Malaria control for Afghans in Pakistan and Afghanistan (1990-2005): a mixed-methods assessment considering effectiveness, efficiency, equity, and humanity

NATASHA HOWARD

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Department of Disease Control

Faculty of Infectious and Tropical Diseases

London School of Hygiene & Tropical Medicine

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Research group affiliations: None

DECLARATION

I, Natasha Howard, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

NATASHA HOWARD

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Introduction

I began Doctor of Public Health (DrPH) studies at the London School of Hygiene & Tropical Medicine (LSHTM) in October 2005. I chose the DrPH over a PhD because the DrPH was designed for those of us whose career plans involved a broader range of global public health activities than academic research alone. DrPH training consisted of three components: (i) a taught component of three compulsory doctoral-level modules and three elective masters-level modules of five weeks each; (ii) an organisational attachment of 3-6 months and research report of not more than 12,000 words; and (iii) a research project of approximately eighteen months and thesis of not more than 50,000 words.

Due to unavoidable work and life commitments during the past twelve years, I took several years of formal and informal study interruptions. This potentially makes me one of the longest-enrolled research degree students in LSHTM's history. University regulations have since changed, to force timely completion by students like me who encounter unanticipated difficulties. In hindsight, a PhD would have been a more straightforward option.

Taught component

The first two compulsory doctoral modules completed were *4005/4006* (now reorganised as one five-week module *5002): Evidence-Based Public Health Practice*. The aim was 'to enable students to locate, assess, synthesize, present and use research-based information to improve public health in a range of settings.' These modules focused on applying research evidence to public health policy-making and examining the processes involved, from collecting appropriate evidence through agenda setting to how changes occur in policy and practice. This was similar to modules I had taken during my MSc, but provided greater depth, and I have since been able to apply elements learnt to my own teaching and research projects.

The third compulsory five-week doctoral module completed was *4004: Leadership and Organisational Management*, since renamed *5001: Understanding leadership, management and organisations.* Its aim was 'to provide students with opportunities to explore a range of issues and theories relating to management, leadership and organisations, to consider the application of these theories in public health organisations and to their own management practice, and to develop an understanding of themselves as leaders and managers in public health.' This module

focused on organisational management theory and practice, e.g. strategic and change management, and personal leadership development. I learnt a number of useful skills, including how to implement and interpret managerial analyses (e.g. SWOT analysis). I was able to apply this to the organisational attachment report and subsequent teaching and consultancy work. It also helped in applying an evaluation framework to the interventions included in this thesis (i.e. Chapter 7).

The three MSc modules I completed as part of my coursework were: (i) *PH208: Financial Management*; (ii) *3141: Vector Sampling, Identification & Incrimination*; and (iii) *1807: Principles and Practice of Health Promotion*. I chose module PH208 as the topic was not sufficiently covered in the doctoral modules and have since been able to apply some of the skills developed in consultancy work and to the costing sections of Chapter 3. I chose module 3141 to improve my ability to identify and differentiate malaria vectors, which was extremely useful on its own, and I was able to apply some of it to chapter background sections (e.g. Chapter 1). I chose module 1807 to deepen my knowledge of health promotion theory and methods, some of which were applicable to Chapter 5 on insecticide-treated net purchasing and the discussion (Chapter 7). Completion of three elective MSc modules is no longer required, which could help speed completion of the degree.

I additionally attended three MSc modules to strengthen my technical and theoretical grounding in specific subject areas necessary to the thesis, which could not be included as course modules due to timing and prerequisites. These were: (i) *1103: Introduction to Health Economics*; (i) *1501: Economic evaluation*; and (ii) *3189: Ethics, Public Health & Human Rights*. Module 1103 was a prerequisite for module 1501, and could not be taken the first year as timing conflicted with doctoral modules, while the latter helped provide the necessary analytical skills to complete Chapter 3. Module 3189 helped with the analysis of equity and humanity considerations in Chapter 7.

As an unforeseen benefit of being a self-funded student and later academic staff-member, I had opportunities to develop, organise, and teach on a number of other MSc modules, several of which were relevant to my DrPH studies. For example, I organised PHM101 *Basic Epidemiology* and PHM104/IDM403 *Health Management* for three years and GHM104 *Issues in Global Health Policy* for a year. I co-organised SM3457 *Designing Disease Control Programmes in Developing Countries* for four years and taught on SM3196 *Analysis & Design of Research Studies* and SM1402 *Conflict & Health.* Additionally, I co-authored the second edition of *Introduction to*

Epidemiology with Ilona Carneiro[1], developed the textbook and module for PHM214 Conflict & Health[2], and coordinated development of the distance learning MSc course in Global Health Policy. These additional teaching and development opportunities deepened my understanding of broader contextual, programmatic, and policy issues, which related to the thesis topic.

Organisational and Policy Analysis (OPA) project

For my organisational attachment, I worked at the Malaria Consortium in London for six months supervised by Global Technical Director Dr Sylvia Meek. Established in 2003, the Malaria Consortium describes itself as "*one of the world's leading non-profit organisations specialising in the prevention, control and treatment of malaria and other communicable diseases among vulnerable populations*." As my primary deliverable, we prepared a technical report on malaria financing mechanisms for the All-Party Parliamentary Malaria Group now the All-Party Parliamentary Group on Malaria and Neglected Tropical Diseases (APPMG)[3]. The Rt. Honourable Hilary Benn, then Secretary of State for International Development, launched the report on 15 March 2007 at the Palace of Westminster.

This second APPMG report used evidence presented to the group during the previous year to advocate for mobilising US$3.2 billion annually from all donors to meet the malaria-related Millennium Development Goals and Abuja targets for the 82 most-affected countries. It recommended creating and/or strengthening global financing mechanisms (e.g. Aid Guarantee Facility, Affordable Medicines Facility, International Finance Facility, debt conversion, UNITAID, air ticket solidarity levy) to fill the gap between existing funding, reported as US$600 million for 2004, and the US$3.2 billion estimated as necessary to meet global targets[3].

My professional attachment report, now called an organisational and policy-analysis report, was titled *Piloting advocacy evaluation*. Its aim was examine how the Malaria Consortium could measure its effectiveness in international advocacy, using its role in development of the malaria financing report as a case study[4]. The APPMG report was aimed at influencing policy change on aid financing through data-driven advocacy, while the implicit social-change purpose was improving the lives of the poorest in Africa. Data were collected by participant-observation, key informant interviews, and document review. Data were analysed thematically, informed by an adaptation of the Anne E Casey Foundation framework proposed by Reisman *et al*[5-7].

DrPH research thesis

As a self-funded student and lone parent, I was not able to travel to collect my own data. Therefore, I drew from existing operational research data from HealthNet International (now Health Works) in Afghanistan and Pakistan, an organisation for which I had worked and with which I had completed my MSc research. Completion of the thesis required a range of quantitative and qualitative analytical skills, given the diversity of the datasets available. I prepared each results chapter for submission as an article, allowing the thesis development process to serve a dual purpose.

Conclusions

Despite the challenges and frustrations I encountered, successful completion of this degree will definitely be worthwhile. I believe that the very circuitous route that I have taken to reach this stage, while I would not recommend it to others, has contributed to making me a more capable global public health researcher and leader. The objective of initiating the DrPH programme at LSHTM was to develop future global public health leaders, recognising that strong research skills are necessary but insufficient and the abilities to translate research evidence into meaningful engagement with diverse audiences and the leadership to inspire and manage large initiatives and teams, were equally vital. This is still an idea that I support and I think that the DrPH course, including my many tangents, has equipped me well for the next stages in a global health career.

ABSTRACT

Increased global attention and funding has provided opportunities to strengthen malaria control. One cross-border control programme researched a range of prevention and treatment interventions over twenty years to reduce the malaria burden for Afghans in Pakistan and Afghanistan. Malaria in these areas is unstable and seasonal. Primary vectors include *Anopheles culicifacies, An. fluviatilis*, and *An. stephensi*. Objectives were to evaluate malaria control interventions in refugee settlements in Northwest Pakistan and returnee settlements in Eastern Afghanistan. Findings offer lessons for programmes in other fragile and conflict-affected settings, while helping inform regional and global malaria control efforts.

A mixed-methods study design included two study sites. The northwest Pakistan site covered 248 camps on malarious land near the Afghan border. The eastern Afghanistan site covered 200 villages near Jalalabad. As the national border separating study sites was relatively porous and both populations mobile, there were no notable sociodemographic differences between sites. Notable differences related to national malaria control policies, infrastructure, and priorities. Data were collected as part of operational research by HealthNet-Transcultural Psychosocial Organisation (HNTPO) between 1990 and 2005. Economic and quantitative data were analysed using Microsoft Excel™ and Stata®11-14. Qualitative data were analysed thematically using inductive and deductive coding.

Cost-effectiveness analysis of adding indoor residual spraying to case management in Pakistan (1990-95) showed favourable incremental cost-effectiveness ratios per case prevented and DALY averted. A clinical trial of extended-dose chloroquine in Pakistan (1998) showed that while increasing chloroquine dosage reduced recrudescence, approximately 50% failure was still too high for first-line treatment. Qualitative analysis of men's and women's perspectives on malaria prevention during the Taliban regime in Afghanistan (2000), showed women and men had similar knowledge, while lack of money was a major disincentive to ITN purchasing. Clinical and epidemiological analysis of pregnant and reproductive-age women in Afghanistan (2004-2005), showed malaria prevalence was much lower than anaemia prevalence in pregnancy and women were well-informed about malaria risks, but their autonomy was limited.

Key findings are discussed in relation to the study framework, providing overall lessons, implications, and potential limitations.

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ABBREVIATIONS

ACBAR	Agency Coordinating Body for Afghan Relief
ACPR	Adequate clinical and parasitological cure rate
ACT	Artemisinin-based combination therapy
AIM	*Action and investment to defeat malaria (2016-2030)*
ANC	Antenatal Care
AOR	Adjusted odds ratio
AZG	Artsen zonder Grenzen
BHC	Basic Health Centre (Afghanistan)
BHU	Basic Health Unit (Pakistan)
BPHS	Basic Package of Health Services
CEA	Cost-effectiveness analysis
CFR	Case fatality rate
CM	Case management
CQ	Chloroquine
DAC	Development Assistance Committee
DALY	Disability-Adjusted Life Year
DDT	Dichloro-diphenyl-trichloroethane
DFID	UK Department for International Development
DHLG	Days of healthy life gained
EA	Economic analysis
EC	European Commission
ECHO	Humanitarian Aid Office of the European Union
EMRO	Eastern Mediterranean Region Office-WHO
EPI	Expanded Programme on Immunisation
ETF	Early treatment failure
FCT	Fever clearance time
FGD	Focus group discussion
Gavi	The Vaccine Alliance
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
g	gram
GSK	Glaxo Smith Kline
GTS	Global Technical Strategy for Malaria
Hb	haemoglobin
HIS	Health Information System
HIV	Human Immunodeficiency Virus
HNTPO	Healthnet-Transcultural Psychosocial Organization
ICER	Incremental cost-effectiveness ratio
IDI	In-depth interview
IDPF	International Drug Purchase Facility
IFF	International Finance Facility
IMF	International Monetary Fund
IPR	Intellectual Property Rights
IPT	Intermittent Preventive Treatment
IPTi	Intermittent Preventive Treatment for Infants
IPTp	Intermittent Preventive Treatment in Pregnancy
IRS	Indoor residual spraying
ITN	Insecticide-treated mosquito net
IV	Intravenous
KAP	Knowledge, attitudes and practices
kg	Kilogram
KPK	Khyber-Pakhtunkhwa province
l	Litre
LBW	Low-birthweight
LLIN	Long-lasting insecticidal net
LSHTM	London School of Hygiene & Tropical Medicine
LTF	Late treatment failure
MAP	Malaria Atlas Project
MDGs	Millennium Development Goals
µg	Microgram
mg	Milligram
MMV	Medicines for Malaria Venture
MOH	Ministry of Health
MoPH	Ministry of Public Health
MSF	Médecins Sans Frontières
NB	*nota bene* (note well)
NGO	Non-Governmental Organisation
NWFP	North-West Frontier Province
ODA	Official Development Assistance
OR	Odds ratio
PCR	Polymerase chain reaction
PDH	Project Department for Health
P.	Plasmodium
PMI	US President's Malaria Initiative
PO	*per os* (by mouth)
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
SDGs	Sustainable Development Goals
SEQ	Socioeconomic quartile
SES	Socioeconomic status
SP	Sulfadoxine-pyrimethamine
SSA	Sub-Saharan Africa
t.i.d.	*ter in die* (3x daily)
TNY	Treated net years
UK	United Kingdom
UN	United Nations
UNICEF	United Nations Children's Fund
USA	United States of America
USAID	United States Agency for International Development
US-CDC	US Centers for Disease Control and Prevention
WB	World Bank
WBC	White blood cells
WHO	World Health Organisation
WTO	World Trade Organisation
WRA	Woman of reproductive age
YHLG	Years of healthy life gained

CHAPTER 1 INTRODUCTION

Overview

The aim of this thesis is to assess several interventions implemented by the malaria control programme provided for Afghans during the period 1990 to 2005, primarily considering effectiveness, but also aspects of efficiency, equity, and humanity. The thesis is divided into seven chapters. Chapters 1 and 2 cover background and methods. Chapters 3 to 6 cover sub-study results. Chapter 7 draws on sub-studies and an evaluation framework to synthesise key results and provide overall discussion and conclusions.

This introductory chapter provides background context. The first section summarises relevant malaria control policies and strategies. The second section describes malaria epidemiology and control efforts in Pakistan and Afghanistan, focusing on refugee settlements in Khyber-Pakhtunkhwa (KPK) province, formerly Northwest Frontier Province (NWFP), Pakistan and returnee settlements in Nangarhar Province Afghanistan. The third section describes the evaluation framework and research approaches selected. The fourth section examines the potential value of using operational data to inform policy and practice. The final section provides aim and objectives.

Malaria control policy and strategies

Malaria Control era achievements (1990-1999)

At the beginning of the 1990s, there were an estimated 300-500 million malaria cases and 1.5-2.7 million deaths annually[8]. Multidrug-resistant falciparum malaria was spreading, since its detection in Southeast Asia in the 1980s, threatening control efforts in other parts of the world[9]. The successes of the Global Eradication Campaign (1956-1969) had not been sustainable and a deteriorating situation convinced the World Health Organization (WHO) Executive Board to propose a Ministerial Conference on Malaria to mobilise the international community and affected countries to intensify malaria control efforts[8]. The Ministerial Conference on Malaria Control, held in Amsterdam in 1992, adopted a World Declaration on the Control of Malaria and Global Malaria Control Strategy that was confirmed by the World Health Assembly in 1993, and by the forty-ninth Session of the United Nations General Assembly in 1994[8]. This strategy differed from eradication era approaches in that it was grounded in the primary healthcare approach and called for flexible, decentralized programmes, based on disease rather than parasite control; strengthening of national capacities; and the rational and selective use of effective malaria control tools supported by operational research[8]. However, due to insufficient financial and human resources, the objective of reducing malaria mortality by at least 20% from the 1995 level in at least 75% of affected countries by the year 2000, was not achieved[8].

Millennium Development Goal era achievements (2000-2015)

Malaria gained increasing global attention during the Millennium Development Goal (MDG) period of 2000-2015, leading to significantly increased political commitments, expanded regional collaboration, availability of substantial and more predictable financing, and improved control interventions[10]. Between 2000 and 2015, increased control efforts contributed to a 41% reduction in malaria case incidence and a 62% reduction in malaria deaths globally[11]. The estimated number of malaria cases globally declined by 19% from 262 million in 2000 (range 205–316 million) to 212 million in 2015 (range 149–303 million), while estimated numbers of deaths declined by 49% from 839,000 (range 653,000-1.1 million) to 429,000 (range 236,000-635,000)[11]. Countries and territories considered endemic for malaria reduced from 108 to 91 during this period[11].

The malaria-specific target C of MDG 6, '*to have halted and begun to reverse the incidence of malaria globally by 2015*,' was achieved, with 57 countries meeting the World Health Assembly and Roll Back Malaria Partnership (RBM) target of reducing malaria incidence by 75% by the end of 2015[12]. Similarly, with global malaria incidence estimated to have decreased by 37% and the global malaria mortality rate estimated to have decreased by 60% between 2000 and 2015, substantial progress was made towards the World Health Assembly target of reducing the global malaria burden by 75% and the RBM target of reducing global malaria deaths to near zero by 2015[12].

Sustainable Development Goal era initiatives (2016-2030)

With the ending of the MDGs in 2015, and the transition to the era of the Sustainable Development Goals (SDGs) covering the years to 2030, affected countries and the international community have begun setting new malaria control goals and targets[13]. WHO's *Global Technical Strategy for Malaria 2016-2030* (GTS) and RBM's *Action and investment to defeat malaria 2016–2030: for a malaria-free world* (AIM) succeed the *Global Malaria Action Plan: for a malaria-free world 2008–2015*, with the aim of ensuring that global malaria trends remain on a downward trajectory[10, 11, 13].

