drug resistance to chloroquine in Mpumulanga from *in-vivo* studies
- % drug resistance to SP in Mpumulanga from *in-vivo* studies

Source: Craig, Kleinschmidt, et al. 2004a

9.2.5.2. Transmission

The model also predicts that transmission rises substantially, with a four-fold increase in the annual number of new cases and 25-fold increase in recrudescence cases as a result of resistance rising from one to 100%. Although this rise in incidence may seem extreme, there is some evidence to suggest that the model predictions are plausible. As shown in Figure 9-4, the incidence of malaria in KwaZulu-Natal increased exponentially from about 600 cases in 1991/92 to more than 30,000 cases in 1999/2000¹ resulting in an incidence of 250-800 cases per 1000 in 1998-1999 (Barnes, Durrheim et al. 2005). Although there are several possible causes for this increase, including HIV, climatic determinants, agricultural developments, migration, insecticide resistance and changes in case reporting, there was a strong correlation with drug resistance (Craig, Kleinschmidt et al. 2004a). The authors identify persistent infections following treatment as a source of increase in the number of infections. In 1984 only 1.2% of hospital treated cases remained positive compared to 9% in 1985, and three years later

¹ An estimated 600,000 live in malaria-risk areas (Barnes, Durrheim et al. 2005).

patients remained positive having been treated four times⁷⁷. In the model, when resistance has reached 100%, recrudescence infections account for around 700 out of 4,000 infections.

Laxminarayan's model predicts that after the initial increase in the number of infections associated with the rise in drug resistance, there is a rapid return to lower than previous levels of infections due to the impact of increasing immunity. However immunity is handled simplistically and when modelled more realistically, as it is in the thesis model, the incidence of malaria infections is predicted to remain at a relatively high level. This is probably a more accurate prediction of what would happen in reality if drug policy is not changed in response to the epidemic. This is because unlike viral infections, in malaria, immunity is only gained after sustained exposure. In the base-case scenario, even when drug resistance has reached 100%, the annual incidence of patent infections is around 3,000 cases, so that each individual has less than a one-in-three chance of being infected each year. One would therefore not expect the average level of immunity in the population to increase sufficiently to cause an overall decrease in susceptibility to infection.

9.2.5.3. Importance of migration

During the development of the model, it was found that in low transmission areas, the incidence of malaria fell to zero, effectively reflecting the eradication of malaria. In order to ensure continued transmission, an input of infections from outside was required and this became an additional feature of the model and is interpreted as either "migrant" or reactivated "dormant" infections. In fact, this observation does reflect the importance of such infections in the maintenance of malaria transmission in areas of low and unstable transmission intensity. In KwaZulu-Natal from 1986 to 1992, it was estimated that between 20-40% of cases were imported (Craig, Kleinschmidt et al. 2004a). In Thailand the continued transmission of malaria is widely believed to be due to cross-border migration from Myanmar and Cambodia. From Mae Sot province on the Thai-Myanmar border, "foreigners" were responsible for more than half of the malaria cases in 2001 (Zhou, Sirichaisinthop et al. 2005). Other models have also noted the importance of migration in sustaining transmission (Gu, Killeen et al. 2003).

9.2.5.4. Severe malaria and mortality

The model suggests that the spread of resistance from one to 100% is associated with a seven-fold increase in the number of severe cases and deaths. There are a lack of data linking drug resistance to the incidence of severe malaria or mortality in low transmission settings. However from studies in high transmission settings in Africa, it has been estimated that the rise in drug

⁷⁷They also propose that the increase in gametocytes in the blood that has been noted following treatment with SP also contributed to the increased infectiousness of the population.

resistance has been associated with between two to 11-fold increase in mortality attributable malaria (Snow, Trape et al. 2001; Trape 2001; Bjorkman and Bhattarai 2005).

9.2.5.5. The impact of ACT

The results from the model suggest that the introduction of an ACT of drug AB at full coverage in a low transmission setting has a dramatic effect on both the spread of drug resistance to drug A, and the epidemic increase in the incidence of malaria and treatment failures, suggesting a decrease in annual incidence in new cases from 739 to 686 (8% reduction) when introduced at 1% resistance to drug A.

Therefore, even in the short term (one year) setting, the introduction of ACTs is cost-effective so that when the switch is made at 1% resistance, the incremental drug cost per DALY averted is around \$130. By the end of five years the cumulative incremental drug cost per DALY is \$4.7 and after another five years this falls by an order of magnitude. Although these results are obtained under the assumption that coverage is 100% which may not seem plausible, data from low transmission areas where high coverage rates were achieved suggest that similar results are possible in reality.

In north-west Thailand, a 47% decline in malaria cases was observed within one year of the introduction of ACT (artesunate plus mefloquine). This increased to a six-fold reduction over 10 years (Price, Nosten et al. 1996; Nosten, van Vugt et al. 2000). In South Africa, there was a 94% decline in incidence of malaria in KZN in the two years following the introduction of both artemether-lumefantrine and the re-introduction of indoor residual spraying with DDT. It was estimated that around 37% of the reduction in incidence was attributable to the change in first-line drug (Muheki, McIntyre et al. 2004). Two years after the interventions the number of outpatient visits, admissions and deaths due to malaria had fallen by almost 100% (Barnes, Durrheim et al. 2005). Cost-effectiveness in terms of average cost-per-life-saved was estimated at US\$18 compared with \$158 with SP. Costs savings from the perspective of the provider were estimated at US\$201,065 for that sub-district (Muheki, McIntyre et al. 2004).

In Vietnam, the provision of free microscopic diagnosis and ACTs at the village level was provided from pre-existing and new health posts as part of a nationwide policy of early diagnosis and treatment of malaria launched in 1993 (Giao, Vries et al. 2005). This resulted in a reduction in presumptive self-treatment of malaria, a decrease in the delay between first symptoms and seeking treatment and a concomitant decline in incidence of uncomplicated and severe malaria.

In the model by Goodman et al, it was found that in low transmission areas, if it was assumed that ACT reduced the growth rate of SP resistance by greater than 47%, then the cost-effectiveness of ACT would be under \$150 per DALY averted. ACT was found to be more cost-effective even when the impact on drug resistance was assumed to be less marked (Goodman, Coleman et al. 2000).

9.2.5.6. The importance of the coverage rate with ACT

The results from running the model with different levels of coverage with combination therapy suggest that even with low levels of coverage there is a noticeable impact on the incidence of infections. Therefore, although initially there is a direct correlation between the level of coverage and the annual costs of first-line drugs because of the higher costs of drugs, as the number of cases increases inversely proportionate to the level of coverage, by year 10 there is an inverse relationship between coverage rate and the annual cost of first-line drug. In terms of the total costs of treating malaria, ACT is cost saving compared to monotherapy within a few years and the higher the coverage rate, the greater the cost saving. In terms of cumulative cost-effectiveness, at two years, the incremental cumulative drug cost per DALY averted ranges from \$7 at 10% coverage to \$54 at 100% coverage. However over the following years the cumulative DALYs averted as a result of higher coverage rates compensate for the higher cost of drugs incurred in the earlier years and there is little difference in cost-effectiveness at year 10 with the cost per DALY averted lying at less than \$1. The results also suggest that beyond a coverage rate of around 50-60%, there are decreasing returns to increasing coverage. There are few practical or theoretical examples with which to compare these predictions of the impact of coverage on the effectiveness of ACTs.

Although Laxminarayan explores the effect of treatment coverage rates on outcomes, the model is set up differently, so that malaria patients who are not “covered” with the combination therapy are treated with some other effective drug not containing either of the drugs in the combination. The model explores the spread of resistance to the combination under different levels of coverage. The findings suggest that a coverage rate of 60% is sufficient to completely suppress the spread of drug resistance but with coverage rates of 40% and 60%, the beginning of exponential growth of resistance started at around five years and seven years respectively, reaching 100% within one or two years (Laxminarayan 2004).

In the recent generalised cost-effectiveness study of malaria control strategies, Morel et al. evaluated interventions including the introduction of different antimalarials at 50%, 80% and 95% coverage over a 10-year time frame (Morel, Lauer et al. 2005). The analysis suggested that there were increasing returns to increasing coverage especially in Africa E regions (Southern East and Central Africa). At 50% coverage with an ACT, the average cost per DALY

averted was \$39 compared to \$14 at 80% coverage, and \$12 at 95% coverage. In Africa D regions (West Africa) the coverage had little effect on cost-effectiveness with a cost per DALY averted of between \$9 and \$13. These values are higher than the ones predicted in this model and reflect substantial differences in approaches and parameter inputs. For example in their model both incidence of malaria and the spread of drug resistance is fixed and adherence to ACT is assumed to be 40%.

9.2.5.7. Application of the model to the Cambodian data

The analysis based on the Cambodian data suggests that although less cost-effective compared to the ideal situation, the replacement of monotherapy with an ACT may still be cost-effective and potentially cost saving in similar settings where access and utilisation of public health facilities is very low. This is mainly because even at the low levels of coverage with ACTs, there are fewer treatment failures, fewer severe outcomes and transmission is potentially reduced.

Delivery of diagnosis and treatment with ACTs through outreach clinics and VMVs are both very cost-effective to the provider. The outreach intervention was found to increase the coverage rate with ACT to 32%. The cumulative incremental drug cost per DALY averted is estimated to be \$48 at five years and \$16 at 10 years. Delivery through VMVs increased coverage to 90% and was associated with a cumulative incremental drug cost per DALY averted of \$68 at five years and \$19 at 10 years.

From a societal perspective, taking into account direct and indirect costs to patients and providers, the delivery interventions become cost saving in terms of annual costs, by year 6. Of note, both interventions, but especially the VMV scheme, result in a substantial shifting of costs from patients to providers. A switch to the ACT in the absence of any delivery interventions results in total annual direct costs to patients of \$1,616 in the first year, rising to \$14,439 at 10 years. The implementation of VMVs results in the total annual cost to patients remaining at \$65 throughout the 10 years. With outreach, the cost savings are much less, with the total annual cost rising to \$824 by year 10. This is due to both the higher proportion of patients seeking treatment from the informal sector but also because there is a higher incidence of malaria due to the lower level of coverage with ACT compared to the VMV villages.

9.3 Conclusion

The key strengths of the thesis are that it has an integrated approach, combining biology with economics and that the resulting model is based on an extensive amount of primary and

secondary data. This helps to ensure both biological realism and policy relevance. A number of limitations and omissions have also been discussed. The most important relate to the restriction of the focus to the spread of drug resistance, the complexity of the model, the lack of important data and practical difficulties during the primary data collection in Cambodia. However despite the latter, the findings clearly suggest that in similar settings with poor healthcare infrastructures, coverage rates are likely to be low and the use of artemisinin monotherapy widespread. Improving access to appropriate management through village malaria workers and outreach clinics significantly improved both of these outcomes. This is important as the results from running the model suggest that in order to impact on the spread of drug resistance once it has already arisen to one of the partner drugs, high levels of coverage with the ACT are needed. However the other key findings from the application of the model are that ACTs are likely to be cost-effective and to result in total cost-savings compared to monotherapy under a wide range of conditions, including at low coverage rates. In low transmission settings much of this benefit is due to the reduction in treatment failures and malaria transmission.

CHAPTER 10

DISCUSSION II:

POLICY IMPLICATIONS AND RESEARCH PRIORITIES

In this chapter the findings from the process of developing the model, collecting and reviewing the primary and secondary data and the application of the model are all brought together in order to discuss the implications for policy and to make recommendations for further research. The final conclusions of the thesis are then presented.

10.1 Policy implications

10.1.1 Drug resistance and ACTs

It is clear that antimalarial drug resistance is one of the most important health issues in tropical countries and that the impact of antimalarial drug resistance is enormous. In this study it is estimated that in a low transmission setting, drug resistance can rise from 1% to almost 100% in five years. In a population of 10,000 in a low transmission setting it is estimated that the annual total (indirect and direct) cost of treating malaria would increase at least three-fold (from \$10,600 to \$32,800) as a result, with almost half the cost being due to the indirect costs resulting from treatment failures. We know that this represents a significant underestimate of the actual negative impact of antimalarial drug resistance and that if a macroeconomic approach had been taken the impact would be much more (Sachs and Malaney 2002; Smith, Yago et al. 2005).

In reality these high levels of resistance have already been reached in many countries where ineffective monotherapy drugs continue to be the first-line treatment in practice, if not in policy. It is now generally accepted that the ideal choice of treatment is an ACT. There is therefore an urgent need for affordable (or free) effective treatment to be made widely available to the vulnerable rural poor who are most at risk of dying of malaria and are least able to access appropriate treatment.

However, there continue to be concerns about how ACTs should be implemented, which combination to switch to and what coverage levels need to be attained if benefits of a reduction in the growth of drug resistance are to be achieved. The existing examples of successful implementation of ACTs have come from South Africa and Thailand where treatment rates in the public sector have been high and therefore high rates of coverage have been achievable.

Thus in KwaZulu-Natal, 93% of those reporting a recent case of malaria had been treated at no charge in a public sector facility (Muheki, McIntyre et al. 2004). There have been concerns that these levels of coverage are exceptional and are unlikely to be replicated elsewhere. The results from the data collection in Cambodia certainly lend credence to these concerns - less than 10% of antimalarial treatment was with the recommended ACT.

10.1.2 Coverage

However, the implications from the modelling scenarios with different coverage rates suggest that the prospects of a low level of coverage should not in itself be a deterrent to switching to an ACT. Although in low transmission settings, very high levels of ACT coverage (above 80%) are required in order to delay significantly the spread of drug resistance to an already failing drug, other benefits are seen at much lower levels of coverage. This is because the greater efficacy of the ACT compared to failing monotherapy results in an immediate benefit to patients in terms of fewer recrudescence infections, and immediate and future externalities in terms of decreased transmission. The higher the coverage level attained the greater the proportion of patients who benefit directly and the greater the effect on decreasing transmission. Although there are decreasing returns to coverage above a certain level (50-60% coverage), this does not mean necessarily that maximum coverage should not be sought. The level of coverage aimed for depends on the decision-makers willingness to pay for coverage and alternative ways of spending money.

The other policy implication implicit in this discussion is that there is a need to monitor the implementation of ACTs to ensure that they reach the targeted population.

10.1.3 Artemisinin monotherapy

Although high coverage rates are desirable, policy makers need to be aware that unrestricted access to artemisinins is not the answer. In Cambodia, artesunate was found to be widely available and was four times more likely to be taken without mefloquine than with it. Although resistance to artemisinins is theoretically very unlikely to emerge, the consequences would be truly disastrous should this occur. Therefore it is of paramount importance that efforts to increase the use of artemisinins in effective combinations are matched by efforts to limit their use on their own. There are a number of policy actions to ensure that only co-formulated ACTs are available and used. Very recently the WHO has issued an unprecedented directive banning the use of artemisinin monotherapy with the possibility of blacklisting manufacturers who continue to produce artemisinin derivatives on their own (WHO 2006c). This is a major step and will hopefully contribute to a limitation of the availability of the monotherapy by deterring at least the large pharmaceutical companies from their production.

However in settings such as Cambodia, there is low utilisation of the public health sector, the drug market is relatively unregulated, borders are porous and law enforcement weak. In such circumstances restrictions on the production, importation or selling of artemisinin monotherapy are unlikely to succeed. Raising awareness through information campaigns and training are also likely to have limited effect, as long as the artemisinin derivatives are available on their own and are cheaper to buy. This is because from the patients' perspective, there may appear to be no additional benefit of using combinations. Artemisinins on their own work as fast as the combination in relieving symptoms, have few side effects and, where they have been used before, are familiar to the community. The infections are much more likely to recrudescence because a longer duration of therapy is required but rarely adhered to. However the recrudescence infection may occur several weeks after the initial infection and from the patient's perspective, is unlikely to be interpreted as a treatment failure.

Thus ensuring that patient with malaria have access to free, or heavily-subsidised co-formulated ACTs is the major challenge facing those involved in the control of malaria (Arrow, Panosian et al. 2004).

10.1.4 An integrated approach

The results from the study in Cambodia emphasize the need to take an integrated approach to the treatment of malaria, one that considers both the formal and the informal sector as well as community-based treatment, depending on the pre-existing healthcare providers and infrastructures. Disappointingly, the findings from the study suggested that providing free ACT in the public health facilities was not a sufficient incentive to effect a significant shift in treatment seeking behaviour from the informal to the formal sector, and that even in the public health facilities, use of ACTs was low. Although the reasons for this are not entirely clear, large stocks of quinine and tetracycline remained stocked in health centres and continued to be used as first-line treatment. This is in contrast to the experience in KwaZulu-Natal, where the old stocks of antimalarial drugs were physically removed from clinics concomitantly with the introduction of artemether-lumefantrine. The implication is that this must become standard practice if change is to be affected successfully.

There was also evidence of the leakage of blister-packaged A+M from the public sector into shops in Cambodia. A+M is specially packaged and is intended for use only in public health facilities where it is provided free. However there is very little control on the use of drugs once they have been distributed from the Central Medical Stores and leakage can occur easily from the provincial level down to the level of individual health centres. Health workers are poorly paid in the public sector and many therefore work in clinics and pharmacies. There is therefore

an incentive for them to treat patients with A+M in the private sector where they can sell it for profit rather than to provide it for free in public health facilities.

The active involvement of the informal sector is therefore essential. In Cambodia, this has been attempted by social marketing of both the pre-packaged artesunate-mefloquine (Malarine®) and Paracheck® RDTs. Experience from the initial phases of implementation suggested that there was poor penetration of the products both in terms of availability and awareness. Malaria treatments bought in the informal sector were sometimes very costly, especially if they included parenteral treatments, and therefore the potential loss of seller earnings associated with providing cheap, effective treatment may be a significant deterrent to changing prescribing behaviour. However, during discussions with informal sector providers, it was clear that many were keen to learn about the appropriate diagnosis and treatment of malaria and appeared willing to try using both RDTs and Malarine®. Experience from other settings have shown that shopkeepers and market vendors can be successfully trained to improve the case management of fever of children (Marsh, Mutemi et al. 1999; Luby, Zaidi et al. 2002; Tavrow, Shabahang et al. 2003; Marsh, Mutemi et al. 2004). For the successful implementation of ACTs, the utilisation of such strategies will need to be explored, where the informal sector is an important source of treatment.

10.1.5 Community based interventions

In some areas there is limited access even to informal sector providers. In such settings, the provision of effective treatment with or without biological diagnosis must be considered at the level of the community. The study in Cambodia found that villagers themselves could be trained to diagnose malaria using RDTs and to prescribe blister-packaged artesunate and mefloquine. The rate of coverage, in terms of proportion of respondents with malarial symptoms appropriately treated was over 90%. Villagers also proved to be a reliable source of surveillance data, especially because the RDTs were kept as “evidence” of cases treated. This was despite initial misgivings that the VMVs, who were largely illiterate, would find the diagnostic tests and treatment regimes too complicated. There is a significant cost involved in ensuring adequate training, monitoring and supervision resulting in the fixed costs of the programme being higher than the variable costs of RDTs and drugs. However the results from running the model using the Cambodian data suggest that VMVs can be highly cost-effective and that high enough coverage rates can be achieved to impact on the spread of drug resistance as well as transmission. The results from the household survey also suggest that the scheme decreased costs for the targeted population who were particularly poor, and therefore an additional attraction of such schemes is that they are inherently “pro-poor”.

However there are situations in which a VMV scheme is not a practical alternative, for example where the population is highly mobile and there is a lack of social cohesion. In such situations, outreach clinics, such as the one implemented in Anlong Veng district in Cambodia, are a viable policy option. The coverage rates are lower and fixed cost per patient tested and treated are significantly higher than the VMV intervention. When the long-term cost-effectiveness of outreach was evaluated using the model to incorporate the impact on drug resistance and transmission, it was clear that this was cost-effective.

Both types of interventions, particularly VMVs, can therefore be strongly recommended as a means of implementing ACTs. However there are a number of caveats. These predictions are based on the assumption that the same level of coverage will be maintained over time and this may not be the case. It was apparent from discussions with members of the communities, and the providers themselves, that there was some dissatisfaction with the services. The most common complaint was that only treatment for malaria and specifically *P. falciparum* malaria was provided. As this represented less than a quarter of the cases seen, the majority of patients did not receive any treatment. This may be why in villages with VMVs, patients appeared to have waited longer before seeking treatment, although comparison with pre-intervention behaviour is not available. In recognition of this problem, and in the hope that the number of patients with malaria may decrease as a result of the intervention, an expanded role for VMVs has been discussed in Cambodia. Other countries considering similar interventions should perhaps, from the outset, consider a more holistic approach in which the consequences of a negative RDT are recognised and the management of diseases other than malaria are considered. One possibility is to integrate the use of RDTs into the integrated management of childhood illness (IMCI) approach and train village health volunteers to also recognise and treat diarrhoeal disease and acute respiratory infections in children.

Finally, it remains to be seen whether the short term success as documented here continues into the future and how well similar schemes work in other settings. Past experience with village health workers has shown that such schemes can be difficult to scale up and to sustain in the long run.

10.1.6 Adherence

The results of the systematic review of adherence to antimalarial drugs and the results of the drug usage study in Cambodia indicate that adherence to ACTs are good when then they are provided free, by trained providers and either co-formulated or blister-packaged. The implication for policy is therefore that poor adherence should not be a deterrent to switching to an ACT but that they must be provided either co-formulated or blister-packaged and either free or at a truly affordable price so that patients do not feel that they must ration doses in order to

retain tablets for the treatment of future fevers. Other simple efforts can significantly improve adherence. This includes ensuring that patients and their carers are given adequate information on how to take drugs correctly and that those prescribing the regimes have sufficient training and support so that this happens.

10.1.7 Biological diagnosis

As mentioned earlier, if the singular goal of antimalarial drug policy was to maximise coverage with the first line drug then the most straightforward solution might be to make ACTs available in every home so that treatment could be instituted without delay following the onset of symptoms. There have been a number of studies where mothers have been trained to make presumptive diagnosis and provide treatment for their children and this has been found to be a feasible and affordable approach (Pagnoni, Convelbo et al. 1997). Most encouragingly, this approach has been found to significantly reduce under-five mortality in a large-scale cluster RCT in Tigray, Ethiopia (Kidane and Morrow 2000). However, there are substantial costs and risks of presumptive home-based treatment with ACTs and there is an ongoing debate about the trade-off between maximising coverage and minimising the wastage of drugs, the costs, and the risk of resistance to the combination by limiting the use of ACTs to those who have biologically confirmed malaria (D'Alessandro, Talisuna et al. 2005).

In the case of Cambodia, the introduction of RDTs with ACTs through VMVs and outreach demonstrated that they were popular and could easily be used by members of the community, as well as health staff. Given a test positivity rate of around 20-25% and cost of \$0.83 for a *P. falciparum* specific test, compared to an adult course of A+M at \$3.80, they are highly cost-effective. The socially marketed RDTs, which were made available to retailers at \$0.50, were reportedly more popular than the blister-packaged Malarine®. Further work needs to be undertaken to explore the optimal level of subsidy for both so that the practice of confirming diagnosis prior to treatment with the combination can be promoted. Utilisation of RDTs in public health facilities was disappointingly low, and this appeared to be partly due to stock-outs and low staff motivation. The implications for policy are that in a low transmission setting, biological diagnosis prior to treatment with ACTs should be standard and that RDTs are a practical and cost-effective means of achieving this. The caveats are that it is essential to ensure adequate stocks and to routinely monitor the quality and use of the tests (Lon, Alcantara et al. 2005). The problem with introducing an accurate biological diagnosis for a single disease has already been noted, and ideally improving the case management of malaria should be integrated with other diseases.

10.1.8 Choice of combination therapy and timing of switch

The results from the scenario analysis showed that with a 10-year time frame, any ACT is cost-effective compared to a failing monotherapy and that the earlier the switch is made, the more cost-effective. This is because switching earlier averts recrudescence and severe infections that occur with the monotherapy as drug resistance rises prior to the switch. Previous international guidelines suggest different levels of clinical failure at which countries should move towards switching first-line antimalarial treatment: a grace period (0-4%), alert (5-14%), action (15-24%) and then change at 25% (Kitua 1999). More recent guidelines suggest a change at levels of clinical failure of 15% (WHO 2005a). However both the results of the modelling and recent evidence from the field suggest that these levels of resistance are often reached within a few years of drug resistance emerging. As the process of switching drug policy takes at least two years, it is therefore recommended that the process of policy change be initiated as soon as there is evidence that drug resistance to the first-line therapy has emerged.

The results from the modelling scenario analysis also show that although artemether-lumefantrine is almost twice the cost of artesunate and SP, even under ideal conditions where coverage is 100% and the switch is made at a low level of resistance to SP, there is little difference in cost-effectiveness between the two drugs. At 10 years the cumulative incremental drug cost per DALY averted with artemether-lumefantrine is \$1 compared to \$0.6 for artesunate and SP. With a more realistic coverage rate and with higher levels of resistance to SP, the difference between the two regimes will be less or possibly reversed. The results of the modelling show that unless coverage with artesunate-SP is over 80%, the spread of resistance to SP will not be significantly affected by the addition of artesunate. Artesunate will thus become increasingly exposed over time, although this may not become apparent clinically for years. The implications in terms of the possible emergence of resistance to the artemisinin derivatives have already been noted.

The recommendations for policy makers are therefore that the switch should be made to an ACT to which there is no resistance to the partner drug. Because resistance to the older monotherapies is now so widespread, at the moment, this means a switch to artemether-lumefantrine in most cases. However the co-formulated combination of dihydroartemisinin-piperaquine (with or without other antimalarials), has been available for several years as Artekin® or CV8, in China, Vietnam and increasingly in Cambodia. Piperaquine has not been widely used on its own and clinical trials have shown that the combination is efficacious and safe. It only requires once-a-day dosing, does not need to be taken with fat in the diet and currently costs less than artemether-lumefantrine (Tran, Dolecek et al. 2004; Ashley, McGready et al. 2005). For some time the main obstacle to its wider use was that it was not manufactured to international good manufacturing practices standard. However this has recently been

achieved and the combination is now in phase three trials. A priority for policy is to ensure that on completion of the trials, the registration process of the drug is facilitated.

The model was also applied to explore concerns regarding the use of presumptive therapy and the spread of drug resistance. It suggests that in a low transmission setting, even if 10% of the population were assumed to have inhibitory levels of drug in their blood, that there was little effect on the spread of drug resistance. This analysis is being extended to explore the impact in higher transmission settings where there is greater use of presumptive therapy. However this does not address the concerns regarding the effect of presumptive therapy on the emergence of drug resistance and this will require further research.

10.2 Research priorities

In this section the priorities for research arising from this study are discussed. In Chapter 7, suggestions for further research specific to Cambodia were discussed and in Chapter 5 suggestions for future studies on the adherence to and effectiveness of antimalarial drugs were made. These are summarised here and are followed by a more general discussion of studies of treatment seeking and adherence and the implementation of ACTs. Other gaps in the data that arose during the process of data collection are then reviewed with suggestions for how these may be addressed. This is followed by a discussion of research priorities for modelling, concentrating on validation of the model, further development and its application to explore a range of policy relevant questions. Finally other approaches to modelling the economics of antimalarial drug resistance are discussed.

10.2.1 Antimalarial drug usage in Cambodia

The collection of data in Cambodia revealed poor levels of coverage with ACT, and biological diagnosis, both of which improved with delivery interventions, in particular VMVs. Being a relatively small study with an emphasis on collecting information from both intervention and non-intervention areas and information on both treatment seeking and adherence, there was a need for a larger more representative study to validate the findings and to ensure that sufficient information was gathered on high risk sub-populations including children and pregnant women. Fortunately this was subsequently undertaken the following year and some of the results were discussed earlier. It was also felt that in order to improve coverage, a better understanding was required of the “supply-side” of the antimalarial drug market, and further qualitative studies were required with both the community and the providers, aimed at identifying barriers and incentives to change behaviour.

10.2.2 Treatment seeking behaviour and antimalarial drug usage

10.2.2.1. Treatment seeking for “malaria”

Community drug usage studies are constrained by not knowing whether a patient actually had malaria or not and therefore whether the choice of treatment was in fact appropriate. Microscopy at the time of interview is not useful as patients who genuinely may have had malaria should become non-parasitaemic soon after starting treatment. For this reason RDTs were used in the collection of primary data in Cambodia. Although this revealed significant issues in terms of undertaking blood tests during such studies and also in interpretation of results, it is an approach that possibly warrants further exploration. In relatively low transmission settings, antibody tests could be also be explored as they remain positive for much longer. However they too may be difficult to interpret (Edelman, Hoffman et al. 1993; Biswas, Tomar et al. 2005).