The malaria-related SDG Target 3.3, '*by 2030 to end epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases, and combat hepatitis, water-borne diseases, and other communicable diseases*' relates to SDG 3 '*Ensure healthy lives and promote wellbeing for all at all ages*'[11]. WHO equates achieving this malaria component with attaining GTS and AIM targets by 2030, to: (i) reduce malaria incidence and mortality rates globally by at least 90% compared

with 2015 levels; (ii) eliminate malaria from at least 35 countries in which malaria was transmitted in 2015; and (iii) prevent re-establishment of malaria in all countries currently malaria free[11].

Malaria burden and the increased importance of vivax malaria

WHO has indicated that the main ongoing and emerging challenges in malaria control for the next decades are gaps in intervention coverage, health system weaknesses and resource constraints, insecticide and antimalarial resistance, slower transmission declines in high-burden countries, and increasing vivax malaria risks[11].

Despite major improvements, malaria remains a significant concern globally. Almost 3.3 billion people in 91 countries are still estimated to be at risk[11, 13]. Malaria remains a leading infectious cause of death worldwide, along with respiratory infections, human immunodeficiency virus (HIV), diarrhoeal diseases, and tuberculosis[13]. Recent estimates indicated 212 million malaria cases (range 148-304 million) and 429,000 deaths (range 235,000–639,000) in 2015[11]. Most 2015 malaria cases (88%) and deaths (92%) were estimated to have occurred in the WHO African Region, followed by the WHO South-East Asia Region (10% and 6% respectively) and the Eastern Mediterranean Region (2% of both cases and deaths), which includes Afghanistan and Pakistan[11].

Of the five Plasmodia species known to infect humans[14], *Plasmodium falciparum* followed by *P. vivax* causes an estimated 90% of human malaria infections worldwide[11]. *P. falciparum* is most prevalent on the African continent and responsible for most malaria deaths. However, *P. vivax* has a wider geographical distribution, because it survives in higher altitudes and cooler climates and has a dormant hypnozoite liver stage that enables it to persist for extended periods in the absence of Anophelines, e.g. during winter, and cause relapsing symptoms months later[11, 12]. About 4% of estimated cases globally, and 41% outside the African continent, are caused by *P. vivax* [11].

Most researchers and policy-makers focus on *P. falciparum* in sub-Saharan Africa, which is responsible for approximately 90% of both global malaria cases and global malaria mortality[11, 13, 15-17]. However, as the global malaria burden reduces, this focus is beginning to broaden. Malaria still poses a significant burden to populations in parts of Asia and South America, partly because vivax malaria is not as benign as was once thought[18-26]. Vivax malaria remains a significant public health issue in many parts of the world, including countries such as Afghanistan and Pakistan, causing an estimated 13.8 million cases globally in 2015[11]. Most vivax cases occur

in the WHO South-East Asia Region (58%) and Eastern Mediterranean Region (16%), with over 75% of global cases estimated to occur in just four countries, i.e. Ethiopia, India, Indonesia, and Pakistan [11].

Severe vivax cases and deaths have been reported from all endemic regions. In 2015, the total number of vivax malaria deaths globally was estimated at 3,100 (1,800-4,900) with 86% occurring outside sub-Saharan Africa[11]. Thus, the importance of vivax malaria appears to be growing, though information on population-attributable risks of severe disease and death due to *P. vivax* remains sparse, with further research required[20, 26, 27]. The four countries accounting for most vivax cases also accounted for 81% of estimated vivax deaths in 2015 (i.e. Ethiopia, India, Indonesia, Pakistan)[11].

Malaria control funding and cost-effectiveness estimates

The increased global commitment to malaria control is particularly noticeable in international and domestic funding increases. Average global commitments to malaria control in the 1990s ranged below US$100 million annually, increasing to an estimated US$0.3 billion in 2003, US$1.7 billion in 2009, and US$2.9 billion in 2015[11]. In 2015, the United States was the largest single international malaria control funder, accounting for approximately 35% of global funding, followed by the United Kingdom (16%), and France (3.2%)[11]. Approximately 45% of international funding is channelled through the Global Fund to Fight AIDS, Tuberculosis and Malaria[11]. Spending on malaria control commodities, e.g. artemisinin-based combination therapies (ACTs), rapid diagnostic tests (RDTs), insecticide treated mosquito nets (ITNs), insecticides and equipment for indoor residual spraying, was estimated to have increased from US$40 million in 2004 to US$1.6 billion in 2014, and accounted for 82% of international malaria spending in 2014[11, 12]. Domestic spending through national malaria control programmes in endemic countries, while still a relatively small proportion of total funding, increased to US$612 million in 2015 with malaria patient care another US$332 million[11].

WHO estimated that a cumulative 1.3 billion fewer malaria cases and 6.8 million fewer malaria deaths occurred globally between 2001 and 2015 than would have occurred had incidence and mortality rates remained at 2000 levels[11]. Malaria interventions are highly cost-effective, and with an estimated 70% of the cases averted between 2001 and 2015 due to malaria interventions, they provide some of the highest returns on public health investment[10, 11, 13]. When the Copenhagen Consensus Center initially ranked development options across all sectors by cost-effectiveness, malaria control investments were ranked among the top four development priorities[17]. Again, as part of the Post-2015 Consensus, halving global malaria

infections was identified as one of the 19 most cost-effective development targets across sectors[28]. In malaria-endemic countries, efforts to reduce and eliminate malaria are increasingly viewed as high-impact strategic investments for public health, poverty alleviation, equity, and development[10, 11]. Malaria elimination is being attempted in areas of unstable transmission, with the ultimate goal of global elimination encouraged by economic modelling estimates such as those done by the Copenhagen Consensus Center, increased investments in new control technologies, and initial successes in areas of Viet Nam and Zanzibar[28, 29]. An increasing number of countries are moving towards elimination, with only 13 countries estimated to have fewer than 1,000 malaria cases in 2000 and 19 countries estimated to have achieved this in 2015[11].

To achieve global targets, WHO estimated that annual global investments in malaria control and elimination need to increase to US$6.4 billion annually by 2020 to achieve a 40% reduction in malaria incidence and mortality rates, increase to US$7.7 billion by 2025 to achieve a 75% reduction, and increase to an estimated US$8.7 billion by 2030 to achieve a 90% reduction[10, 11]. However, current malaria funding, calculated at US$2.9 billion for 2015, remains far short of required estimates[11]. For example, while international funding for malaria control outside of Africa rose steeply from less than US$17 million in 2000 to US$300 million in 2010, the amount committed falls short of the resources required to achieve universal access to life-saving malaria prevention and control measures outside sub-Saharan Africa, estimated at approximately US$3 billion per year[11, 30].

Malaria control strategies and interventions

Increased funding has brought significant changes in antimalarial drug policies from monotherapies and limited ITN distribution to ACTs, mass distribution of ITNs, and corresponding declines in malaria incidence[28]. The *Global Technical Strategy for Malaria 2016-2030* is built on three pillars: (1), to ensure universal access to malaria prevention, diagnosis, and treatment; (2), to accelerate efforts towards elimination of malaria and attainment of malaria-free status; and (3), to transform malaria surveillance into a core intervention[10]. The core WHO-recommended control interventions advocated under Pillar 1 are quality-assured vector control, chemoprevention, and diagnostic testing and treatment[10, 11]. Elements of these interventions, specifically cost-effectiveness of indoor residual spraying, effectiveness of extended dosage chloroquine, acceptability of chemoprevention in pregnancy, and purchasing of ITNs are assessed in later chapters.

WHO now recommends implementing prevention and case management interventions in a complementary way: (i) prevention strategies based on vector control, and chemoprevention if

appropriate, and (ii) universal diagnosis and prompt effective treatment of malaria in public and private health facilities and at community level[10]. These interventions are time-tested and recommendations are not dramatically different from the WHO Global Malaria Programme recommendations for 2005-2015 to scale-up three primary interventions to help achieve Abuja Declaration and MDG targets: (i) diagnosis of malaria cases and treatment with effective medicines; (ii) distribution of ITNs to achieve full coverage of populations at risk of malaria; and (iii) indoor residual spraying (IRS), including, where indicated, the use of dichloro-diphenyl-trichloroethane (DDT)[17, 31-33].

The two most broadly applicable vector control interventions are ITNs, particularly long-lasting insecticidal nets (LLINs), and IRS. Preventive treatment interventions, which currently target falciparum malaria, suppress existing infections and prevent the consequences of parasitaemia [10]. The most widely researched is intermittent preventive treatment (IPT) of pregnant women. Universal diagnostic testing of all suspected cases requires parasitic confirmation by quality-assured microscopy or RDT, to prolong the effectiveness of WHO-recommended antimalarials, particularly ACTs[10]. Of the estimated 663 million cases averted globally between 2001-2015 due to malaria control interventions, 69% (range 63-73%) were estimated averted due to ITN usage, 21% (range 17-29%) due to ACT treatment, and 10% (range 6-14%) due to IRS[11, 12].

Insecticide-treated mosquito nets for malaria prevention

Considerable published research demonstrates the effectiveness and cost-effectiveness (efficiency) of ITNs and LLINs for malaria control in a variety of epidemiological settings[34-48]. Sleeping under ITNs has been shown to reduce malaria incidence and case fatality by an average of 50% and 20% respectively with average cost-effectiveness ratios of international $35-100 per disability adjusted life-year (DALY) averted at 95% coverage[11, 49]. ITN effectiveness against *P. vivax* incidence appears similar once relapses are accounted for, though DALY-based cost-effectiveness ratios are less informative due to much lower mortality rates for *P. vivax* of well below 1%[27, 50-54]. Real effectiveness and cost-effectiveness are lower, as ITN coverage rarely reaches 95%. However, most malaria endemic countries have adopted policies promoting universal access to ITNs, which has significantly improved coverage[11]. For example, WHO reports that an estimated 54% of Africans slept under ITNs in 2015 compared to 2% in 2000, though coverage of children under five (at 68%) remained below universal targets[11, 12].

Indoor residual spraying for malaria prevention

IRS has regained some of its former popularity in the past two decades. IRS, mainly using DDT, eliminated malaria as a public health issue in large areas of Asia, Europe, and the Americas

during the 1950s[55]. Despite continued controversy over the use of DDT for in-house spraying, a significant body of literature exists on the epidemiology and cost-effectiveness of IRS[39, 42, 56-86]. IRS protective efficacy is roughly 50%, though a Cochrane review put the range at 6-93% (the wide range appeared to be due to the limited number of studies meeting review criteria) and indicated that IRS may be more effective in unstable/seasonal transmission settings, such as many areas of South Asia[87]. Costs per person-year protected were calculated at about US$3-4, though this varied considerably with transmission levels and insecticide used[47, 86, 88]. However, IRS arguably requires significant technical capacity, structured programmes and sustainable financing, and implementation lags behind that for ITNs[55]. Additionally, transitions from pyrethroids to more expensive carbomates due to insecticide resistance, have contributed to reductions in spraying from a global peak of 5.7% coverage of populations at risk in 2010 to 3.1% in 2015[11]. Approximately 116 million people are currently protected by IRS worldwide[11, 12].

Intermittent preventive treatment in pregnancy for malaria chemoprevention

Chemoprevention among vulnerable groups is a key element of WHO's multipronged strategy to reduce the global malaria burden[10]. WHO-recommended malaria chemoprevention includes IPT of pregnant women (IPTp), IPT of infants (IPTi), and seasonal chemoprevention for children under 5 years, to suppress existing infections and prevent the consequences of parasitaemia[10]. At the time of the studies included here, IPTp was still being assessed in a variety of settings including South Asia, though it is now only recommended in areas of moderate-to-high malaria transmission in sub-Saharan Africa[89, 90].

Microscopy for malaria diagnosis

Accurate parasitic diagnosis and prompt treatment with effective antimalarials remain successful for case management, though clinical diagnosis and usage of ineffective first-line treatment drugs persist in many resource-constrained settings, including among private and informal providers in Pakistan and Afghanistan[91-94]. Diagnostic confirmation by quality-assured microscopy or RDT before treatment became an official WHO recommendation in 2010, strengthened in the current global technical strategy as universal diagnosis[10, 11]. However, the proportion of suspected cases receiving a diagnostic test at public facilities has remained relatively steady at around 65% in WHO's Eastern-Mediterranean region[11]. While microscopy requires more infrastructure and training than RDTs do, the lack in some malaria parasites of histidine rich protein 2 (HRP2, the most common target antigen used in RDTs to detect *P. falciparum*) first reported in 2010 in Peru and detected more broadly since, demonstrates the ongoing value of quality-assured microscopy[11]. However, WHO now recognizes that testing and safe radical treatment of vivax malaria requires two diagnoses: (i) the presence of *P. vivax*

parasites and (ii) glucose-6-phosphate dehydrogenase status, due to the risk of haemolytic anaemia in some populations, including those in South Asia[10].

Antimalarials for treatment

WHO now recommends that after diagnostic confirmation, all patients with uncomplicated *P. falciparum* malaria should be treated with quality-assured ACTs and, in areas where chloroquine-susceptible *P. vivax* is present (e.g. Pakistan and Afghanistan), uncomplicated non-falciparum malaria should be treated with either chloroquine (with primaquine for radical cure where feasible) or an ACT known to be effective in the area[10]. Prolific research programmes have contributed extensively to global malaria case-management policy and literature, with the original advocacy push for ACTs originating in Thailand[95, 96]. With artemisinin resistance confirmed in Cambodia in 2009 and observed in a further four Mekong sub-region countries, monitoring therapeutic efficacy and molecular markers of drug resistance and developing new antimalarials continue to be priorities[10, 11]. The economic literature related to malaria case-management is relatively extensive, particularly on diagnosis, drug resistance, and usage of ACTs in sub-Saharan Africa[58, 61, 63, 96-111].

Equity and humanity in malaria control

Malaria disproportionately affects the poorest, though causal mechanisms are complex[112]. Thus, equity has received increased attention in control programmes and research in the past decades[110, 113-124]. WHO defines equity as the absence of avoidable or remediable differences among groups of people, whether defined socially, economically, demographically, or geographically. Equity is a concept that combines equality, social justice, and fairness[125]. It thus involves more than just equality of health determinants, but also overcoming inequalities that infringe on human rights norms and fairness[126, 127]. Achieving health equity requires creating fair opportunities for health and eliminating gaps in health outcomes between different social groups[125]. As with most health equity literature, that for malaria control has focussed on distributive justice (e.g. access to interventions such as ITNs or diagnosis and treatment by those in need)[118, 128-133] and horizontal equity (e.g. all people in equivalent circumstances are treated equally) or vertical equity (e.g. those deemed at greatest need, such as biologically and economically high-risk groups, receive targeted support)[110, 113, 117, 118, 121, 122, 134-137].

Humanity is a multidimensional concept that lacks a specific definition in the context of health services provision, but generally draws from the four principles of biomedical ethics, e.g. autonomy, justice, beneficence and non-maleficence, with dignity sometimes included as well[125, 138]. Recent ethical reviews have considered aspects of humanity in malaria control

implementation and research, noting this as an area of growing interest and importance[139-142]. Humanity is increasingly considered, though not always explicitly highlighted, in the malaria case-management literature[143-145]. Perhaps unsurprisingly, most focus has been on autonomy and non-maleficence in clinical drug trials[146-149]. However, justice is particularly relevant in situations where resources are constrained (e.g. health systems in Pakistan and Afghanistan) to help determine the range and quality of interventions provided so as to ensure humane and safe treatment[125].

Malaria among Afghans in Afghanistan and Pakistan

While global strategies are an important starting point, lessons learned at national and sub-national levels must be incorporated and applied. A specialist international technical NGO has been working with national malaria control programmes and available partners to research and implement the control tools and strategies described above to successfully reduce the malaria burden among 3 million Afghan refugees in Pakistan and communities of returnees in Afghanistan, for over twenty years[150, 151]. Programmatic experiences and data can offer lessons for current global malaria-control agendas[51, 150, 152-154].

The malaria control programme for Afghans

HealthNet International (now *Health Works*), a Dutch NGO working to support health systems strengthening and health services delivery in areas affected by war or disaster, was started as an initiative from *Médecins Sans Frontières* (MSF) in 1992 to bridge the gap between emergency relief and structural development. *Artsen zonder Grenzen* (MSF-Holland) initiated a malaria control programme for Afghan refugees in Pakistan in 1989, which was handed over to the newly created HealthNet International in 1992. In 2005, HealthNet International merged with the *Transcultural Psychosocial Organization* (TPO), becoming *HealthNet-TPO* (HNTPO) and gaining psychosocial and mental health care expertise in addition to its core work reinforcing healthcare systems and the prevention, diagnosis, and treatment of infectious diseases. In 2017, HNTPO changed its name to *Health Works*, to make itself 'more appealing' without changing its core mission[155]. This thesis will refer to the organisation as HNTPO to retain consistency and because the former name remains familiar at the time of writing and most appropriate for the time-period covered.