10.2.2.2. Adherence

The review of the literature revealed that there were wide discrepancies in the definition and measurement of “adherence”. In the future, clearer definitions of adherence should be provided to assist in interpretation and comparison across studies, and ideally this should be based on dose, frequency and duration. However, as the study in Cambodia revealed, patients are unlikely to be able to recall this amount of detail accurately, therefore as a compromise a pragmatic operational definition is needed.

Furthermore, although there is some evidence to support that self- or carer-reported drug histories may be reliable (Kofoed, Lopez et al. 2003; Marsh, Mutemi et al. 2004), other studies have shown that they can be subject to bias and error (Nwanyanwu *et al.* 1996). It would therefore be helpful to have more studies that validate drug histories with biological markers of adherence using modern population pharmacokinetic approaches (Simpson et al. 2001). However, these can only be undertaken with drugs that have a half-life of at least a few days and therefore can not be carried out on the artemisinin derivatives.

It is particularly difficult to study adherence to the first-line drug in a community setting when the actual usage of the drug of interest is low. As the experience in Cambodia revealed, it would be much more efficient to identify patients supplied with the first-line drug at shops or clinics and to follow them up at home. Although there may be problems with this approach as discussed earlier, it may be the only way to obtain sufficient data.

10.2.2.3. Effectiveness

It may be, however, that too much emphasis has been put on adherence, rather than focusing on the actual consequence of poor adherence, the main one being treatment failure. The emphasis

should therefore shift more towards measuring the real-life effectiveness of treatments, where patients obtain and take drugs outside of clinical trial settings and are followed up clinically and parasitologically to find out whether or not they are cured. The results can then be compared to the efficacy of the drugs when taken supervised (Krause and Sauerborn 2000; Nsungwa-Sabiiti, Tomson et al. 2005). This entails a shift from the traditional clinical “efficacy” trials to “effectiveness” trials, a shift that is already underway (Smithuis, van der Broek et al. 2004; Depoortere, Guthmann et al. 2005; Piola, Fogg et al. 2005). These recent studies also address one of the gaps identified in the review of antimalarial drug usage studies, which was that there was need for studies of the effectiveness of ACTs in sub-Saharan Africa.

10.2.2.4. Interventions to improve community drug usage

There was a lack of good quality studies documenting the effectiveness and cost-effectiveness of interventions aimed at improving the treatment of malaria in the community. Ideally these should be community-based RCTs in which communities or clusters of communities are randomised into different intervention or non-intervention arms. The disadvantage with such studies is that they can be difficult and costly to undertake. However with sufficient planning and support, it should be possible to conduct useful operational research in the context of the planned implementation of ACTs. Many countries that have received money from the Global Fund for the introduction of ACTs do not plan to implement universal and nationwide coverage immediately. There is usually some plan for a phased introduction or a targeted approach. One of the important lessons from Cambodia is to encourage the exploitation of these opportunities as natural experiments. If the implementation strategy is well planned and the collection of appropriate data is organised from the outset, then the resulting information could be extremely useful. Differences in outcomes could be compared in communities before and after the introduction of the policy change and any accompanying interventions to improve access could be evaluated. Such studies should include information on costs and how they are calculated in order for policy makers to make informed decisions around policy change and implementation.

10.2.3 Malaria and antimalarial drug resistance

A modelling approach was taken in this thesis because of the uncertainty about the development of drug resistance and the effect of ACTs in different settings. Empirical data based on longitudinal epidemiological studies of antimalarial drug resistance would help address much of the uncertainty. Such studies should ideally be carried out in different epidemiological conditions and should monitor the use of antimalarial drugs in the community. Where the first-line antimalarial drug is artemether-lumefantrine, the monitoring of drug resistance will be dependent mainly on the *in-vivo* studies, until reliable molecular markers of the component drugs are found. The identification of such markers is therefore another important priority for research. In undertaking *in-vivo* studies, it is essential that follow-up is adequate - at least 42

days for drugs with a long half-life such as lumenfantrine. Otherwise, drug resistance will not be detected until it is already well established, because most treatment failures occur after 28 days (Stepniewska, Taylor et al. 2004). Now that re-infections can be distinguished from recrudescence infections using molecular techniques, this should become standard even in high transmission settings. For the drugs for which molecular markers of drug resistance have been identified, more studies describing the relationship between carriage of resistant mutants and the clinical outcomes would be useful.

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The exercise of gathering data was instructive in revealing important gaps in our current knowledge on certain aspects of malaria infection. For the purpose of the modelling, there was uncertainty to a number of parameters to which the model outcomes were particularly sensitive, particularly pertaining to aspects of malaria infection in the human host. For some of these gaps, it may not be technically possible to gather the necessary information, however in other areas it should not be too difficult.

Ethical problem!

Better estimates of the duration of malaria infections would be extremely useful. These could be based on longitudinal genotypic studies examining the duration of infection in different age groups and at different transmission intensities and could be related to the parasite density of infections and the onset of symptoms. This would help to elucidate the interaction between the intra-host dynamics of malaria infection, the role of general and specific immunity in controlling infection, and the importance of sub-patent infection in transmission.

Much uncertainty still exists around the factors affecting the transmission of malaria and in particular the factors affecting gametocytogenesis and the relationship between gametocyte carriage, infectiousness and immunity. Some of the most eloquent work on gametocytes comes from work done almost 50 years ago (Eyles and Young 1951) and fortunately there has been a renewed interest in this area. As a first step in the further gametocyte research it would be desirable to agree upon a common means of measuring the rate at which asexual parasites switch to gametocytes. It would also be useful to have a uniform means of measuring the infectiousness in terms of gametocyte density and duration (Sowunmi and Fateye 2003). As most clinical trials of antimalarial drugs currently follow-up patients parasitologically on a weekly basis, it requires little additional effort to report the gametocyte density as well as asexual parasite density before and up to 42 days after treatment, and from this establishing a “gametocytes switching rate” following treatment with different drugs (Barnes, Durrheim et al. 2005). There is also a lack of data on recrudescence infections themselves, as their onset usually represents the end-point of clinical trials. However they are an important source of malaria transmission and the spread of drug resistance and it would therefore be useful to have more information about them, particularly in relation to the density and duration of gametocytaemia.

For the purpose of a model such as the one presented here, in which immunity plays a central part, it would be useful to have more complete data on several age-stratified clinical outcomes at a range of EIRs. In particular, there is a lack of published data on age-stratified rates of treatment failure. Again, when clinical trials are carried out this information is inevitably collected and therefore only requires analysis and reporting. Other data are much more difficult or impossible to collect. Specifically, data on human susceptibility to infection are lacking and there is still a great deal of uncertainty about the existence and role of transmission-blocking immunity.

Finally, for the accurate estimation of the burden of disease caused by antimalarial drug resistance and therefore the benefit of interventions aimed at its control, more precise estimates of the incidence of malaria, severe malaria and deaths are needed. In addition studies that elucidate the relationships between malaria and anaemia, neurodisability and other infections will be important in quantifying the full burden of disease.

10.2.4 Further development of the thesis model

The development of the model to this stage was the aim of the thesis and was all that was possible within the constraints of time and the computing facilities. However, there is clearly room for further refinement and validation and to fully exploit the application of the model. This section firstly describes how the model could be checked for validity and then describes further developments of the model that would either make it easier to use or more realistic. Finally some of the potential applications of the model are discussed in the context of current policy issues.

10.2.4.1. Checking the model for validity

The process of developing the model was a continuous iterative process involving the construction of the model, running it and making modifications in light of the findings. Ideally the robustness and validity of the model should be further explored by extending the sensitivity analysis and by comparing the results of the model to more datasets, especially in high transmission settings. Sensitivity analysis should ideally be extended to include testing of the immunity functions. Immunity forms a core part of the model and the shapes of the functions are key determinants of the model outcomes. Although the data on which some of the functions were based were comprehensive and the resulting functions described a good fit, for other functions there were fewer data, and the resulting functions are less precise. In addition there is an inherent uncertainty in using the immunity functions as proxy measures of the facets of immunity described in the model. It would therefore be useful to vary the shape of the

functions, essentially to describe more or less steep relationships between facets of immunity, age and EIR, in order to explore how this affects the outcome of the model.

The best way of validating the model is to see how accurately it predicts outcomes and this was done for a low transmission setting, using data from KwaZulu-Natal in South Africa and Northern Thailand. There are several large-scale implementation programmes currently underway in both low and high transmission areas, which will provide opportunities for further validation. Such a programme is now being instituted in a large mining community in Papua where a switch is being made from chloroquine to artemether-lumefantrine. A rich set of clinical, parasitological and entomological data is currently being collected and there are plans to use this data to validate the model (Ric Price, personal communication).

10.2.4.2. Developing and modifying the model

The model, as it stands, is more comprehensive than preceding work and can already be applied to address policy relevant questions. However there is plenty of scope to develop it further. These developments mainly fall into the category of either increasing the realism of the model or improving its user friendliness or speed of running.

Integration with a model of the emergence of drug resistance

As mentioned at the beginning of the chapter, perhaps the greatest need is to incorporate the emergence of drug resistance. It is clear that once resistance has emerged and survived, its subsequent spread is rapid and therefore measures including the use of ACTs that impact on the likelihood of emergence will have a far greater effect on health outcomes and costs than those that only impact on the spread of drug resistance. It will also help to address concerns about the emergence of resistance to artemisinin derivatives in light of potential widespread use of the monotherapy. An emergence model is currently being developed. The next step will therefore involve dovetailing the two models so that the “spread” model starts at the point at which the “emergence” model ends, which is when there are enough resistant parasites to be reasonably certain of transmission and spread.

Individual-based simulations

As discussed earlier, the main limitations to the realism of the model are that it is deterministic and population-based and it therefore does not allow for the exploration of micro-heterogeneity in the population and for the stochastic nature of events. The latter is particularly important in realistically simulating rare events and would therefore be most useful in modelling transmission in low transmission settings and in the modelling of the emergence and survival of drug resistance. Therefore one of the next aims of this work is to adapt and transcribe the model to another programme such as Simul8® which is designed to keep track of individuals. In this

way individual or ethnic variation, for example differences in the risk of exposure and immunity, can be introduced and the effect on model outcomes explored. This could also be useful in investigating outcomes in pregnant women and their contribution to transmission and the spread of drug resistance.

Pharmacokinetics and other refinements

Currently the model handles the phenomenon of chemoprophylaxis simplistically by presuming that a fixed proportion of potentially patent sensitive infections are eliminated at the beginning of each iteration. Recently it has become clear that the half-life of the drugs in combination therapies is important in determining the rate of re-infection in high transmission settings (Staedke, Mpimbaza et al. 2004; Mutabingwa, Anthony et al. 2005)⁷⁸. Ideally the model should therefore be adapted so that the pharmacokinetics of drugs is handled more realistically. This will most likely entail the introduction of an intermediate level of drug resistance (Res1) between the complete resistance and complete sensitivity assumed in the current model (Hastings, Watkins et al. 2002).

Other refinements

Other possible refinements to the biological model include allowing for superinfection, *var* gene switching, a group of symptomatic but untreated patients with the immune characteristics of the latter, and a third arm of treatment where patients are treated with a drug other than the monotherapy and combination therapy.

In addition, there are changes that could be made to the sub-models to enable more detailed modelling of the outcomes and costs. For example a proportion of patients with severe malaria should be assumed to be treated in the informal sector where the likelihood of mortality and costs are different from the formal sector.

At the moment the model is not particularly easy to share with others and requires transferring of datasets from S-plus® to Excel®. In order to make it more accessible and useful it needs to be integrated and transcribed to a more user-friendly programme such as Modelmaker® or Simul8®.

⁷⁸ The study in Tanzania showed that although the PCR adjusted day 28 cure rates with amodiaquine-artesunate was 88% compared to 97.3% for artemether-lumefantrine, there were more re-infections in the latter so that the unadjusted “clinical cure” rates were the same (Mutabingwa, Anthony et al. 2005). In the Ugandan study, a similar observation was made between a group treated with amodiaquine-SP and a group treated with artesunate-SP (Staedke, Mpimbaza et al. 2004).

10.2.4.3. Applying the model

There are many avenues for applying the model to investigate the spread of antimalarial drug resistance and the effectiveness and cost-effectiveness of measures aimed at its control. Some of these have been visited in this thesis but others remain unexplored.

Macroeconomic analysis

As discussed at the beginning of the thesis, the economic analysis takes a “micro” approach. In order to capture the full impact of drug resistance and the benefits of controlling its development, the results of this model could be fed into a macroeconomic analysis (Smith, Yago et al. 2005). The latter require data generated from micro studies including estimates of the impact of drug resistance on health outcomes.

High transmission settings

The focus of this thesis has been the spread of drug resistance in a low transmission setting. However, there has been much debate about the impact of combination therapy in high transmission settings and the model was constructed so that it could address this question. Preliminary results from applying the model to a high transmission setting show that the model predicts that resistance spreads more slowly than in low transmission settings and that whilst the introduction of ACT slows this spread further, the effect is much less marked than in low transmission settings. As expected, the model predicts that ACTs do not appear to have any impact on malaria incidence (Annex 10). Because of the higher incidence of infections, the incremental costs of first-line drugs are much greater and the cost-effectiveness less, especially if only a short term perspective is taken. Clearly, there is much more scope for using the model to explore the implications of implementing ACTs in a high transmission setting.

Targeting

Perhaps the most exciting application is the use of the model to compare the effectiveness and cost-effectiveness of specific policy options, especially after it has been coupled with the emergence model. The most pertinent questions relate to addressing the trade-off between maximising access to ACTs versus limiting or targeting their use to those who are most biologically and/or economically vulnerable. The aims of targeting are to reduce the cost of drugs; decrease the wastage of a scarce resource; reduce the risk of the inappropriate treatment of non-malarial fevers and the associated delays; and finally reduce drug pressure and therefore the risk of resistance arising. The most obvious target group is children and the model in its current form can be applied to compare the long term impact and cost-effectiveness of targeting children versus universal coverage.

Biological diagnosis and social marketing

The model can also be used to address the question of whether or not the use of ACTs should be restricted to those who have biologically confirmed *P. falciparum* malaria. The question of the cost-effectiveness of biological diagnosis irrespective of the impact of resulting drug use on drug resistance is an important one and is actively being pursued by collaborators and it is hoped that their analysis will be able to inform this model (Catherine Goodman, personal communication). Inclusion of the costs and effects of introducing diagnostics immediately introduces the need to consider the segment of the population who are uninfected with malaria, but who have similar symptoms for which they seek treatment. Those that receive antimalarial drugs presumptively may contribute to the spread of resistance and as mentioned earlier, this would ideally involve adapting the model to include an intermediate level of drug resistance.

The impact and cost implications of socially marketing ACT can also be explored using the model. In particular, the distribution of costs between patients, the private sector and the government can be estimated in different scenarios.

Choice of drug

Making two switches, first to artesunate-SP (or artesunate-amodiaquine) and then later to a co-formulated ACT such as artemether-lumefantrine, has been the policy option chosen by a number of countries. The main incentive is the lower cost of artesunate-SP. As discussed earlier, the danger of such a policy is that the spread of resistance to SP or amodiaquine is likely to go unchecked by the addition of artesunate. The results of the model suggest that under perfect conditions where coverage is 100% and the switch is made when resistance is still low (<20%), artesunate-SP is marginally more cost-effective than artemether-lumefantrine over a 10-year time frame and it may be reasonable to implement such an "intermediate switch". However, in less than ideal circumstances, artesunate and SP may soon become less cost-effective than artemether-lumefantrine, necessitating an early switch. This problem warrants further exploration with the model. In doing so it will be important to incorporate the cost of making an additional change in policy, such as the costs of meetings, training, printing and raising public awareness.

Time frame

In this thesis, a time frame of 10 years was used. However, the time frame of the economic analysis is clearly important and some of the benefits of ACT may not be fully realised until after this. Extending the duration of the analysis will therefore be essential, especially when the "emergence model" is incorporated. Currently, one of the disincentives to using longer time frames is the length of time it actually takes to run the model. One of the major advantages of

Migration, dormant infections and seasonality

In terms of transmission and the spread of antimalarial drug resistance, the model has a number of features that have not been exploited so far and warrant further investigation. This includes exploring the inclusion of external source of infections (migrant or dormant infections) and the effect of seasonality. The role of migration infections and their importance in maintaining transmission in a low transmission setting has already been noted. So far in this thesis, this group have been assumed to have the same characteristics in terms of immune profile and level of drug resistance compared to the main population. However, the model allows both of these to vary, as well as the size and the timing of their introduction into the population. By varying these characteristics and the size of migrant group the effect of migration on malaria transmission and the spread of drug resistance can be explored.

The effect of seasonality on the transmission of malaria can also be explored by specifying the timing of the external infections in order to simulate the phenomenon of sub-patent infections that survive through the dry months to re-emerge the following year. Seasonality can also be explored by varying the vectorial capacity from month to month

Immunity

Because the model handles immunity in a more sophisticated way than previous models, it can be exploited to investigate the effect of interventions on the immunity profile of the population. For example there are concerns that the introduction of vaccines, vector control or effective drug treatment in infants and young children will result in a shifting of the age and severity of clinical disease upwards towards the older age groups. Although not constructed for this purpose, there is no reason that the model can not be used to explore these issues.

10.2.5 Alternative modelling approaches

In this thesis, a microeconomic approach was used, in which the underlying epidemiological model was population-based and when the total cost of malaria was considered, a human capital approach was used. There are a number of alternative analytic strategies that could be explored.

10.2.5.1. “Micro” approaches

Other “micro” approaches that have been used to study the economics of antimalarial drug resistance and ACT, and warrant further exploration, include the decision-tree based models (Goodman, Coleman et al. 2001; Coleman, Morel et al. 2004) and adaptation of existing compartment models of malaria transmission and drug resistance (Laxminarayan 2004a). The former have also been used to explore the value of obtaining additional information for variables to which the cost-effectiveness of ACT is sensitive but for which there is significant uncertainty (Sam Shillcutt, personal communication). For the more realistic modelling of the

former have also been used to explore the value of obtaining additional information for variables to which the cost-effectiveness of ACT is sensitive but for which there is significant uncertainty (Sam Shillcutt, personal communication). For the more realistic modelling of the epidemiology of malaria transmission and antimalarial drug resistance, models based on individuals rather than on the population will be necessary. Such models allow the exploration of the impact of individual variation in risks and behaviours on overall outcome including the total cost of malaria inclusive of the indirect costs of lost productivity. They also allow the amount of variation in the impact of drug resistance on individuals to be explored. As mentioned earlier such a model could be developed from a pre-existing population-based model such as the one presented in this thesis.

Most economic analysis of malaria and antimalarial control strategies have utilised a human capital approach to measure the cost of health in monetary terms. Studies employing a “willingness-to-pay” approach could provide valuable information on the amount of money decision-makers are willing to pay in order to decrease the risk of the emergence or spread of drug resistance. Although, the complexity of the issues involved make it challenging to explore such questions in malaria-affected communities, it would be useful to estimate how much individuals are willing to pay for such externalities.

10.2.5.2. “Macro” approaches

Although macroeconomic approaches have been employed to study the economic impact of malaria (McCarthy, Wolf et al. 2000; Gallup and Sachs 2001) and of antimicrobial drug resistance (Smith, Yago et al. 2005), so far they have not been used in the economic analysis of antimalarial drug resistance. Such studies are needed in order to estimate the impact of antimalarial drug resistance on the economy more comprehensively than is possible with traditional microeconomic approaches. Possible means of doing this could include either using logistic regression analysis similar to those conducted previously on malaria or one using a computable equilibrium analysis. One of the disadvantages of the former is that although it may be useful in describing the link between antimalarial drug resistance and economic indicators, it cannot be easily manipulated to study the cost and impact of interventions to control drug resistance. This may however be possible by using a computable general equilibrium analysis as described by Smith et al. This could be undertaken by mathematically describing the economy of a country or region in a state of equilibrium, with a given level of malaria transmission and no drug resistance. Drug resistance could then be introduced as a “shock” to the system and the effects on the different sectors of the economy, observed. The effect of different strategies for controlling drug resistance could possibly be explored by varying the size of this initial shock or by the introduction of a second shock to the system.

10.3 Final conclusions

This thesis started by stating the nature of problem of antimalarial drug resistance and the policy dilemmas facing decision-makers responsible for changing and implementing antimalarial drug policy. The core of the problem is that artemisinin-based combination therapies are more costly than the older failing monotherapies and there is a need to ensure that they are used to save the lives of those threatened with malaria now, whilst at the same time prolonging their useful life for the future. There are, in particular, concerns about how effective ACTs will be in practice when implemented in settings with poor health care infrastructure where low coverage rates can be anticipated.

In order to address this problem with this study, a comprehensive bio-economic model of the spread of antimalarial drug resistance has been developed and an extensive amount of data collected, including empirical data from Cambodia where ACTs were first implemented. The model has been applied to a low transmission setting and run with the Cambodian data, in order to explore the spread of resistance and the costs and consequences of switching from a monotherapy to an ACT.

The results from this study suggest that in a low transmission setting, ACTs are cost-effective and result in overall cost-savings in a wide range of scenarios. Much of the benefit in this setting is due to an impact on the transmission of malaria as the recrudescence infections that are responsible for much of the transmission are averted. The longer the time frame of the analysis, the more cost-effective the switch, as more cases and treatment failures in the future are averted. Although benefits are seen even at low coverage rates, higher coverage rates are important in maximising benefit to both current and future populations. The model predicts that high coverage rates of 80% or above are required to cause a noticeable delay in the spread of drug resistance to a partner drug to which resistance has already emerged. Choice of drug is important. Although the addition of an artemisinin to an already failing drug will result in short-term benefit and may be less costly in the short term, unless coverage rates are very high and the switch is made early, the artemisinin component will be left exposed as a monotherapy. Clinically, this may not be detected for years, as the majority of patients will continue to be cured. Therefore switching to the co-formulated ACTs is strongly recommended.

The findings from the empirical data collection in Cambodia highlight the challenges facing those implementing the switch to ACTs in similar settings. Without specific strategies to improve access to ACTs and biological diagnosis, uptake of the new policy was extremely low and most worryingly the inappropriate use of artemisinins on their own was widespread. However delivery intervention, such as outreach clinics and in particular village malaria

volunteers appear to be an effective way of increasing coverage of ACTs. The benefits are multiple. The most vulnerable populations are targeted; biological confirmation to use of ACTs is ensured; the correct use of the drugs increased; artemisinin monotherapy use reduced; and the societal costs of malaria substantially ameliorated.

The human and economic cost of antimalarial drug resistance is high. This has finally been recognised and a major change in global antimalarial drug policy is currently underway. Global subsidies have been advocated to ensure that co-formulated ACTs are available for free, or at very low cost to the populations at-risk of malaria (Arrow, Panosian et al. 2004). It is important to ensure that sufficient resources are also made available for their effective implementation and to evaluate the cost and effectiveness of different strategies including the social marketing of the drugs with or without RDTs. The bio-economic model developed in this study is intended to contribute to such evaluations.

There is a trade-off between the complexity needed to ensure biological realism and the simplicity and clarity required to facilitate application to policy. However, by combining biology and economics within a single framework, this model has the advantage of ensuring that the economic analysis is based on realistic biological predictions. It therefore enables a wide range of scenarios to be explored by altering the values of the epidemiological, behavioural and cost inputs. By applying the model to both low and high transmission settings, it is hoped that it will serve as a useful tool in the further elucidation of policy decisions.

ANNEX 1 Background information

A.1.1. Artemisinin

History

Artemisinin or Qinghaosu was first isolated by Chinese army scientists in 1972, searching for new antimalarials amongst the traditional Chinese remedies¹. However details of the process were not released and it was not until 1984 that researchers outside of China successfully isolated artemisinin derivatives from plants found near the Potomac river in Washington D.C.. The plant in fact is common in temperate areas although commercial production until now has been concentrated in China and Vietnam. Artemisinin can be found in all parts of the plant except the roots and is most highly concentrated in the flowers. Artemisinin yield is associated with plant age and varies from 5kg/hectare to 30kg/hectare.

Formulations

The most widely used derivatives are artesunate, artemether and dihydroartemisinin (DHA). Artesunate is the most widely available in tablet form on its own, in gel suppositories and in powder form in a vial for injection following reconstitution with 5% sodium bicarbonate. Artemether is available in tablet form on its own but and is more widely available co-formulated with lumefantrine. It is also formulated in peanut oil for intramuscular injection. Dihydroartemisinin is available mainly in Southeast Asia where it is usually co-formulated with piperazine.

Mechanism of action

Artemisinins have a unique chemical structure, containing a endoperoxide bridge that is central to its mechanism of action. Artemisinins cause a peroxidation of lipid membranes due to the formation of free radicals when they comes into contact with intracellular heme or iron. They may have a more specific action on malaria parasites by acting on a calcium transporter.

Uncomplicated malaria

The first RCTs on ACTs conducted in Asia, with the combination of three days of artesunate and single dose mefloquine showed that the combination was rapidly efficacious, improved cure rates, decreased gametocyte carriage and was well tolerated (Price, Nosten et al. 1997; Nosten, van Vugt et al. 2000). Subsequent trials elsewhere including the largest RCTs ever conducted in Africa, have confirmed these findings with different ACTs. The first of these was a multi-centre RCT of three-day amodiaquine plus artesunate against amodiaquine plus placebo, involving 941 children. The artesunate plus amodiaquine combination was found to be significantly more efficacious in Gabon (85% versus 71%, $p=0.02$) and Kenya (68 versus 41%, $p<0.0001$) and equivalent in efficacy in Senegal (Adjuik, Agnamey et al. 2002). In Gambia, the combination of three days of artesunate and a single dose of sulfadoxine-pyrimethamine (SP) was found to result in a significantly higher cure rate than SP alone, at a time that SP was still effective. Gametocyte carriage was also noted to be significantly lower with the artesunate-SP combination (21% versus 68%, $p=0.001$) (von Seidlein, Milligan et al. 2000). In contrast when the same combination was evaluated in Uganda where drug resistance to SP was already established, a significant proportion of infections treated with the artesunate-SP combination recrudesced.

The fixed dose combination, artemether-lumefantrine (Coartem®), is currently the only co-formulated ACT on the market, and contains a partner drug that has not been widely used previously. It has the disadvantages of requiring twice daily dosing and the need for dietary intake for optimal absorption. Clinical efficacy studies have shown it to be extremely efficacious and well tolerated in Asia (van Vugt, Looareesuwan et al. 2000; Lefevre, Carpenter et al. 2002) and Africa (Falade, Makanga et al. 2005). A recent randomised study in Uganda compared efficacy (supervised) with the effectiveness (unsupervised) and using pharmaco-

¹ Interestingly, this programme was in response to an appeal for help from Ho Chi Minh to Zhou En Lai during the Vietnam war.

pharmacokinetics in 644 patients. PCR-corrected cure rates were 98% in both groups although the plasma concentrations of lumefantrine were lower in the unsupervised group (Piola, Fogg et al. 2005). However in another study in Zambia with 169 patients, effectiveness was significantly lower at 63.4% compared to efficacy at 83.5% (Depoortere, Guthmann et al. 2005).

Severe malaria

Recently the largest clinical trial of the treatment of severe malaria found that patients treated with intravenous artesunate had a mortality rate of 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; an absolute reduction of 34.7% (95% CI 18.5-47.6%; $p=0.0002$). Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3.2, 1.3-7.8; $p=0.009$) (Dondorp, Nosten et al. 2005). Artesunate can also be administered as a rectal suppository, making it easy to administer quickly to children and adults with severe malaria. Its widespread availability in peripheral health facilities and in communities therefore has the potential of significantly reducing the delay in treatment of severe infections, thereby reducing malaria deaths. It has been shown to be highly effective and safe in a number of randomised and open-label studies in both Asia and Africa (Cao, Bethell et al. 1997; Awad, Alkadru et al. 2003; Barnes, Mwenechanya et al. 2004; Aceng, Byarugaba et al. 2005).