The HNTPO programme supporting Afghans began as a response to a falciparum and vivax malaria epidemic in refugee camps of Northwest Frontier Province in Pakistan, renamed Khyber Pakhtunkhwa (KPK) province in 2010. Pakistan had a long history of malaria control, initiating eradication in the 1960s, switching to the control agenda in 1975-1985, and joining the RBM

movement in 2006[156]. However, malaria control for refugees was primarily the responsibility of UNHCR and humanitarian NGOs[157]. Once the initial epidemic in northwest Pakistan was controlled, the HNTPO programme then shifted to focus on reducing malaria in eastern Afghanistan[152]. Malaria control has a long history in Afghanistan dating back to formation of the Directorate General of Preventive Medicine and Primary Health Care in 1948[115, 152, 153, 158-179]. Early vector control focused on DDT spraying and *An. superpictus* was almost eradicated by 1970[179]. However, after the Soviet invasion, the national malaria control programme weakened and almost ceased functioning, while health infrastructure was destroyed during decades of war[179-183]. After the fall of the Taliban in 2001, the Afghan Ministry of Public Health (MoPH) and donors worked to improve health indicators quickly by contracting out basic health services to non-governmental providers[184-186]. While formal subcontracting of health services was a relatively new initiative in low-income countries, HNTPO has supported the majority of malaria-control activities in Afghanistan since 1991[151, 185, 187].

HNTPO programme principles have been to apply appropriate control techniques and strategies on a large scale after operational research demonstrated efficacy, cultural acceptability, and safety[152]. The programme has emphasised research capability and developed several innovative control tools, some of which are now being tested outside the region, e.g. insecticide treated materials, cattle sponging[162, 188, 189]. HNTPO maintained detailed records, recording epidemiological and entomological efficacy, social awareness, costs, and the evolution of operational strategy. Thus, it is possible to analyse data retrospectively on prevention and case-management interventions. Efficacy findings have already had influence on regional malaria control policy, for example first-line treatment regimens and ITNs for vector control[190, 191].

Research approach and framework

Major questions in public health intervention evaluation generally involve prevalence, causes and effects of supply and demand, relations between prevention and treatment, and interdependences with other sectors, including education, business, and technology[192]. As such, it has not yet needed its own research methodology, instead adapting theories and methods from existing disciplines[192]. Thus, the research approaches used in designing and analysing the sub-studies come from epidemiology and social sciences, e.g. economics.

Evaluating public health interventions

As the sub-studies included are topically and methodologically diverse, and conducted over varying time-periods, a programme evaluation framework was chosen to help guide analysis.

Details of how the evaluation framework was selected are provided in the sub-section entitled '*Study design and framework selection'* in Chapter 2.

Evaluation frameworks draw from quantitative and qualitative research approaches, enabling a broader understanding than might be possible from any one method[193]. Trochim defined evaluation as 'the systematic acquisition and assessment of information to provide useful feedback about some object'[194]. The Organisation for Economic Co-operation and Development (OECD) Development Assistance Committee (DAC) Criteria, often cited in the evaluation literature, add relevance, efficiency, impact and sustainability to analysis of effectiveness[195]. Public health intervention evaluation should thus be 'a systematic method of collecting, analysing and using data' to 'improve and account for public health actions by involving procedures that are useful, feasible, ethical, and accurate'[196, 197]. While each evaluation cannot include all aspects suggested in the literature, the sub-studies included were diverse enough to enable consideration of aspects of effectiveness, efficiency, equity, and humanity within the malaria programme, represented in Figure 1[125, 198].

Relevant evaluation types

The health programme evaluation literature is substantial. Health programme evaluation can include over thirty-five different evaluation types - such as needs assessment, accreditation, audit, cost-benefit, effectiveness, efficiency, pluralistic, goal-based, process, or impact[199]. Almost thirty years ago, Hopkins noted a distinction between formative and summative evaluations that continues today, with the specific type selected depending on needs, skills, time-frame, and resources[200]. For example, if the evaluation asks whether a specific strategy is a good way to prevent malaria then formative evaluation helps implementers do it better in their specific context, process evaluation lets implementers describe how they are doing it, and outcome/impact evaluation tells stakeholders whether implementers did what was intended or not.

Table 1 shows several common types of evaluation under which studies in results chapters 3-6 fit. The top section on formative evaluation shows the original purpose of each study, while the lower section shows how summative secondary analysis of the study data included in this thesis now fits.

Table 1. Common evaluation types and purposes

Evaluation types	Purpose	Relevant chapters
Formative	During - to strengthen or improve what is evaluated	Initial analysis
Needs assessment	for determining what the need is, how great, and how it might be addressed (i.e. gaps between current and desired conditions)	Ch 6
Developmental	for assessing ongoing programmes during their construction to implement improvements	Ch 4
Process	for investigating the process of programme delivery, including alternative procedures	Ch 3
Pluralistic	For examining stakeholder perspectives, influence, and involvement	Ch 5
Audit	For assessing validity, reliability and internal control to improve programme or organisational quality	NA
Summative	After - to examine the effects or outcomes of what is evaluated	Secondary analysis re-examining data to address new questions or with new methods
Outcome	For measuring change in outcomes (e.g. disease rates, behaviours) against objectives that may or may not be due to the programme (e.g. investigates whether interventions caused demonstrable effects on specifically defined target outcomes	Ch 4, 5
Impact	For measuring the extent to which programme activities changed outcomes, consistent with objectives (i.e. assesses the overall or net effects - intended or unintended - of the programme)	Ch 3, 6
Economic	For examining costs and consequences in standardised economic terms	Ch 3
Meta-analysis	for integrating outcome estimates from multiple studies to provide summary judgement on an evaluation question	NA

NB: Adapted from http://www.socialresearchmethods.net/kb/intreval.htm and http://info.k4health.org/inforeports/BCCtools/7.shtml

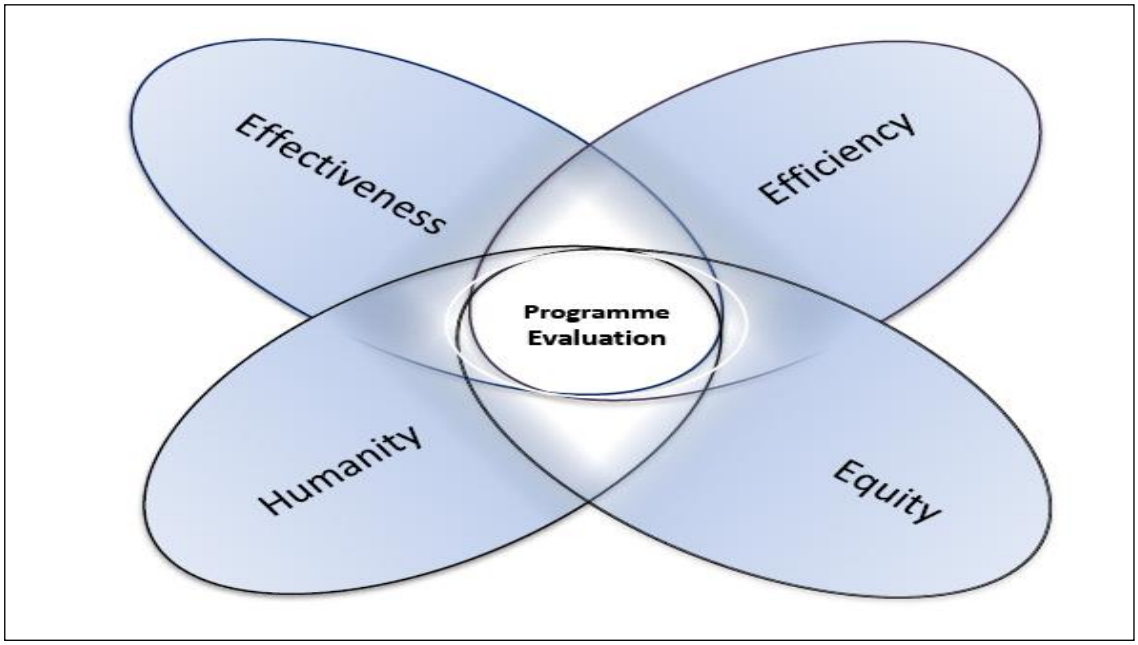
Evaluation framework selected

The malaria control programme for Afghans consisted of multiple interventions during 1990 to 2005 (e.g. indoor residual spraying, insecticide treated mosquito nets, diagnostics, treatment drugs), multiple settings (e.g. acute humanitarian support for refugee camps in Pakistan and chronic-emergency support for villages in Afghanistan), and multiple funding sources, programme targets, and outcome measures. However, the goal remained to reduce the malaria burden among vulnerable Afghan populations in Pakistan and Afghanistan.

Each sub-study contributes indicators and associated baseline and targets to an overall outcome-based evaluation of selected HNTPO interventions. Such a multi-method approach is supported by the literature on evaluation of complex interventions - those "made up of various interconnecting parts"[201] – and the British Medical Research Council framework for the development and evaluation of complex interventions to improve health was used as a theoretical guide[202]. It is worth noting that this thesis does not attempt to assess the whole HNTPO programme for Afghans, as data for such an evaluation were not available. Thus, only the relevant interventions were assessed.

The framework selected (Figure 1) was for an outcome evaluation and considered the four dimensions of effectiveness, efficiency (cost-effectiveness), equity, and humanity proposed by Black and Gruen in Smith *et al* and again in Tsang and Cromwell[125, 198].

Figure 1. Conceptual framework for four-dimensional evaluation



NB: Developed from Black and Gruen[125, 198, 203]

Effectiveness

The epidemiological methods used in analytic and experimental studies help determine programme effectiveness through examining hypothesised relationships, statistical associations, and causality[198, 204]. Social sciences (e.g. economics, anthropology, psychology) contribute methods of determining and interpreting effectiveness, such as multilevel regression modelling, to health research[205].

Efficiency

Improving public health programme and intervention efficiency in resource-constrained settings requires comparison and prioritisation of interventions that provide the greatest benefit per unit of cost[206]. Without systematic analysis of costs and outcomes, identifying relevant alternatives is difficult[207]. Economic analysis has become increasingly popular among donors and aid agencies in low-income countries as implementing agencies must increasingly demonstrate value-for-money. The analytic perspective or viewpoint chosen can be that of the individual, provider, health system, or society, with each having important implications for interpretation as what is good value for the individual or provider may not be for society and vice versa[207]. While costs are analysed in a common format, benefits (outcomes) are approached in several ways[206, 207]. Key economic exposure measures used here were total, average, and incremental cost, while outcome measures used included cases prevented and disability-adjusted life years (DALYs) averted. The main economic method used, cost-effectiveness analysis, enables comparison of interventions to determine maximum health gain for given expenditure[125].

Equity

Equity encompasses fairness, justice and equality, and is generally assessed in health in terms of opportunities or outcomes[125]. *Horizontal equity* refers to equal treatment for equal needs, while *vertical equity* refers to unequal treatment for unequal needs (e.g. preferential treatment for pregnant women and under-five children)[125, 198, 208]. Measuring the equity of an intervention involves comparing selected inputs, processes and outputs between selected groups and by clinical need, e.g. the capacity to benefit from the intervention[125, 209]. Needs vary according to various geographical, socioeconomic, ethnic, gender, age, and co-morbidity factors and can be estimated using standardised techniques, such as indices and socioeconomic classifications (e.g. residential area or asset indices[210]) or co-morbidities (e.g. Charlson Index[211]), and direct or indirect standardisation (e.g. standardised mortality ratios)[125, 204].

Mooney outlined seven measures of equity: (i) equality of expenditure per capita, (ii) equality of inputs per capita, (iii) equality of input for equal need, (iv) equality of access for equal need, (v) equality of usage for equal need, (vi) equality of marginal met need, and (vii) equality of health[212]. Most published literature on equity in health focuses on distributive justice (e.g. access, usage, health service financing), rather than on whether these inequalities are unfair or unjust[125, 208].

Humanity

Providing healthcare in northwest Pakistan and Eastern Afghanistan, or other dangerous resource-constrained settings, necessitates consideration of humanity issues to avoid these being superseded by efficiency considerations[213, 214]. Evaluating humanity in public-health programming minimally involves consideration of the three 1979 Belmont Report ethical principles (i.e. autonomy, justice, beneficence), expanded by Beauchamp & Childress to four: (i) *autonomy*, the right to informed choice, (ii) *justice*, the right to fair treatment, (iii) *beneficence*, choosing to do good, and (iv) *non-maleficence,* avoiding harm[138, 215]. *Dignity*, the right to respect, is often added[125, 216, 217].

Operational data for informing policy and practice

All data for this thesis came from operational research datasets. Operational public health research consists of "*investigating strategies, interventions, instruments, or knowledge that can enhance the quality, coverage, effectiveness, or performance of health systems, health services, or disease control programmes*"[218]. Coming from military and industrial modelling, as the discipline of applying advanced analytical methods to decision-making, operational research has been widely used in the commercial sector but remains less developed in health programmes[218]. It can be used directly to inform policy, as it is designed for improving programme outcomes, assessing the feasibility of new approaches or interventions, and advocating policy change[219]. By showing what works and what does not in various contexts, operational research can provide evidence to help policy-makers adapt health interventions and services for maximum public health benefit[220].

Research that does not tangibly affect policies and practices is particularly ineffective and wasteful in resource-constrained settings, such as Afghanistan and Pakistan, in which disease burden is high[221]. Operational research in low-income countries thus has a key role in filling the gap between what is known from research and what is done with it, referred to by Zachariah and others as the implementation, or 'know-do,' gap[221]. The two main approaches to operational research are analysing secondary data and conducting primary research[218]. Operational research can thus include a range of study designs, primarily categorised as: (i) descriptive, including cross-sectional and qualitative; (ii) case-control; and (iii) retrospective or prospective cohorts[219, 222].

Unlike basic science research and most randomised controlled clinical trials that primarily address efficacy questions, operational research should have direct and practical relevance for policy and practice[219]. However, large amounts of routine data that are collected within health

systems and by non-governmental organisations remain underused, neither fully analysed nor widely disseminated, thus reducing the potential effect of research on policy and practice[220]. Operational research could have a much larger role than it currently does in influencing policy and practice, if more operational data were analysed and reported as has been attempted in this thesis and related publications[89, 115, 223-225].

There is an ethical imperative for ensuring that operational data that are collected are not wasted. Operational research ethics is based on four principles of duty: (i) to alleviate suffering, (ii) to show respect for human beings, (iii) to be sensitive to cultural differences, and (iv) not to exploit the vulnerable[219]. None of these principles can be achieved if data are not fully used.

Aim and objectives

The study aim was to assess interventions implemented by the malaria control programme provided for Afghans during the period 1990 to 2005, using existing secondary operational data and primarily considering effectiveness, but also considering aspects of efficiency, equity, and humanity. It was not possible to conduct a full programme evaluation given the nature of the available data. Thus, findings on individual interventions were treated as indicative of programme capacity and discussed qualitatively in Chapter 7.

Each results chapter (Chapters 3-6) includes specific objectives for individual sub-studies. The overall objectives of this DrPH research were to (i) evaluate whether malaria control interventions provided for Afghans were effective and efficient, according to standard definitions provided, using epidemiological and economic analysis methods on data gathered in refugee camps in KPK Pakistan and villages in eastern Afghanistan between 1990 and 2005; (ii) discuss the equity and humanity of programme interventions, according to standard definitions, using social science data gathered between 2000 and 2005; and (iii) consider implications for malaria control policy and practice specific to each sub-study and broader lessons that could inform future research.

CHAPTER 2 METHODS

Overview

The four sub-studies in chapters 3-6 each include specific and more detailed methods sections. This chapter provides an overview of methodological approaches used. The first section details the two study sites and population. The second section describes study design and framework selection. The third section discusses secondary dataset selection and issues around using secondary data. The fourth section describes methods used in reviewing the literature for each sub-study. The fifth section discusses data collection. The sixth section discusses data analysis, including quantitative and qualitative measurement of exposures and outcomes. The final section describes ethics considerations.

Study sites and population

Both Afghanistan and Pakistan are geographically part of South Asia, which includes one fifth of the global population and covers approximately 5.1 million km² (i.e. 11.5% of the Asian continent and 3.4% of global land-surface area)[226]. The other South Asian countries are Bangladesh, Bhutan, India, Maldives, Nepal, and Sri Lanka. South Asia is important for health policy and practice because: (i) with 1.7 billion people, it is the most populous and densely populated geographical region globally; (ii) it has the highest number of the world's poor, at approximately 500 million; and (iii) it is one of the world's least stable sub-regions, with all eight countries regularly ranking below average on global fragility indices and Afghanistan and Pakistan routinely among the worst performers[227, 228]. Not only does this consume substantial global resources for development and humanitarian assistance, peace-keeping, and stabilisation, but continued sub-regional tensions have been leveraged globally (e.g. entrenching extremist ideologies, as a 'training ground' for global terrorism, nuclearisation[228]).