ANNEX 2 Cambodian development and economic indicators

Table A2-1: Cambodian economic indicators

Indicator	Value
Gross Domestic Product (GDP) (US\$)	3.4 (UNDP 2002)
GDP per capita (US\$)	263 (NIS 1999), 278 (UNDP 2002)
Purchasing Power Parity (PPP) (US\$)	22.8 billion (UNDP 2002)
PPP per capita (US\$)	1,860 (UNDP 2002)
Overseas Developmental Assistance (ODA) received (net disbursement) – Total (US\$)	408.7 million (UNDP 2002)
ODA received (net disbursement) Per capita (US\$)	30.3 (UNDP 2002)
ODA received (net disbursement) As % of GDP	12 (UNDP 2002)
Total debt service As % of GDP	0.6 (UNDP 2002)
Health expenditure Public as % of GDP	1.0-2.0 (UNDP 2002)
Health expenditure Private as % of GDP	6.1 (UNDP 2002)
Health expenditure per capita PPP (US\$)	97 (UNDP 2002)

Table A 2-2: Household expenditure and consumption data from Cambodian socio-economic survey 1999 (NIS 1999)

		Urban	Rural
Average monthly expenditure (US\$1999)	Per household	94.8	74.6
	Per capita	18.6	14.7
Average monthly household consumption (Riel)	Total	361,736	284,444
	For medical care	21,189 (5.9%) 1 st decile 3352 =2.4%, 10 th decile 92,620 = 8.8%	18,696 (6.6%)
	For food and tobacco	222,757 (61.6%)	198,831 (70.0%)
	For housing	61,915 (17.1%)	309,619 (10.8%)
Average monthly per capita consumption (riels)	Total	71,077	55,956
	For medical care	4,095 (5.8%)	3,564 (6.4%)
	For food and tobacco	43,443 (61.1%)	38,853 (69.4%)
	For housing	12,568 (17.7%)	6,368 (11.4%)
Monthly income (US\$1999)	Per HH	105.7	82.4
	Per capita	20.8	16.4

Table A2-3: Poverty indicators

Indicator	Value
Gini index	40.4 (UNDP 2002)
% pop below national poverty line	36% (NIS 1999)
Share of income or consumption Poorest 10%	2.9% (UNDP 2002)
Share of income or consumption Richest 10%	33.8% (UNDP 2002)
% of households with access to safe drinking water	29% (23.7% in rural) (NIS 1999)
% of households with electricity as main source of light	15.1% (8.6% in rural) (NIS 1999)
% of households having toilet facility within premises	14.5% (8.6% in rural) (NIS 1999)

Table A2-4: Health related indicators from the Cambodian general population census (NIS 1999) and the demographic and health survey (NIS 2001)

Indicator	Value
Under-five mortality rate (per 1000 live births)	124 (NIS 2001)
Infant mortality rate (per 1000 live births)	95 (NIS 2001)
Maternal mortality rate (per 100,000 live births)	437 (NIS 2001)
Life expectancy at birth (Male)	54.5 (NIS 1999)
Life expectancy at birth (Female)	58.3 (NIS 1999)
Maternal mortality rate (per 100,000 live births) 1985-2001	440 (NIS 1999)
% female literates	57% (NIS 1999)
One-year olds fully immunised against TB	64% (UNDP 2002)
One-year olds fully immunised against measles	59% (UNDP 2002)
Physicians (per 100,000)	30 (UNDP 2002)

Table A2-5: Other indicators from Cambodian socio-economic survey (included for comparison of results with this thesis)

Indicator		All	Rural
Wall construction	Bamboo, thatch	48.4%	54.7%
	Wood	2.5%	2.8%
	Plywood	37.3%	34.8%
Roof construction	Thatch	39.8%	44.4%
	Tiles	29.1%	31.7%
	Iron/aluminium	22.5%	18.8%
Clean source of water (piped, protected well or bought)		64%	24%
Household durables	Bicycle	64.5%	67.1%
	Motorcycle	24.9%	16.6%
	Radio	45.3%	41.3%
	TV	26.4%	20%

ANNEX 3 Classification for *in-vivo* antimalarial drug resistance studies

A.3.1. WHO 1996 Classification

ETF – Early Treatment Failure

- Danger signs or severe malaria on day 1, 2, or 3 in the presence of parasitaemia
- Fever* on day 2 and parasite density greater than on day 0
- Fever and parasitaemia on day 3
- Parasite density on day 3 is $\geq 25\%$ than on day 0

LTF – Late Treatment Failure

- Danger signs or severe malaria in the presence of parasitaemia on any day from day 4 to day 14, without previously meeting any of the criteria for ETF
- Fever and parasitaemia on any day from day 4 to day 14, without previously meeting any of the criteria for ETF
-

ACR - Adequate Clinical Response

- Absence of parasitaemia on day 14, irrespective of fever status, without previously meeting any of the criteria for ETF or LTF.
- Absence of fever irrespective of the parasitaemia status, without previously meeting any of the criteria for ETF or LTF

A.3.2. Revised WHO Guidelines - 2002 Classification

ETF – Early Treatment Failure: Days 0,1,2 and 3

- Development of danger signs or severe malaria on days 0 to 3 in the presence of parasitaemia
- Parasitaemia on day 2 higher than on day 0, irrespective of temperature
- Parasitaemia on day 3 with fever
- Parasite density on day 3 $\geq 25\%$ of count on day 0

LCF – Late Clinical Failure: Days 4 to 14 (for intense transmission area) or 28 (for low-to moderate transmission area).

- Development of danger signs or severe malaria after day 3 in the presence of parasitaemia, without previously meeting any of the criteria for ETF.
- Fever (or history of fever in past 24 hours in low-to-moderate transmission area), in the presence of parasitaemia without previously meeting any of the criteria for ETF.

LPF - Late Parasitological Failure: Days 7 to 14 or 28

- Fever and presence of parasitaemia on day 14 in intense transmission area, or on any day from day 7 to 28 in low-to-moderate transmission area, without previously meeting any of the criteria for early or late treatment failure

ACPR – Adequate Clinical and Parasitological Response

- Absence of parasitaemia on day 14 in intense transmission area, or on day 28 in low-to-moderate transmission area, irrespective of fever, without meeting any of the previous criteria for failure

*Fever is defined as axillary temperature $\geq 37.5^{\circ}\text{C}$

Source: *Susceptibility of Plasmodium Falciparum to antimalarial drugs: Report of global monitoring 1996-2004. WHO 2005*

ANNEX 4 Antimalarial drug policy and incidence of malaria in Cambodia

Cambodian national antimalarial guidelines from year 2000 (CNM 2002)

First-line treatment for uncomplicated *P. falciparum* malaria

For 6 months to 6 years old children, the 1st line treatment is artesunate 50mg suppositories (P) during 5 days and mefloquine (M) dispensed by pharmacist/other health worker on D₂.

Table A4-1: Dosing of artesunate suppositories for children under 6 years old

Weight (w)	Age (a)	Day D ₁		D ₂	From D ₃ to D ₅
6kg ≤ w < 10kg	6 months ≤ a < 2 years	1P		1P+½M	1P / day
10kg ≤ w < 14kg	2 years ≤ a < 4 years	1P		1P+1M	1P / day
14kg ≤ w < 16kg	4 years ≤ a < 6 years	Morning 1P	Evening 1P	1P+1½M	1P / day

For others, the 1st line treatment is artesunate (or artemether) (A) + mefloquine (M), for 3 days. (A) is given as 50 mg tablets and (M) as 250 mg tablets.

Table A4-2: Dosing of blister-packaged artesunate and mefloquine

Weight (w)	Age (a)	Day D ₁		D ₂	D ₃
		Morning	Evening		
16kg ≤ w < 25kg (A+M ₂)	6 years ≤ a < 11 years	1M+1A	1M+1A	2A	2A
25kg ≤ w < 35kg (A+M ₃)	11 years ≤ a < 15 years	1M+1A	2M+2A	3A	3A
w ≥ 35 kg (A+M ₄)	a ≥ 15 years	2M+2A	2M+2A	4A	4A

During the 1st trimester of pregnancy, the 1st line treatment is not recommended, and quinine given for 7 days. During the 2nd and 3rd trimester of pregnancy, the treatment of uncomplicated malaria is A+M.

First line treatment of non *P. falciparum* malaria

The total dose of chloroquine is 25 mg/kg over 3 days.

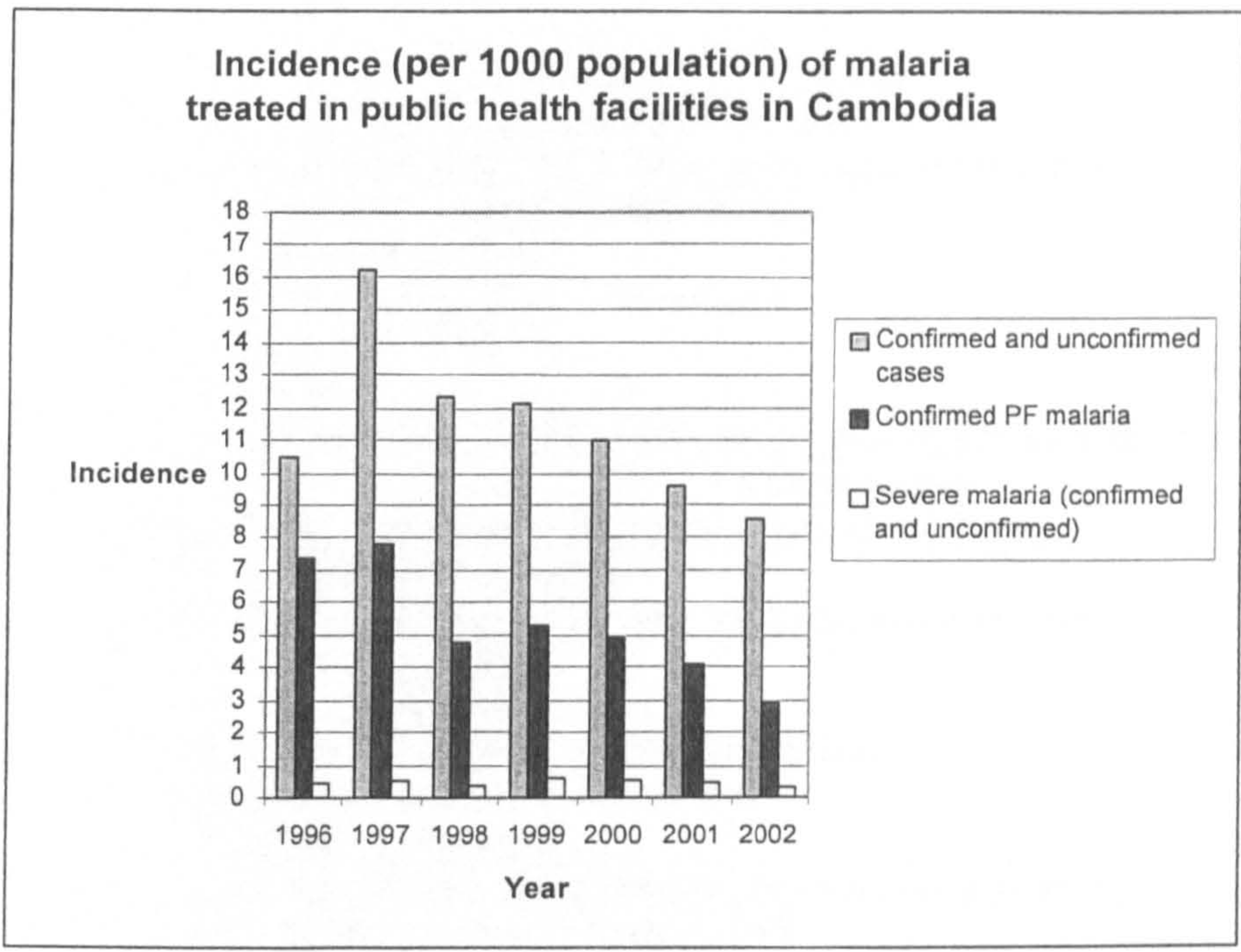
D₁ = 10 mg/kg single dose

D₂ = 10 mg/kg single dose

D₃ = 5 mg/kg single dose

Figure A4-1: Incidence of malaria in Cambodia

Source: Soley L. 2003, personal communication



ANNEX 5 Conceptual frameworks for economic analysis

Table A5-1: Types of costs and consequences relevant to the economic evaluation of health programmes

Costs	
I	Organising and operating costs, within the health sector (e.g. health care professionals' time, supplies, equipment, capital costs)
II	a. Costs borne by patients and their families <ul style="list-style-type: none"> ▪ Out of pocket expenses ▪ Patient and family inputs into treatment b. Time lost from work <ul style="list-style-type: none"> ▪ Psychic costs
III	Costs borne external to the health care sector, patients and their families.
Consequences	
I	Change in physical, social or emotional functioning (effects)
II	Change in resource use (benefits) For organising and operation services within the health care sector <ul style="list-style-type: none"> ▪ For the original condition ▪ For unrelated condition Relating to activities of patients and their families <ul style="list-style-type: none"> ▪ Savings in expenditure or leisure time ▪ Savings in lost work time
III	Changes in the quality of life of patients and their families (utilities)

Source: Adapted from Drummond & Stoddart, 1987

Table A5-2: Conceptual framework of economic analyses of malaria control from "Guidelines for cost-effectiveness analysis of vector control" (Phillips, Mills et al. 1993)

- I. The objective of improving health (choice of malaria control versus other means of health improvement);
- II. The objective of malaria control (choice of vector control versus case detection and treatment and various mixes of both);
- III. The objective of (a) vector control and (b) case detection and treatment (choice of strategies for each); and
- IV. The objective of delivering a pre-determined strategy (choice of means of blood slide examination, choices of different mixes of staff for various activities, choices of organisational pattern, etc.)

ANNEX 6 Parameter estimates

A.6.1. Order of presentation

The parameters are presented in the following order:

1. Malaria infection in the human host
2. Immunity functions
3. Asymptomatic infections
4. Symptomatic infections
5. Recrudescence infections
6. Vector dynamics
7. Clinical outcomes-Severe malaria and mortality
8. Behaviour - diagnosis and treatment seeking
9. Implementation
10. Costs
 - a. Direct costs of uncomplicated malaria
 - b. Direct costs of severe malaria
 - c. Indirect costs

In reality there is obviously much overlap between the groupings and the relationships between the parameters forms a complex web rather than distinct linear constructions. In order to make this clearer, for each parameter, its relationship to other parameters is indicated in the "dependent on" and "affects" columns. Clearly, not all permutations could be included in the model and therefore those relationships that were not actually incorporated into this model are placed in italics. Mean or median parameter estimates, and their estimated or observed distributions, are listed for use in sensitivity analysis. Where distributions could not be deduced from the literature, the most likely characteristics were ascribed.

A.6.2. Rows and Columns

Each row in the tables represents a different parameter with information presented in 9 columns. These are explained in Figure A6-1.

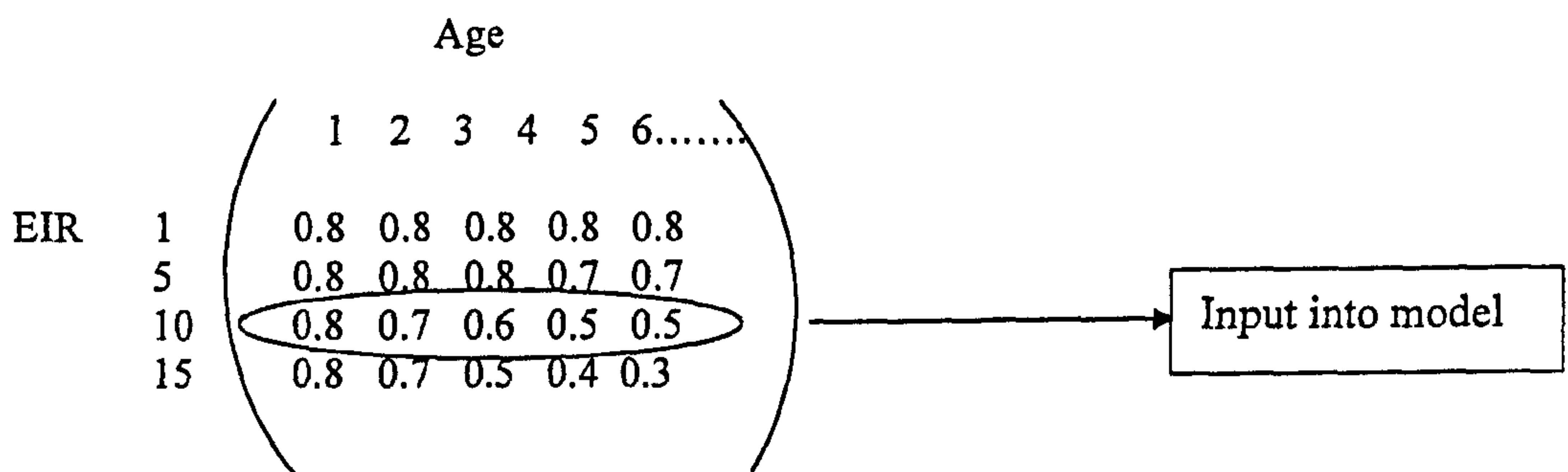
Figure A6-1: Example of column headings

1.	2.	3.	4.	5.	6.	7.	8.	9.
No.	Parameter	Dependent on	Influences	Value and range	Distribution	Quality level (QL)	Notes	Source
M4	Incubation period (Time between inoculation and first febrile response)	Size of inoculation Immunity	<i>Calculation of time lag between inoculations and symptomatic infections</i>	12 days 13.1 (1) 15 (2)	Point	A	Assumed to be same as time to maximum parasite density	1)Kitchen in Boyd's (p. 995) 2)Dietz 1974 (p.354)

1. No. - Parameter number (to aid cross-referencing)
2. Parameter - Usually self-explanatory and if not then a brief definition is included
3. Dependent on - This indicates the factors that influence this parameter. If this relationship is incorporated into the model it is written in italics.

4. Influences – This indicates the parameters “downstream” to this parameter. As above, if the relationship is incorporated it is written in italics
5. Value and range – The first value in italics is the one used in the model. The other values are those obtained from the literature. The number in brackets is a reference to the source which is detailed in the last column.
6. Distribution – This is the distribution of the range of values for use in the sensitivity analysis e.g. uniform, normal or log-normal. For parameters for which there is little uncertainty a “fixed” input is used either as single value or as a vector e.g. age-stratified blood volume.

As the product of the each immunity function is a matrix of age and EIR dependent values, the actual input into a single iteration of the model is the vector of age-dependent values for the EIR in that iteration. This is illustrated in the example below where the values in the matrix could represent likelihood of symptomatic infection and the EIR for the given iteration is 10.



7. Quality level (QL) – This indicates the degree of confidence in the quality of the data and was defined as follows:
 - A Much data available, little uncertainty
 - B Some data available, some uncertainty
 - C Little or no data available, much uncertainty.
8. Notes – Useful information about the data and assumptions made in using the parameter in the model are included in this column.
9. Source – The full references are given at the end of the thesis.

Table A6-1: Malaria infection in the human host

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
M1	Population age structure	Socio-economics Migration	<i>Distribution of infections</i>		Fixed	A	Can be adapted for atypical age structures eg in predominantly migrant populations	(UN 2005)
M2	Age-stratified blood volume per person	Age-weight structure of population	<i>Used to calculate no. parasites/per infected person</i>	0.8 – 5 litres <i>Based on weight/age (1) and mean blood volumes (2)</i>	Fixed	A	Assume: Average adult weight: 60kg female 65kg male Blood volume: 75 ml/kg (2)	(1) Standard Growth charts (WHO and other websites) (2) Scientific tables
M3	Time taken to acquire immunity after infection		<i>Frequency that immunity profile of population is updated</i>	90 days	Fixed	C	Is the same for different facets of immunity	
M4	Incubation period (Time between inoculation and first febrile response)	Size of inoculation (1) Parasite multiplication rate	<i>Used to check time lag between inoculations and symptomatic infections</i>	13.1 (1) 15 (2)	Fixed	A	Assumed not to be associated with immunity ²	(1) (Kitchen 1949) page 995 (2) (Dietz, Molineaux et al. 1974) (page 354)
M5	Pre-patent period Time taken from inoculation to detectable parasitaemia	Size of inoculation	<i>Calculation of time lag between inoculations resulting in infectiousness</i>	10 days 11 days (1) 7-13 days (2) 6-28 days (3)	Fixed	A	Assume not to be associated with immunity	(1) (Kitchen 1949) page 995 (2) (Eyles and Young 1951) (3) (Eyles and Young 1951; Collins and Jeffery 1999)

² In re-infected patients the mean pre-patent period was 11.5 days and said to be “in the same range as those reported previously for patients following primary challenge” (Collins and Jeffery 1999).

(Table A6-1 continued: *Malaria infection in the human host*)

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
M6	Time from parasite patency to gametocyte (ie gametocyte maturation)		<i>As for M5</i>	10 days 10 days (1) & (2)	Fixed	A		(1) (Thomson 1911) (2) (Jeffery and Eyles 1955)
M7	Gametocyte half life	Gametocidal drugs	<i>Infectivity</i>	2.4 days (1) About 4 days (2) ³	Normal (2)	A	Gametocytes once mature remain infective throughout their life (1) Gametocytes clear at constant rate	(1) (Smalley and Sinden 1977) (2) (Eichner, Diebner et al. 2001)
M8	Minimum parasite density detectable by microscopy		<i>Used to interpret prevalence data</i>	20/ul (10 parasites/adult) 20/ul (1) 5/ul (2)	Fixed	A		(1) (Bruce-Chwatt 1993) (2) (Petersen, Hogg et al. 1991)
M9	Multiplication rate per 48 hours		<i>Duration and density of parasitaemia before it reaches a maximum</i>	x10 x 8 (90% prediction interval 5.5-12.3)(1)	Fixed	B	Data modelled on neurosyphilis data	(1) (Simpson, Aarons et al. 2002)
M10	Proportion of human population with inhibitory concentration of antimalarials in their blood at any one time	Transmission intensity Treatment seeking behaviour Access to treatment	<i>Likelihood that a sensitive infection will survive to become patent</i>	10% 18% of children with detectable SP 5% of children with detectable CQN		B		(1) (Eriksen, Nsimba et al. 2005)

³ Average (geometric mean) circulation time after inoculation was 7.4 days which was double that predicted by Smalley.

Table A6-2: Age-stratified data used in immune functions

No.	Parameter	Dependent on	Influences Role in model	Value and range Value in model	Distribution	QL	Notes and assumptions	Source
Im 1	Age-stratified probability of clinical symptoms in humans with a patent infection.	Transmission intensity	Used to construct Immunity Function 1	0.94-1.0 (1) Thailand, EIR 1 0-0.25 (2a) Chonyi, Kenya EIR 50 0-0.5 (2b) Ngerenya, Kenya, EIR 20 0.008-0.28 (3) Siaya, Kenya, EIR 270	-	B	From x-sectional prevalence surveys	(2) (Nosten F, personal communication) (3) (Mwangi T, personal communication) (3) (Bloland, Boriga et al. 1999)
Im 2	Age-stratified parasite density (parasites/ul)	Transmission intensity	Used to construct Immunity Function 2	117 - 1922 Ghana, EIR 300 (1) 5 024 to 97 591 Laos, EIR 1 (2) 40 - 439 179 Kenya, EIR 50 (3a) 40 - 694 629 Kenya, EIR 20 (3b) 40 - 1 528 753 Thailand, EIR 1 (4) 8801 - 55 228 PNG, EIR 40 (5) 250 - 52052 Senegal, EIR (6) 500 to 4500 Siaya, Kenya, EIR 270 (7)	-	A	Assume that detectable limit is 20/ul (=10 ⁷ parasites in adult)[16] All data from x-sectional prevalence surveys except (4)	(1) (Owusu-Agyei, Smith et al. 2002) (2) (Mayxay M, personal communication) (3) (Mwangi T, personal communication) (4) (Nosten F, personal communication) (5) (Cox, Kum et al. 1994) (6) (Trape, Rogier et al. 1994) (7) (Bloland, Boriga et al. 1999)
Im 3	Age-stratified risk of severe malaria	Transmission intensity	Used to construct Immunity Function 3	0 - 80 cases per 1000 persons/year. 3 places in Kenya, 2 places in Gambia (Children only <9 years only) (1) 0 - 90 cases per 1000 persons/year. (All ages) (2)	-	B		(1) (Snow, Omumbo et al. 1997) (2) (Luxemburger, Ricci et al. 1997)

Table A6-3: Input parameters for non-immune host for "zeroing" immune function

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
Im 4	Maximum susceptibility ie maximum probability of developing a patent infection following inoculation		<i>Used to calculate susceptibility to infection</i>	0.8 0.79 non-immune adults after first inoculation (1)	Normal	C	After 1 inoculation 75% of neurosyphillis patient became parasitaemic with symptomatic with and 4% parasitaemic only	(1) (Ciuca, Ballif et al. 1934)
Im 5	Maximum likelihood of treatment failure (Same as an untreated infection)		<i>Used to "zero" calculate age-stratified probability of treatment failure</i>	0.85 1 (1) 0.7 (2)		A	Based on clinical trials with 28 day follow up using ineffective drugs	(1) (Bunnag, Viravan et al. 1991) ³ (2) Expert opinion
Im 6	Maximum likelihood of symptoms given a patent infections			0.8 0.89 (<5 year olds, Uganda) (1) 0.92 (0.8-1) South Africa (2) 0.95 ⁴ (malariatherapy patients) (3) 0.84 (Thailand) (4) 0.28 (Kenya) (5)		B	Based on monthly follow up ⁵	(1) (Njama-Meya, Kanya et al. 2004) (2) (Barnes K, personal communication) (3) (Ciuca, Ballif et al. 1934) (4) (Luxemburger, Thwai et al. 1996) (5) (Bloland, Boriga et al. 1999)

³ Thailand, Artesunate 1-2 days 10mg/kg.

⁴75/79 in non-immune adults after first inoculation.

⁵ But not based on genotyping so not definite if symptomatic episodes following a period of asymptomatic parasitaemia were really due to same clone but strong temporal correlation. Therefore unlike the Sudan study (Babiker 1998) where progression to symptomatic malaria was associated with both persistent strains and the appearance of new strains.

(Table A6-3 continued: Input parameters for non-immune host for "zeroing" immune function)

No.	Parameter	Dependent on	Influences Role in model	Value and range Value in model	Distribution	QL	Notes and assumptions	Source
Im 7	Maximum duration of untreated infection		<i>Influences population rate of loss of infections</i> <i>Influences time before individual re-enters susceptible pool or starts recrudescent infection</i>	80 days 121+/- 9 (1)89-228 days (2) 75% loss by 2 months ⁶ (3) 9.5 months (4) 52-555 days (derived value) (5) 200-300 days (6) Median of <4 weeks, max 40 weeks (age < 2years, with genotyping) (7) 9 to 48 days depending on age ⁷ (longitudinal study, no genotyping)(8) >15 months (with genotyping) (9)	Log-normal for SA	B		(1) (Eyles and Young 1951) (2) (Collins and Jeffery 1999) (3) (Kitchen 1949) (p1011) (4) (Anderson and May 1991)(p378) (5) (Molineaux, Storey et al. 1980) (6) (Anderson and May 1991)(p279) (7) (Franks, Koram et al. 2001) (8) (Bruce, Donnelly et al. 2000) (9) (Babiker, Abdel-Muhsin et al. 1998)
Im 8	Minimum parasite reduction ratios (PRR) with different drugs at different levels of immunity and resistance	<i>Dependent on drug and resistance</i>	<i>Used to derive duration of infections and rate at which parasites are cleared from the population</i>	1.3-10000 fold reduction per life cycle (1) Results in duration of infection of 2-7 days	Fixed	A	Assumes: -that the reduction in parasite population is log-linear - that treatment is given at point of maximum parasitaemia	(1) (White 1997)

⁶ All lost by 6 months.

⁷ >48 days for age <4 years, 9 days for age 5-9 years, 15 days for age 10-14 years, 12 days for adults.

Table A6-4: Characteristics of asymptomatic infections

No.	Parameter	Dependent on	Influences Role in model	Value and range Value in model	Distribution	QL	Notes and assumptions	Source
A1	Parasite density of asymptomatic infection relative to symptomatic infections		<i>Infectiousness of untreated "immune" patients</i>	0.5 (0.1-0.9) 207-259 versus 9550-15366 0.01-0.03 (Vauatu (EIR 7), age <10 years ⁸) (1) 0.744 (PNG) (2) 0.55 (Mali) (3) 0.7 (Ghana) (4)	Uniform	A	That this ratio is fixed across age-groups	(1) (Maitland, Williams et al. 1996) (2) (Cox 2002) (3) (Sagara, Sangare et al. 2002) (4) (Owusu-Agyei, Koram et al. 2001)
A2	Gametocyte switching rate (GSR) (probability of an asexual parasite switching to a gametocyte)		<i>Infectiousness of untreated "immune" patients</i>	0.0019 in "acute" cases 0.019 in "chronic" cases ⁹ (1) 0.64 (0.00027-0.135) (2)	Log-normal (2)	B	One rate used throughout parasitaemia and for all untreated patients Input as a factor of GSR of symptomatic infections treated with monotherapy. <i>A factor of 1 is used in the base-case scenario</i>	(1) (Thomson 1911) (2) (Eichner, Diebner et al. 2001)

⁸ but part of definition of symptomatic includes minimum density.