More positively, South Asia is increasingly important to the global economy, due particularly to the economic rise of India. The sub-region is covered by two economic cooperation agreements, the South Asian Association for Regional Cooperation (SAARC) established in 1985 and incorporating Afghanistan in 2009, and the South Asia Free Trade Agreement (SAFTA), which incorporated Afghanistan in 2011[228]. At its most basic, improved community health and disease control contributes to individual security, which in turn increases national and regional stability and prosperity[229, 230].

Politically and culturally, the two countries are often included as part of the 'Middle East' of predominantly Muslim-majority countries. For example, public health guidance and policy for both countries is managed through WHO's Eastern Mediterranean Regional office, which covers

22 countries and territories in the Middle East, North Africa, and Horn of Africa [231]. Aside from the obvious geopolitical importance, malaria research in Afghanistan and Pakistan is relevant to global practice for two major reasons.

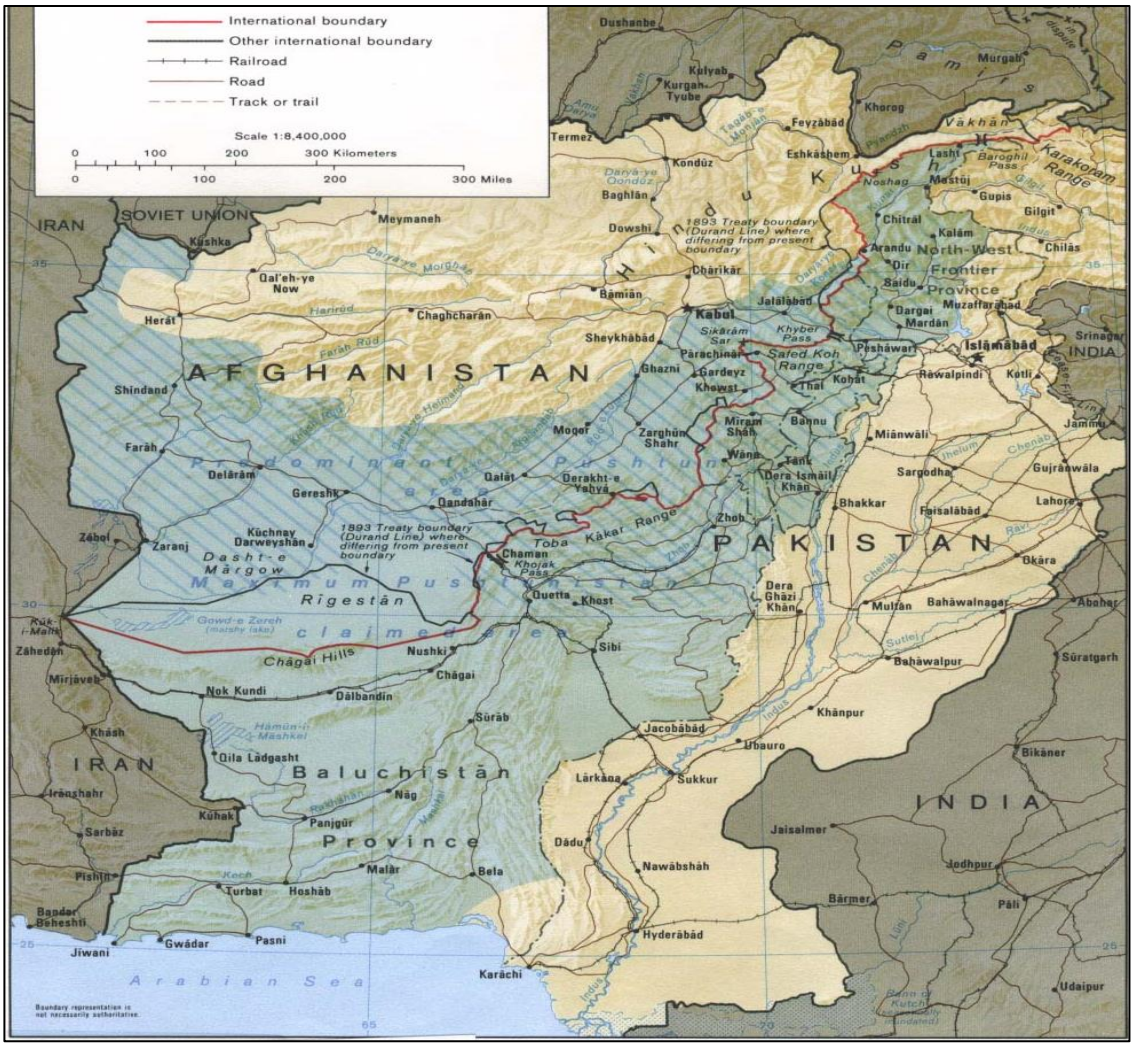
First, malaria epidemiology in South Asia is considerably different from that in sub-Saharan Africa or Southeast Asia, where most malaria research has been conducted, and thus requires different control approaches and priorities. Despite global improvements, Pakistan was one of five high-burden countries in Asia that did not achieve the malaria-related MDG or World Health Assembly targets by the end of 2015[11, 30]. The malaria burden in Afghanistan has decreased more than that in Pakistan, but increased violence and conflict and potential reductions in funding continue to threaten gains made.

Second, experiences in strengthening malaria prevention and treatment services in these conflict-affected settings can provide important lessons for the next stages in malaria control. If current efforts are sustained or increased, and malaria transmission continues to decline globally, more adults will be at risk as lower malaria exposure means immunity is not acquired; malaria may become increasingly concentrated in marginalised hard-to-reach populations or border areas, potentially worsening existing inequities; transmission intensity may become increasingly heterogeneous and migration from or to higher-transmission areas will increase the risk of outbreaks; antimalarial and insecticide resistance is likely to increase; and *P. vivax* may become increasingly important, as it can tolerate a wider variety of environments and is harder to control[30].

Each of these potential global concerns have been considered or researched, though obviously on a smaller scale, as part of the twenty-five year malaria control and research programme for Afghans in the border areas of northwest Pakistan and Eastern Afghanistan.

Figure 2 shows the two countries and the 1896 'Durand line' border between them, bisecting the traditional Pashtun tribal area, shown as a shaded area on both sides of the border. As in many regions where modern national boundaries have divided traditional tribal lands, Pashtuns on both sides of the border often have more affinity with each other than with the rest of their respective nations.

Figure 2. Map of Afghanistan and Pakistan including border area



Source: Wikipedia Commons.

https://upload.wikimedia.org/wikipedia/commons/5/50/Durand_Line_Border_Between_Afghanistan_And_Pakistan.jpg

Pakistan is a lower-middle-income country with a semi-industrialised economy and growing services sector. Since separating from India in 1947, Pakistan has had a series of civilian and military governments and been affected by regional and civil conflicts[232]. Healthcare is overseen by the Ministry of Health (MoH) at the federal level and by health departments at provincial levels[233]. Primary healthcare facilities include basic health units, rural health centres, primary healthcare centres, dispensaries, first aid posts, mother and child health centres, and lady health visitors[233].

Afghanistan is a low-income country with very poor human development indicators. A series of coups, beginning in 1973 with the overthrow of King Zahir Shah, were followed by years of civil war that devastated the country[234]. Healthcare, overseen by the Afghan MoPH since 2001, has been significantly reconstructed since the fall of the Taliban in the same year. During the study period, most primary health services were provided by informal providers, charitable

organisations, and a few NGOs[183, 186]. According to MoPH data, only 9% of Afghans had access to health services in 2003, while as much as 67% had access in 2016 to the Basic Package of Health Services and Essential Hospital Services in over 2,200 health facilities in all 34 provinces[235].

The Basic Health Unit or Basic Health Centre was the smallest and simplest community-based primary healthcare facility in Pakistan (BHU) and Afghanistan (BHC) during the study period, as differentiated from community health-worker services that were normally provided from home. BHU/BHCs focused on immunization, sanitation, malaria control, and maternal and child health. Services normally included antenatal, delivery, and postpartum care; routine immunizations; management of childhood diseases; treatment of malaria and tuberculosis; and identification, referral, and follow-up care for those with mental and physical disabilities. BHU/BHC catchment populations were approximately 15,000-30,000, depending on local geography and population density[233, 236]. BHU/BHCs typically had 7-13 staff, usually including a male nurse or health assistant; a female community, auxiliary, or nurse midwife; a community health/nutrition supervisor; a sanitary inspector; a lab technician/microscopist; a drug dispenser; 1-2 lady health visitors; 1-2 vaccinators, a guard, and a cleaner[233, 236]. BHU/BHCs also supervised the community health-workers and birth-attendants working from home in their catchment areas[233, 236].

The health systems of both Pakistan and Afghanistan are a mix of public and private, formal and informal, modern and traditional medicine[237]. Thus, in addition to government/NGO facilities, many Afghans attended informal and for-profit providers during the study period[237, 238]. Reasons included easier access, preferred treatments, and better availability of drugs and 'doctors'[237]. Private healthcare was not adequately regulated at the time of research, and many spent significant sums for wrong or insufficient diagnoses and treatments[237, 239].

Study site and population in northwest Pakistan

The United Nations High Commissioner for Refugees (UNHCR) has responsibility for Afghan refugee camps and informal settlements in Pakistan. Pakistan was not a signatory to the 1951 Refugee Convention or the 1967 Protocol Relating to the Status of Refugees and the temporary stay of registered Afghan refugees in Pakistan was regularised by means of Proof of Registration cards [240]. Afghan refugees in Pakistan were never a homogeneous group, instead arriving and leaving in conflict-inspired waves starting with the Soviet invasion and war of 1979-1989. Pakistan hosted the majority of Afghan refugees globally, which peaked at approximately 5 million in the 1980s due to its 'open-door' policy [241]. Most (60-80%) were housed in 340 camps

or settlements in NWFP (now KPK[1]) along the Afghan-Pakistan border[157]. Most (85%) were ethnic Pashtuns, while 15% were Uzbeks, Tajiks or other ethnic minorities [240].

While most urban refugees and economic migrants lived in slum areas of Pakistan's major cities, low-income rural refugees in KPK camps were sited on marginal or waterlogged land capable of supporting extensive mosquito breeding [242, 243]. Malaria in Pakistan is typically unstable and seasonal, with major transmission post monsoon, i.e. August to November. *Anopheles stephensi* and *An. culicifacies* were considered primary malaria vectors, while *An. fluviatilis*, *An. superpictus*, and *An. subpictus* were also known vectors [242, 244]. The initial malaria epidemic in Pakistan, for which UNHCR requested specialist technical support, was caused by the influx of three million non-immune Afghans to KPK refugee camps and informal settlements. In 1991, at the height of the epidemic, approximately 150,000 cases of vivax and 40,000 cases of falciparum malaria were diagnosed and treated annually [224].

The UNHCR malaria control programme in KPK followed WHO guidelines as part of integrated housing, education and health services for refugees. Implementers were the governmental Project Department for Health (PDH) and local and international non-governmental organizations (NGOs). From 1985, AZG provided health support to the camps, including malaria control until HNTPO took on this role. From 1992, HNTPO was funded to monitor malaria incidence, train technical staff, supervise malaria diagnosis, and organise vector control.

The malaria epidemic was eventually controlled by improving the quality of both diagnostic and treatment services in 200 BHUs and laboratories, improving refugee health awareness through basic malaria-focussed health education campaigns, and primarily by reviving annual targeted IRS usage in traditional mud-brick houses and nomad tents[245]. IRS was conducted by refugee workers at the onset of peak falciparum transmission (July-August) in camps reporting malaria incidence above 0.5% for falciparum or 3.0% for vivax. *Malathion* and later *permethrin* were used. BHUs provided case management, which was free to service-users. Positive cases received first-line treatment in accordance with national guidelines. By 1995, annual numbers had fallen to 30,000 vivax and 4,500 falciparum cases respectively in an estimated population of 1.2 million refugees. However, malaria remains a significant public health concern in Pakistan, which is listed as a major focal point in the WHO-EMRO region [11].

[1] As most research data were gathered prior to 2010, this document will use both 'NWFP' for historical accuracy, and 'Khyber Pakhtunkhwa', or KPK to aid clarity.

Figure 3. Map of Pakistan's Khyber-Pakhtunkhwa Province (NWFP) and Federally Administered Tribal Areas (FATA), showing districts

Source: Wikipedia Commons. https://commons.wikimedia.org/wiki/File:Map_showing_NWFP_and_FATA.png

Study site and population in eastern Afghanistan

In contrast to the situation in northwest Pakistan, the 1990s malaria resurgence in eastern Afghanistan resulted from repatriating infected refugees to a fragile conflict-affected country in which health infrastructure and malaria control services had ceased to function. Many former refugees resettled in and around Nangarhar Province (Figure 4). Similarly to northwest Pakistan, primary vectors in this area were *An. culicifacies, An. superpictus,* and *An. stephensi*, while *An. fluviatilis* and *An. pulcherrimus* were found nationwide[246]. Malaria transmission was from June to September in Nangarhar Province, and malaria was hyper-endemic in rice producing areas[85]. *An. stephensi* breeds in residual water, while *An. superpictus* favours mountain lakes. *An. superpictus* and *An. fluviatilis* are exophilic and exophagic, while other species are generally

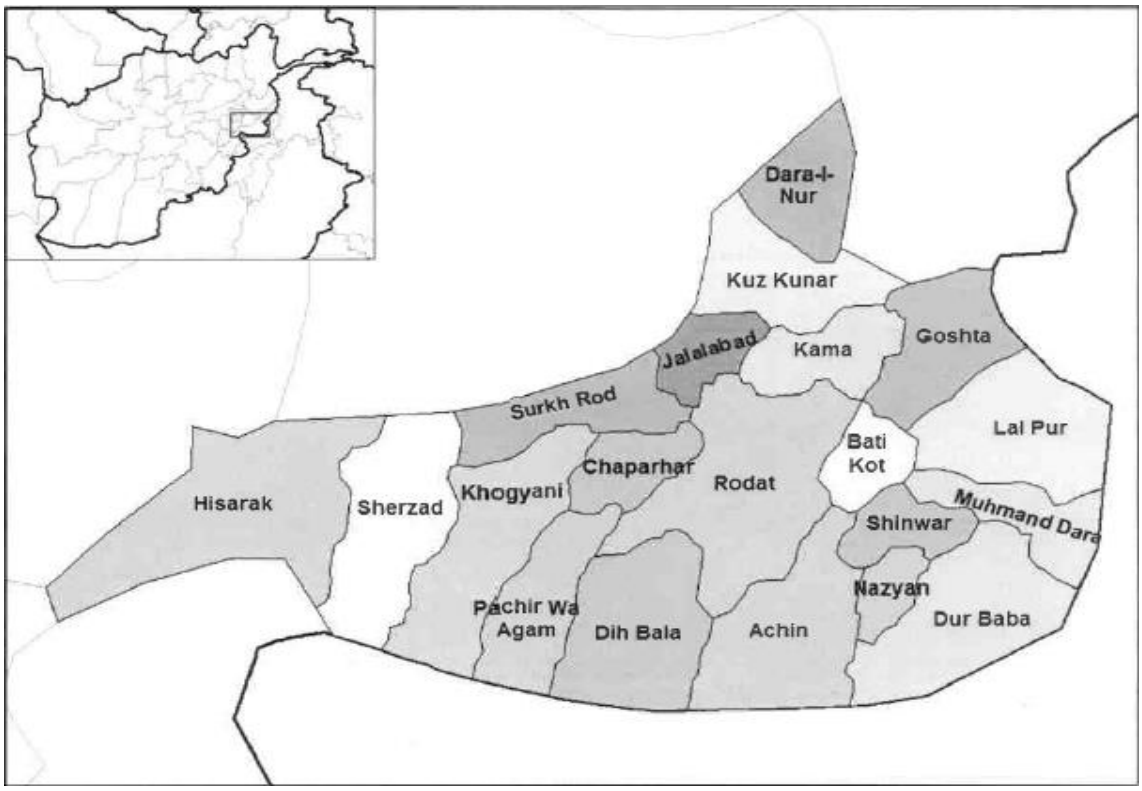
endophilic and endophagic. Small species, such as *An. stephensi*, can penetrate untreated mosquito nets and have a flight radius of 1-2 kilometres[246].

Before Afghanistan's extended conflict, malaria was almost eliminated as a public health issue through vertical governmental IRS and chloroquine (CQ) treatment[52, 152, 246]. As control infrastructure deteriorated during over thirty years of conflict malaria rates increased, peaking during the mid-1990s[152, 246]. From 1992, eastern Afghanistan became stable enough to establish a network of NGO-supported clinics, standardize training and monitoring of microscopists and clinical staff, and distribute ITNs and insecticide retreatment.

Malaria prevalence in Afghanistan is heterogeneous, believed to be endemic in areas below 2,000 meters elevation and highly prevalent in river valleys under rice cultivation[152]. Transmission seasons vary throughout the country, and the population is effectively non-immune to malaria[225]. While malaria incidence has reduced significantly in the past fifteen years, malaria remains a health concern in Afghanistan[11, 224, 247, 248]. Large areas of Afghanistan are malaria endemic due to both *P. vivax* (approximately 70-90% of infections) and *P. falciparum*[150, 246]. Approximately 60% of the population - nearly 25 million people - are considered at risk[11]. Malaria outbreaks have re-emerged as a concern since 2001 (e.g. in Kundoz, Takhar, and Badakhshan provinces) due to refugees returning from neighbouring countries, intensified rice cultivation close to populated towns, and insufficient coverage of vector-control measures[249, 250]. WHO estimated that approximately 300,000-510,000 malaria cases occurred in 2015, more than 30% of them in eastern Afghanistan[11].

HNTPO coordinated malaria control in eastern Afghanistan from 1992, extending its malaria operations from Peshawar Pakistan to Jalalabad Afghanistan[152]. As no effective government seemed likely to evolve in Afghanistan during the nineties, malaria control efforts were quite different from those in KPK refugee settlements. Instead of working through or creating a vertical programme, HNTPO attempted to encourage self-sufficiency and personal or household-level protective measures. Despite initial donor scepticism, HNTPO introduced ITNs on a broad scale. Over 200,000 family-size ITNs were sold at subsidized prices, covering almost 1 million inhabitants. Few Afghans had used mosquito nets previously and this was one of the largest programmes of its kind in the South Asian or Middle-East regions until creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in 2002 enabled free mass distribution of ITNs.

Figure 4. Nangarhar Province Afghanistan, showing districts



Source: Wikipedia Commons https://commons.wikimedia.org/wiki/File:Nangarhar_districts.png

During the mujahedeen (1992-1996) and Taliban (1996-2001) eras, HNTPO focussed on interventions shown through operational research to be effective, popular and not requiring significant government involvement or inputs[52, 153, 188, 246, 251]. Government infrastructure and external support remained minimal until well into the US-led occupation (2001-2014) and is arguably still weaker than had been anticipated when the Taliban first fell [248]. In South Asia, both IRS and ITNs have been shown to be effective for malaria control[39, 52, 251-254]. However, sustainability of prevention efforts requires effective government structures to either stimulate local production of necessary supplies and equipment or regulate supply and distribution, which has not yet occurred in Afghanistan.

Study design and framework selection

A mixed-methods study design was chosen, including economic analysis of routine cost and outcome data (Chapter 3), epidemiological analysis of clinical, laboratory, and socioeconomic data (Chapters 4 and 6), and qualitative analysis of interview and focus group data (Chapter 5).

A review of evaluation literature for public health and healthcare was conducted, described below in the *Literature review* sub-section, to identify relevant work undertaken and potentially suitable frameworks to guide analysis and interpretation. A number of potential evaluation

frameworks were identified, predominantly from the healthcare literature. The most notable, which were considered for use, were: (i) Donabedian's seminal work, including his 1988 use of programme evaluation theory to assess quality of healthcare through structure, process, and outcomes and his 1966 dimensions of effectiveness, efficacy, efficiency, acceptability, legitimacy, and equity[255, 256]; (ii) the 1991 OECD-DAC dimensions of effectiveness, efficiency, relevance, sustainability, and impact; (iii) the 1999 US Centers for Disease Control and Prevention (US-CDC) Framework for Program Evaluation in Public Health, which considers utility, feasibility, propriety, and accuracy[257]; (iv) Black and Gruen's dimensions of effectiveness, efficiency, equity, and humanity for assessing healthcare services[258]; and (v) the 2006 OECD framework dimensions of effectiveness, cost/expenditure, responsiveness, needs, safety, and accessibility[259].

Table 2. Comparing evaluation frameworks

Framework	Focus	Domains included	Strengths	Weaknesses
Donabedian (1966)	Clinical services	▪ Acceptability ▪ Effectiveness ▪ Efficacy ▪ Efficiency ▪ Equity ▪ Legitimacy	▪ Widely recognised. ▪ Includes equity explicitly.	▪ Focused on clinical care. ▪ Available data and research focus is on effectiveness rather than efficacy. ▪ Legitimacy would be challenging to assess with available data.
OECD-DAC (1991)	Development assistance	▪ Effectiveness ▪ Efficiency ▪ Relevance ▪ Sustainability ▪ Impact	▪ Widely recognised and reasonably comprehensive.	▪ Does not explicitly include equity or humanity. ▪ Impact data not available. ▪ Relevance and sustainability hard to measure.
US-CDC (1999)	Public health programmes	▪ Accuracy ▪ Feasibility ▪ Propriety ▪ Utility	▪ Designed for public health programmes.	▪ The interpretation of some domains is not obvious. ▪ Overly complex for this purpose.
Black and Gruen (2005)	Health services	▪ Effectiveness ▪ Efficiency ▪ Equity ▪ Humanity	▪ Broadly applicable. ▪ Understandable and relevant, yet flexible. ▪ Only one to include humanity explicitly.	▪ Minimal guidance on thresholds, e.g. for humanity indicators.
OECD (2006)	Healthcare	▪ Accessibility ▪ Effectiveness ▪ Cost/Expenditure ▪ Needs ▪ Responsiveness ▪ Safety	▪ Explicitly includes safety and responsiveness.	▪ Only includes equity in terms of access and need. ▪ Responsiveness would be difficult to assess with available data.
Kruk et al (2010)	Health services	▪ Effectiveness ▪ Efficiency ▪ Equity	▪ Includes the three key domains. ▪ Broadly applicable.	▪ Does not improve on Black and Gruen, as it excludes humanity. ▪ Domains treated as qualitative themes.
Reeve et al (2015)	Health services	▪ Accessibility ▪ Appropriateness ▪ Continuity ▪ Effectiveness ▪ Efficiency ▪ Responsiveness	▪ Improves on Black and Gruen by including appropriateness and continuity (sustainability).	▪ Only includes equity in terms of access and does not include humanity.

Black and Gruen's framework was selected as it included the three key domains of effectiveness, efficiency, and equity, and was the only framework to include humanity. It was recognised from the beginning that equity and humanity would be more difficult domains than effectiveness and efficiency to assess with the secondary data available. However, the attempt seemed worthwhile as a contribution to evaluation approaches using operational research data in complex settings.

The initial literature review, conducted prior to 2008 DrPH review, was updated prior to thesis finalisation, and two additional relevant frameworks considered: (i) Kruk *et al*'s use of 'Effectiveness, Equity, and Efficiency' to review the contribution of primary care in low and middle-income countries[260]; and (ii) the more comprehensive health services evaluation framework developed by Reeve *et al* for rural and remote communities in Australia (Figure 12)[261]. Neither were selected as Kruk *et al*'s framework did not progress from Black and Gruen's, while Reeve *et al*'s framework additionally included structure, process, outcome, and key foundations (i.e. sustainability, quality of care, national performance indicators, community health determinants) that required considerably more time and external data to the programme than were available.

Dataset selection and secondary data usage issues

Dataset selection

Despite the wealth of operational datasets collected by HNTPO, most had already been published or were maintained by someone intending to analyse and publish them. Thus, only a limited number was available for potential inclusion in this thesis research. Potential datasets consisted of: (1) cost-effectiveness data of the malaria programme in KPK camps from 1990-1995; (2) cost-effectiveness data of ITNs and IRS in KPK camps in 1991-1994; (3) clinical trial data of extended-dose CQ in KPK camps in 1998; (4) cost-effectiveness data of IRS with lambda-cyhalothrin versus malathion in KPK camps in 1996; (5) cost data of static versus mobile distribution of ITNs in Nangarhar province in 1997; (6) clinical trial data of CQ versus SP chemoprophylaxis in KPK camps in 1998; (7) semi-structured interviews and cross-sectional household survey data of malaria knowledge, prevention and treatment practices, and ITN usage in Nangarhar in 2000; and (8) clinical survey, cross-sectional survey, and case-control data of malaria and pregnancy in Nangarhar in 2004-2005.

A minimum of three datasets were required for inclusion, while a maximum of five could have been included with some loss of depth. To provide the broadest view of the malaria control programme in both countries, a range of study types and topics in both study settings were

necessary. Thus, the eight datasets were checked against binary selection criteria (Yes/No), and the six that were of satisfactory or good quality were ranked from best to worst per criterion as shown in Table 3.

Table 3. Dataset selection criteria and ranking

Criteria	Datasets	Ranking (best to worst)[a]	Score values[b]	Included[c]
Data quality				
Good	5; 7	7; 5	[6;5]	7
Satisfactory	1; 2; 3; 8	8; 1; 3; 2	[4;3;2;1]	8; 1; 3
Unsatisfactory	4; 6	Excluded	Excluded	Excluded
Addresses framework				
Effectiveness	1; 2; 3; 4; 6; 7; 8	1; 3; 8; 2; 7	[6;5;1;0;0]	1; 3; 8; 7
Efficiency	1; 2; 4; 5	1; 5; 2	[6;5;1]	1
Equity	1; 2; 7; 8	7; 1; 8; 2	[6;5;1;0]	7; 1; 8
Humanity	7; 8	7; 8	[6;5]	7; 8
Type				
Epidemiological	3; 6; 8	3; 8	[6;1]	3; 8
Economic	1; 2; 4; 5	1; 5; 2	[6;1;0]	1
Qualitative	7	Included	[6]	7
Setting				
Pakistan	1; 2; 3; 4; 6	1; 3; 2	[6;5;0]	1; 3
Afghanistan	5; 7; 8	7; 8; 5	[6;5;0]	7; 8
Time-period				
1990-1999	1; 2; 3; 4; 5; 6	1; 5; 3; 2	[6;5;1;0]	1; 3
2000-2005	7; 8	7; 8	[6;5]	7; 8

NB: [a]Datasets were ranked 'best to worst' from left to right according to selected criteria. [b]Each dataset was assigned a numerical score from 6-0 according to how well it achieved each criterion, and scores for each criterion were summed to provide a total for each dataset. [c]Those datasets included in thesis research are shown in this column in-line with the criteria they satisfy.

Two datasets failed quality criteria and were immediately excluded (Datasets 4 and 6), while only one dataset was qualitative and so immediately included (Dataset 7), though it would have achieved the second highest score of '36' anyway. The remaining five were ranked by score: (Dataset 1) 38; (Dataset 8) 22; (Dataset 3) 19; (Dataset 5) 16; and (Dataset 2) 2, with the top three highest scoring datasets being included with Dataset 7. Dataset 5 scored well enough to be included, but was not as strong an economic dataset as Dataset 1 and did not contribute to any criterion not already covered by included datasets, and was thus deemed unnecessary. Thus, a total of four datasets were included (i.e. Datasets 1, 3, 7, and 8 were used in Chapters 3, 4, 5, and 6 respectively).

Data issues

The obvious advantages of using secondary data were time and cost savings, and the potential for new and additional insights combined with the ethical benefit of ensuring that data involving human subjects were analysed and disseminated and therefore not wasted. However, the main methodological challenges, compounded by the age of some datasets, were inappropriateness of some data variables and lack of control over data quality. First, secondary data could not

always answer research questions directly and thus questions had to be adjusted to fit the data available. Second, it was not always easy to determine how data were collected or what quality assurance procedures had been used and some assumptions were required that were detailed in specific sub-studies. Third, missing and incongruous data could not always be checked with data collectors or original paper files and similarly assumptions were required that were described in sub-studies. Fourth, more effort was required to ensure results were relevant to the issues of today than would have been the case, for example, with data collected within the past eighteen months.

Each dataset had to be assessed to determine original purpose, collection methods, collection period, types of variables, ethics considerations and any local approval process, and data consistency and accuracy. Despite the age of some datasets, most of this information was available (primarily because these issues were considered during the selection process described above). Data quality (e.g. consistency and accuracy) were hardest to determine directly. However, HNTPO had an established reputation for epidemiological research, economic data were collected by an LSHTM researcher who was still employed at the School, and qualitative data were collected by another LSHTM researcher - who was still employed at the School - and the DrPH candidate. Thus, original principal investigators were able to answer a number of questions that could not be determined from quality checks on variables. It is worth noting that when most of these data were collected, ethics approval was not routinely required for operational research. Therefore, one of the first steps was to apply for retrospective ethics approval for these datasets and overall approval for secondary analysis. These approvals provided further assurance that study approaches, data collection, and analyses complied with ethical principles.

Literature reviews

Multiple sources were searched to increase comprehensiveness. First, a review of relevant peer-reviewed published literature was conducted in the main electronic databases, e.g. PubMed, EMBASE, Science Citations, Social Science Research Network (SSRN), ISI Web of Knowledge, Health Economic Evaluations Database (HEED), and Cochrane Central and specialised registers. Second, a purposive online review of relevant documentary sources was conducted. Search engines Google (https://www.google.co.uk/) and Google Scholar (https://scholar.google.co.uk/) were used to access additional academic, non-academic and grey literature, including global and regional policy documents, conference proceedings, study reports, evaluation reports, website information, presentations, online tutorials, organisational data, and news articles. As the quality of this data varied considerably, it was only included for context or if the methodology

was cited in an academic publication. Third, a purposive hand-search of publications and reference lists from the HNTPO control programme was conducted.

To identify and support the evaluation framework, a review of evaluation literature published between 1990 and 2015 was conducted for public health, healthcare, humanitarian aid, complex interventions, and development sectors. PubMed, Popline, SSRN, and ISI Web of Knowledge were searched for relevant journal publications. Search terms included '*evaluation'*, '*public health,' 'malaria control,' 'effectiveness,' 'efficiency,' 'equity (equity of access),'* and *'humanity (autonomy, beneficence, non-maleficence, dignity, justice),'* adapted to the MESH headings for each database. A Google search, and snowballing of relevant article reference lists, was also conducted.

Separate literature reviews were conducted for each sub-study, though a number of publications were relevant to more than one chapter.

The first study in chapters 3, assessing cost-effectiveness of adding malaria prevention to case management for Afghan refugees, drew on health economics literature. A search of PubMed, SSRN, and HEED databases was conducted. Initial broad search terms, adapted to database MESH headings, included 'cost-effective,' 'cost', 'economic,' 'incremental cost effectiveness ratio', or 'CEA' and 'malaria' or '*Plasmodium falciparum', 'Plasmodium vivax*,' 'disease control,' 'Pakistan,' 'Afghan' and 'refugee.'

Chapter 4, assessing CQ resistance among refugees in Pakistan, related to the epidemiological literature on drug resistance and access to effective diagnosis and treatment drugs. PubMed, EMBASE, and Cochran registers were searched using initial broad search terms, adapted to database MESH headings, including 'chloroquine resistance,' 'ECQ' and '*pfcrt*,' or '*pfmdr1*,' 'Pakistan,' 'Afghanistan,' and 'refugee.'

Chapter 5, assessing malaria-related perceptions and behaviours among Afghans under the Taliban, related to the social science literature (particularly in South Asia) on health education, behaviour change, gender, equity, and humanity. PubMed, SSRN, and Google Scholar were used. Initial broad search terms, adapted to database MESH headings, included 'qualitative,' 'social/socio*,' 'knowledge attitudes and practices' or 'KAP,' and 'ITN' or 'malaria,' 'risk perception,' 'behaviour,' 'gender,' 'women' or 'female,' and 'Afghanistan.'

Chapter 6, assessing prevalence, clinical indicators, and women's perceptions of malaria in pregnancy, relates to the epidemiological literature on malaria in pregnancy (particularly in South Asia) and the social science literature on behaviour change and equity. PubMed, SSRN, Cochran databases, and Google Scholar were used. Initial search terms, adapted to database MESH headings, included: 'malaria' or 'vivax' and 'pregnancy', 'antenatal,' 'prenatal', 'perinatal', 'postnatal/postpartum,' 'risk perception,' 'women,' and/or 'Afghanistan.'

Data collection

All primary and secondary datasets were collected as part of HNTPO's operational research from 1990 to 2005. Economic data for Chapter 3 were collected by a consultant in 1996 as part of a retrospective review of UNHCR's health programme for Afghan refugees from 1990 to 1995. Drug resistance data for Chapter 4 were collected for an open-label double-blind randomised controlled trial of CQ treatment for uncomplicated falciparum malaria in Pakistan refugee camps, conducted by HNTPO research staff in 1993 to help inform programme antimalarial policy. Socioeconomic data for Chapter 5 were collected by the DrPH investigator when working for HNTPO in 2000 to determine service-user preferences, knowledge and practices so as to help inform ITN programme expansion. Clinical and knowledge, attitudes and practices (KAP) data for chapter 6 were collected from women of reproductive age as part of a Unicef and WHO-funded study of malaria in pregnancy conducted by the DrPH investigator and HNTPO staff in 2004-2005 to help inform national Safe Motherhood policy.