⁹ Based on gametocyte to asexual parasite ratio which was 1 to 535 in "acute" cases and 1 in 52 to 81 in "chronic cases".

Table A6-5: Characteristics of symptomatic infections

No.	Parameter	Dependent on	Influences Role in model	Value and range Value in model	Distribution	QL	Notes and assumptions	Source
S1	Treatment rate (Probability that a symptomatic infection will be treated with an antimalarial)	Access to treatment and treatment seeking behaviour	Likelihood of cure, duration of infection and GSR	0.95 0.40-0.92 (1) 0.96 (Kenya) (2) 0.93 (Uganda) (3) 0.80 (Ethiopia) (4) 0.92-0.95 (South Africa) (5) 0.84 (Tanzania) (6) 0.80 (Philippines) (7)	Skewed	A	Patients receive either monotherapy (drug A) or combination therapy (drug AB or BC)	(1) (McCombie 1996) (2) (Munguti 1998) (3) (Nuwaha 2002) (4) (Deressa, Ali et al. 2003) (5) (Barnes K, personal communication) (6) (Eriksen, Nsimba et al. 2005) (7) (Espino and Manderson 2000)
S2	Coverage rate with ACT (Likelihood that a treated patient receives ACT)	Access to treatment and treatment seeking behaviour	Likelihood of cure, duration of infection and GSR	0.1 to 1 depending on coverage rate 0.08 – 0.9 0.97-0.99 (2)	Fixed (but varied in scenario analysis)	A	Patients not covered with ACT receive monotherapy	(1) Cambodia, primary data collection, 2002 (2) (Barnes K, personal communication)
S3	Time between onset of symptoms and treatment	Access to treatment and treatment seeking behaviour	Duration of parasitaemia and therefore infectiousness	1.2 days 1-2 days (43%), 3-4 days (31%) (1) 0.6 +/- 0.8 days (2) 2 days (s.d.0.9) (3) 4 days (4)	Negative skew	A		(1) (Deressa, Ali et al. 2003) (2) (Ruebush, Kern et al. 1995) (3) (Luxemburger, Thwai et al. 1996) (4) (Barnes K, personal communication)
S4	Gametocyte switching rate (GSR) with different drugs	Drug	Infectiousness of treated patients	0.003 for monotherapy 0.0009 for ACT	Log-normal	B	Calculated from trial data as described in Chapter 4 Assumed to be independent of immunity	(1) (Robert, Awono-Ambene et al. 2000) (2) (von Seidlein, Drakeley et al. 2001) (3) (Price, Nosten et al. 1996)

Table A6-6: Recrudescent infections

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
R1	Infectiousness of recrudescent infections relative to primary infections	GSR <i>Duration of recrudescence Parasite density</i>	<i>Used to check GSR in recrudescent infection</i>	x4 x4 (based on duration of gametocytaemia (1) x14 (based on AUCgam in Cqn res compared to Cqn sens) (2)	Log-normal	C		(1) (Price, Nosten et al. 1996) (2) (Sowunmi and Fateye 2003)
R2	Mean parasitaemia in recrudescent infection relative to primary infection	<i>Immunity</i>	<i>Infectivity of resistant infections</i>	x0.5 0.1 (1) 1 (2) 4-7X less in non-immune non-treated (3)	Log-normal	B		(1) (Sowunmi and Fateye 2003) (2) (Barnes K, personal communication) (3) (Collins and Jeffery 1999)
R3	Gametocyte switching rate in recrudescent infection relative to that in initial infections		<i>Infectivity of resistant infections</i>	x20 x 53 (0.051 versus 0.00097), based on gametocyte to parasite ratio in primary versus recrudescent infections (1)	Uniform	C	Same assumptions as for GSR in initial infection	(1) (Sowunmi and Fateye 2003)
R4	Time between onset of symptoms and treatment	<i>Same factors that affect delay in initial treatment seeking</i>	<i>Infectivity of resistant infections</i>	1.2 days 3.8 days (0-14) (1)	Skewed	C		(1) (Sowunmi and Fateye 2003)
R5	Time to recrudescence (Time between treatment of initial infection and peak parasitaemia in recrudescent infection)	<i>Immunity</i>	<i>Infectivity of resistant infections</i>	28 days 24-33 days depending on drug half life (1)	Normal	B	Used to calculate duration of undetectable parasitaemia between initial and recrudescent infections (14 days in base-case scenario)	(1) (Stepniewska, Taylor et al. 2004)
R6	Number of recrudescent peaks	<i>Treatment received</i>	<i>Infectivity of resistant infections</i>	3 peaks 1-5 after which they are "barely detectable" (1)		B	Assumed not to be related to immunity	(1) (Collins and Jeffery 1999)

Table A6-7: Vector factors

No.	Parameter	Dependent on	Influences Role in model	Value and range Value in model	Distribution	QL	Notes and assumptions	Source
V1	Vectorial capacity (VC)	- Human biting rate (ma) - Anopheles survival (p) - Vector control	<i>Inoculation rate</i>	0.1 in low transmission settings 0.48-1.28 dry season, Thailand (1) 0.34-1.42 <i>An. Arabiensis</i> , Tanzania (2) 0.009-0.43 <i>An. Dirus</i> , Laos (3) 0 - 0.82 <i>An Dirus</i> , depending on season, India ¹⁰ (4) 15 <i>An. gambiae</i> , Nigeria (5)	Fixed	C	VC particularly sensitive to duration of anopheles survival (p)	(1) (Rosenberg, Andre et al. 1990) (2) (Ijumba, Moshia et al. 2002) (3) (Toma, Miyagi et al. 2002)[36] (4) (Prakash, Bhattacharyya et al. 2001) (5) (Garrett-Jones and Shidrawi 1969)
V2	Likelihood that a mosquito will be infected after biting a human carrying gametocytes	Gametocyte density in humans Packed cell volume	<i>Mosquito infectivity</i>	0.15-1 depending on gametocyte density 0.21 (gametocyte density <10/ul) 1 (gametocyte density >1000/ul) (1) Mean 0.25 & Max 0.77, membrane fed, Tanzania (2) Mean 0.19, direct fed, Cameroon (3) 0.15 +/- 0.029, PNG (4) 0.58 Gambia (5) 0.42 Tanzania (5)	Fixed	A	Calculated parameter within model iterations, based on references (1) and (3) Not affected by age of human (1)	(1) (Jeffery and Eyles 1955) (2) (Drakeley, Secka et al. 1999) (3) (Bonnet, Gouagna et al. 2000) (4) (Graves, Burkot et al. 1988) (5) (Drakeley, Akim et al. 2000)

¹⁰ 0 - 0.07 Oct - Feb, 0.65 - 0.82 March-Sept.

(Table 6-7 continued: *Vector factors*)

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
V3	Duration of sexual stage in mosquito		<i>Time lag of between human infections</i>	12 days 11 days summer 28 days winter (1)	Normal	A		(1) (Dietz, Molineaux et al. 1974)
V4	Seasonality (months where most (>75%) of transmission occurs)	Climate Vector type	<i>Number of months of low/high VC</i>	12 in base-case scenario 1-12 (review from 159 sites in 15 countries) (1)	Normal	A	No seasonality in base-case scenario	(1) (Hay, Rogers et al. 2000)
V5	Difference in daily EIR between wet and dry season	Climate Vector type	<i>Relative value of VC in low/high season</i>	x0 in base-case scenario x2.7 (0.24-0.65) Dielmo (1) x8.5 (0.02-0.17) Ndiop (1) x3.0 (0.29-0.86) Madang (2)		A	No seasonality in base-case scenario	(1) (Fontenille, Locheuarn et al. 1997) (2) (Burkot, Graves et al. 1987)

Table A6-8: Clinical outcomes-Severe malaria and mortality

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
O1	Case fatality per malaria case depending on treatment and resistance (ie probability of death per case)	Transmission intensity (immunity)	<i>Used in producing sigmoid function relating drug resistance to severe malaria</i>	0.002-0.0015 (1) 0.002-0.008 in <5 year olds (moderate EIR)(2) 0.00045-0.02 depending on age and drug resistance (3) 0.2 (Low EIR) (4) 0.0025-0.023 in adults depending on resistance (rise 9.7% per year) 0.03-0.06 in children depending of resistance (rise 5.2% per year) ¹¹ (5) 0.11 if treated with Cqn 0.33 if treated with SP (6)	Fixed	B	10X increase in 0-4 year olds mortality because of resistance (2)	(1) (Murphy and Breman 2001) (2) (Trape 2001) (3) (Sudre, Breman et al. 1990) (4) (Luxemburger, Ricci et al. 1997) (5) (Brinkmann and Brinkmann 1991) (6) (Zucker, Ruebush et al. 2003)
O2	Likelihood of severe malaria	Immunity Drugs Drug resistance Access to treatment	<i>Used in producing sigmoid function relating drug resistance to severe malaria</i>	0.05 base-case for symptomatic 0.15 maximum for untreated 0 for non-immune 0.08 (1) 0.12 (2) 0.05-0.11 (3) 0.007-0.019 (4) 0.09 -0.23 depending on age ¹² (5) 0.05 (6)	Fixed	B		(1) (Brinkmann and Brinkmann 1991) (2) (Luxemburger, Thwai et al. 1996) (3) (Sirima, Konate et al. 2003) (4) (Goodman, Coleman et al. 2000) (5) (Baird, Masbar et al. 1998) (6) (Luxemburger, Ricci et al. 1997)

¹¹ 0.02-0.05 all ages.

¹² 148/639 (0.23) in non-immune adults, 36/420 (0.09) in non-immune children <15, (RR=2.5 CI 1.8-4.2).

(Table A6-8 continued: *Clinical outcomes-Severe malaria and mortality*)

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
O3	Probability of death if severe malaria	Access to treatment Drugs Drug resistance Immunity Pregnancy	<i>Mortality rate</i>	0.2 0.15-0.22 (1) 0.035 PNG (2) 0.08-0.18 (18.4% in non pregnant women and 7.6% in men)(3) 0.05 (4) (under 5) 0.094 – 0.57 (5) 0.005-0.63 (6)	Fixed	A		(1) (Dondorp, Nosten et al. 2005) (2) (Allen, O'Donnell et al. 1996) (3) (Kochar, Thanvi et al. 1999) (4) (Trape 2001) (5) (Baird 1998) (6) (Kitchen 1949) p1014

Table A6-9: Behaviour – Diagnosis and treatment

No.	Parameter	Dependent on	Influences <i>Role in model</i>	Value <i>Value in model</i>	QL	Notes and assumptions	Source
B1	Probability that a patient with malaria goes to public sector	Setting	CT coverage rate Costs	0-1 0.10-0.97(1) 0.92 Ethiopia (2) 0.08-0.92 (3) 0.87 Kenya (4) 0.29 Uganda (5)	A		(1) (McCombie 1996) (2) (Deressa, Ali et al. 2003) (3) (Brinkmann and Brinkmann 1991) (4) (Munguti 1998), (5) (Nuwaha 2002)
B2	In public sector – likelihood of receiving ACT	Setting	CT coverage rate Costs	0-1 0.43 (1) 1 (2)	A		(1) Cambodia, primary data collection, 2002 (2) (Barnes 2003)
B3	Likelihood of receiving biological diagnosis	Setting Other symptoms Age (2)	Costs Treatment rate	1 0-1 (1) 0.46 (2)	A		(1) Cambodia, primary data collection, 2002 (2) (Barat, Chipipa et al. 1999)
B4	If patient clinically diagnosed as positive, probability they actually have malaria	Setting Season	Costs Clinical outcome	0.045 in dry season and 0.54 in wet season (1) 0.38 (2) 0.4-0.5 (3)	A		(1) (Olivar, Develoux et al. 1991) (2) (Nsimba, Massele et al. 2002) (3) (Brinkmann and Brinkmann 1991)
B5	If patient clinically diagnosed negative, probability that they actually have malaria	Setting Season	Costs Clinical outcome	0.48 (1) low transmission	A		(1) (Luxemburger, Nosten et al. 1998)

Table A6-10: Implementation - strategies to improve adherence

No.	Parameter	Dependent on	Influences	Value and range <i>Value in model</i>	Distribution	QL	Notes and assumptions	Source
C1	Probability of increased adherence with blister packaging*	Setting Drug regime	Cure rate Cost	0.33 to 0.82 (1) 0.42 to 0.91 (2)	Uniform	B		(1) (Yeboah-Antwi, Gyapong et al. 2001) (2) (Ansah, Gyapong et al. 2001)
C2	Probability of increased adherence with patient IEC in public sector	Setting Drug regime	Cure rate Cost	0.37 to 0.52 picture inset only to 0.73 with verbal too (1)	Uniform	B		(1) (Okonkwo, Akpala et al. 2001)
C3	Probability of increased adherence with IEC to private sector	Setting Drug regime	Cure rate Cost	0.03 to 0.11 with poster , to 0.21 with video (1)	Uniform	B		(1) (Denis 1998)

Table A6-11: Direct costs – OPD treatment of uncomplicated malaria (cost per patient in US\$2002)

No.	Item	Cost	Source
UC1	Clinic Outpatient consultation	1.00 (0.34-12.37) 1.33 (0.56-2.75) (1) 0.72 (0.34-12.37) ¹³ (2) 0.09 China (3) ¹⁴ South Africa (4) 0.14 for adults and 0.08 for children (patient user fee) (5) 7.52-13.50 (inclusive of drugs) (6)	(1) (Fabricant 2002) (2) (Goodman, Coleman et al. 2000) (3) (Jackson, Sleight et al. 2002) (4) (Wilkins, Folb et al. 2002) (5) (Agnamey, Brasseur et al. 2005) (6) (Muheki, McIntyre et al. 2004)
UC2	Cost of patient transport, food and other	1.00 (0.3-2.0) 0.81 median, Cambodia (1) 0.31 China (2) 0.74 (0.18-1.67) review average(3) 1.18 (0.74-1.66) Sri Lanka (4)	(1) Cambodia-primary data collection 2002 (2) (Jackson, Sleight et al. 2002) (3) (Goodman, Coleman et al. 2000) (4) (Konradsen, Steele et al. 1999)
UC3	Hospital OPD cost	3.9 (0.91-90.48) ¹⁵ (1) 23.5-31.3 (2) (inclusive of drugs)	(0) (Goodman, Coleman et al. 2000) (1) (Muheki, McIntyre et al. 2004)
UC4	% of OPD visits that take place at hospital	0 (0-0.32) 0.32 (1) 0 ¹⁶ (2)	(1) (Goodman, Coleman et al. 2000) (2) (Fabricant 2002)

¹³ 0.61 (0.29 – 1.14) for very low income countries (VLIC) (4 studies), 0.96 (0.63-1.29) for middle income countries (MIC) (4 studies), 7.51 (4.16 – 10.48) high income countries (HIC) (2 studies) (in US1995\$). US\$1 in 1995=1.18US\$ in 2002.

¹⁴ \$1.06 for SP, 1.36 for Cqn (US\$1995) for staff cost.

¹⁵ 3.3 (0.77-5.15) for VLIC, 4.97 (1.08-13.66) for MIC, 38.43 (6.24-76.68) for HIC. US\$1 in 1995=1.18US\$ in 2002.

¹⁶ Hospital OPD visits data not reliable but in district hospitals average of 83 (range 22-226) (all cases) visits/month compared to 803 (range 173-1829) for health centre. Ratio of district hospitals to health centre is approx. 1:17 in malarious areas therefore proportion of malaria cases seen in hospitals is negligible.

(Table A6-11 continued: Direct costs – OPD treatment of uncomplicated malaria (cost per patient in US\$2002))

No.	Item	Cost	Source
UC5	Diagnosis by microscopy – Cost/test	0.60 (0.13-1.57) 0.51 ¹⁷ Sri Lanka (1) 0.73-1.57 ¹⁸ Cambodia (2) 0.13-0.43 (3) 0.20 (4) 0.53-0.65 ¹⁹ (5) 0.3 (6)	(1) (Kusumawathie 1996) (2) Cambodia, primary data collection, 2002 (3) (WHO 2000) (4) (Jackson, Sleight et al. 2002) (5) (Goodman, Coleman et al. 2000) (6) (Agnamey, Brasseur et al. 2005)
UC6	Diagnosis by RDT –Cost/test	0.80 (0.65-2.70) 1.12 Sri Lanka (1) 0.83 Laos (2) 0.75-0.88 Cambodia (3) 0.65–2.70 (4)	(1) (Kusumawathie 1996) (2) (Mayxay M, personal communication 2002) (3) Cambodia, primary data collection, 2002 (4) (WHO 2000)
UC7	Total cost –no microscopy (UC1+UC2)	2.0 (0.64-14.37) 1.83-3.67 (1)	(1) (Etting and Shepard 1991)
UC8	Total cost with microscopy (UC7+UC5)	2.6 (0.77-15.94) 1.30-2.20 (1) 0.44 (2)	(1) (Konraden, Steele et al. 1999) (2) (Jackson, Sleight et al. 2002)
UC9	Total cost with RDT (UC7+UC6)	2.80 (1.44-17.07) 14.76 +/-2.48 ²⁰ (1)	(1) (Wilkins, Folb et al. 2002)

¹⁷ 325 Sri Lankan rupees. CPI 163.1 rupees in 1995=314.9 rupees in 2002 (x1.94). 1 rupee = US\$0.010 (2002).

¹⁸ Fixed non-salary cost 317.2/year, Salary cost=360-2400, Recurrent cost 0.05/slide). Slides/hc/year=1000-4000 (US\$2002)

¹⁹ 0.31-0.58 in VLIC, 0.37-0.73 in MIC, 0.84-1.85 in HIC (US\$ 1995). Quoted figures are the means costs in US\$2002 for VLIC and MIC respectively.

²⁰ This was the mean cost of treating a malaria patient with SP assuming a resistance rate of 5.5%, excluding drug costs.

Table A6-12: Direct cost -IPD treatment of complicated malaria (cost per patient in US\$ 2002)

No.	Item	Value	Source
IC1	IPD cost per day	12 (1.67-235.15)	(1) (Goodman, Coleman et al. 2000)
		16.70 (4.59-277.48) ²¹ (1)	(2) (Fabricant 2002)
		8.50 (1.67-14.10) Cambodia (2)	(3) (Gogtay, Kadam et al. 2003)
		12.45 India ²² (3)	(4) (Muheki, McIntyre et al. 2004)
		24.8-33.9 South Africa (4) 3.06-6.12 Rwanda (5)	(5) (Ettling and Shepard 1991)
IC2	Cost of food, transport and other to patient per day	1.0 (0.24-2.08)	(1) Cambodia, primary data collection, 2002
		0.98 ²³ (1)	(2) (Goodman, Coleman et al. 2000)
		0.85 (0.24-2.08) ²⁴ (2) 0.86 ²⁵ (3)	(3) (Gogtay, Kadam et al. 2003)
IC3	Average length of stay for malaria IPD (days)	4.5 (3.8-9)	(1) (Goodman, Coleman et al. 2000)
		4.5 days (1)	(2) Cambodia, primary data collection, 2002
		4.5 days (2)	(3) (Thap L., personal communication)
		6.5 ²⁶ days (3)	(4) (Ettling and Shepard 1991)
		3.8 - 9 days (4)	(5) (Shepard, Ettling et al. 1991)
		6 days Congo (5) 7 days (6)	(6) (Muheki, McIntyre et al. 2004)
IC4	Cost of investigations and consumables	5.0 (3-48.93)	(1) (Gogtay, Kadam et al. 2003)
		4.46 (1)	(2) (Kirigia, Snow et al. 1998)
		5.98- 48.93 (2)	
IC5	Cost of adverse events	0.25	(1) (Gogtay, Kadam et al. 2003)
		0.21-0.31	
IC6	Cost of IPD stay excluding drugs (IC4 +IC5)	63.75 (10.51-2184.25)	

²¹ 11.99 (3.89-20.74) in VLIC, 17.11 (4.22-36.08) in MIC, 129.17 (34.11-235.15) in HIC in US\$1995.

²² 100 rupees for nursing care, 500 rupees for "ICU".

²³ Mean IPD cost of \$4.43/ (range 0-11.54). Mean number of days =4.5 days,) although transport is mainly fixed but have to pay for relative visiting.

²⁴ \$3.84 (1.10-9.36) per stay. Mean IPD days=4.5 days.

²⁵ 3.86 per stay. Mean days stay not stated but assume same as average elsewhere ie 4.5 days.

²⁶ 9.5 days for the 8 out of 122 patients who had quinine.

(Table A6-12 continued: Direct cost - IPD treatment of complicated malaria (cost per patient in US\$ 2002))

No.	Item	Value	Source
IC7	Cost of drugs for adult Artemether intramuscularly 5 days + mefloquine orally 1 day	9.04 (5.12-11.52) (1)	(1) Cambodia, primary data collection, 2002
IC8	Cost of drugs Quinine 3 days intravenously, 4 days PO	2.5 (1.61-7.90)	(1) Cambodia, primary data collection, 2002
		2.42 (1.61-6.48) (1)	(2) (Kirigia, Snow et al. 1998)
		2.39- 7.90 ^{z/} (2)	(3) (Gogtay, Kadam et al. 2003)
		2.60 (3)	
IC9	Total cost if treated with A+M (IC8+IC9)	72.79 (15.62-2195.77) (1)	(1) Cambodia, primary data collection, 2002
IC10	Total cost if treated with Q+T (IC8+IC10)	66.17 (12.12-2192.15)(1)	(1) Cambodia, primary data collection, 2002
		45.73-147.30 (2)	(1) (Kirigia, Snow et al. 1998)
		20.87 (3)	(2) (Gogtay, Kadam et al. 2003)

^{z/}Type of drugs not specified.

Table A6-13: Indirect costs (US\$ 2002)

No.	Item	Value	Source
PC1	Days of lost productivity for uncomplicated episode (patient and carer)	5 days (3-10) 5-7 days (median) (1) 10 days, China (2) 3.8-9.5 days disabled 1-2.6 days partially disabled (3) 5.33 (4)	(1) Cambodia, primary data collection, 2002 (2) (Jackson, Sleight et al. 2002) (3) (Mills 1994) (4) (Jayawardene 1993)
PC2	Days of lost productivity for severe episode (patient and carer)	10 days (3.8-18) 18 days ²⁸ (1) 3.8-9 ²⁹ days, Rwanda (2)	(1) Cambodia, primary data collection, 2002 (2) (Etting and Shepard 1991)
PC3	Cost per day of lost productivity	1.5 1.17 (1) 1.6 (\$45/month minimum wage for garment worker in Cambodia in 2004) (2)	(1) (Godfrey, Sovannarith et al. 2001) (2) (International Labour Organisation 2004)
PC4	Cost of lost productivity for uncomplicated episode (PC1xPC3)	7.5 6.52-6.74 (1) 0.16- 0.61 Thailand (2) 1.7 China (3)	(1) (Gogtay, Kadam et al. 2003) (2) (Etting and Shepard 1991) (3) (Jackson, Sleight et al. 2002)
PC5	Cost of lost productivity for severe episode (PC2xPC3)	15 (8.7-31.5) 8.70 (1)	(1) (Gogtay, Kadam et al. 2003)

²⁸For those who had 3 more treatments.

²⁹Length of stay 6 days in hospital, 2.8 days in dispensary. Adults lose hospital time + 3 days at home. For child, carer loses hospital time plus one day at home.

Table A6-14: Estimated minimum cure rates in the non-immune host dependent on adherence and drug resistance

Drug regime	Adherence						Estimated minimum cure rates in non-immune												
	Estimated adherence rates			Likely regime if non-adherent			If adherent				If non-adherent				Resistant				
	Best	Low	High	Best	Low	High	Best	Low	High	Best	Low	High	Best	Low	High	Best	Low	High	
							Sensitive	Resistant			Sensitive			Resistant					
Monotherapy																			
Chloroquine (C) (1x/day, 3 days)	0.5	0.3	0.69	2 days, median dose 12.8 mg/kg															
Sulphadoxine-Pyrimethamine (SP) (single dose)	0.85	0.85	0.95	Half dose															
Mefloquine (M) (single dose 25mg/kg)	0.8	0.7	0.9	Half dose															
Amodiaquine (AQ) (1x day, 3 days)	0.5	0.3	0.69	2 days															
Artesunate (A) (1x,day, 7 days)	0.3	0.2	0.42	3 days															
Quinine (Q) (3x/day, 7 days)	0.22	0.09	0.47	3 days															
Combinations																			
A+AQ (3 days)	0.5	0.3	0.7	Fewer tabs of either	0.95	0.80	1.0												
A+SP loose (3 days A, 1 dose SP)	0.6	0.39	0.78	Fewer tabs															
A+M- blister pack (3 days, 1 dose M)	0.88	0.72	0.97	Fewer tabs of either															
A+M- loose (3 days, 1 dose M)	0.13	0.8	0.25	No mefloquine 3 days artesunate	0.5	0.35	0.65												
Q+Tetracycline (T) (3x day, 7 days)	0.3	0.22	0.72	No tetracycline 3 days quinine															
Artemether -lumefantrine (Co-formulated, 2x/day, 3 days)	0.8	0.7	0.95	Fewer tabs Low fat diet															
Dihydroartemisin-piperaquine (Co-formulated, 3 days)	0.8	0.7	0.95	Fewer tabs															

ANNEX 7 Immune functions and formula for calculating infectivity of humans to mosquitoes

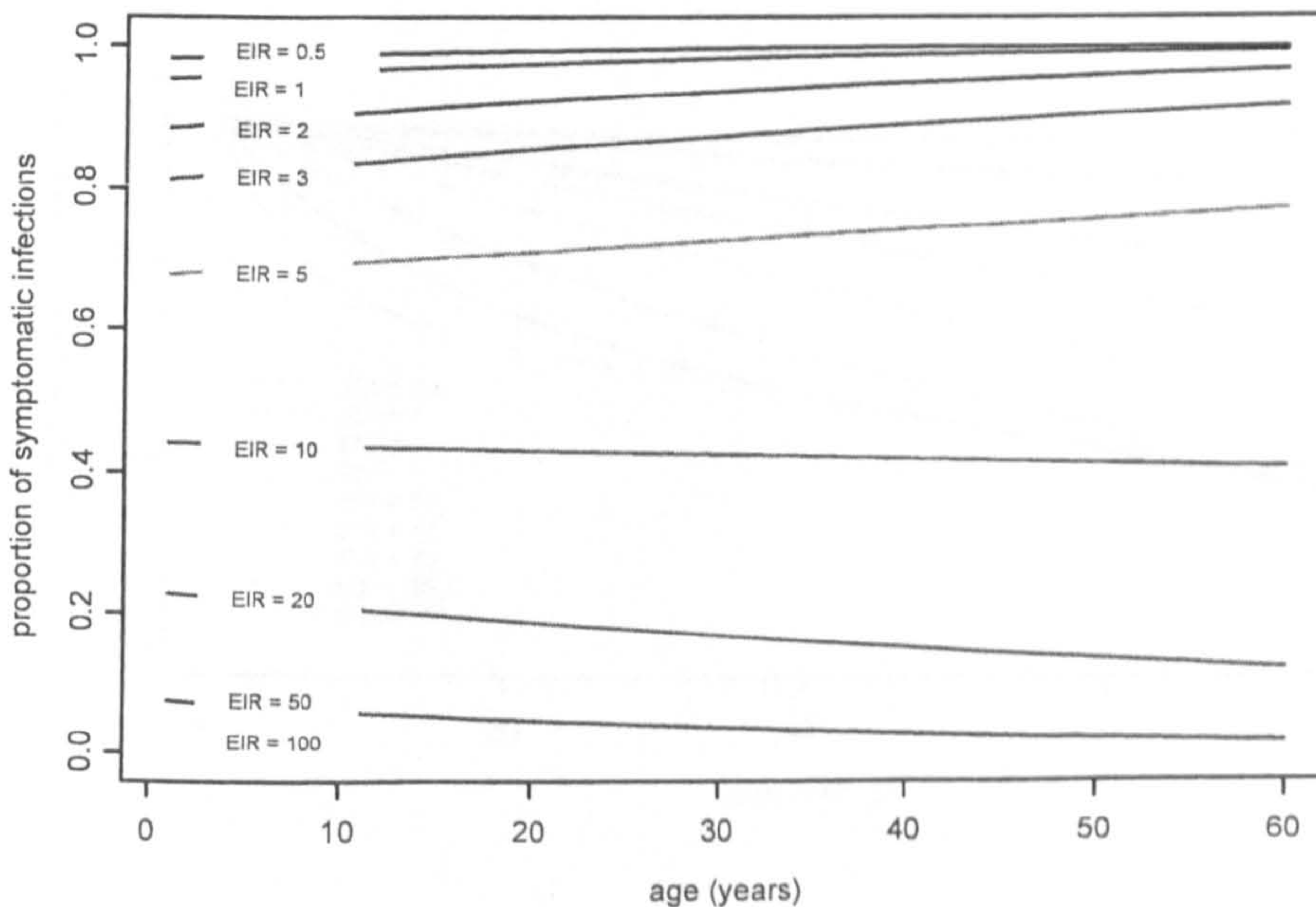
A.7.1. Immunity Function 1 (based on likelihood of symptomatic malaria)