Data analysis

Economic data were analysed using Excel™. Quantitative socioeconomic and clinical data were analysed using Stata® versions 11-14. Qualitative data were analysed manually using thematic coding.

Epidemiological measurement of occurrence and association

Epidemiological measures of occurrence, association and impact include incidence, prevalence, and odds[1]. Disease occurrence was measured through incidence rates and point prevalence[198, 262]. Association of interventions with outcomes was measured through odds ratios, using logistic regression tested statistically using χ^2 for categorical data and t-tests for continuous data[263].

The likelihood that findings were due to chance was minimised in sub-study design. Statistical tests of significance, based on probability theory (e.g. the null hypothesis of no difference between groups), increased the likelihood that associations were not due to chance. The conventional p-value of <0.05 and 95% confidence intervals were used (i.e. 95 of 100 times

observed differences were other than those expected by chance and true values between upper and lower confidence limits). A statistical power of 1-β=0.80 was used*, a priori* or *post-hoc*, to determine whether a meaningful association could be observed for expected effect sizes or specific sample sizes, given specified significance levels. Sample sizes were calculated using Stata or EpiCalc.

Internal validity was addressed in sub-study design and analysis. Selection bias was limited through randomised selection or allocation where feasible and distribution measurement of case-mix variables (e.g. age, sex, residence). Information bias was limited through standardised data collection and measurement, and blinding where feasible. Confounding was addressed at sub-study design stage by collecting data on *a priori* confounders. The effects of confounding and interaction were controlled for in analysis by restriction, stratification, or multivariate regression techniques. External validity was increased at selection, by ensuring study samples were as representative of the wider population as possible. Bradford Hill's criteria were used to infer evidence of causality[264]. Of these nine criteria, four (temporality, strength and consistency of association, and dose-response relationship) appeared to provide strongest evidence[265].

Economic measurement of cost and utility

Economic costs encompass the value of forgone opportunities, resulting from engaging resources in any activity[207]. Cost-effectiveness analysis, such as in Chapter 3, is used to determine technical efficiency. It examines the costs and consequences of alternate interventions (i.e. IRS added to case management versus case management alone) expressed per unit of health outcome. A societal perspective was chosen, as it is the most comprehensive economic perspective (i.e. including all others) and therefore preferred when data are sufficient to allow for it. Economic measures used for costing included direct, indirect, fixed and variable costs, discounting, and time preference, while outcome measures included utility values and disability-adjusted life years (DALYs)[207]. Data concerns were addressed using sensitivity analysis.

Social science measurement of equity and humanity

The equity measure initially chosen was equity of usage, which is a function of supply and demand (i.e. supply, by providing equal services for equal need, and demand, by requiring those with greatest need to choose to use services)[125, 198]. It appeared to be the most relevant allocational definition, as using a definition encompassing health equity would have been beyond the anticipated scope of a malaria-control programme[212]. The humanity measures initially chosen were autonomy (based on perceived independence and informed choice) and

dignity (based on perceived fair and respectful treatment). Justice was also considered, within equity of usage.

Both qualitative and quantitative social science methods were used. Quantitative methods, such as household surveys, were used to describe social phenomena such as malaria knowledge, attitudes and reported practices, and to test theories (e.g. that Afghans purchase ITNs to protect themselves from malaria). Qualitative methods, such as in-depth interviews (IDIs), were used to generate and explain social data (e.g. why children are prioritised for sleeping under ITNs). Measures used include comparative (i.e. items were compared directly with each other – "Do you prefer CQ or SP for malaria treatment?") and non-comparative (i.e. each item scaled independently – "How do you feel about using malaria treatment during pregnancy?") scaling[266, 267].

Ethics

Ethics approval for secondary analysis of data-sets was granted by the Research Ethics Committee of the London School of Hygiene & Tropical Medicine (LSHTM), reference number *5508*. Approval for specific sub-studies was granted by the relevant coordination bodies in Pakistan and Afghanistan. Studies conducted in KPK refugee camps (i.e. Chapters 3 and 4) were developed with inputs and coordination from UNHCR, which supported the malaria control programme financially, and received local ethics approval from UNHCR and Pakistan MoPH authorities. The clinical trial in Chapter 4 was also registered with ClinicalTrials.gov, reference number *NCT01019408*. Studies conducted in Nangarhar Province Afghanistan (i.e. Chapters 5 and 6) were funded by UNHCR, WHO and UNICEF Afghanistan. The sub-study in Chapter 5 was conducted when there was no functioning national ethics review committee in Afghanistan and thus received local approval from UNHCR, WHO and the acting governor for the Taliban in Jalalabad. The epidemiological and KAP study in Chapter 6 received approval from Afghan MoPH authorities.

CHAPTER 3 COST-EFFECTIVENESS OF ADDING INDOOR RESIDUAL SPRAYING TO CASE MANAGEMENT IN AFGHAN REFUGEE SETTLEMENTS IN NORTHWEST PAKISTAN DURING A PROLONGED MALARIA EPIDEMIC (1990-1995)

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Author contributions:
NH designed the retrospective study, analysed and interpreted data, and wrote the manuscript.

Abstract

Introduction

Financing of malaria control for displaced populations is limited in scope and duration, making cost-effectiveness analyses relevant but difficult. This study analyses cost-effectiveness of adding prevention through targeted indoor residual spraying (IRS) to case management in Afghan refugee settlements in Pakistan during a prolonged malaria epidemic.

Methods

Taking a societal perspective, provider and household costs of vector control and case management were collected from provider records and community survey. Health outcomes (e.g. cases and DALYs averted) were derived and incremental cost-effectiveness ratios (ICERs) for cases prevented and DALYs averted calculated. Population, treatment cost, women's time, days of productivity lost, case fatality rate, cases prevented, and DALY assumptions were tested in sensitivity analysis.

Findings

Malaria incidence peaked at 44/1,000 population in year 2, declining to 14/1,000 in year 5. In total, 370,000 malaria cases, 80% vivax, were diagnosed and treated and an estimated 67,988 vivax cases and 18,578 falciparum and mixed cases prevented. Mean annual programme cost per capita was US$0.56. The additional cost of including IRS over five years per case prevented was US$39; US$50 for vivax (US$43 in years 1-3, US$80 in years 4-5) and US$182 for falciparum (US$139 in years 1-3 and US$680 in years 4-5). Per DALY averted this was US$266 (US$220 in years 1-3 and US$486 in years 4-5) and thus 'highly cost-effective' or cost-effective using WHO and comparison thresholds.

Conclusions

Adding IRS was cost-effective in this moderate endemicity, low mortality setting. It was more cost-effective when transmission was highest, becoming less so as transmission reduced. Because vivax was three times more common than falciparum and the case fatality rate was low, cost-effectiveness estimations for cases prevented appear reliable and more definitive for vivax malaria.

Background

Despite almost two decades of radically increased public funding and significant gains, malaria control remains challenging as resistance develops to existing insecticides and antimalarials [268-271]. WHO recommends an integrated control approach of early diagnosis and treatment, vector control, epidemic surveillance and response, and improved information systems [10, 268, 272]. Despite these advances, financing of malaria control for populations displaced by crises and conflicts is by definition limited in scope and duration [137, 248]. Cost-effectiveness analyses, by comparing costs and consequences of alternative interventions, can increase effective programme management, but are particularly difficult to conduct in complex, resource-constrained settings. Thus, no studies were found exploring full operational costs or cost-effectiveness of integrated malaria control in refugee settings or including epidemic transmission, and minimal published cost-effectiveness research was found for malaria prevention in South Asia [39, 54].

Parts of Afghanistan and KPK province, Pakistan remain malaria endemic [160, 249, 273, 274]. Breakdown of control infrastructure during decades of conflict led to a high annual malaria burden for Afghanistan during 1990-2010 [152, 248, 273]. Inflows of over 3 million Afghan refugees to Pakistan in the 1980s and 1990s led to increased transmission in newly-settled areas [85, 150, 153, 275]. Refugee populations were particularly vulnerable, due to being predominantly non-immune and settled in areas prone to Anopheline breeding [85, 171, 243, 275, 276]. To inform future refugee programme design and implementation, data from the 1990-1995 epidemic were retrospectively evaluated, as primary healthcare services in settlements changed relatively little over this chronic emergency period.

This study aimed to determine whether adding targeted malaria prevention using IRS to case management using quality-assured microscopy and national first-line treatment was a better use of limited resources than case management alone during five years of epidemic malaria control in Afghan refugee settlements in Pakistan. Objectives were to: (i) calculate costs of the integrated control programme and vector control and case management components; (ii) determine costs per malaria case and death prevented, year of healthy life gained (YHLG), and disability-adjusted life-year (DALY) averted; and (iii) calculate incremental cost-effectiveness ratios (ICERs) for integrated control relative to case management alone.

Methods

Study design

Following Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines

[277], an intervention study design was selected to determine the cost-effectiveness of adding a vector control intervention to existing malaria case management, using a societal perspective. A societal perspective requires that costs related to all stakeholders (e.g. health system/programme, government and private providers, service-users) are included, so that cost-effectiveness calculations account for costs and benefits for the whole of society and 'reflect broad public interest'[278]. Programme implementation costs, outcomes (i.e. cases and deaths prevented, YHLG, DALYs), and cost-effectiveness (ICERs) were calculated.

Study site and population

The study population resided in Afghan refugee settlements near the Afghanistan-Pakistan border. In Year 0, a population of almost 2.5 million Afghan refugees was supported by 193 BHUs (the lowest level of primary healthcare facility) in over 100 settlements in KPK (Table 1a). By Year 5, this had dropped to 1.2 million refugees supported by 71 BHUs. As the refugee population declined and NGOs reduced activities, numbers of operational BHUs reduced by nearly two-thirds.

Refugee populations were non-immune and constantly changing, having originated in areas where malaria was previously controlled and engaging in considerable cross-border movement. Refugee settlements were sited on marginal land and housing was rapidly constructed from mud-brick, lacking piped water or sewerage. UNHCR provided integrated housing, education, and health services for refugees. The UNHCR malaria control programme responded to a late 1980s malaria epidemic and operated for over fifteen years. Implementers were governmental Project Department for Health (PDH) and local and international NGOs. HNTPO, a specialist technical NGO, conducted research and provided technical support, quality-assured malaria microscopy training, monthly field laboratory monitoring, malaria surveillance, vector control, and evaluation.

Intervention

The UNHCR-subsidised intervention consisted of: (i) case management through strengthening malaria diagnosis and treatment at BHUs in all settlements during years 0-5; and (ii) vector control using annual IRS in a sub-set of higher-incidence settlements during years 1-5. Case management, conducted by BHU health-workers, consisted of diagnosis by quality-assured microscopy and treatment of malaria cases according to national guidelines[275]. Microscopy was the only diagnostic method used. Continuous training and quality checks, through bimonthly monitoring of each BHU laboratory (i.e. experienced microscopists checked a randomly-selected series of negative and positive malaria slides from each microscopist), maintained a diagnostic

accuracy of above 98%[275]. RDTs were not available at test sites, but it was deemed unlikely by investigators that their usage would have improved the level of accuracy achieved. Positive cases received a 3-day course of CQ as first-line treatment, with primaquine (PQ) administered as a gametocytocidal drug for falciparum malaria and as a 5-day course for vivax malaria, though this was later abandoned as a trial demonstrated insufficiency for radical treatment[279]. UNHCR procured CQ locally and primaquine internationally. All cases were recorded for surveillance purposes and asked to return for a follow-up slide, with most doing so, and treatment failures receiving sulphadoxine-pyrimethamine (SP). National guidelines have since changed for confirmed falciparum malaria, to more effective and more expensive SP-artesunate therapy [280], and this substitution was modelled in sensitivity analysis.

IRS vector control was conducted by refugee workers, supervised by implementing partners, in an annual campaign held before the onset of peak annual transmission (July-August). Refugee settlements were spatially discrete, ranging from approximately 5,000 to 30,000 population, and separated from local Pakistani villages. Settlements were generally quite densely populated. Though density sometimes varied, it was not difficult for the malaria control programme to identify spatially the perimeters of each settlement and houses within them, all of which were eligible for IRS. IRS targeting was based on a threshold reported malaria incidence rate per settlement of above 5 falciparum cases per 1,000 person-years or 30 vivax cases per 1,000 person-years in the previous year. Pumps and insecticide were donated by UNHCR. The organophosphate insecticide malathion and the pyrethroid lambdacyhalothin were used for IRS (Table 1a). All services were provided free to end-users.

Effectiveness calculations

Effectiveness measures used were cases prevented, deaths prevented, YHLG, and DALYs averted. YHLG were reported because DALYs were very low due to low recorded mortality and for comparison with studies not reporting DALYs. Malaria incidence per 1,000 population was estimated from BHU-diagnosed malaria cases, as 87% of refugees surveyed reported using BHUs for healthcare[85, 281]. Population figures were taken from biannual UNHCR records and crosschecked with HNTPO data, NGO family registrations, and spraying records, but potentially over-represented due to population mobility. As population estimates affected incidence calculations, a reduced population set was included in sensitivity analysis.

Cases prevented by vector control were calculated in sprayed settlements as 'the number of actual cases' minus 'the number of cases that would have occurred in the absence of spraying'. Unsprayed settlements were used for controls and matched with sprayed settlements with

similar populations and incidence rates from the same district, using randomised controlled trial principles. As some unsprayed settlements had lower incidence rates, which could have underestimated cases prevented, a higher transmission reduction was tested in sensitivity analysis. Inversely, the inherent variability in caseloads between villages and over years could have overestimated cases prevented, and a lower transmission reduction was also tested in sensitivity analysis.

Cases prevented by case management could not be calculated readily, as no counterfactual settlements without case management existed. Thus, the worst-case scenario was used in which case management prevented no additional cases and thus had no impact on transmission, with higher estimates modelled in sensitivity analysis.

Deaths prevented were calculated as the product of the number of falciparum cases prevented multiplied by the case fatality rate (CFR). This enabled comparison across vector control and case management and derivation of YHLG. Vivax CFR was estimated as zero. A falciparum CFR of 0.71% (i.e. 44 deaths out of 6,210 falciparum cases) for Afghan refugees was obtained from two years of mortality data in study settlements in Hangu district[282]. As household deaths were seldom reported and not directly attributable to malaria, and CFR data were collected during epidemic conditions, both a higher CFR and lower non-epidemic CFR were tested in sensitivity analysis.

Years of healthy life gained (YHLG) summed morbidity and mortality gains from cases prevented. Mean days of illness per episode, obtained by household survey, were 12 for vivax and 18.4 for falciparum. Mean age at death for falciparum, obtained from BHU records, was 16.4 years. Age-disaggregated life expectancy data were obtained from WHO life tables for Afghanistan over the study time-period [283] and used for calculating years of life lost, as it was anticipated based on discussion with local experts that these rates would be more similar to refugee death rates than would those for the host population. Calculations using BHU and Afghan life table data were compared and found to be similar. However, it is worth noting that neither could be assumed to be completely accurate, but instead seen as the best available to model years of life lost, and results should be interpreted accordingly. Morbidity gains per case averted were calculated as mean days ill multiplied by percentage of nonfatal cases (i.e. 1 minus CFR). Mortality gains per case averted were calculated as: 'life expectancy at age of death' minus 'mean age at death' multiplied by 1 minus CFR. A 3% discount rate was used, to capture present valuation of future benefit or harm [284], as its common usage in other studies improved comparability [285-287]. YHLG were obtained by dividing day results by 365.

DALYS averted were calculated for falciparum and vivax combined according to WHO methods, with 3% discounting, 0.053 disability weighting for moderate infectious disease, and uniform age weighting [288, 289], as: 'years of life lost to malaria mortality plus years of malaria-related disability in the absence of the intervention' minus 'years of life lost to malaria mortality plus years of malaria-related disability in the presence of the intervention'. Major DALY assumptions (i.e. discount rate, age weighting, disability weighting, life expectancy, CFR) were tested in the sensitivity analysis.

Cost calculations

Using a standard ingredients approach, total costs were calculated over five years for the whole control programme and for vector control and case management components individually. *Provider cost data* were collected from UNHCR, HNTPO and four implementing partners providing healthcare services covering 80% of settlements. Shared provider costs, associated with both vector control and case management (i.e. malaria inspectors and supervisors, administrative and finance staff, general health-staff, overheads, storage, transport) were allocated per programme component. *Household cost data* were estimated by facility exit survey. The survey was conducted by two male CHWs, experienced in interviewing, of 623 malaria outpatients at four BHUs in Naguman, Kotki, and Azakhel settlements, to calculate weighted average household costs. Settlements were purposively selected to represent lower, middle, and higher-income households. Data collected on: (i) malaria species diagnosed; (ii) travel and waiting times for BHU providers; (iii) travel and waiting times for non-BHU providers; (iv) payments at non-BHU providers; and (v) time and productivity lost from illness were used to estimate direct and indirect household costs per malaria episode.