Data for this function were obtained from three cross-sectional prevalence studies where signs and symptoms of malaria in subjects were also recorded and from one longitudinal cohort study. One set of cross-sectional data was obtained from the Shoko refugee camp along the Thai-Burmese border in the north-western part of Thailand, with an estimated EIR of one in 1997 (Nosten F, personal communication). Two sets of data were obtained from Kenya, from Ngerenya, with an estimated EIR of 20 and from Chonyi, Kenya, with an estimated EIR of 50 (Mwangi T, personal communication). The longitudinal final data were taken from a published paper from Siaya, Tanzania with an estimated EIR of 270 (Bloland, Boriga et al. 1999). The equation describing the best fit to the data and a graphical representation of the results are shown below:

Equation A7-1

$$y = 0.26 * \exp(-0.3AGE) + 0.02 * \exp(-0.06AGE) + 1.09 * \exp(-0.1EIR) - 0.28 * \exp(-0.21AGE * EIR)$$

Figure A7-1: Simulated curves of the proportion of symptomatic infections by ages in different transmission intensities by the non-linear immunity function described by Equation A7-1



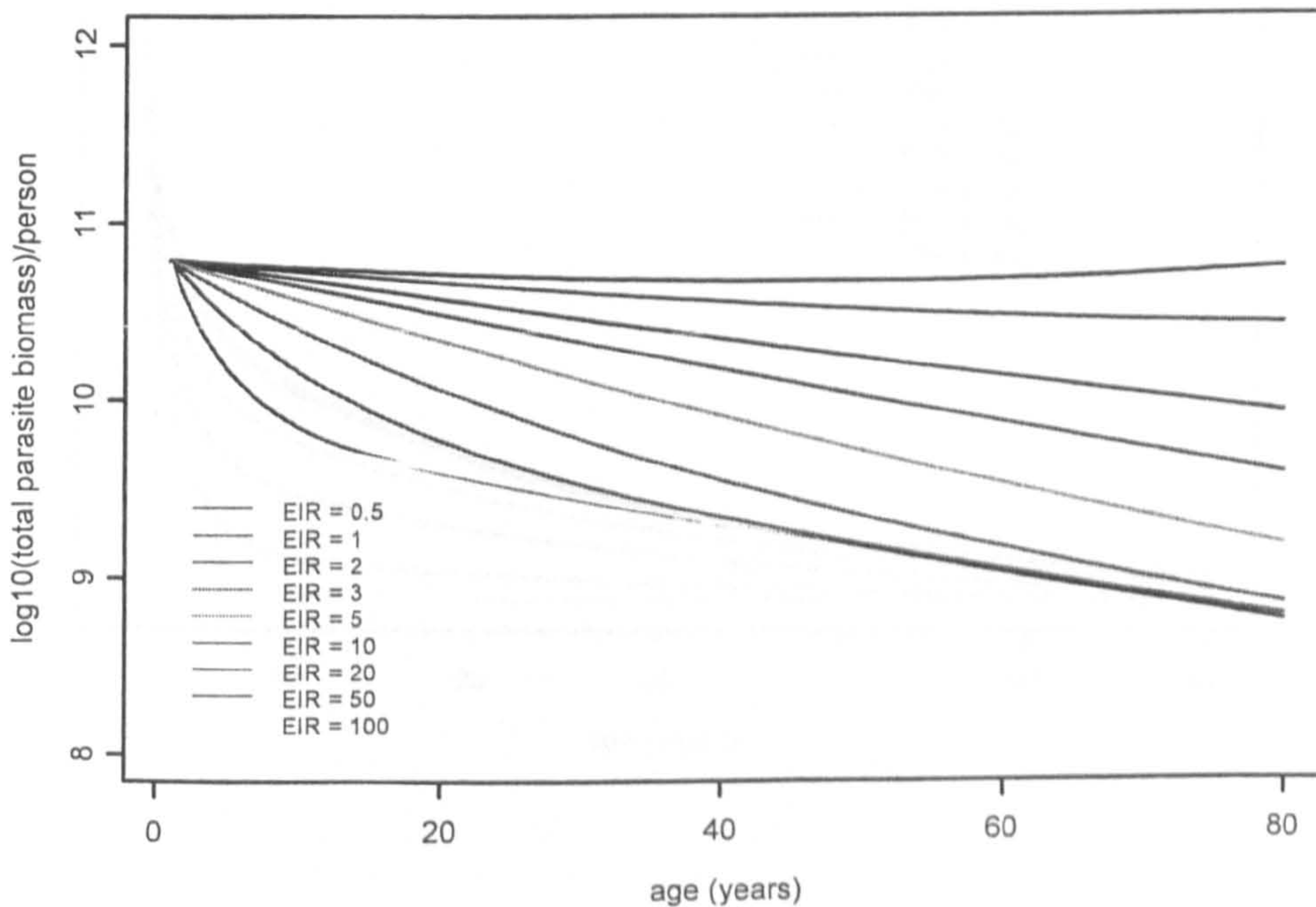
A.7.2. Immunity Function 2 (based on parasite density)

Eight sets of data with age-stratified parasite densities were used including the four datasets used in Immunity Function 1. In addition, three published sources of data were used: data from Madang in Papua New Guinea with an EIR of 40 (Cox, Kum et al. 1994); data from Ghana with and EIR of 300 (Owusu-Agyei, Smith et al. 2002) and data from Dielmo, Senegal with and EIR of 200 (Trape, Rogier et al. 1994). One additional data set from a low transmission setting (EIR of 1) was obtained from Lao PDR (Mayxay M, personal communication). For model consistency the standard parasite detectable limit was assumed to be 20 parasites/ul of blood in a thin film and equivalent to 10^8 parasites in an adult. The parasite biomass for each age was calculated as described in Chapter 4. The optimal immune function derived from this data and the resulting curves are shown below.

Equation A7-2

$$y = 9.8 \exp(-(0.001AGE - 0.0001EIR + 0.000002AGE * EIR)) + 0.97 \exp(0.011AGE + 0.003EIR - 0.0045AGE * EIR)$$

Figure A7-2: Simulated curves of $\log_{10}(\text{parasite biomass})$ in different age groups and different transmission intensities as described by Equation A7-2



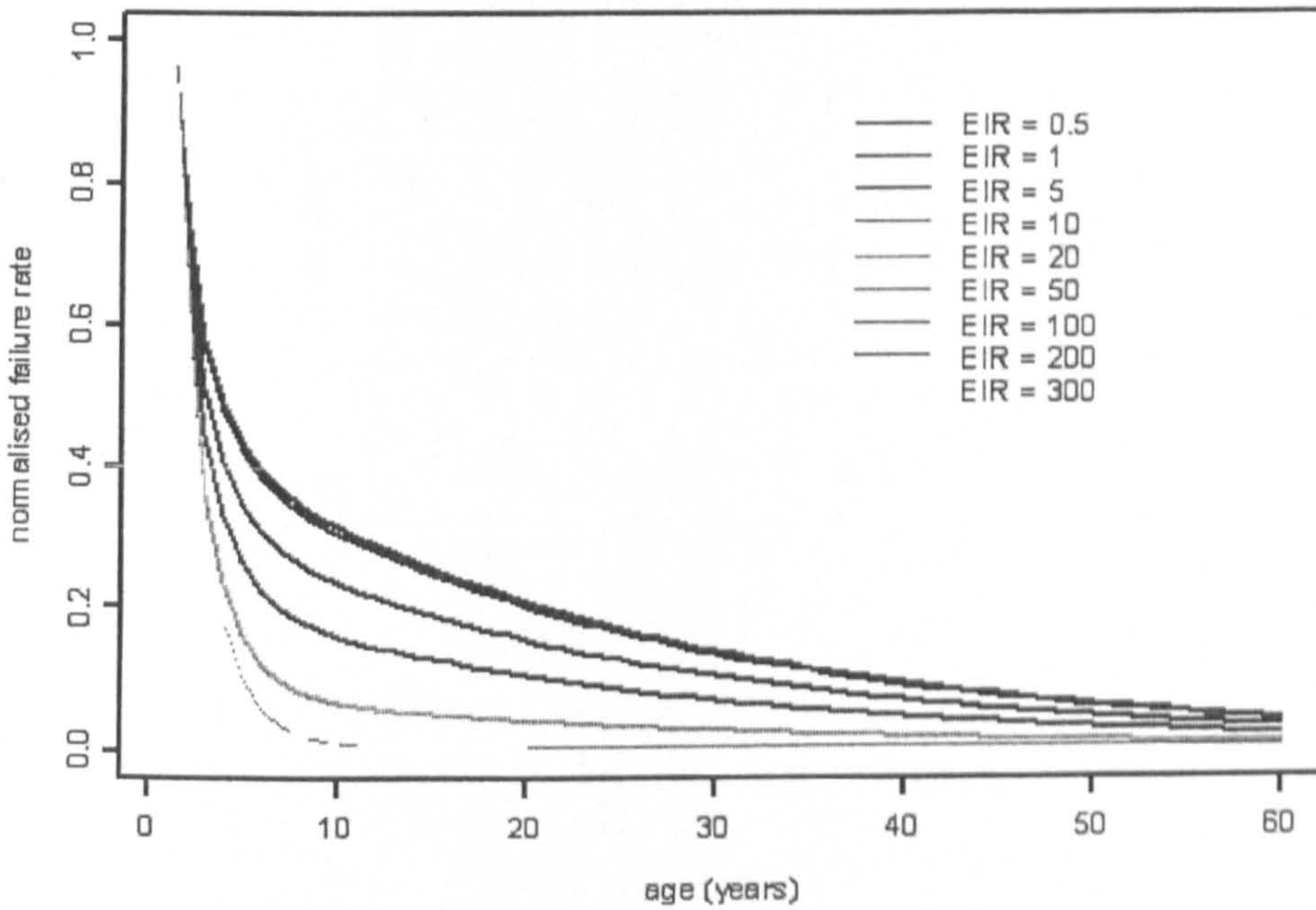
A.7.3. Immunity Function 3 (based on likelihood of severe malaria)

Data for this immunity function was derived from data on adults and children in Shoklo, Thailand with an EIR for one (Nosten 2001) and from a large published study of severe malaria morbidity in children in sub-Saharan Africa (Snow, Omumbo et al. 1997). The four areas included in this study were: Bakau, The Gambia with an EIR of 0.5; Sukuta, The Gambia with an EIR of two; Kilifi, northern Kenya with an EIR of 120 and Siaya, western Kenya with an EIR of 100. The two-term exponential function that best described this data is shown below. Within the biological model, this function was used to describe the relationship between age, EIR and treatment failure and this is shown in Figure A7-3.

Equation A7-3

$$y = 1.28 \exp(-(0.59 \text{AGE} + 0.003 \text{EIR})) + 0.63 \exp(-(0.04 \text{AGE} + 0.11 \text{EIR}))$$

Figure A7-3: Simulated curves of the normalised data of treatment failure rate in different age groups and different transmission intensities based on Equation A7-3



Equation A7-4: Formula used to calculate mosquito infectivity based on the gametocyte number

$$y = \frac{1.02}{(1 + \exp(-1.03 * (\log_{10}x - 8.55)))}$$

Where y (or i) is human infectiousness or probability of infecting mosquitoes, x is total gametocyte number. In the model any effect of transmission blocking immunity is ignored due to conflicting data.

**ANNEX 8 Original documentation from community-based survey in Cambodia
(also translated into Khmer)**

A.8.1. Letter to Head of village

Village
Commune
Province

Dear _____

My name is Shunmay Yeung, I work for a University in the UK and am doing a study on malaria ("Kroon chang"). I want to learn about how much of a problem Kroon Chang is and what people do if someone gets the symptoms. To do this, I would like to visit the households in your village and ask them some questions if they have had fever or malaria in the last 3 weeks. I would also like to do a finger prick test for malaria and to look for the anti-malarial medicine in their blood. I will come with four Khmer research assistants. We would like to stay for about 2 days. Each interview will take about 45 minutes. We hope to arrive on the (Date and time). We will be happy to discuss what we are doing at a community meeting when we arrive. People are free not to participate if they do not want to and can leave at any time. We hope that the results of the survey will be helpful for learning how to improve the provision of care to this and other villages and we will be happy to share the results with you at the end of the study if you are interested.

If you have any questions or doubts please tell us either now or at any time. My contact details are below.

Thank you very much for your help

Shunmay Yeung

Tel.: 012 723 108 (Cambodian mobile no.)
E-mail Shunmay.Yeung@lshtm.ac.uk

Address: Wellcome Unit
Faculty of Tropical Medicine
420/6 Rajivithi Road
Bangkok 10400

A.8.2. Consent form

Household ID code	
Interviewer initials	
Date	

Consent form (Form B)

Fill one form for each person who had malaria/fever in the last 3 weeks.
 If the person is less than 18 years old then ask the parent for consent
 If the person is not available and you are interviewing the relative then ask the relative for consent
 If the person can not read, then read aloud the information sheet and statement and if they agree, put YOUR signature
 If they do not agree, thank them for their time and move on to next person or next household

Line number (from form A)	Name of head of household	Name of person with fever

 I understand the information in the information sheet and agree to participate.
 I understand that I can choose freely and can withdraw at any time

If patient is present and an adult: Signature of patient: _____

If patient is not present or is a child: Name of relative: _____

Relationship of relative to patient: _____

If patient or relative cannot write: Interviewer signature: _____

A.8.3. Questionnaires

General household questions (Form D)

សំណួរទូទៅតាមផ្ទះ (ទម្រង់ D)

Interviewer (Initials and date) ឈ្មោះអ្នកសំភាសន៍ (លេខកូដ និង ថ្ងៃខែ)	_ / _ / _
Checked (Initials and date) អ្នកពិនិត្យ (លេខកូដ និង ថ្ងៃខែ)	_ / _ / _
Data entry (Initials and date) អ្នកបញ្ចូលព័ត៌មាន (លេខកូដ និង ថ្ងៃខែ)	_ / _ / _

A. Identification អត្តសញ្ញាណ

Commune ឃុំ	Village ភូមិ	Line number (from form A) បន្ទាត់លេខរៀងទម្រង់ A	Name of Head of Household ឈ្មោះមេគ្រួសារ	Personal ID numbers (Form C)

Name of person answering questions ឈ្មោះអ្នកដែលឆ្លើយនឹងសំណួរ	Age អាយុ	Sex ភេទ	Position in household in relation to the head of household តួនាទីទំនាក់ទំនងជាមួយមេគ្រួសារ
		M F ប្រុស ស្រី	1. Head of household មេគ្រួសារ 2. Spouse ប្រពន្ធ ឬ ប្តី 3. Brother/sister បងប្អូនបង្កើត 4. Mother/father ឪពុកម្តាយ 5. Child កូន 98. Other ផ្សេងៗ (Specify) _____ បញ្ជាក់

B. Background ព័ត៌មានមូលដ្ឋាន

1. How long have you lived in this house?
តើអ្នករស់ នៅទីនេះប៉ុន្មានឆ្នាំហើយ?

____ years ឆ្នាំ ____ months ខែ

2. How many people in this household?
ក្នុងគ្រួសារមានចំនួនប៉ុន្មាននាក់?

3. How many adult men and women in this household?
តើមានមនុស្សធំពេញវ័យប្រុសស្រីប៉ុន្មាននាក់ក្នុងផ្ទះនេះ?

Males
ប្រុស

Females
ស្រី

Not including adults who moved away.
មិនរាប់បញ្ចូលមនុស្សពេញវ័យចេញទៅឆ្ងាយទេ

4. How many people can work?
មានមនុស្សប៉ុន្មាននាក់អាចធ្វើការបាន?

5. How many children are there in this household?
តើមានកុមារប៉ុន្មាននាក់ក្នុងផ្ទះនេះ?

Including students supported by family
រាប់បញ្ចូលសិស្សដែលទទួលបានការឧបត្ថម្ភពីក្រុមគ្រួសារ

6 Have you given birth to any live babies since the last Khmer New Year?
 តាំងពីឆ្នាំទៅមិញ អ្នកមានសំរាលកូន ហើយនៅរស់ ឬទេ ?

- | |
|---|
| 1. No ទេ |
| 2. Yes, 1 live birth បាទ, រស់ម្នាក់ |
| 3. Yes, 2 live births បាទ, រស់ពីរម្នាក់ |

C. Mortality មរណភាព

7 Have any children died since the last Khmer New Year?
 តាំងពីឆ្នាំទៅមានកុមារណាម្នាក់ស្លាប់ទេ ?

- | | | |
|----------|------------|---|
| 1. No ទេ | 2. Yes បាទ | If "No" go to 9. បើសិនទេ រំលងទៅលេខ 9
If "Yes", ask if you can ask about them?
បើបាទ សួរគាត់ បើសិនសួរបានអំពីរឿងនោះ |
|----------|------------|---|

8	Age អាយុ	Sex ភេទ	When did they die? តើក្នុងនោះស្លាប់ ពេលណា?	Cause of death (if known) មូលហេតុនៃការស្លាប់ (បើសិនដឹង)	What symptoms did they have? តើកុមារនោះមានអាការៈឈឺដូចម្តេចខ្លះ?	How long were they sick? តើឈឺមានរយៈពេល ប៉ុន្មានថ្ងៃដែរ?
1						
2						

9 Did any adults die since the last Khmer New Year?
 តើមានមនុស្សធំពេញវ័យស្លាប់ទេ តាំងពីឆ្នាំទៅ នោះ ?

- | | | |
|----------|------------|--|
| 1. No ទេ | 2. Yes បាទ | If "No" go to 11. បើសិនទេ រំលងទៅលេខ 11
If "Yes", ask if they mind talking about it
បើបាទ សួរគាត់ បើសិនសួរបានអំពីរឿងនោះ |
|----------|------------|--|

10	Age at death អាយុ ពេលស្លាប់	Sex ភេទ	Which year did they die? តើឆ្នាំស្លាប់ពេលណា?	Cause of death មូលហេតុស្លាប់	What symptoms did they have? តើមានអាការៈឈឺដូចម្តេចដែរ?	How long were they sick? តើគាត់ឈឺរយៈពេល ប៉ុន្មានថ្ងៃ-ខែ?

D. Socio-economic status ស្ថានភាព សេដ្ឋកិច្ច

11 How much rice land do you own?
តើអ្នកមានដីស្រែទំហំប៉ុន្មានដែរ?

	Ha ហិចតា
--	----------

12 How much rice did you produce since last Khmer New Year?
តើផលស្រូវកាលពីឆ្នាំទៅ បានប៉ុន្មានដែរ ?

	Kg គីឡូ
--	---------

13 Did you have to borrow money to buy rice ?
មានបានខ្ចីប្រាក់គេដើម្បីទិញស្រូវអង្កាម ?

1. No ទេ	2. Yes បាទ	If "No" go to 15 បើទេ សួរទៅសំណួរទី 15
----------	------------	--

14 How many months did you have to borrow money to buy rice?
តើរយៈពេលប៉ុន្មានខែដែរ ដែលអ្នកបានខ្ចីប្រាក់គេទិញអង្កាម

--

15 Did you sell surplus last year ?
តើអ្នកបានលក់ស្រូវដែលសល់ពីហូបដែរឬទេ?

1. No ទេ	2. Yes បាទ	If "No" go to 17 បើទេ សួរទៅសំណួរទី 17
----------	------------	--

16 How much did you sell?
តើអ្នកលក់ស្រូវបានប៉ុន្មានគីឡូក្រាម ?

	Kg គីឡូ
--	---------

17 What other source of income does this household have? Eg hired labor
តើមានប្រភពចំណូលផ្សេងទៀតទេ? ឧ. ស៊ីល្អិតល្អន់

--

18 What is the roof of the house made of
ដំបូលផ្ទះប្រក់អ្វីដែរ ?

<p>1. No roof គ្មានដំបូល</p> <p>2. Leaves or bamboo ស្លឹក ឬ ឫស្សី</p> <p>3. Wood ឈើ</p> <p>4. Concrete or brick ប៊្រិក ឬ ក្រៀង</p> <p>98. Other ផ្សេងទៀត _____</p>
--

19 What are the walls of the house made of
ជញ្ជាំងផ្ទះប្រក់អ្វី ?

<p>1. No walls គ្មានជញ្ជាំង</p> <p>2. Leaves or bamboo ស្លឹក ឬ ឫស្សី</p> <p>3. Wood ឈើ</p> <p>4. Concrete or brick ប៊្រិក ឬ ក្រៀង</p> <p>98. Other ផ្សេងទៀត _____</p>

20 How many cows/buffaloes or horses do you own?
តើអ្នកមាន គោ-ក្របី-សេះ ប៉ុន្មាន?

--

22 What kind of transport do you own?
តើអ្នកមានមធ្យោបាយធ្វើដំណើរអ្វីខ្លះ?

- 1. None គ្មាន
- 2. Ox cart រទេះគោ
- 3. Bicycle កង់
- 4. Motorcycle ម៉ូតូ
- 98. Other ផ្សេងៗ _____

23 Do you own a radio or TV?
តើអ្នកមានវិទ្យុ ទូរទស្សន៍ដែរទេ?

- 1. None គ្មាន
- 2. Radio វិទ្យុ
- 3. TV ទូរទស្សន៍

26 Source of drinking water in dry season?
ប្រភពទឹកប្រើប្រាស់សំរាប់បូបនៅរដូវប្រាំង?

- 1. Drill well with pump អណ្តូងស្នប់
- 2. Other well អន្តូងផ្សេងទៀត
- 3. River/lake/pond ស្ទឹង-បឹង-ត្រពាំង
- 98. Other ផ្សេងៗសូមបញ្ជាក់ _____

27 How many years of schooling did you receive?
តើអ្នកចូលសាលារៀនប៉ុន្មានឆ្នាំដែរ?

years ឆ្នាំ

24 Have you seen or heard any information about dipstick diagnosis?
តើអ្នកធ្លាប់ឃើញ ឬបានឮព័ត៌មានអំពីការធ្វើរោគវិនិច្ឆ័យដោយប្រើ ឱបស្ទិកឬទេ ?

- 1. No ទេ
- 2. Yes, radio បានធ្លាប់ឮតាមវិទ្យុ
- 3. Yes, TV បានធ្លាប់ឮតាមទូរទស្សន៍
- 98. Yes, other បាន តាមរបៀបផ្សេងៗ _____

25 Have you seen or heard any information about malarine?
តើអ្នកបានឃើញ ឬបានឮព័ត៌មានអំពីថ្នាំ មាលារីន ដែរទេ ?

- 1. No ទេ
- 2. Yes, radio បានធ្លាប់ឮតាមវិទ្យុ
- 3. Yes, TV បានធ្លាប់ឮតាមទូរទស្សន៍
- 98. Yes, other បាន តាមរបៀបផ្សេងៗ _____

E. What is an affordable price for diagnosis and treatment?

Show them the dipstick and explain to them that the dipstick is a test for the dangerous type of malaria. Explain that is a very quick and easy test to perform and that it has the benefit that the patient can also see the result and can tell if they need anti-malaria medicine.

26 If the nearest private provider could do dipsticks. How much are you happy to pay for dipstick?
បើសិនជាសេវាព្យាបាលឯកជននៅជិតជាងគេបំផុតដែលអាចធ្វើឱបស្ទិកបាន ។
តើតំលៃប៉ុន្មានសមរម្យដែលគាត់ពេញចិត្តនឹងចំណាយ ?

27 How much are they happy to pay for tablets that will always cure malaria?
តើគំលែប៉ុន្មានក្នុងការព្យាបាលជំងឺគ្រុនចាញ់ជាសះស្បើយ ហើយគាត់ពេញចិត្ត?

28 If they could pay a little more for special quality tablets that would make sure that the cure was longer and that malaria did not come back . How much more do they need to pay?
បើគាត់ចំណាយប្រាក់តិចតួចបន្ថែម សំរាប់ថ្នាំគ្រាប់ពិសេសដែលធ្វើអោយប្រាកដថា ការព្យាបាលយូរអង្វែង និងមិនធ្វើអោយជំងឺគ្រុនចាញ់កើតឡើងវិញ ។ តើគាត់ត្រូវចំណាយប្រាក់ប៉ុន្មាន ?

If you took a dipstick, record the result at the end of form C.
Explain the result and give treatment if necessary

The End

“That is the end of the interview. Thank you very much for your time and participation. Do you have any comments or questions?”

Participants comments or questions អ្នកដែលចូលរួមសំភាសន៍មានយោបល់ ឬ សំនួរ

Interviewer's comments or questions សំនួរ ឬ យោបល់អ្នកធ្វើសំភាសន៍

Supervisor 1 comments or questions សំនួរ ឬ យោបល់អ្នកអភិបាលការងារទី ១

Data entry comments of questions សំនួរ យោបល់ អ្នកបញ្ចូលព័ត៌មាន

Pha Pharmacy like this but better quality

Personal ID No. 263

Interviewer (initials and date) ឈ្មោះអ្នកសំភាសន៍ (លេខកូដ និង ថ្ងៃខែ)		/ /
Checked (initials and date) អ្នកពិនិត្យ (លេខកូដ និង ថ្ងៃខែ)		/ /
Data entry (initials and date) អ្នកបញ្ចូលព័ត៌មាន (លេខកូដ និង ថ្ងៃខែ)		/ /

Malaria - Individual questionnaire (Form C)

សំណួរសំរាប់បុគ្គល (ម្នាក់ៗ) (ទម្រង់ C)

A. Identification អត្តសញ្ញាណសំគាល់

Commune ឃុំ	Village ភូមិ	Line No. (Form A) លេខរៀងបន្ទាត់ (ទម្រង់ A)	Name of Head of Household ឈ្មោះមេគ្រួសារ	Household ID No. លេខផ្ទះ (Form D)

Name of person who had fever ឈ្មោះបុគ្គលដែលគ្រុនក្តៅ	Age អាយុ	Sex ភេទ
		1.M ប្រុស 2.F ស្រី

B. Description of illness ការពិពណ៌នាអំពីជំងឺ

1 When did your last episode of fever start?
តើអ្នកឈឺចាប់ពីពេលណាមក ?

days ago
ថ្ងៃកន្លងទៅ

Try to get this as accurately as possible
ខំធ្វើយ៉ាងណាឱ្យបានច្បាស់បើអាច
ធ្វើទៅបាន

An "episode" of fever is where there is fever every day, followed by at least 3 days without fever

2 For how many days did you have fever?
តើអ្នកឈឺចាប់ប៉ុន្មានថ្ងៃមកហើយ ? (ប្រហាក់ប្រហែល)

days ថ្ងៃ

3 Do you think you have fever today?
តើអ្នកគិតថាមានគ្រុនទេនៅថ្ងៃនេះ ?

1. No ទេ	2. Yes បាទ	99 Don't know មិនដឹង មិនអាចដឹងបាន
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4 What other symptoms did you suffer?
តើអ្នកមានអាការៈរោគដូចម្តេចខ្លះ?

Do not read aloud answers. Tick the ones they say
កុំអានចម្លើយ ។ ចុះតួសម្បយអ្វីដែលគេបាននិយាយ ។

- 1. Fever គ្រុនក្តៅ
 - 2. Chills ញាក់
 - 3. Headache ឈឺក្បាល
 - 4. No energy អស់កំលាំង
 - 5. Body pain ឈឺរមាត់ព្រួន
 - 6. Nausea or vomiting ចង្ហាវ ឬ ត្អូក
 - 7. Dizziness វិលមុខ
 - 8. Convulsions ប្រកាច់
 - 98. Other ផ្សេងៗ
- (specify) (សូមបញ្ជាក់) _____



5 Before this episode, have you had fever in the last 2 months ?

មុនដំណាក់កាលនេះ តើអ្នកមានគ្រុនទេ ក្នុងរយៈពេល២ខែដុះ?

1. No ទេ 2. Yes បាទ ឬអ 99. Don't know មិនដឹង	If No then go to C បើទេ ទៅសំណួរ C
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6 How many fever free days between these two episodes?

តើអ្នកមានពេលខ្លះអស់គ្រុនទេ ក្នុងចន្លោះដំណាក់កាលទីពីរនេះ ?

1. < 7 days តិចៗ 2. 7 - 14 days ៧ទៅ១៤ថ្ងៃ 3. 15 - 30 days ១៥ទៅ៣០ថ្ងៃ 4. 31-60 days ៣១ទៅ៦០ថ្ងៃ 5. > 60 days >៦០ថ្ងៃ 6. Continuous intermittent fever គ្រុនរលាកជាប់រហូត 98. Other ផ្សេងៗ _____ 99. Don't know មិនដឹង	If >60 days. continuous or don't know go to C បើ>៦០ បន្តសំណួរ បើមិនដឹង សួរទៅសំណួរ C
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7 For how many days did you have fever the previous episode ដំណាក់កាលដំបូង តើអ្នកគ្រុនរយៈពេលប៉ុន្មានថ្ងៃ?

days ថ្ងៃ

C. Diagnosis រោគវិនិច្ឆ័យ

8 Did you have a blood test for malaria? តើអ្នកមានបានជំនួយសរសៃឈាមមើលមេរោគគ្រុនចាញ់ទេ ?

1. No test មិនបានពិនិត្យ 2. Yes, Dipstick ប្រើខ្ទឹបស្លឹក 3. Yes, Slide ប្រើកញ្ចក់ឈាម 99. Don't know មិនដឹង	"No" go to D បើសិនមិនបានពិនិត្យ សួរទៅសំណួរទី D
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9 What was the result? តើលទ្ធផលឈាម យ៉ាងណាដែរ?

1. Negative គ្មានមេរោគគ្រុនចាញ់ 2. Positive មានមេរោគគ្រុនចាញ់ 3. 1+ 4. 2- 5. 3-4- 99. Don't know មិនដឹង
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10 How many days ago? ប៉ុន្មានថ្ងៃហើយ?

days ago ថ្ងៃ

11 Tested where? តើជំនួយសរសៃឈាម ពិនិត្យនៅឯណា ?

2. Went to private phet ទៅកន្លែងពិនិត្យឯកជន-ពេទ្យឈ្នួល 3. Public health center/hospital ទៅពេទ្យរដ្ឋ 4. At home by private phet ហៅពេទ្យឈ្នួលមកផ្ទះ 5. Village malaria worker ទៅកម្មករស្រែចិញ្ចឹម-ជនបង្គោល 6. MSF Outreach team ក្រុមពេទ្យអង្គការដឹកនាំពេទ្យរដ្ឋចុះមកជួប 98. Other ផ្សេងៗ _____ 99. Don't know មិនដឹង

If they had more than one test in the last 2 months then write the details here

D. Inpatient stay ការសំរាកព្យាបាលក្នុងសេវាថែទាំសុខភាព

12 Did you stay over night in a clinic/hospital (public/private)?
តើអ្នកមានសំរាកព្យាបាលក្នុងផ្ទះពេទ្យឈ្នួល ឬមន្ទីរពេទ្យរដ្ឋដែរឬទេ?

1. No ទេ	2. Yes បាទ	If No go to E បើទេ សូរទៅសំនួរ E
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13 Which place did you stay?
តើអ្នកទៅសំរាកព្យាបាលកន្លែងណា?

2. Private clinic ទៅកន្លែងនិសាធិស្ថាន ពេទ្យឈ្នួល
3. Public health centre/hospital ទៅពេទ្យរដ្ឋ
98. Other ផ្សេងៗ _____

14 How many nights did you stay?
តើអ្នកសំរាកព្យាបាលនៅទីនោះ ប៉ុន្មានយប់ដែរ?

	nights យប់
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E. Drugs kept from this episode តើមានសល់ថ្នាំប្រើក្នុងដំណាក់កាលនេះឬទេ ?

15	Do you have any medicines kept from this episode តើគាត់មានថ្នាំសល់ក្នុងដំណាក់កាលនេះទេ ?	1. No ទេ	2. Yes បាទ	If No go to F បើទេ សូរទៅសំនួរ F
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16 Write down here the name or description of any drugs they show you and how many there are.

ចូរសរសេរឈ្មោះថ្នាំ និងវិចិត្រព្យាបាល និងថ្នាំមួយៗដែលពួកគាត់បានបង្ហាញយើង និង ចំនួនគ្រាប់ថ្នាំដែលមាន ។

Name and form រាងរោង និងឈ្មោះថ្នាំ	Number of tablets/amps ជំនួនគ្រាប់ថ្នាំ/ អំពូល	Where did you get it? តើអ្នកបានមកពីណា ?	Why do you keep this medicine? ហេតុអ្វីបានជាអ្នកទុកថ្នាំនេះ ?	Other comment យោបល់ផ្សេងៗ
eg Quinine 600mg tabs	6	Drug seller អ្នកលក់ថ្នាំ	Take to forest យកទៅព្រៃ	

F. Providers and drug usage អ្នកផ្តល់ការព្យាបាល និង ការប្រើប្រាស់ថ្នាំ

54	For the last (most recent episode of fever). How many days did you have fever before you tried western medicine?		days	Go to next page if they only had one episode of fever in the last 2 months
55	For the previous (second to last episode of fever). How many days did you have fever before you tried western medicine			

Please tell me about all the treatment you took, starting from treatment that you received from the last provider and then going back in time to any previous providers. Please include any traditional medicine you took

មេត្តាប្រាប់ខ្ញុំ ពីការព្យាបាល និងការចាប់ផ្តើមលេបថ្នាំ ដែលអ្នកបានទទួលការប្រើប្រាស់ពីសេវាផ្តល់ថ្នាំលើកក្រោយ ហើយបន្ទាប់មកក្នុងពេលដែល មានបានត្រឡប់ទៅសេវាដទៃទៀតទេ ? សូមមេត្តារាប់បញ្ចូលការប្រើប្រាស់ថ្នាំបុរាណផង ។

Last provider information

17 Who was the last provider that you received treatment from?
 តើសេវាប្រយោជន៍របស់អ្នកទទួលបានការព្យាបាលចុងក្រោយ ពី គេ ?

1. Simple seller ទៅកន្លែងលក់ថ្នាំ
2. Go to private phet ទៅកន្លែងឱសថស្ថាន ពេទ្យឈ្នួល
3. Public clinic/hospital ទៅពេទ្យរដ្ឋ
4. Private phet came to home ទៅពេទ្យឈ្នួលមកផ្ទះ
5. VMW ទៅកម្មករស្រែចំការ-ជនបង្គោល
6. Outreach team ក្រុមពេទ្យដំណើរការទៅផ្ទះមកជួប
98. Other ផ្សេងៗ

18 How many days ago did you receive this treatment?
 តើអ្នកចាប់ផ្តើមយោបថ្នាំបន្តិចថ្ងៃណាស់
 មកដល់ពេលនេះ ? days ថ្ងៃ

19	Drug name or what does it look like? ឈ្មោះថ្នាំតាមការទំនាច់ តំបន់មានរូបភាព	Code No. ល.រ ថ្នាំ	Drug name after helping with examples ឈ្មោះថ្នាំក្រោយពេលព្យាបាលបានប្រសើរឡើង	Code No. ល.រ ថ្នាំ	Dose កំរិតប្រើប្រាស់ថ្នាំជាក់លាក់				No. of days ចំនួនថ្ងៃ	Did the provider tell the dose? តើអ្នកផ្តល់ថ្នាំបាន ត្រូវបានប្រាប់អ្នកដឹង?	What did the provider tell you? តើអ្នកផ្តល់ថ្នាំបានប្រាប់អ្នកដឹង?
					Day 1	Day 2	Day 3	Other			
Eg.	White label with mosquito គ្រាប់ថ្នាំពណ៌ស មានសញ្ញារូបឈ្នួល	19	Chloroquine	13	2X2	1X2			3	Y	5 days but I felt better ៥ថ្ងៃ ខ្ញុំបានត្រូវប្រើ ។
	If they know name Clo to បើពាក់ស្លាកលើឈ្មោះថ្នាំដូចជា										

20 After starting this treatment, what happened to the fever?
 បន្ទាប់ពីការព្យាបាលនេះ លើក្រអួតយ៉ាងម៉េចដែរ ?

<ol style="list-style-type: none"> 1. Fever did not stop ក្រអួតមិនធាត់ 2. Fever stopped 1-3 days after starting treatment ធាត់ក្រអួតរយៈពេល១-៣ ថ្ងៃបន្ទាប់ពីការព្យាបាលរួច ។ 3. Fever stopped 4-7 days after starting treatment ធាត់ក្រអួតរយៈពេល៤-៧ ថ្ងៃបន្ទាប់ពីការព្យាបាលរួច ។ 4. Fever stopped 1-3 days after starting treatment but came back ធាត់ក្រអួតរយៈពេល១-៣ ថ្ងៃបន្ទាប់ពីការព្យាបាល រួចត្រឡប់មកវិញ ។ 5. Fever stopped 4-7 days after starting treatment but came back ធាត់ក្រអួតរយៈពេល៤-៧ ថ្ងៃបន្ទាប់ពីការព្យាបាល រួចត្រឡប់មកវិញ ។ 98. Other ផ្សេងៗ 	If fever did not come back go to 22 បើក្រអួតមិនលាប់ឡើង វិញទៅ សួរទៅសំនួរ 22
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21 After how many days of no fever did the fever come back?
 តើរយៈពេលអត់ក្រអួតរួចរាល់ថ្ងៃ ដែលចាប់ផ្តើមក្រអួតម្តងទៀត?

<ol style="list-style-type: none"> 1. No ទេ 2. Yes, treatment for same episode បាន ព្យាបាលដូចពីមុន 3. Yes, treatment for previous episode បាន ព្យាបាលពីមុន 98. Other ផ្សេងៗ 	If No go to G បើទេ សួរទៅសំនួរ G
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22 Before you tried this treatment did you try any other treatments for this episode or a previous episode in the last 2 months?
 មុនពេលដែលអ្នកសាកព្យាបាលក្នុងដំណាក់កាលនេះ តើមានការព្យាបាលផ្សេងៗណាមួយដែរឬទេ? ពេលពីរ ២ខែមេមេ ?

<ol style="list-style-type: none"> 1. Simple seller ទៅកន្លែងតូចលក់ 2. Go to private phet ទៅកន្លែងឯសឺស្តា-ពេទ្យឯស្រុក 3. Public clinic/hospital ទៅពេទ្យរដ្ឋ 4. Private phet came to home ទៅពេទ្យឯស្រុកមកផ្ទះ 5. VMW ទៅកម្មករស្រូវ-ជនបទភ្នំពេញ 6. Outreach team ប្រុបពេទ្យអង្កាមនិងពេទ្យរដ្ឋចុះមកជួប 98. Other ផ្សេងៗ 	How many between the last provider and this one? រយៈពេលប៉ុន្មានថ្ងៃរវាងពេទ្យចុងក្រោយ និង ពេទ្យនេះ ?
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Second to last provider លេខពីរចុងក្រោយ

117 Who was the previous (second to last) provider you received treatment from?
 តើលេខពីរចុងក្រោយដែលអ្នកទទួលបានការព្យាបាលមុនគេ?

<ol style="list-style-type: none"> 1. Simple seller ទៅកន្លែងតូចលក់ 2. Go to private phet ទៅកន្លែងឯសឺស្តា-ពេទ្យឯស្រុក 3. Public clinic/hospital ទៅពេទ្យរដ្ឋ 4. Private phet came to home ទៅពេទ្យឯស្រុកមកផ្ទះ 5. VMW ទៅកម្មករស្រូវ-ជនបទភ្នំពេញ 6. Outreach team ប្រុបពេទ្យអង្កាមនិងពេទ្យរដ្ឋចុះមកជួប 98. Other ផ្សេងៗ 	How many between the last provider and this one? រយៈពេលប៉ុន្មានថ្ងៃរវាងពេទ្យចុងក្រោយ និង ពេទ្យនេះ ?
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days ថ្ងៃ

Second to last provider messages:

119	Drug name or what does it look like? ឈ្មោះថ្នាំតាមការទង់ចាំ ស្ថិតណាម៉តិថ្នាំ	Code No. ល.រ ថ្នាំ	Drug name after helping with examples ឈ្មោះថ្នាំព្រាងឈេល ឃើញ	Code No. ល.រ ថ្នាំ	Dose ពិពណ៌នាប្រែសម្រួលថ្នាំ				No. of days ចំនួនថ្ងៃ	Did the provider tell the dose? តើអ្នកជួយផ្តល់ការព្រាងឈេល ឃើញ ឬទេ?	What did the provider tell you? តើអ្នកជួយផ្តល់ការព្រាងឈេល ឃើញ អ្វីខុសប្រាប់អ្នកជាមុន?
					Day 1	Day 2	Day 3	Other			
Eg.	White tablet with mosquito ព្រាងឈេលស្រពិលស ជាប់រយ រូបមូស	19	Chloroquine	13	2X2	1X2	-	-	3	Y	5 days but I felt better ៥ថ្ងៃ ខ្ញុំបានប្រាន់បើ ។
1											
2											
3											
4											
5											

120 After starting this treatment, what happened to the fever?
បន្ទាប់ពីការព្យាបាលនេះ តើគ្រុនក្តៅយ៉ាងម៉េចដែរ ?

<ol style="list-style-type: none"> 1. Fever did not stop គ្រុនមិនឈប់ 2. Fever stopped 1-3 days after starting treatment ធាត់គ្រុនរយៈពេល១-៣ ថ្ងៃបន្ទាប់ពីការព្យាបាលរួច ។ 3. Fever stopped 4-7 days after starting treatment ធាត់គ្រុនរយៈពេល៤-៧ ថ្ងៃបន្ទាប់ពីការព្យាបាលរួច ។ 4. Fever stopped 1-3 days after starting treatment but came back ធាត់គ្រុនរយៈពេល១-៣ ថ្ងៃបន្ទាប់ពីការព្យាបាល រួចត្រឡប់មកវិញ ។ 5. Fever stopped 4-7 days after starting treatment but came back ធាត់គ្រុនរយៈពេល៤-៧ ថ្ងៃបន្ទាប់ ពីការព្យាបាល រួចត្រឡប់មកវិញ ។ <p>98. Other ផ្សេងៗ</p>	<p>If fever did not come back go to 122 បើគ្រុនមិនឈប់ឡើយ វិញទៅ សួររាល់សំណួរ 122</p>
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121 After how many days of no fever did the fever come back?
តើរយៈពេលអត់គ្រុនប៉ុន្មានថ្ងៃ ដែលចាប់ផ្តើមគ្រុនម្តងទៀត?

<input type="text"/>	days ថ្ងៃ
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122 Before you tried this treatment did you try any other treatments for this episode or a previous episode in the last 2 months?
មុនពេលដែលអ្នកសាកល្បងព្យាបាលក្នុងដំណាក់កាលនេះ តើមានជម្រកសាកល្បងព្យាបាលក្នុងដំណាក់កាលមុនរយៈពេលពីរ ខែចេញទេ ?

<ol style="list-style-type: none"> 1. No ទេ 2. Yes, treatment for same episode មាន ព្យាបាលដូចជាដំណើរការ 3. Yes, treatment for previous episode មាន ព្យាបាលពីដំណើរការ <p>98. Other ផ្សេងៗ</p>	<p>If No go to C បើទេ សួររាល់សំណួរ C</p>
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Third to last provider and treatment អត់ដឹងពីថ្ងៃសេវាបីចុងក្រោយ

217 Who was the previous (third to last provider?)

តើសេវាយុវណ្ណដែលអ្នកទៅកាន់ការព្យាបាលមុនគេ ថ្ងៃសេវាសុខភាពមី?

- 1. Simple seller លក់ថ្នាំឯង
- 2. Go to private phet ទៅលក់ថ្នាំឯងសឺសឺសឺ - ពេទ្យឃ្នាល
- 3. Public clinic/hospital ទៅពេទ្យរដ្ឋ
- 4. Private phet came to home ហៅពេទ្យឃ្នាលមកផ្ទះ
- 5. VMW ទៅកម្មសង្រ្គមចិត្ត - ជនបង្គោល
- 6. Outreach team ក្រុមពេទ្យដំណើរការនិងពេទ្យជំនុំមុខមកផ្ទះ
- 98. Other ផ្សេងៗ

218 How many days between this provider and the second to last one?

តើមានរយៈពេលប៉ុន្មានថ្ងៃចន្លោះពីសេវាលើកនេះ ដល់ សេវាលើកមីពីរ ?

days ថ្ងៃ

219	Drug name or what does it look like? ឈ្មោះថ្នាំតាមការចងចាំ ពិពណ៌នាអំពីថ្នាំ	Code No. ល.រ ថ្នាំ	Drug name after helping with examples ឈ្មោះថ្នាំគ្រោយពេល ឃើញ	Code No. ល.រ ថ្នាំ	Dose គិតប្រើប្រាស់ថ្នាំកំឡែង			No. of days ចំនួនថ្ងៃ	Did the provider tell the dose? តើអ្នកផ្តល់ថ្នាំកាល គ្រោយពេលអ្នកឃើញ ឬ?	What did the provider tell you? តើអ្នកផ្តល់ថ្នាំអោយគ្រាប់អ្នកដូចម្តេច ?
					Day 1	Day 2	Day 3			
Eg.	White tablet with mosquito គ្រាប់ថ្នាំពណ៌ស មានសញ្ញាប្រដាប់មូស	19	Chloroquine	13	2X2	1X2	-	3	Y	5 days but I felt better ៥ថ្ងៃ ខ្ញុំបានគ្រាន់បើ ។
1										
2										
3										
4										
5										

220 After starting this treatment, what happened to the fever?
 បន្ទាប់ពីការព្យាបាលនេះ តើ គ្រុនក្ដៅ យ៉ាងម៉េចដែរ ?

<ol style="list-style-type: none"> 1. I ever did not stop គ្រុនអីមធាត់ 2. Fever stopped 1-3 days after starting treatment ធាត់ គ្រុនរយៈពេល ១-៣ ថ្ងៃបន្ទាប់ពីការព្យាបាលរួច ។ 3. I ever stopped 4-7 days after starting treatment ធាត់ គ្រុនរយៈពេល ៤-៧ ថ្ងៃបន្ទាប់ពីការព្យាបាលរួច ។ 4. Fever stopped 1-3 days after starting treatment but came back ធាត់ គ្រុនរយៈពេល ១-៣ ថ្ងៃបន្ទាប់ពីការព្យាបាល រួច គ្រឿងមកវិញ ។ 5. Fever stopped 4-7 days after starting treatment but came back ធាត់ គ្រុនរយៈពេល ៤-៧ ថ្ងៃបន្ទាប់ ពីការព្យាបាល រួច គ្រឿងមកវិញ ។ <p>98. Other ចៀបប្រទេស</p>	If fever did not come back go to 222 បើ គ្រុនមិនចាប់ផ្ដើម វិញទេ សូមទៅសំណួរ 222
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221 After how many days of no fever did the fever come back?
 បន្ទាប់ពី រៀង គ្រុនរយៈពេល ប៉ុន្មាន ថ្ងៃ ដែល ធាត់ គ្រុន ម្ដង ម្កេត ?

days ថ្ងៃ

G. Mefloquine history ប្រវត្តិការប្រើប្រាស់មេហ្វូគីន

Show them the tablets, Mefloquine A+M & Malarine. បង្ហាញត្រាប់ថ្នាំដល់គាត់ មេហ្វូគីន. A+M. មាលារីន

23 Did you ever take Mefloquine, A+M or Malarine តើអ្នកធ្លាប់លេបមេហ្វូគីន. A+M or Malarine ទេ ?

1. Never មិនធ្លាប់	If 1. or 99. go to 31
2. Yes, already described បាន. ធ្លាប់លេបហើយ	បើ 1 ឬ 99 ទៅ 31
3. Yes, not yet described បាន. មិនធ្លាប់ទេ	If 2. go to 24
99. Don't know មិនដឹង	បើ 2 ទៅ 24
	If 3. go to 26
	បើ 3 ទៅ 26

24 Did you vomit within 1 hour of taking Mefloquine/A+M/Malarine? តើអ្នកមានកូតចេញថ្នាំទេ បន្ទាប់ពីលេបថ្នាំរួច ?

1. No ទេ	2. Yes បាន	99. Don't know មិនដឹង
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25 Was this the first time you took Mefloquine, A+M or Malarine? តើនេះជាលើកទីមួយឬ ដែលអ្នកប្រើថ្នាំ មេហ្វូគីន. A+M ឬ មាលារីន

1. No ទេ	2. Yes បាន	99. Don't know មិនដឹង	If Yes go to 31 បើបាន. សូរទៅសំណួរ 31
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Previous time ពិពេលមុន

26 Which one did you take the previous time? កាលពីលើកមុន តើអ្នកប្រើថ្នាំណាមួយ ?

1. Mefloquine
2. A+M4
3. A+M3
4. Malarine 4
5. Malarine 3
99. Don't know

27 How many days or weeks ago did you take it? តើប៉ុន្មានអាទិត្យនៃហើយដែលអ្នកលេបថ្នាំនេះ ?

___ weeks អាទិត្យ	___ months ខែ	If more than 2 months ago go to 31 បើលើសពី 2 ខែ សូរទៅ សំណួរទី 31
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28 Did you finish the packet? តើអ្នកលេបថ្នាំអស់ ទាំងអស់ឬ?

1. No ទេ	2. Yes បាន	99. Don't know មិនដឹង
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29 How many tablets of Mefloquine did you take? តើអ្នកលេបថ្នាំ មេហ្វូគីន ប៉ុន្មានត្រាប់?

If they took A+M or Malarine then calculate the number បើប្រើថ្នាំ A + M ឬ មាលារីន . ចូរគណនាចំនួន

30 Did you vomit up the medicine? តើអ្នកមានកូតចេញថ្នាំទេ បន្ទាប់ពីលេបថ្នាំរួច?

1. No ទេ	2. Yes បាន	99. Don't know មិនដឹង
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H. Lost productivity បាត់បង់ផលិតផល

31 What work were you doing before the last episode of fever?

តើអ្នកប្រកបការងារអ្វី មុនអ្នកត្រូវបានលើកក្រោយនេះ ?

- 1. Working in field ធ្វើស្រែ
- 2. Working in forest ចូលព្រៃ
- 3. Looking after children and home មើលក្មេងនៅផ្ទះ
- 4. Child staying at home កូនសំរាកនៅផ្ទះ
- 5. Child following parent to chamkar ក្មេងទៅជំរកការពារ ធិពុកម្តាយ
- 6. Child going to school ទៅសាលារៀន
- 98. Other ផ្សេងៗ (សូមបញ្ជាក់) _____

32 How many days work/study did you miss because of the last episode of fever? តើអ្នកខានធ្វើការងារ ឬរៀនសូត្រប៉ុន្មានថ្ងៃហើយក្នុងពេលចុងក្រោយនេះ ?

days ថ្ងៃ

33 Who else had to stop work to help take care of sick person during the last episode of fever?

តើមានអ្នកណាទៀតដែលខានធ្វើការងារដើម្បីជួយថែរក្សាអ្នក?

1.	Put the relationship of the person If no one go to 35 សរសេរថា តើគ្រូជាអ្វីនឹងអ្នកជម្ងឺ. បើគ្មានទេ សូរទៅសំណួរ 35
2.	

34 How many days work did each person miss? Not including patient

តើម្នាក់ៗខានធ្វើការងារប៉ុន្មានថ្ងៃ ? ដោយមិនគិតពីអ្នកជម្ងឺ

1.	days ថ្ងៃ
2.	days ថ្ងៃ

Not including patient
ដោយមិនគិតពីអ្នកជម្ងឺទេ

I. Transport and costs មធ្យោបាយធ្វើដំណើរ និង តម្លៃ

Start with last provider and ask all questions about that provider before asking about the 2nd last provider
 ចាប់ផ្តើមពីសេវាសុខភាពចុងក្រោយ និង សួរសំណួរទាំងអស់អំពីសេវានោះមុន និងសួរទៅ សំណួរសេវាទីពីរចុងក្រោយទៀត

	Last provider សេវាសុខភាពចុងក្រោយ	2 nd to last provider សេវាសុខភាពទីពីរចុងក្រោយ	3 rd to last provider សេវាសុខភាពទី៣ចុងក្រោយ
35	Provider Copy from page 4.5.7 សេវាសុខភាព បំណងគាំទ្រទំព័រ 4.5.7		
36	How did you travel there? តើអ្នកធ្វើដំណើរដោយមធ្យោបាយណា ?	1. At home សំរាកនៅផ្ទះ 2. Walk ដើរ 3. Bicycle កង់ 4. Moto ម៉ូតូ 5. Car ឡាន 98. Other ផ្សេងៗ	1. At home សំរាកនៅផ្ទះ 2. Walk ដើរ 3. Bicycle កង់ 4. Moto ម៉ូតូ 5. Car ឡាន 98. Other ផ្សេងៗ
If they stayed at home then go to 40 បើសិនគាត់នៅផ្ទះ សួរទៅសំណួរទី 40			
37	How many people travelled? តើមានមនុស្សប៉ុន្មាននាក់ ដែលទៅជាមួយ?		
38	How much time to go and return? តើអ្នកធ្វើដំណើរទៅហើយនិងមកប៉ុន្មានម៉ោង មានរយៈពេលប៉ុន្មានម៉ោង?		
39	Total cost of Transport តើសរុបថ្លៃធ្វើដំណើរទៅ ដំណើរមកប៉ុន្មាន?		
40	Treatment and diagnosis cost ? តើថ្លៃព្យាបាលទាំងអស់ប៉ុន្មាន?		
41	Food/fruit/ drink? តើអ្នកចំណាយអស់ប៉ុន្មាន សំរាប់ថ្លៃបាយទឹក?		
42	Other costs ? តើការចំណាយផ្សេងៗទៀតដែរទេ?		
43	What were "other costs"? តើមានចំណាយអ្វីផ្សេងៗទៀត ដូចជាបន់ស្រន់ទេ ?		
44	TOTAL សរុប		

How much?
ប៉ុន្មាន?

45 How did you pay?
តើអ្នកឱ្យលុយតាមវិធីណា?

Wait for their reply រង់ចាំចម្លើយរបស់គាត់

1. Ready cash លុយខ្លួនឯងមានស្រាប់	
2. Borrowed from neighbour ខ្ចីលុយពីអ្នកជិតខាង	
3. Credit from provider ជំពាក់ពេទ្យ	
4. Sold land, animals or gold លក់ដី លក់គោ-ក្របី លក់មាស-របស់របរឱ្យគេ	
98. Other ផ្សេងៗ (សូមបញ្ជាក់)	

J. Weight and blood test ថ្ងៃទម្ងន់ និង ជុសឈាម

Is the patient present? តើបុគ្គលនេះមានវត្តមាននៅជូរទេ?	1. No ទេ	2. Yes បាទ	If No go to K ប្រសិនបើ ទៅសំណួរ K
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46	Weight ទម្ងន់		Kg (គីឡូ)	
47	Axillary Temperature វាស់កំដៅ តាមឃ្មៅក			
48	Spleen size ទំហំអណ្តើក		Cm (សង្ឃឹម៉ែត្រ)	
49	If female is she pregnant? ប្រសិនបើស្ត្រី តើមានផ្ទៃពោះឬទេ?	1. No ទេ	2. Yes បាទ	99. Don't know មិនដឹង
		If No or don't know go to 51 បើមិនដឹង រំលងទៅសំណួរ 51		
50	How many months pregnant មានផ្ទៃពោះប៉ុន្មានខែ ?		Months ខែ	

51	Dipstick result លទ្ធផលឱបស្វិត	1. Negative អវិជ្ជមាន	2. Positive វិជ្ជមាន	3. No result គ្មានលទ្ធផល Why not? មូលហេតុអ្វី _____
52	Treatment given ការព្យាបាលដែលបានអោយគាត់			

53	Filter paper taken?	1. No ទេ	2. Yes បាទ	
54	Slide taken?	1. No ទេ	2. Yes បាទ	

K. Other people? មនុស្សផ្សេងទៀត

53 Did any one else in this household have fever/ malaria in last 3 weeks.
តើមានអ្នកណាផ្សេងទៀតមានគ្រុន ឬ គ្រុនចាញ់ក្នុងរយៈពេល ២អាទិត្យមុននេះទេ?