Total annual case management costs were estimated as: ('provider cost per case' plus 'household cost per case') multiplied by 'number of cases diagnosed and treated annually'. Case management costs per strain and per year were calculated as: ('number of positive slides recorded' multiplied by 'cost per case diagnosed and treated') plus ('number of negative slides recorded' multiplied by 'cost per slide'), with mixed cases assumed to incur falciparum costs and negative results costed as: slide plus reagent plus 'microscopist time per slide'. Provider costs for case management summed direct costs from all participating providers. Specific costs were laboratory technicians, microscopes, slides and reagents, antimalarials, training, and monitoring. Shared costs were allocated as described above for vector control. Household costs for case management summed direct and indirect costs for service-users, which were estimated per episode by the exit survey then multiplied by numbers of cases to estimate total annual

costs. Direct costs were costs incurred through treatment. Indirect costs were costs incurred through travel and the value of time lost from regular activities, due to illness, and due to caring for those ill. Service-user costs per case were: 'direct costs' plus 'indirect costs' plus 'carer costs' plus 'productivity lost to morbidity or mortality'.

Direct household costs were: 'average per-case test and treatment costs for non-BHU providers' plus 'average per-case travel costs'. Estimated travel costs for patients and carers were: 'travel costs to and from a facility' multiplied by 'number of journeys per person per episode'. As polypharmacy was common among private providers, meaning malaria patients received non-essential tests and drugs they would not have incurred without malaria infection, these were included as direct costs.

Indirect household costs were: ('travel time to and from facilities' multiplied by 'number of journeys per person per episode' plus 'time per person spent in facilities waiting and consulting' plus 'additional non-productive time spent ill') multiplied by 'time value for patients and carers'. Time spent ill was estimated from survey data as 12 days for vivax and 18.4 days for falciparum malaria. As this was potentially overestimated, a lower estimate was tested in sensitivity analysis. Time, for both service-users and carers, was valued as 'time in days' multiplied by 'daily wage' multiplied by '% in paid employment' using the average daily wage of US$1.65 paid by PDH and estimating that 34.7% of adult refugees (i.e. 65% of men, 1% of women) earned wages based on HNTPO interview data[290]. As this estimation undervalued women's unpaid domestic work, higher estimations were tested in sensitivity analysis. For cost of death an adapted human capital approach was used to estimate potential life-long productivity losses as data did not allow for willingness-to-pay estimations. Estimated length of productive life was calculated by subtracting 16.4 years, the mean age at death from falciparum malaria, from median Afghan life expectancy using an Afghan life table, as no life table was available for Afghan refugees [291]. Productivity valuation was: 'discounted value of future income' multiplied by 'the value of one year of income' multiplied by 'case fatality rate'. A discount rate of 3% was assumed and productivity lost to mortality estimated using both epidemic and non-epidemic case fatality rates (CFR). While non-working children could not be disaggregated, malaria was most frequent in working ages. Carers were normally women or unemployed householders, thus replacement-cost valuation using the generalist daily wage paid to refugee labourers (i.e. US$1.65) was selected.

Total annual vector control costs summed provider and service-user costs associated with vector control. Costs for participating providers were entomologists, spray-personnel, spray pumps,

protective gear, and insecticide. Implementing partners provided specific and shared cost data (e.g. overheads, vehicles, personnel) from expenditure records, budget files and staff interviews. As malaria control was part of integrated health-service delivery, shared support cost allocation differed by provider. Cost allocation approaches were: (i) personnel costs multiplied daily wages by estimated time in post; (ii) annual training was calculated as (number of trainees for NWFP programme/number of trainees for all programmes) multiplied by (total training costs); transport and overheads were split by number of operational sectors weighted by numbers of malaria staff or similar indicator of programme size; and monitoring costs were estimated from HNTPO interviews. Household costs associated with vector control, estimated by provider interview, summed time lost to women's unpaid work during house preparation, time waiting for IRS/drying, and post-spraying house reorganisation, based on replacement cost of a domestic worker. Household costs were very small and thus treated as zero for simplicity.

Annual per-capita case management costs were calculated by dividing total case management costs by total recorded settlement population. *Annual per-capita vector control costs* were calculated by dividing total vector control costs by the total recorded population of settlements sprayed.

All costs were converted to US$2015 constant prices using Pakistan's national GDP deflator and International Monetary Fund statistics[292-294]. Capital costs were annualised using the World Bank discount rate for Pakistan of 10% and expected useful lifespan (i.e. BHU buildings and microscopes at 20 years, vehicles at 10 years, and computers, photocopiers, and spray pumps at 5 years).

Cost-effectiveness calculations

Cost per case prevented by vector control was calculated as: 'total programme and household costs of vector control and case management' divided by 'total number of malaria cases prevented'. No cases were prevented by case management in the main analysis, so costs were calculated as zero. The incremental cost-effectiveness ratio (ICER) for cases prevented by vector control was then calculated as difference in cost divided by difference in effect: ('total programme and household costs of vector control and case management' minus 'total programme and household costs of case management alone') divided by ('number of cases prevented by the whole programme' minus 'number of cases prevented by case management alone'). Costs and ICERs for malaria deaths prevented, per YHLG, and per DALY averted were calculated similarly. The WHO cost-effectiveness threshold for DALYs of 3 times Pakistan's GDP per capita in year 0, i.e. US$1,436 (range US$537-US$3,864), was used because preference

elicitation data were unavailable and it remains an established threshold[295, 296]. However, given criticisms of the WHO threshold by Shillcutt and others[297, 298], Wood *et al*'s threshold values for Pakistan, i.e. US$87-US$669, were also compared[299].

Sensitivity analysis

A univariate sensitivity analysis was conducted, as probabilistic analysis would have been difficult without cost and effect distributions. Inputs for major assumptions of population, malaria treatment costs, valuation of women's time, days of productivity lost to illness, CFR, cases prevented, and DALY assumptions were varied and resulting costs compared with effectiveness outcomes. To test the effects on the ICER for cases prevented of:

1. increasing falciparum treatment costs, a higher estimate using SP+Artesunate was tested;
2. reducing population size, an additional annual incidence set was calculated using a population of one-half recorded size;
3. varying cases prevented by vector control, both increased and reduced rates of 50% were tested[85, 300];
4. increasing cases prevented by case management above zero, rates of 30% and 50% were tested[111];
5. reducing days of productivity lost to malaria illness, lower estimates from Nepal (i.e. 7.9 days for vivax, 10.9 days for falciparum) were used[253];
6. reducing valuation of women's time, two additional daily rates of $1.00 and $0.00 were used.

To test the effects of varying DALY assumptions on the ICER for DALYs averted:

- the 3% discount rate was compared with a rate of 5% and 10%[301];
- uniform age weighting was compared with non-uniform weighting;
- disability weighting of 0.053 for an acute moderate infection episode was compared with 0.005 for a mild episode and 0.254 for post-acute consequences as estimated for the 2010 Global Burden of Disease[289];
- historic Afghan life expectancy was compared with a 2014 Afghan life table[283]; and
- the 0.71% CFR was compared with a possible non-epidemic estimate of 0.05% (an estimated midrange CFR for Pakistan for 2003-2013[302]) and a doubled epidemic estimate to account for potential underreporting of deaths, as there was no required death registration.

Ethics

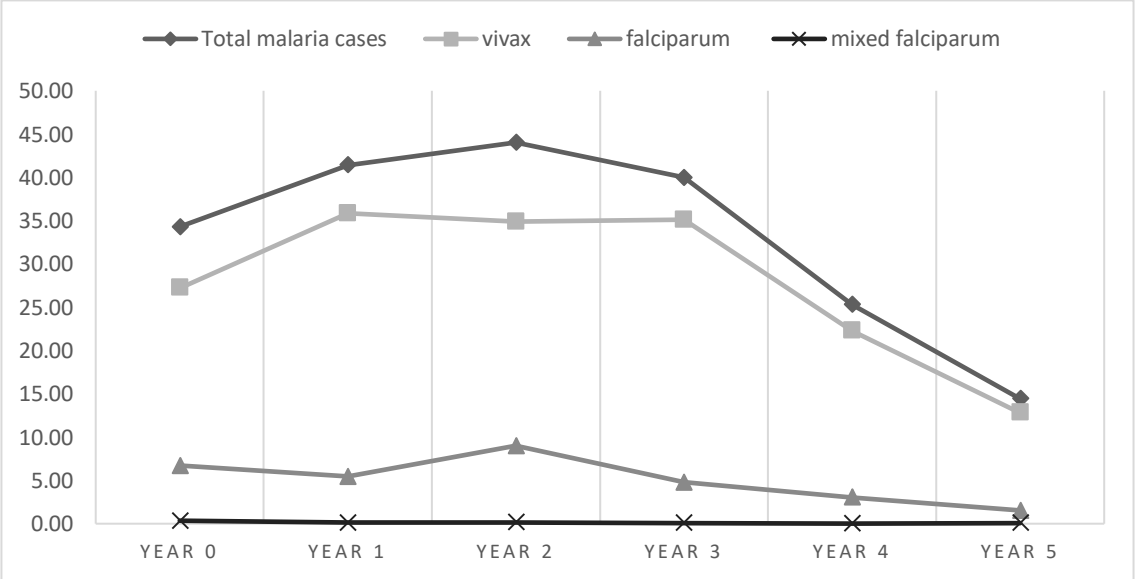
Local ethics approval for operational research was provided by UNHCR Pakistan office. Approval for retrospective data analysis was provided by the LSHTM research ethics committee (reference 5508). All patient data were anonymised prior to inclusion.

Results

Epidemiology and response

Figure 5 shows malaria incidence in refugee settlements rose from 34 per 1,000 person-years in year 0 to a peak of 44 per 1,000 person-years in year 2, then declined steadily to 14 per 1,000 person-years in year 5. Table 4a shows annual population, malaria incidence, and programme responses. At baseline in year 0, 193 health facilities provided case management for 2.4 million refugees (0.8/10,000 population). The number of facilities peaked in years 2-3 with 1.0/10,000, decreasing to 0.6/10,000 in year 5. From year 1 onwards, high-incidence settlements also received IRS, peaking in year 3 with 50% (77/155) of BHU catchment settlements covered and reducing to 41% (29/71) of remaining settlements in year 5. Programme effectiveness and cost-effectiveness results are reported for years 1-5 only, as year 0 did not include IRS.

Figure 5. Malaria incidence per thousand in KPK refugee settlements, Year 0 to Year 5



Effectiveness analysis

Cases and deaths prevented: Table 4b shows that over years 1-5, an estimated 67,988 vivax cases (annual average 13,598), 18,578 falciparum and mixed-infection cases (annual average 3,716), and 132 deaths (annual average 26) were prevented through IRS.

Table 4. Epidemiology, programme effectiveness, and cost-effectiveness by year

a. Epidemiology	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Population	2,402,726	2,386,726	1,832,077	1,541,577	1,298,006	1,236,325
P. vivax cases	65,410	85,560	63,909	54,096	28,898	15,815
P. falciparum cases	16,121	12,984	16,495	7,376	3,941	1,895
Mixed falciparum cases	829	282	253	133	15	122
Total cases	*82,360*	*98,826*	*80,657*	*61,605*	*32,854*	*17,832*
Vector control response (%)						
Number of settlements sprayed with malathion	0	64 (100)	76 (100)	39 (51)	19 (56)	13 (45)
Number of settlements sprayed with lambda-cyhalothrin	0	0 (0)	0 (0)	33 (43)	15 (44)	13 (45)
Number of settlements sprayed with permethrine	0	0 (0)	0 (0)	5 (6)	0 (0)	3 (10)
Total settlements sprayed	*0*	*64*	*76*	*77*	*34*	*29*
Case management response						
total BHUs	193	190	180	155	101	71
per 10,000 population	0.80	0.80	0.98	1.01	0.78	0.57

b. Effectiveness indicators	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Cases prevented						
P. vivax	..	13,979	19,406	21,181	11,769	1,653
P. falciparum/mixed	..	3,106	6,144	7,754	1,087	487
Total cases		17,085	25,550	28,935	12,856	2,140
Deaths prevented	..	22	44	55	8	3
Years healthy life gained						
P. vivax	..	460	638	696	387	54
Discounted *P. vivax*	..	460	619	656	354	48
P. falciparum	..	949	1,878	2,370	332	149
Discounted *P. falciparum*	..	949	1,823	2,234	304	132
DALYs averted	..	2,511	3,756	4,253	1,890	315

c. Cost-effectiveness indicators	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Cost per case prevented						
P. vivax	..	US$142	US$88	US$85	US$106	US$539
P. falciparum/mixed	..	US$641	US$278	US$233	US$1,152	US$1,829
Total cases	..	US$116	US$67	US$63	US$97	US$416
Cost per death prevented	..	US$90,224	US$39,182	US$32,886	US$257,576	US$116,415
Cost per YHLG	..	US$1,412	US$679	US$590	US$1,741	US$4,383
Cost per discounted YHLG		US$1,412	US$700	US$626	US$1,903	US$4,948
Cost per DALY averted	..	US$792	US$455	US$426	US$662	US$1,033

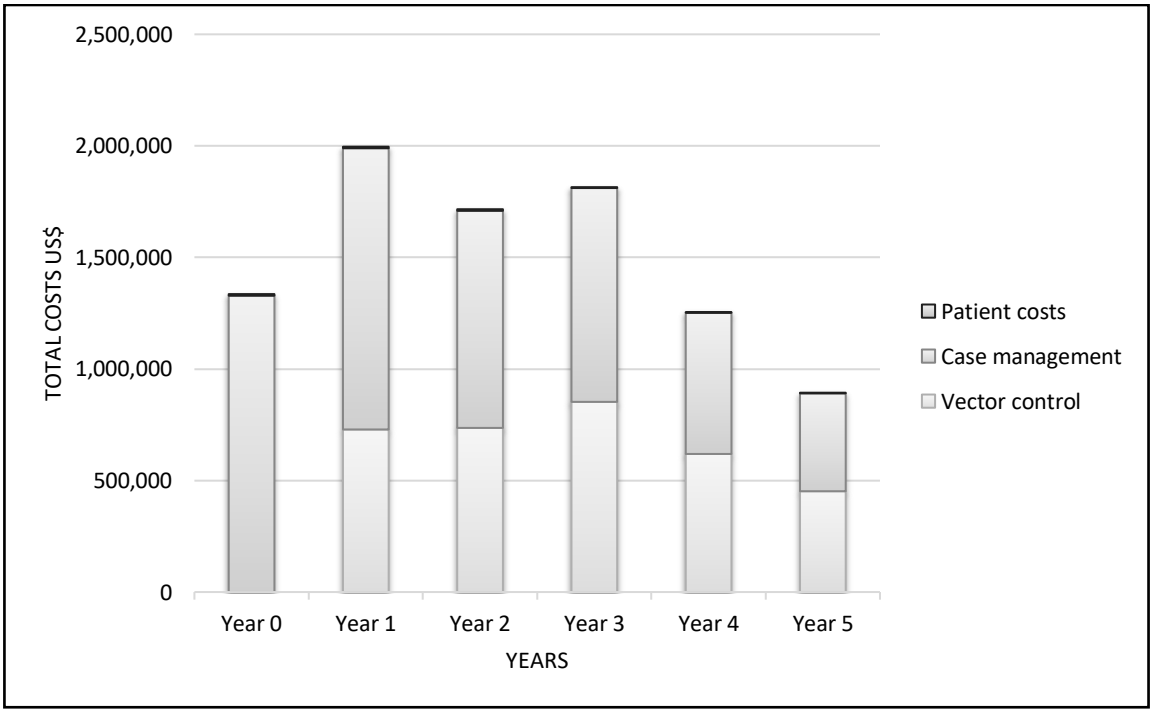
YHLG: Days of healthy life gained per case prevented were 12 for *P. vivax*, 111 for *P. falciparum*. Per case estimates were multiplied by cases prevented and then by 365 to obtain a total 2,235 YHLG for vivax prevention (annual average 447) and total 5,678 YHLG for falciparum prevention (annual average 1,136). Discounted YHLG totalled 2,138 (annual average 428) for vivax prevention and 5,443 (annual average 1,089) for falciparum prevention (Table 4b).

DALYs averted: Disability-adjusted life-years averted were estimated as 0.147 per case prevented for total cases, thus accounting for vivax and falciparum morbidity and mortality. This was then multiplied by cases prevented to obtain a total of 12,725 DALYs averted (annual average 2,545) during years 1-5 (Table 4b).