- 1. No គ្មាន
- 2. 1 person មនុស្សម្នាក់
- 3. 2 person មនុស្សពីរនាក់
- 98. Other ដទៃទៀត _____
- 99. Don't know មិនដឹង

Check form A ពិនិត្យទម្រង់ A
 If No, then continue with form D
 បើសិនទេ បន្ទាប់មកបន្តរូបសម្រាប់ទម្រង់ D
 If Yes, try to fill in another form C.
 បើសិនចាស ចូរបំពេញទម្រង់ C
 If you cannot then write down as much as you can
 បើសិនអ្នកមិនអាចបំពេញទម្រង់ C
 ចូរអ្នកសរសេរតាមលទ្ធភាពដែលអាច

Age ឈ្មោះបុគ្គល _____ years Sex ភេទ 1.M 2.F

When did they have fever? តើគាត់ចាប់គ្រុនពីពេលណាមក ?

Other information (What treatment they took, where they got it, how many days they took the medicine, any delay?
 ព័ត៌មានផ្សេងៗ. (តើគាត់បានលេបថ្នាំអ្វីខ្លះ? បានមកទីណា . លេបប៉ុន្មានថ្ងៃ . មានយឺតយ៉ាវក្នុងការលេបទេ ?)

Age ឈ្មោះបុគ្គល

Sex ភេទ

When did they have fever? តើគាត់គ្រុនពីពេលណាមក ?

Other information (What treatment they took, where they got it, how many days they took the medicine, any delay?
 ព័ត៌មានផ្សេងៗ. (តើគាត់បានលេបថ្នាំអ្វី. បានមកទីណា . លេបប៉ុន្មានថ្ងៃ . មានយឺតយ៉ាវក្នុងការលេបទេ ?)

“While we are waiting for the blood test please tell me about your household”
 ខណៈពេលដែលយើងកំពុងរង់ចាំលទ្ធផលឈាម . យើងអាចសួរសំណួរផ្សេងៗទៀតក៏បាន ?

ANNEX 9 Additional results from the household survey in Cambodia

Table A 9-1: Summary description of the areas in which the community based treatment seeking and drug usage study took place

Intervention	Districts (Province)	No. in study	Description of area	Description of intervention and existing health structure
None	Sampalouen (Battambang)	4 settlements 65 individuals	Mainly maize and bean growing with pockets of hills and forest. The population is a mixture of older inhabitants, new settlers and migrant workers with varying degrees of exposure to the forest and therefore malaria.	Originally selected as an "Intervention" area where the social marketing of Malarine and RDTs had been piloted through 10 vendors in the market town. In fact, no difference from non-intervention areas due to lack of penetration of the scheme into villages and therefore merged into the non-intervention group. Takrey health centre and Sampalouen referral hospital are generally regarded as well functioning health facilities.
	Malai (Banteay Meanchey)	2 settlements 45 individuals	Border town (Thai-Cambodia) Next to Sampalouen and similar in geography and agricultural activity.	Very active private sector with poorly functioning public health centre. Public health clinics on Thai side of border also popular.
	Chik Phat +Thmar Beng (Ko Kong)	5 settlements 91 individuals	One of the most difficult areas to access in Cambodia. Dense tropical jungle. Some villages only accessible by boat. The population use to make good living from hunting and selling forest products, now becoming increasingly poor with the enforcement of anti-hunting and logging laws.	Health centre building exists in Chik Phat but not functioning and nearest public health facilities often more than a day's travel from other villages
	Sotnikum (Siem Riep)	3 settlements 28 individuals	Near and in some areas similar to Anlong Veng district. Mainly poor rice growing populations with many new, "temporary" settlements in remoter areas.	Health centres supported by additional support from MSF but no malaria outreach service.
Outreach	Anlong Veng (Oddor Meanchey)	7 settlements 88 individuals	A remote and heavily forested area. This was a Khmer Rouge stronghold until 1998 when Pol Pot died there. Since then it has been gradually demined and new roads have been built attracting an influx of poor non-immune settlers from lowland areas resulting in local outbreaks of malaria.	Khmer Rouge supported health centre until 1999. Since then, MSF supported health services. The only district in the country with a malaria "outreach" service where each village is visited once or twice per week by a team from the health centres who diagnose and treat <i>P. falciparum</i> malaria with A+M.
Village Malaria Volunteers (VMVs)	Thmar Beng (Ko Kong)	2 settlements 44 individuals	See description of Chik Phat and Thmar Beng	Since January 2002, the only Khmer speaking districts with VMVs. In the 10 villages, VMVs are trained to diagnose and treat <i>falciparum</i> malaria using RDTs and pre-packaged artesunate and mefloquine.

Table A9-2: Size of land owned by households by district

District	N	Mean size (ha)	Median size (ha)	Range (ha)
Anlong Veng	58	1.4	1	1-5
Chik Phat	62	1.0	1	1-6
Malai	36	2.2	0.5	0-17
Sampalouen	46	1.7	1	1-8
Sotnikum	26	1.1	1	0-4
Thmar Bang	35	1.5	1	0-3
Total	263	1.5	1	0-17

Table A9-3: Months of food shortage in the last year

	No. (%)
0-3 months	16 (19.5)
4-6 months	35 (45.6)
7-9 months	17 (22.1)
10-12 months	10 (13.0)
Unknown	8 (9.3)
Total	86

Table A 9-4: Years of schooling (Mean 2.5, median 1, min 0, max 12)

	No. (%)
0	114 (42.1%)
1	22 (8.1%)
2	14 (5.2%)
3	35 (12.9%)
4	26 (9.6%)
5	18 (6.6%)
6	14 (5.2%)
7	10 (3.7%)
8	7 (2.6%)
9	6 (2.2%)
10	3 (1.1%)
11	1 (0.4%)
12	1 (0.4%)

Table A9-5: Building material for walls

	No. (%)
Wood	156 (53.8%)
Leaves or bamboo	116 (40.0%)
No walls	11 (3.8%)
Concrete or brick	2 (0.7%)
Other	5 (1.7%)
Total	290

Table A9-6: Building material for roof

	No. (%)
Leaves or bamboo	203 (70.0%)
Metal	47 (16.2%)
Tile, Brick, Concrete	20 (6.9%)
Wood	9 (3.1%)
Other	10 (3.5%)
Total	290

Table A9-7: Number of draft animals

	No. (%)
0	237 (85.3%)
1	7 (2.5%)
2	20 (7.2%)
3	3 (1.1%)
4	1 (0.4%)
5+	10 (3.6%)
Total	278

Table A9-8: Ownership of means of transport

	No. (%)
None	190 (65.5%)
Oxcart	14 (4.8%)
Bicycle	57 (19.7%)
Motorcycle	28 (9.7%)
Tractor	7 (2.4%)
Total	290

Table A9-9: Ownership of means of telecommunications

	No. (%)
None	183 (64.0%)
Radio only	74 (25.9%)
TV only	18 (6.3%)
Both	10 (3.5%)
Other (video)	1 (0.35%)
Total	286

Table A9-10: Source of water

	No. (%)
Dug well	209 (72.1%)
Natural water	61 (21.3%)
Drill well	20 (6.9%)
Total	290

Table A9-11: Age distribution of sample

Age (years)	No. (%)
0-5	20 (5.5%)
6-10	43 (11.9%)
11-14	45 (12.5%)
15+	253 (70.1%)
Total	361

Table A9-12: Logistic regression analysis of likelihood of being seen by formal provider for recent episode of malaria like illness (adjusted for study design)

Independent variable	AOR	p	95% CI
Outreach area	4.0	0.023	1.12-13.2
VMV area	147.5	0.002	8.46-2570.7
Female	1.0	0.981	0.50-2.04
Child 6-14	3.2	0.004	1.50-6.67
Child <6	3.8	0.016	1.32-10.84
Far*	1.0	0.977	0.30-3.41
Poorest 40%	1.0	0.942	0.42-2.22
Richest 20%	0.3	0.140	0.05-1.58

N=361

Dummy variables: Intervention=none, Sex=male, age=adult>14 years, distance from health centre <2 hours by motorcycle, poverty rank=middle 40%.

Variables in bold are those which significantly affect the adjusted odds ratio.

Table A 9-13: Likelihood of biological diagnosis by district

District	n	% (n)
Anlong veng	88	35% (31)
Chik Phat	91	2% (2)
Malai	42	47% (21)
Sampalouen	65	23% (15)
Sotnikum	28	14% (4)
Thmar Bang	44	34% (15)
	361	

χ^2 P<0.0001

Table A 9-14: Logistic regression analysis of likelihood of receiving biological diagnosis for recent episode of malaria like illness (adjusted for study design)

	AOR	p	95% CI
Outreach area	2.38	0.10	0.83-6.88
VMV area	10.67	0.00	4.70-24.25
Sex (female)	0.80	0.356	0.50-1.30
Age<5	1.09	0.769	0.60-1.97
Age 6-15	2.91	0.035	1.08-7.96
Far	0.65	0.408	0.23-1.87
Poverty lowest 20%	0.99	0.974	0.54-1.83
Povety highest 40%	0.73	0.486	0.28-1.86

N=360

Dummy variables: Intervention=none, Sex=male, age=adult>14 years, distance from health centre <2 hours by motorcycle, poverty rank=middle 40%.

Variables in bold are those which significantly affect the adjusted odds ratio.

Table A9-15: Logistic regression analysis of receiving A+M for recent episode of malaria like illness (adjusted for study design)

	AOR	p	95% CI
Outreach area	2.73	0.053	0.99-7.59
VMV area	7.72	0.007	1.84-28.2
Female	0.94	0.852	0.5-2.0
Child 6-14	1.18	0.602	0.61-2.27
Child <6	0.77	0.757	0.14-4.29
Far from HC	1.19	0.721	0.44-1.17
Poorest 40%	0.86	0.644	0.46-1.62
Richest 20%	0.33	0.164	0.09-1.62

N=297

Dummy variables: Intervention=none, Sex=male, age=adult>14 years, distance from health centre <2 hours by motorcycle, poverty rank=middle 40%.

Variables in bold are those which significantly affect the adjusted odds ratio.

Table A9-16: Average duration of treatment by antimalarial regime

Antimalarial regime	No. (%)	No. with info on duration available	Mean duration	s.d	Median (range)
A+M (+/- other antimalarial)	72 (13.8%)	55	2.89	0.90	3 (1-6)
Artemisinin alone	56 (10.7%)	29	3.09	1.91	3 (1-7)
Artemisinins (+/- other drugs)	52 (9.9%)	36	2.57	1.70	2 (1-7)
Chloroquine and/or tetracycline	94 (18.0%)	64	2.17	1.54	2 (1-7)
Other	8 (1.5%)	5	1.8	1.30	1 (1-4)
Q (+/-others)	33 (6.3%)	24	2.31	1.64	2 (1-7)
Q+T (+/- others)	22 (4.2%)	13	3.85	3.02	3 (1-10)
Traditional or none	119 (22.8%)	53	2.49	1.45	2 (1-6)
Unknown	67 (12.8%)	38	3.87	3.38	3 (1-14)
Total	523 (100%)	317	2.76	1.96	3 (1-14)

Table A9-17: Type of treatment by provider (%)

Provider	A+M (+/- other antimalarial)	Artemisinin alone	Artemisinin derivative with other antimalarial	Chloroquine	Chloroquine +tetracycline	Other antimalarial	Quinine (+/- other antimalarial)	Quinine+tetracycline	Total
Public health facility	3 (17.7%)	0	0	7 (41.2%)	0	2 (11.8%)	3 (17.7%)	2 (11.8%)	17
VMV	14 (100%)	0	0	0	0	0	0	0	14
Outreach	15 (100%)	0	0	0	0	0	0	0	15
Other	6 (28.6%)	3 (14.3%)	2 (9.6%)	5 (23.8%)	0	3 (14.3%)	3 (14.3%)	0	21
Private provider	17 (7.9%)	43 (20.0%)	42 (19.5%)	46 (21.4%)	14 (6.5%)	12 (5.6%)	24 (11.2%)	17 (7.9%)	215
Total	54 (19.2%)	46 (16.3%)	43 (15.3%)	58 (20.6%)	14 (5.0%)	17 (6.0%)	30 (10.6%)	19 (6.7%)	281

ANNEX 10 Modelling results for a high transmission settings

A.10.1. Outcomes

The model was run using a vectorial capacity of 15 in order to simulate a high transmission intensity setting, with an annual entomological inoculation rate (EIR) of around 100-150. In Figure A10-1, it can be seen that, as expected, when drug A is used alone as monotherapy, resistance to it spreads much slower in a high transmission setting than in a low transmission setting, taking six years to reach 20% resistance. This is because a much smaller proportion of patent infections are symptomatic and treated, and therefore less drug pressure is exerted with less opportunity for resistant infections to exhibit their survival advantage. Combination therapy appears to have much less impact on the spread of resistance in high transmission settings compared to low transmission settings because the proportion of parasites in which drug treatment is allowed to affect outcomes represents only a small proportion of all infections. Perhaps surprisingly, the rate of spread of drug resistance appears to be faster with combination therapy in a high transmission setting compared to a low transmission setting. This is partly because in all these simulations, 10% of the potentially patent infections are assumed to be exposed to inhibitory levels of drug A. This means that a substantial proportion of parasites are exposed to the drug pressure that results in selection of resistant mutants. In addition, it is also assumed that there is no fitness cost to drug resistance and therefore an equal chance of survival of resistant mutants in the absence of drug pressure.

Figure A10-1: *The spread of drug resistance in high and low transmission settings*

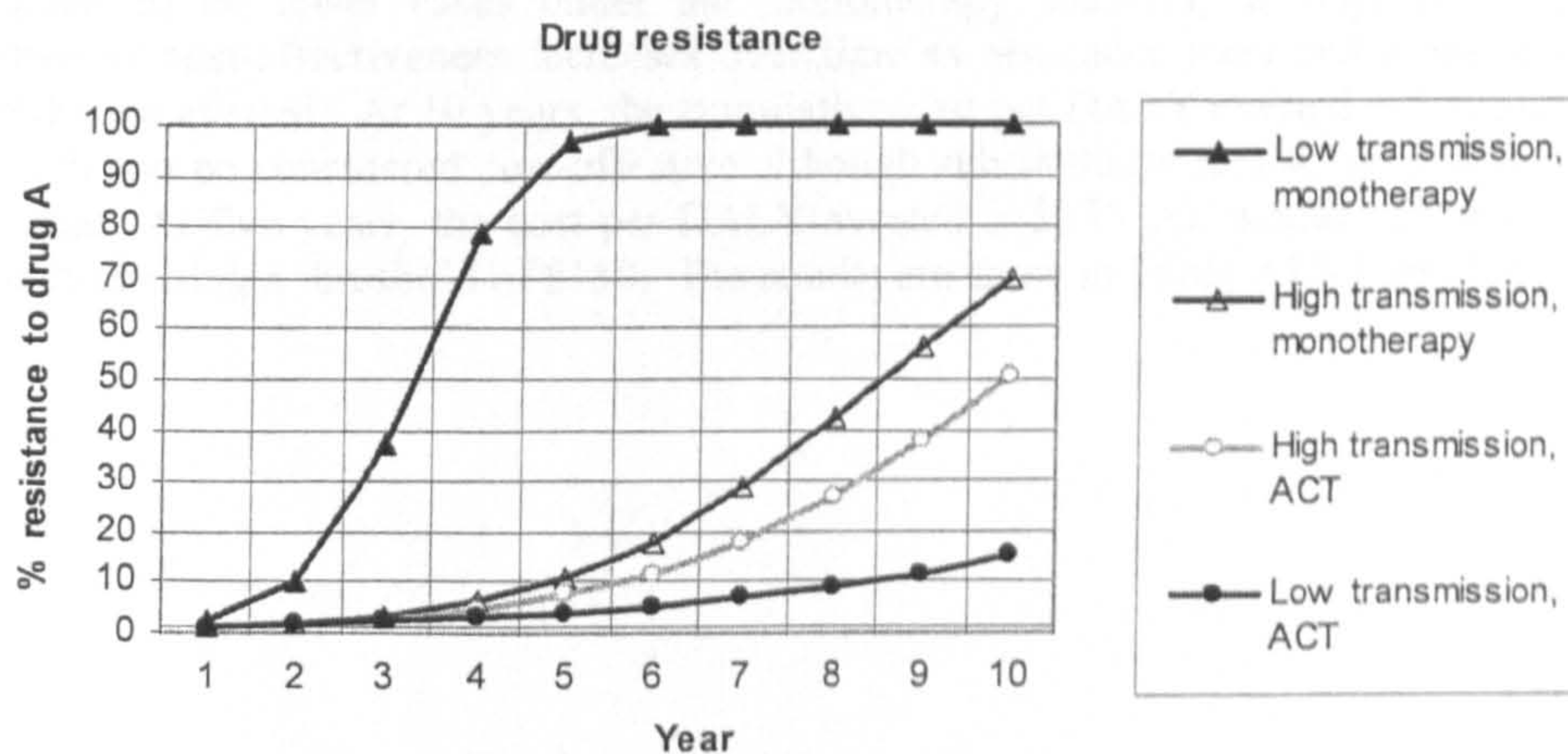


Figure A10-2 shows the incidence of new patent and treated infections. It can be seen that in a high transmission setting, only a small proportion of patent infections are treated, due to the high levels of immunity in the population⁷⁶. The comparison with a low transmission setting seems to suggest that the incidence of symptomatic infections in the epidemic situation in low transmission settings is higher than that in the stable high transmission settings⁷⁷. Figure A10-3 presents the annual incidence of patent and treated infections by age group. Because the immunity function for symptomatic malaria describes a steep decrease in likelihood of symptoms with increasing age, although adults account for the majority of patent infections in absolute terms because they form the largest age-group, they carry the least burden of disease in terms of symptomatic (and therefore treated) malaria.

⁷⁶ Note the scale of the vertical axis.

⁷⁷ Whilst this may be the case initially, we would expect that as immunity developed in the population, the incidence would fall in the low transmission setting.

Annual outcomes in terms of recrudescence infections and disability adjusted life years (DALYs) are presented in Figure A10-4. As expected, as resistance to drug A rises with continued use of monotherapy, the number of recrudescence infections also rises as does the number of severe infections and therefore DALYs. However with combination therapy, the incidence of recrudescence infections and DALYs remains low. This is because the majority of resistant infections that are treated with combination therapy are cured.

A.10.2. Costs

Because CT has little impact on transmission in a high transmission setting, the annual drug costs of combination therapy can be expected to remain greater than if monotherapy was used. This is illustrated in Figure A10-5. In terms of the total costs of treating malaria, because there are fewer recrudescence and severe infections than with monotherapy, we might expect combination therapy to be cost saving overall. However, within the time frame of this analysis, the annual direct cost of malaria with ACT remains greater than monotherapy until after year 10.

A.10.3. Cumulative cost-effectiveness

The resulting cost-effectiveness of combination therapy in a high transmission setting is therefore less than in a low transmission setting. In the first few years, whilst resistance is low and there are few recrudescence infections with monotherapy, combination therapy makes no difference to the number of recrudescence or severe infections and has no impact on transmission intensity. Therefore, if a short time frame is used, combination therapy will not appear to be cost-effective and may even appear to be more costly and less effective if, due to chance, there happen to be fewer cases under the monotherapy scenario, as happens in this example. However cost-effectiveness increases over time as resistance rises and more severe cases and deaths are averted. At 10 years, the cumulative cost per DALY averted is \$41 and therefore the switch can be considered cost-effective although substantially less so than in low transmission settings. At five years, the cost per DALY averted is \$335 and would not be considered cost-effective using a threshold of \$150. The results are shown in Table A10-1 and Figure A10-6.

Figure A10-2: Annual incidence of new patent and treated infections in low and high transmission settings with monotherapy and combination therapy at 100% coverage

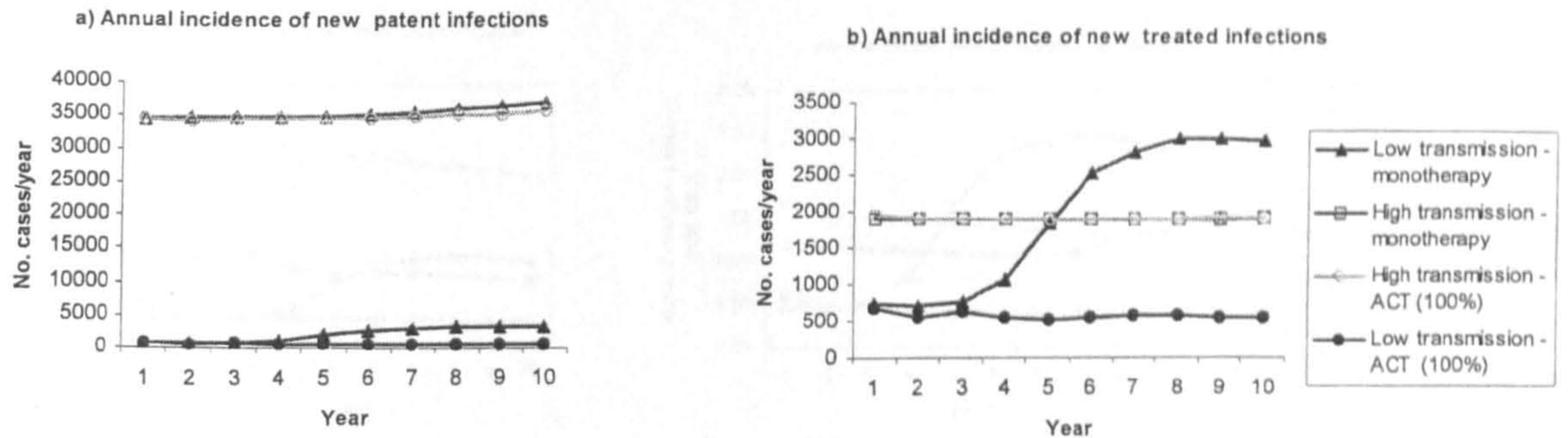


Figure A10-3: Annual incidence of new patent and treated infections with monotherapy in a high transmission setting, by age group

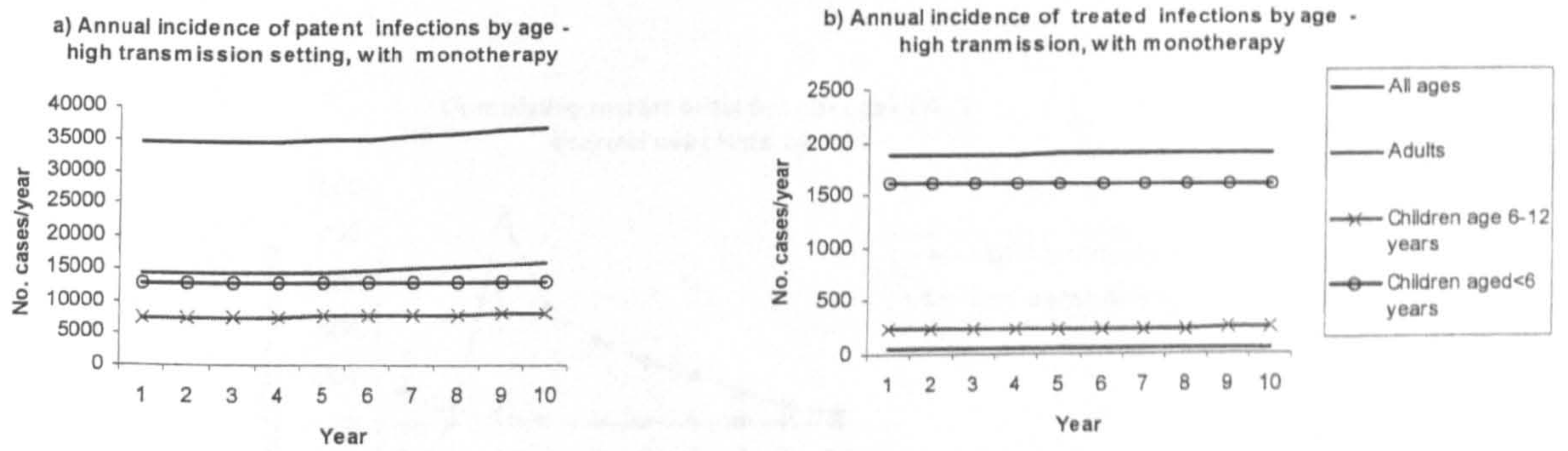


Figure A10-4: Annual incidence of recrudescence infections and number of DALYs

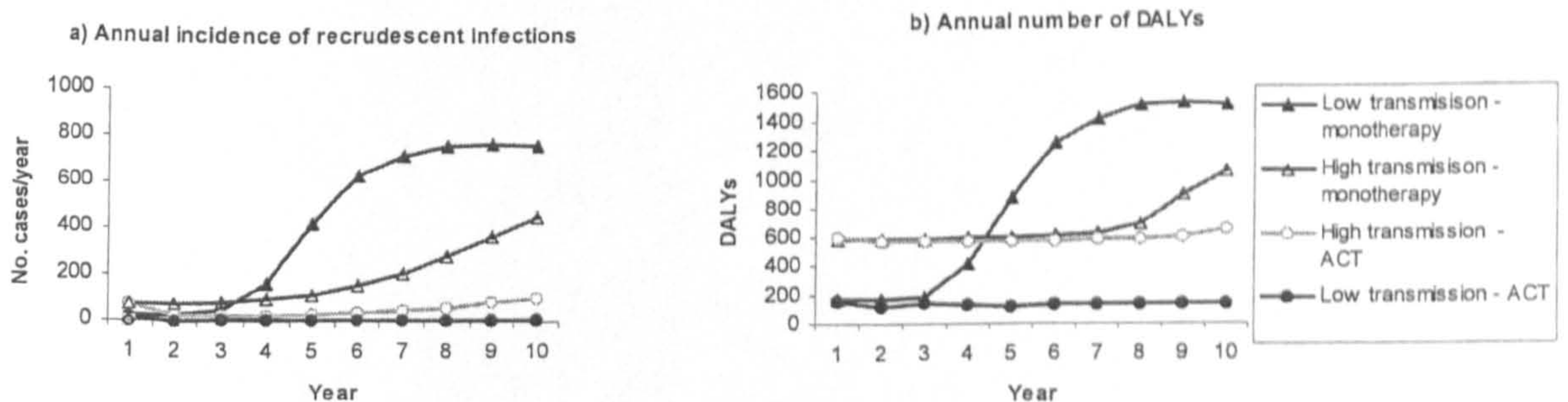


Figure A10-5: Annual direct cost of drugs and of treating malaria (including recrudescent and severe infections, in low and high transmission settings with monotherapy and 100% combination therapy

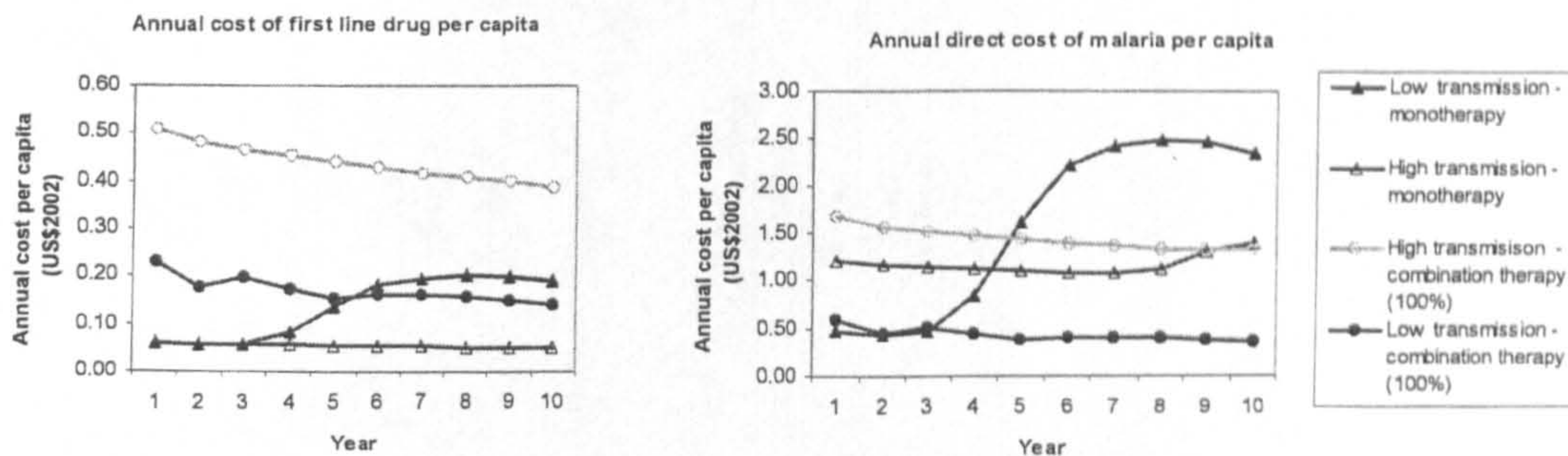


Figure A10-6: Cost-effectiveness of combination therapy (100% coverage) over time in a high transmission setting compared to low transmission setting

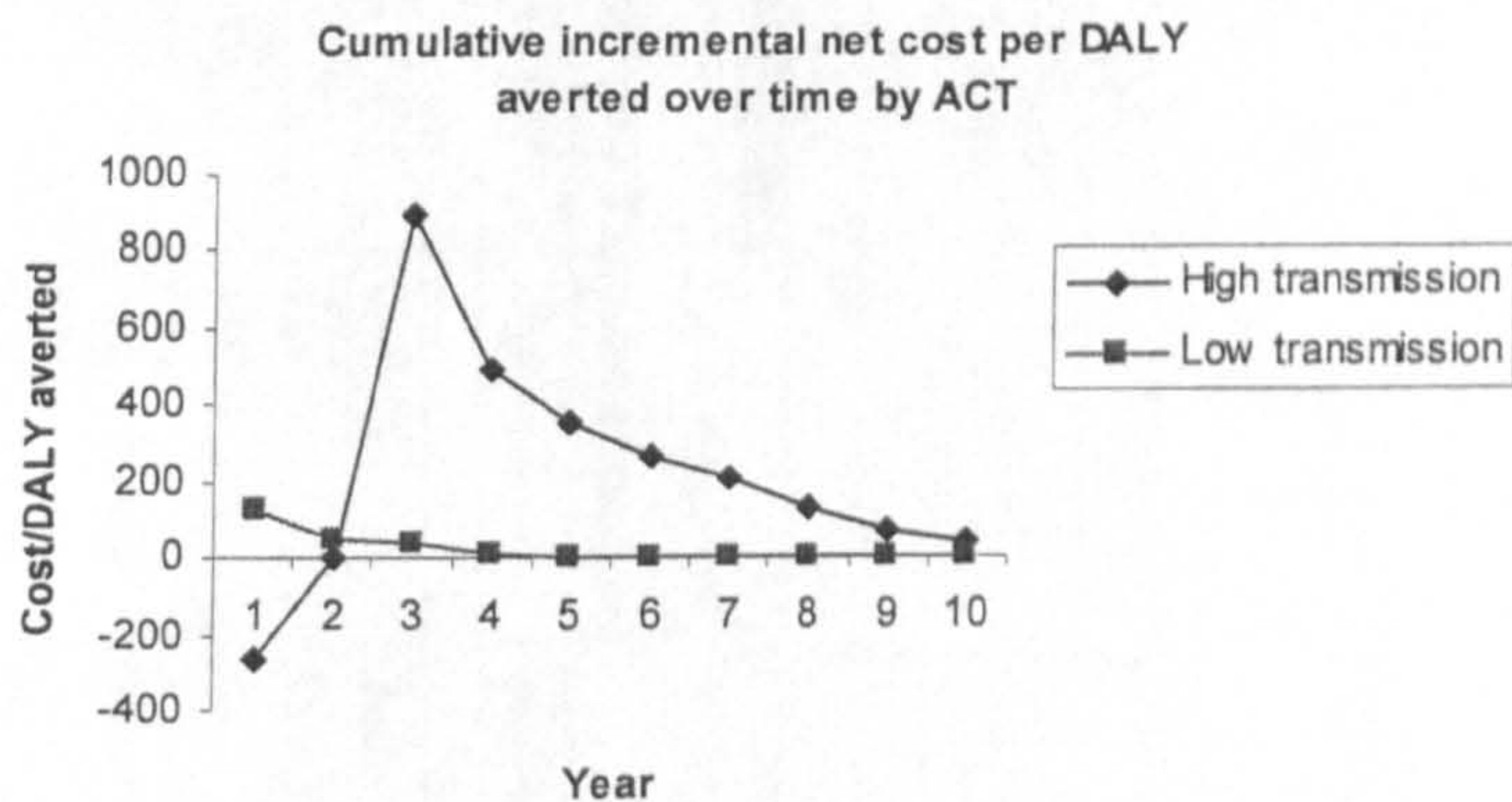


Table A10-1: Cumulative cost-effectiveness of combination therapy (100% coverage) over time in a high transmission setting

	Cumulative costs and effects											
	After 1 year			After 5 years			After 10 years					
	Mono-therapy	CT	Difference (CT-mono)	Mono-therapy	CT	Difference (CT-mono)	Mono-therapy	CT	Difference (CT-mono)	Mono-therapy	CT	Difference (CT-mono)
Number of treated cases	1,889	1,947	58	9,459	9,515	56	18,974	19,049	75			
Number of recrudescences	73	71	-2	453	177	-276	1,911	508	-1403			
Number of severe cases	104	107	3	527	516	-11	1,216	1,050	-166			
Number of deaths	21	21	0	105	103	-2	243	210	-33			
Number of DALYs	587	604	17	2,965	2907	-58	6,845	5,913	-932			
Cost of drug	610	5,084	4,474	2,882	23,465	20,583	5,407	43,802	38,395			
Direct cost of illness	12,098	16,896	4,798	57,612	77,022	19,410	117,926	144,888	26,962			
Total cost (indirect and direct)	27,904	33,139	5,235	132,903	150,715	17,812	266,409	283,476	17067			
Incremental drug cost per consequence averted												
Drug cost (US\$) per	After 1 year			After 5 years			After 10 years					
- case averted		-77.1			-367.6			-511.9				
- recrudescence averted		2,237.0			-74.6			27.4				
- severe infection averted		1,491.3			1,871.2			231.3				
- death averted		-			10,291.5			1,163.5				
- DALY averted		263.2			354.9			41.2				

ANNEX 11 Sensitivity analysis of biological model

Table A11-1: Parameters tested in the sensitivity analysis with code

No.	Parameter	Code
1	Vectorial capacity	I1
2	Host susceptibility	I2
3	Probability of being symptomatic	I3
4	Treatment coverage	I4
5	ACT coverage	I5
6	Relative parasite in non-treated	I6
7	Relative parasite in recrudescence	I7
8	Gametocyte switch rate for monotherapy	I8
9	Relative gametocyte switch rate for ACT	I9
10	Relative gametocyte switch rate in recrudescence	I10
11	Relative gametocyte switch rate in non-treated	I11
12	Plateau stage at the peak parasitaemia	I12
13	Plateau stage during recrudescence	I13
14	Duration of a non-treat infection	I14
15	PRR of drug-sensitive infection treated with monotherapy	I15
16	PRR of drug-resistant infection treated with monotherapy	I16
17	Relative PRR when treated with ACT	I17
18	Failure rate in drug-sensitive infection treated with monotherapy	I18
19	Failure rate in drug-resistant infection treated with monotherapy	I19
20	Relative failure rate in drug-sensitive infection treated with ACT	I20
21	Relative failure rate in drug-resistant infection treated with ACT	I21
22	Resistance level at which ACT is first considered	I22
23	Proportion of uninfected population with residual drug	I23

Scenario A: Low transmission setting and monotherapy

Scenario B: Low transmission setting and ACT

Scenario C: High transmission setting and monotherapy

Scenario D: High transmission setting and ACT

Table A11-2: The partial rank correlation coefficients of the input parameters and the outcomes in low transmission setting with monotherapy (Scenario A)

Outputs	Input parameters																						
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	I17	I18	I19	I20	I21	I22	I23
EIR _{y2}	0.8	0	0	-0.1	0	0	0	0.3	0	0	0.1	0.1	0	0	0	0	0	0	0	0	0	0	0
EIR _{y5}	0.8	0.2	0	0	0	0	0.1	0.2	0	0	0.1	0.1	0	0	0	0	0	0	0	0	0	0	0
EIR _{y8}	0.8	0.1	0	0	0	0	0.2	0.2	0	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0	-0.1
EIR _{y10}	0.8	0.2	0	0	-0.1	0	0.2	0.2	0	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0	0
% treated infection _{y2}	0.6	0.1	0	0.4	0	0	0	0.2	0	0	0.1	0.1	0	0	0	0	0	0	0	0	0	0	-0.1
% treated infection _{y5}	0.4	0	0	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
% treated infection _{y8}	0.3	0	0	0.4	0	0	-0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
% treated infection _{y10}	0.3	0	0	0.4	0	0	-0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
% recrudescent infection _{y2}	0.1	0.1	0	0	0	0	0	0.1	0	0	0	0	0	0	0	0	0	0.1	0	0	0	0	0.1
% recrudescent infection _{y5}	0.7	0.2	0	0.1	-0.1	0	0.1	0.2	0	0	0.1	0.1	0	-0.1	0	0	-0.1	0	0.1	0	0	0	0.1
% recrudescent infection _{y8}	0.5	0.1	0	0.1	-0.4	0	0.1	0.2	0	0	0	0	0	-0.1	0	0	0	0	0.3	0	0.1	0	0
% recrudescent infection _{y10}	0.4	0.1	0	0	-0.5	0	0.1	0.1	0	0	0	0	0	-0.1	0	0	0	0.4	0	0	0.1	0	0
Prevalence _{y2}	0.6	0.2	0	-0.2	0	0	0	0.2	0	0	0.1	0.1	0	0.2	0	0	0	0	0	0	0	0	-0.2
Prevalence _{y5}	0.7	0.2	0	0	-0.1	0	0.1	0.2	0	0	0.1	0.1	0	0	0	0	-0.1	0	0	0	0	0	0
Prevalence _{y8}	0.7	0.2	0	0	-0.1	0	0.2	0.2	0	0.1	0	0.1	0	0	0	0	0	0.1	0.1	0	0	0	0
Prevalence _{y10}	0.7	0.2	0	0	-0.1	0.2	0.2	0.2	0	0.1	0	0.1	0	0	0	0	0	0.1	0.1	0	0	0	0
Resistance _{y2}	0.7	0.2	0	0.1	0	0	0	0.2	0	0	0.1	0.1	0	0	0	0	0	0	0	0	0	0	0.2
Resistance _{y5}	0.7	0.1	0	0.2	-0.1	0	0	0.2	0	0	0.1	0.1	0	-0.1	0	0	0	0	0.1	0	0	0	0.2
Resistance _{y8}	0.1	0	0	0.4	-0.1	0	0	0	0	0	0	0	0.1	-0.2	0.1	-0.1	0	-0.1	0.1	0	0	0	0
Resistance _{y10}	0.3	0	0	0.1	0	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0	0	0	0

Table A11-3: The partial rank correlation coefficients of the input parameters and the outcomes in low transmission setting with ACT (Scenario B)

Outputs	Input parameters																						
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	I17	I18	I19	I20	I21	I22	I23
EIR _{y2}	0.8	0.1	0	0	0	0	0	0.3	0	0	0.1	0.1	0	0	0	0	0	0	0	0	0	0	-0.1
EIR _{y5}	0.8	0.1	0	-0.1	-0.1	0	0	0.3	0.1	0	0.1	0.1	0	0.1	0	0	0	0	0	0	0	0	0
EIR _{y8}	0.8	0.1	0	0	-0.1	0	0.1	0.2	0.1	0	0.1	0.1	0	0	0	0	0	0	0	0	0.1	0	0
EIR _{y10}	0.8	0.1	0	0	-0.1	0	0.1	0.2	0.1	0	0.1	0.1	0	0	0	0	0	0	0	0	0.1	0	0
% treated infection _{y2}	0.6	0.1	0	0.4	0	0	0	0.2	0	0	0.1	0	0	0	0	0	0	0	0	0	0	0	-0.1
% treated infection _{y5}	0.5	0.1	0	0.5	0	0	0	0.2	0.1	0	0.1	0.1	0	0	0	0	0	0	0	0	0	0	0
% treated infection _{y8}	0.6	0.1	0	0.5	-0.1	0	0	0.2	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0.1	0	0
% treated infection _{y10}	0.6	0.1	0	0.4	-0.1	0	0.1	0.2	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0.1	0	0
% recrudescent infection _{y2}	0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.9	0	0	0	0	0
% recrudescent infection _{y5}	0.4	0.1	0	0	-0.3	0	0	0.1	0	0	0.1	0	0	0	0	0	0	0.1	0	0.1	0.4	0.1	0.2
% recrudescent infection _{y8}	0.5	0.1	0	0.1	-0.3	0	0	0.1	0	0	0.1	0	0	0	-0.1	0	0	0	0.1	0	0.5	0	0.2
% recrudescent infection _{y10}	0.4	0.1	0	0.1	-0.3	0	0	0.1	0	0	0	0	0	-0.1	0	0	0	0	0.1	0	0.6	0	0.1
Prevalence _{y2}	0	0.2	0	-0.2	0	0	0	0.2	0	0	0.1	0.1	0	0.2	0	0	0	0	0	0	0	0	-0.2
Prevalence _{y5}	0.6	0.2	0	-0.2	-0.1	0	0	0.2	0.1	0	0.1	0.1	0	0.2	0	0	0	0	0	0	0.1	0	0
Prevalence _{y8}	0.6	0.2	0	-0.1	-0.2	0	0.1	0.2	0.1	0	0.1	0.1	0	0.2	0	0	0	0	0	0	0.1	0	0.1
Prevalence _{y10}	0.6	0.2	0	-0.1	-0.2	0	0.1	0.2	0.1	0	0.1	0.1	0	0.1	0	0	0	0	0	0	0.1	0	0
Resistance _{y2}	0.7	0.2	0	0.1	0	0	0	0.2	0	0	0.1	0.1	0	0	0	0	0	0	0.1	0	0	0	0.2
Resistance _{y5}	0.6	0.1	0	0.1	-0.2	0	0	0.2	0	0	0.1	0	0.1	-0.2	0	0	0	0	0.1	0	0.2	0.1	0.2
Resistance _{y8}	0.6	0.1	0	0.1	-0.2	0	0.1	0.2	0.1	0	0.1	0	0.1	-0.2	0	0	0	0	0.1	0	0.2	0	0.3
Resistance _{y10}	0.6	0.1	0	0.1	-0.2	0	0.1	0.2	0.1	0	0.1	0	0.1	-0.2	0	0	0	0	0.1	0	0.2	0	0.3

Table A11-4: The partial rank correlation coefficients of the input parameters and the outcomes in high transmission setting with monotherapy (Scenario C)

Outputs	Input parameters																							
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	I17	I18	I19	I20	I21	I22	I23	
EIR _{y2}	0.2	0.1	0	0	0	0.4	0	0.4	0	0	0.5	0.1	0	0.1	0	0	0	0	0	0	0	0	0	-0.1
EIR _{y5}	0.2	0.1	0	0	0	0.4	0	0.4	0	0	0.5	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0
EIR _{y8}	0.2	0.1	0	0	0	0.4	0	0.4	0	0	0.5	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0
EIR _{y10}	0.2	0.1	0	0	0	0.4	0	0.4	0	0	0.5	0.1	0	0.1	0	0	0	0	0	0	0	0	0	0
% treated infection _{y2}	-0.2	-0.2	0	0.1	0	-0.4	0	-0.3	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0	0.2
% treated infection _{y5}	-0.2	-0.3	0	0.2	0	-0.4	0	-0.4	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0	-0.1
% treated infection _{y8}	-0.2	-0.3	0	0.2	0	-0.4	0	-0.4	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0	-0.1
% treated infection _{y10}	-0.2	-0.3	0	0.2	0	-0.4	0	-0.4	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0	-0.1
% recrudescent infection _{y2}	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.8	0	0	0	0	0.2
% recrudescent infection _{y5}	0	0	0	0	-0.1	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0.2	0.1	0	0	0	0.8
% recrudescent infection _{y8}	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0.2	0.1	0	0	0.7
% recrudescent infection _{y10}	0	0	0	0	-0.3	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0.2	0.1	0	0	0.6
Prevalence _{y2}	0.1	0.3	0	0	0	0.3	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0	-0.3
Prevalence _{y5}	0.2	0.3	0	0	0	0.4	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0	0.1
Prevalence _{y8}	0.2	0.3	0	0	0	0.4	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0	0.1
Prevalence _{y10}	0.2	0.3	0	0	0	0.4	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0	0.1
Resistance _{y2}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0	0	0	0	0.9
Resistance _{y5}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	0	0.9
Resistance _{y8}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	0	0.9
Resistance _{y10}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	0	0.8

Table A11-5: The partial rank correlation coefficients of the input parameters and the outcomes in high transmission setting with ACT (Scenario D)

Outputs	Input parameters																						
	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	I17	I18	I19	I20	I21	I22	I23
EIR _{y2}	0.8	0	0	0	0	0	0	0.3	0	0	0	0.1	0	0	0	0	0	0	0	0	0	0	0
EIR _{y5}	0.2	0.1	0	0	0	0.4	0	0.4	0	0	0.5	0.1	0	0.1	0	0	0	0	0	0	0	0	0
EIR _{y8}	0.2	0.2	0	-0.1	0.1	0.3	0	0.4	-0.1	0	0.4	0.1	0	0.1	0	0	0	0	0	0	0	0	0
EIR _{y10}	0.2	0.1	0	0	0	0.4	0	0.4	0	0	0.5	0.1	0	0.1	0	0	0	0	0	0	0	0	0
% treated infection _{y2}	-0.2	-0.2	0	0.1	0	-0.4	0	-0.4	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0.2
% treated infection _{y5}	-0.2	-0.3	0	0.2	0	-0.4	0	-0.4	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0
% treated infection _{y8}	-0.2	-0.3	0	0.2	-0.1	-0.3	0	-0.4	0.1	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	-0.1
% treated infection _{y10}	-0.2	-0.3	0	0.2	0	-0.4	0	-0.4	0	0	-0.4	-0.1	0	-0.2	0	0	0	0	0	0	0	0	0
% recrudescent infection _{y2}	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2
% recrudescent infection _{y5}	0	0	0	0	-0.1	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0	0.2	0	0.6
% recrudescent infection _{y8}	0	0	0	0	-0.1	0	0	0	0	0	0	0	0	-0.1	0	0	0	0.1	0	0	0.4	0	0.6
% recrudescent infection _{y10}	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0	0.4	0	0.5
Prevalence _{y2}	0.1	0.3	0	0	0	0.3	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	-0.3
Prevalence _{y5}	0.1	0.3	0	0	0	0.4	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0
Prevalence _{y8}	0.1	0.3	0	0	0	0.4	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0.1
Prevalence _{y10}	0.2	0.3	0	0	0	0.4	0	0.3	0	0	0.4	0.1	0	0.3	0	0	0	0	0	0	0	0	0
Resistance _{y2}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.1	0	0	0	0	0	0	0	0	0.9
Resistance _{y5}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	0.9
Resistance _{y8}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	0.9
Resistance _{y10}	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.2	0	0	0	0	0	0	0	0	0.9

Table A11-6: The results of the sensitivity analysis shown as the statistical summaries of the outcomes in the 4 scenarios

Output		Scenario			
		A	B	C	D
EIR _{y2}	Mean	0.08	0.08	107.95	108.69
	Median	0.05	0.05	89.48	90.91
	Var	0.01	0.01	4527.54	4469.25
	SD	0.09	0.09	67.29	66.85
	SE	0.00	0.00	0.95	0.95
	CV	108.26	110.80	62.33	61.51
EIR _{y5}	Mean	0.50	0.05	119.10	115.90
	Median	0.10	0.03	100.45	97.44
	Var	0.57	0.01	4932.30	4844.75
	SD	0.75	0.08	70.23	69.60
	SE	0.01	0.00	0.99	0.98
	CV	149.25	153.62	58.97	60.05
EIR _{y8}	Mean	0.70	0.08	126.90	121.30
	Median	0.38	0.04	108.30	103.52
	Var	0.61	0.02	5230.75	5113.17
	SD	0.78	0.14	72.32	71.51
	SE	0.01	0.00	1.02	1.01
	CV	111.16	159.45	56.99	58.95
EIR _{y10}	Mean	0.71	0.09	128.63	122.37
	Median	0.40	0.04	110.26	104.72
	Var	0.61	0.02	5273.86	5159.80
	SD	0.78	0.14	72.62	71.83
	SE	0.01	0.00	1.03	1.02
	CV	101.51	151.10	56.46	58.70
Treated infection _{y2} (%)	Mean	86.20	86.11	6.43	6.41
	Median	85.95	85.86	6.01	5.97
	Var	22.15	22.20	3.87	3.71
	SD	4.71	4.71	1.97	1.93
	SE	0.07	0.07	0.03	0.03
	CV	5.46	5.47	30.62	30.04
Treated infection _{y5} (%)	Mean	86.87	84.48	5.87	6.09
	Median	86.70	84.08	5.61	5.69
	Var	28.52	16.41	1.84	2.80
	SD	5.34	4.05	1.36	1.67
	SE	0.08	0.06	0.02	0.02
	CV	6.15	4.79	23.11	27.47
Treated infection _{y8} (%)	Mean	88.36	85.36	5.61	5.88
	Median	88.93	84.74	5.40	5.54
	Var	29.44	23.65	1.35	2.33
	SD	5.43	4.86	1.16	1.53
	SE	0.08	0.07	0.02	0.02
	CV	6.14	5.70	20.75	25.99
Treated infection _{y10} (%)	Mean	88.57	85.72	5.55	5.83
	Median	89.10	85.18	5.35	5.49
	Var	28.46	24.54	1.23	2.25
	SD	5.33	4.95	1.11	1.50
	SE	0.08	0.07	0.02	0.02
	CV	6.02	5.78	19.96	25.69

(Table A11-6 continued: *The results of the sensitivity analysis shown as the statistical summaries of the outcomes in the 4 scenarios*)

Output	Scenario				
	A	B	C	D	
Recrudescence infection _{Y2} (%)	Mean	2.97	2.93	4.02	4.03
	Median	2.99	2.94	4.01	4.01
	Var	0.63	0.60	1.13	1.12
	SD	0.80	0.78	1.06	1.06
	SE	0.01	0.01	0.02	0.01
	CV	26.83	26.48	26.44	26.34
Recrudescence infection _{Y5} (%)	Mean	16.00	3.88	15.01	7.23
	Median	16.52	3.14	11.97	5.77
	Var	62.18	5.60	102.82	15.90
	SD	7.89	2.37	10.14	3.99
	SE	0.11	0.03	0.14	0.06
	CV	49.30	60.93	67.58	55.13
Recrudescence infection _{Y8} (%)	Mean	23.33	6.93	22.40	9.95
	Median	23.89	6.37	28.25	9.72
	Var	10.76	12.47	119.32	24.44
	SD	3.28	3.53	10.92	4.94
	SE	0.05	0.05	0.15	0.07
	CV	14.06	50.95	48.77	49.69
Recrudescence infection _{Y10} (%)	Mean	24.30	8.28	24.71	10.85
	Median	24.30	8.25	29.68	10.94
	Var	3.84	12.11	102.73	24.02
	SD	1.96	3.48	10.14	4.90
	SE	0.03	0.05	0.14	0.07
	CV	8.06	42.05	41.01	45.17
Prevalence _{Y2} (%)	Mean	0.74	0.72	36.33	36.65
	Median	0.63	0.62	34.55	35.21
	Var	0.13	0.12	116.42	118.70
	SD	0.36	0.35	10.79	10.90
	SE	0.01	0.00	0.15	0.15
	CV	48.79	48.10	29.70	29.73
Prevalence _{Y5} (%)	Mean	3.81	0.70	41.27	40.53
	Median	1.61	0.56	40.04	39.37
	Var	15.95	0.25	111.24	117.35
	SD	3.99	0.50	10.55	10.83
	SE	0.06	0.01	0.15	0.15
	CV	104.83	71.67	25.56	26.73
Prevalence _{Y8} (%)	Mean	4.60	0.88	43.20	42.11
	Median	3.47	0.65	42.20	41.04
	Var	14.93	0.47	112.45	119.37
	SD	3.86	0.68	10.60	10.93
	SE	0.05	0.01	0.15	0.15
	CV	83.96	77.86	24.54	25.95
Prevalence _{Y10} (%)	Mean	4.63	0.91	43.62	42.44
	Median	3.52	0.68	42.65	41.48
	Var	14.74	0.48	112.11	119.83
	SD	3.84	0.69	10.59	10.95
	SE	0.05	0.01	0.15	0.15
	CV	82.87	75.89	24.27	25.79

(Table A11-6 continued: *The results of the sensitivity analysis shown as the statistical summaries of the outcomes in the 4 scenarios*)

Output		Scenario			
		A	B	C	D
Resistance _{y2} (%)	Mean	3.21	3.04	2.46	2.40
	Median	2.20	2.12	1.83	1.77
	Var	8.21	5.96	3.15	3.01
	SD	2.87	2.44	1.77	1.74
	SE	0.04	0.03	0.03	0.02
	CV	89.29	80.26	72.14	72.21
Resistance _{y5} (%)	Mean	71.55	33.99	46.23	43.87
	Median	86.85	24.64	39.70	33.80
	Var	952.18	587.88	1454.48	1404.80
	SD	30.86	24.25	38.14	37.48
	SE	0.44	0.34	0.54	0.53
	CV	43.13	71.34	82.50	85.44
Resistance _{y8} (%)	Mean	96.49	65.25	69.43	67.12
	Median	99.93	67.95	94.93	91.73
	Var	74.91	795.96	1456.21	1492.60
	SD	8.65	28.21	38.16	38.63
	SE	0.12	0.40	0.54	0.55
	CV	8.97	43.24	54.96	57.56
Resistance _{y10} (%)	Mean	99.30	78.25	77.01	74.80
	Median	99.98	88.97	99.41	98.79
	Var	7.56	578.19	1231.03	1302.96
	SD	2.75	24.05	35.09	36.10
	SE	0.04	0.34	0.50	0.51
	CV	2.77	30.73	45.56	48.26

ANNEX 12 Additional results from scenario analysis modelling

Table 12-1: Cumulative costs, effects and cost-effectiveness of switching to drug AB (artesunate + SP) from SP at 20% resistance to drug A (SP)

	Cumulative costs and effects											
	After 1 year			After 5 years			After 10 years					
	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)	Mono-therapy	ACT	Difference (ACT-Mono)
Number of treated cases	739	725	-14	5,107	3,337	-1,770	19,438	6,296	-13,142			
Number of recrudescences	21	21	0	688	103	-585	4,316	218	-4,098			
Number of severe cases	33	32	1	342	150	-193	1,682	292	-1,390			
Number of deaths	7	6	0	68	30	-39	336	58	-278			
Number of DALYs	175	172	3	1,828	793	-1,034	9,026	1,551	-7,475			
Cost of drug	53	780	-727	339	3,393	3,054	1,169	5,980	4,811			
Direct cost of malaria	4,068	4,725	-657	34,213	20,645	-13,569	142,927	36,962	-105,965			
Total cost (indirect and direct)	10,081	10,629	-548	77,905	46,427	-31,478	308,952	82,704	-226,248			
	Incremental drug cost of ACT per consequence averted											
Cost of drug (US\$) per	After 1 year			After 5 years			After 10 years					
- case averted		-52.0			1.7			0.4				
- recrudescence averted		-			5.2			1.2				
- severe infection averted		1328.8			15.9			3.5				
- death averted		6643.8			79.3			17.3				
- DALY averted		253.1			3.0			0.6				

Table 12-2: Cumulative costs, effects and cost-effectiveness of switching to drug BC (artemether-lumefantrine) from SP at 20% resistance to drug A (SP)

	Cumulative costs and effects											
	After 1 year				After 5 years				After 10 years			
	Mono-therapy	ACT	Difference (ACT-Mono)		Mono-therapy	ACT	Difference (ACT-Mono)		Mono-therapy	ACT	Difference (ACT-Mono)	
Number of treated cases	739	755	16	5,107	3,252	-1,855		19,438	5,972	-13,466		
Number of recrudescences	21	21	0	688	82	-606		4,316	102	-4,214		
Number of severe cases	33	34	1	342	145	-197		1,682	264	-1,419		
Number of deaths	7	7	0	68	29	-39		336	53	-283		
Number of DALYs	175	179	4	1,828	768	-1,060		9,026	1,398	-7,627		
Cost of drug	53	1,375	1,322	339	5,615	5,276		1,169	9,635	8,466		
Direct cost of malaria	4,068	5,472	1,405	34,213	22,346	-11,868		142,927	38,141	-104,786		
Total cost (indirect and direct)	10,081	11,599	1,517	77,905	47,377	-30,528		308,952	80,844	-228,108		
	Incremental drug cost of ACT per consequence averted											
Cost of drug (US\$) per	After 1 year*				After 5 years				After 10 years			
- case averted		-82.6				2.8				0.6		
- recrudescence averted		-				8.7				2.0		
- severe infection averted		-1769.4				26.7				6.0		
- death averted		-3183.9				133.7				29.9		
- DALY averted		-333.0				5.0				1.1		

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