Cost analysis

Total costs: Programme costs totalled US$8.9 million (US$1.5 million annual average) for the full six years (years 0-5) and US$7.7 million (also US$1.5 million average) for the five years included in cost-effectiveness analysis. UNHCR funded approximately 56% overall with remaining costs divided between HNTPO (i.e. 12% overall) and NGO service-providers (i.e. 32% overall). HNTPO and NGO service-providers' proportional contributions shifted, from 6% and 50% respectively in year 0 to 26% each in year 5. Figure 6 shows an overall decline in costs from US$1.3 million at baseline to US$890,623 in year 5, with two peaks in years 1 and 3. Case management was proportionately higher at US$5.6 million (62%), decreasing from US$1.3 million annually (100%) at baseline to US$438,765 annually (49%) in year 5. Vector control totalled US$3.4 million (38%), peaking in year 3 at US$852,477 (47%). Service-user case management expenditures totalled US$27,861 (0%), decreasing with the epidemic curve from US$7,025 (1%) at baseline to US$1,117 (0%) in year 5.

Figure 6. Total programme costs by year



Component costs: The costliest vector control components were personnel and insecticide at US$2.9 million (85%) total. An increase in vector control costs in year 3 was associated with increased insecticide costs due to initiation of lambda-cyhalothrin for IRS in half of settlements sprayed. The costliest case management component was personnel at US$3.7 million (67%). Locally purchased antimalarials and imported *primaquine*, at US$272,283 (5%) and US$35,692 (1%) respectively, were minor components. Provider transport increased as a share of costs

comparatively over time, from US$153,078 (12%) at baseline to US$83,374 (19%) in year 5. Service-users spent 22% more treating falciparum than vivax malaria (i.e. US$16,899 versus US$10,962 respectively), though these were minor components (0%) of overall societal costs.

Per capita costs: The mean annual cost per capita for the full programme was US$0.56, ranging US$0.36-0.76 over five years. Mean annual costs per capita for vector control and case management separately were US$0.23 and US$0.33 respectively. For vector control, this ranged from US$0.0-0.34, highest in year 3. For case management, this ranged from US$0.23-0.40 and was highest in year 0 (US$0.36) and year 3 (US$0.40).

Per-case costs: Provider costs per case diagnosed and treated averaged US$14.98 for vivax and US$14.93 for falciparum, with the largest component cost being US$10 for staff. Household costs per case were estimated from survey data as US$10.83 for vivax and US$18.91 for falciparum. Given low mortality rates, the largest household component cost per case was productive time lost to illness at US$8.22 for vivax and US$12.63 for falciparum. A malaria death caused an estimated US$16,038 lost productivity, using the assumption that individuals would continue with similar work and wage rates, given the protracted nature of the refugee setting and that at death an individual loses all future life-years and future productivity anyway.

Cost-effectiveness analysis

Table 4c shows changes in programme cost-effectiveness indicators over the course of year 1 to year 5. Table 5 compares cost-effectiveness of the integrated programme versus case management alone for a population of 100,000. It includes costs and ICERs of events averted averaged over the full five-year analysis period (years 1-5), and separately for years 1-3 and 4-5, to compare epidemic peak and ending. In a model population of 100,000, the *cost per case prevented* averaged US$88 (US$77 in years 1-3 and US$143 in years 4-5). For vivax, cases prevented averaged US$111 (US$103 in years 1-3 and US$160 in years 4-5). For falciparum, cases prevented averaged US$442 (US$331 in years 1-3 and US$1,361 in years 4-5). *Cost per death* prevented averaged US$316,734 (US$45,635 in years 1-3 and US$191,715 in years 4-5). *Cost per YHLG* averaged US$1,011 (US$806 in years 1-3 and US$2,323 in years 4-5). *Cost per DALY averted* averaged US$601 (US$524 in years 1-3 and US$972 in years 4-5).

Table 5. Effects, costs, and incremental cost-effectiveness ratios of adding vector control to case management in refugee settlements in Pakistan over five years, and disaggregating years 1-3 and 4-5, in US$2015

Effects per 100,000 population	**Integrated programme**	**Case management**	**Comparison**
	n=100,000	*n=100,000*	*n=100,000*

Vivax cases prevented	835	..	835
Falciparum/mixed cases prevented	209	..	209
All cases prevented	1,044	..	1,044
Deaths prevented	0.29	..	0.29
YHLG	91	..	91
DALYs averted	153	..	153
Costs per 100,000 population	**Average cost-effectiveness ratio**		**Comparison**
Costs of events averted over 5 years	**US$**	**US$**	**ICER US$**
Programme costs per 100,000	92,250	51,406	
Cost per vivax case prevented	111	..	50
Cost per falciparum/mixed case prevented	442	..	182
Cost per case prevented	88	..	39
Cost per death prevented	316,733	..	140,234
Cost per YHLG	1,011	..	448
Cost per DALYs averted	*601	..	**266
Costs of events averted in years 1-3	**US$**	**US$**	**ICER US$**
Programme costs per 100,000	95,643	55,420	
Cost per vivax case prevented	103	..	43
Cost per falciparum/mixed case prevented	331	..	139
Cost per case prevented	77	..	32
Cost per death prevented	45,635	..	19,192
Cost per YHLG	806	..	339
Cost per DALYs averted	*524	..	**220
Costs of events averted in years 4-5	**US$**	**US$**	**ICER US$**
Programme costs per 100,000	84,539	42,284	
Cost per vivax case prevented	160	..	80
Cost per falciparum/mixed case prevented	1,361	..	680
Cost per case prevented	143	..	71
Cost per death prevented	191,715	..	95,825
Cost per YHLG	2,323	..	1,161
Cost per DALY averted	*972	..	*486

NB: *Below WHO cost-effectiveness threshold of US$1,435.86 (3*US$478.62 or Y0 Pakistan GDP per capita) per DALY averted. **Highly cost-effective at <US$478.62 (Y0 Pakistan GDP per capita) per DALY averted. GDP=gross domestic product; <GDP per capita is 'very cost-effective', 1-3*GDP per capita is 'cost-effective', >3*GDP per capita is 'not cost-effective.'

The additional cost of including IRS in a model population of 100,000 averaged over five years per case prevented was US$39 (US$33 in years 1-3 and US$69 in years 4-5). For vivax cases prevented this was US$50 (US$43 in years 1-3 and US$80 in years 4-5). For falciparum cases prevented this was US$182 (US$139 in years 1-3 and US$680 in years 4-5). The additional cost averaged over five years per death prevented was US$140,234 (US$19,192 in years 1-3 and US$95,825 in years 4-5). The additional cost averaged over five years per YHLG was US$448 (US$339 in years 1-3 and US$1,161 in years 4-5). The additional cost averaged over five years per DALY averted was US$266 (US$220 in years 1-3 and US$486 in years 4-5). Adding IRS to routine case management was thus 'highly cost-effective' using the WHO threshold of US$479 per DALY averted (i.e. Y0 Pakistan GDP per capita) when averaged over five years and in years 1-3. This reduced in years 4-5, as the epidemic ended, but remained below the WHO 'cost-

effective' threshold of US$1,436 per DALY averted (i.e. 3 times Y0 Pakistan GDP per capita). The additional costs of adding IRS to case management per DALY averted were cost-effective over all time-periods using Woods *et al*'s threshold of US$87-669.

Sensitivity analysis

Table 6 shows results of varying treatment costs, population, cases prevented, days of productivity lost, time valuation, and DALY assumptions. Increasing falciparum treatment costs to account for ACT, reducing days of productivity lost, and reducing valuation of women's time had no notable effect on the ICER for cases prevented. Reducing the population by one-half increased the ICER from US$39 to US$78. Increasing cases prevented by vector control by 50% reduced the ICER to US$26, while reducing cases prevented by vector control by 50% increased the ICER to US$79. Increasing cases prevented by case management increased the ICER to US$56 for a 30% increase and US$78 for a 50% increase. For DALY assumptions, increasing the discount rate increased the ICER for DALYs averted from US$266 to US$399. Changing to non-uniform age weighting increased the ICER to US$477. Varying disability weighting had little effect, while varying life expectancy had no effect on the ICER. Lowering the CFR to a non-epidemic average increased the ICER to US$3,914. Doubling the CFR lowered the ICER to US$133. Thus, assumptions with the largest effects on the ICER for cases prevented were population size, cases prevented by vector control, and cases prevented by case management. Assumptions with the largest effects on the ICER for DALYs averted were the discount rate, age weighting, and CFR. Life expectancy differences had no effect on the ICER for DALYs averted.

Table 6. Sensitivity to selected parameters of the societal incremental cost-effectiveness ratio (ICER) in US$2015 of cases prevented or DALYs averted

Parameter: Cases prevented[&]	ICER
Study ICER for cases prevented	*39*
Cost of Pf treatment *(US$0.83)*	
Increased by 150%	39
Increased by 300%	39
Population size (2,402,726)	
Reduced by 50%	78
Cases prevented by vector control (63%)	
Increased by 50%	26
Reduced by 50%	79
Cases prevented by case management (0%)	
30% of total cases prevented	56
50% of total cases prevented	78
Time valuation for women (US$1.65/day)	
US$1.00/day	39
US$0.00/day	39
Days productivity lost to illness (12.0; 18.4)	

Parameter: DALYs averted[&]	ICER
Study ICER for DALYs averted	*266*
DALY assumptions:	
Discount rate (3%)	
5%	399
10%	611
Age weighting (uniform K=0)	
Non-uniform	477
Disability weighting (0.053)	
0.005	323
0.254	320
Life expectancy (2000)	
2014 table	266
Case fatality rate (0.71%)	
Lower non-epidemic (0.05%)	3,914

Pv 7.9 days	39	Higher epidemic (1.42%)	133
Pf 10.9 days	39		

NB: [&]Actual parameter values used for the study are in parentheses.

Discussion

Primary findings

This study is the first to model the cost-effectiveness of adding vector control to case management during an epidemic in a co-endemic vivax-predominant setting. It is one of the first to estimate costs per case averted and first to estimate costs per DALY averted by IRS in South Asia, where IRS has traditionally dominated as a means of malaria prevention[54, 303].

Annual indicators showed increasing then decreasing programme efficiency over six years as population and malaria incidence increased then declined. Similarly, the rise and sustained fall in household costs reflected fewer service-users due to population decline, reduced numbers of BHUs, and falling incidence. IRS prevented approximately 266% more vivax than falciparum cases (i.e. 67,988 vivax versus 18,578 falciparum), due to the dominance of *P. vivax* in the area. Conversely, IRS enabled approximately 154% more YHLG from falciparum than vivax prevention (i.e. 5,678 falciparum YHLG versus 2,235 vivax YHLG), because falciparum prevention was worth more YHLG (i.e. 0.30 years for falciparum versus 0.03 for vivax). DALYs averted, which included both vivax and falciparum, were relatively low due to the low estimated falciparum CFR.

IRS appeared to improve horizontal equity (providing equal access to all those with equal needs) because it cost less than case management for households. Household case management costs, though insignificant within overall programme terms, were likely difficult for low-income service-users. Direct household costs were low because IRS was provided free to service-users and most attended BHUs, thus receiving free treatment to which they were able to walk. However, indirect case management costs such as income lost due to illness were a concern for low-income households. Additionally, those who attended private providers could pay significant amounts for less reliable diagnosis and treatment.

Adding IRS appeared highly cost-effective in epidemic conditions and less so as cases and CFR reduced. This intervention supported refugees during prolonged epidemic conditions in refugee settlements, but cost-effectiveness can be compared with other programmes using costs to the health system (per capita), per case diagnosed and treated, and per case or DALY averted[86]. For example, health system costs per capita for five years (calculated by dividing total programme costs by total population in the study area), were US$0.73 for the full programme, US$0.62 for case management, and US$0.84 for vector control. These compared favourably to health system

costs for malaria control found by Shretta *et al* globally (US$2013 2.50), for sub-Saharan Africa (US$2013 1.21-3.47), and for South Asia (Afghanistan US$2013 1.34; India US$2013 0.30-9.39; Nepal US$2013 0.45-1.36)[86]. Average cost per patient diagnosed and treated (US$14.95) was similar to findings by Hansen *et al* for microscopy diagnosis and treatment in moderate (US$2013 10.64) and low (US$2013 22.38) transmission settings in Afghanistan and by Bualombai *et al* (US$2013 13.23) in Thailand, though higher than by Davis *et al* (US$2013 4.36) in Papua New Guinea per child vivax case diagnosed and treated[26].

Due to low morbidity and mortality compared with high-endemicity predominantly falciparum malaria settings, costs per event averted were relatively high, making cost-effectiveness results for IRS higher than in many endemic settings[47, 303, 304]. For example, average cost per case averted (US$88) was higher than findings by Smithuis *et al* (US$2013 16.54) or Kamolratanakul et al (US$2009 2.7) for IRS with DDT in Myanmar and the Thai-Myanmar border respectively, but lower than findings by Bhatia *et al* (US$2013 126.39) for IRS with deltamethrin in Gujarat[26, 303]. Given DDT was considerably cheaper than other IRS insecticides, this is perhaps unsurprising. Average cost per DALY averted (US$601) was considerably higher than findings by Yukich *et al* (US$2008 119-132) for IRS in Mozambique and KwaZulu-Natal[47]. The programme was more effectively compared with South Asian programmes, as malaria transmission patterns were similar. However, while Bhatia *et al* reported costs per case averted, no other South Asian studies were found reporting costs of cases or DALYs averted through IRS[26, 39]. It is possible that researchers in South Asia have tended to avoid calculating DALYs for malaria prevention interventions as relatively low incidence and proportionally high vivax transmission means fewer cases, lower mortality, and thus elevated costs per DALY averted. However, study results indicate that cost-effective results per DALY averted are still feasible in the region. Additionally, while it would have been useful to compare cost-effectiveness with interventions in epidemic situations, such evidence remains minimal as already noted by Worrell *et al* in 2004[53].

As incidence continued to fall in the refugee settlements, the malaria control strategy evolved away from targeted IRS to insecticide-treated net (ITN) social marketing and then targeted free distribution of ITNs to communities at highest malaria risk[115, 152]. ITNs have generally been found to be more cost-effective than IRS, with a review by White *et al* finding the median ICER per DALY averted from a provider perspective was US$2009 27 for ITNs (range US$2009 8-110 from 15 African studies) versus US$2009 143 for IRS (range US$2009 135-150 from two southern African studies)[303]. It is possible that the incremental cost of adding prevention using ITNs would be lower than for IRS. However, this cannot be assumed as IRS is generally more effective for transmission control in South Asia than it is in Africa and should be compared in the same

setting[281]. The policy of CQ treatment for *P. vivax* infection has not changed in Pakistan and vivax remains the predominant malaria species[223].

Implications

Despite malaria incidence being relatively lower than in sub-Saharan Africa and vivax predominating, ICER results showed that adding malaria prevention with targeted IRS to routine case management was cost-effective using both WHO's aspirational and potentially overly-generous threshold of three times GDP and Woods *et al*'s more conservative range for Pakistan of US$87-669[296, 299]. Results can potentially provide lessons outside South Asia as malaria control progresses toward elimination. Considerations additional to cost will become increasingly important as countries transition to elimination and costs per event averted likely increase[270, 271, 305]. Additionally, in mixed *Plasmodium* species settings, *P. falciparum* is more easily reduced by vector control, leaving *P. vivax* as the majority species[85]. Therefore, cost-effectiveness analyses of malaria control interventions in low-endemicity, unstable, and epidemic settings could become increasingly important.

Sensitivity analyses indicated that the key assumptions for the ICER for cases prevented were population size, cases prevented by vector control, and cases prevented by case management, while those for DALYs averted were the discount rate, age weighting, and CFR. Changes in any of these assumptions could significantly change the ICER. This appeared to be a greater issue for ICER for cases prevented than for DALYs averted, as two of the three latter assumptions depended on societal values (e.g. perceived value of future versus present day, perceived value of the young). However, assumptions related to population size, cases prevented, and CFR relied primarily on data accuracy and would therefore require more attention from decision-makers when choosing interventions.

Methodologically, accurate cost-effectiveness analysis for *P. falciparum* depends primarily on the accuracy of CFR calculations. The CFR estimate used was taken from a camp survey and BHS data[282]. Because no formal system for death notification existed for refugees, who had no incentive to report deaths, reported causes of death were not confirmed and CFR estimates were subject to unverifiable assumptions. Estimates for vivax and falciparum cases prevented were more reliable than deaths prevented because they were based on quality-assured microscopy of actual cases and on differences in clinical incidence between matched sprayed and unsprayed camps during the study period[85, 150]. Vivax malaria was three times more common than falciparum malaria and CFR was zero for vivax. Thus, cost-effectiveness analysis for vivax made fewer assumptions than for falciparum and can be assumed to be more accurate.

However, given this is an assumption it was still worthwhile to report falciparum and mixed infection results.

Programmatically, changes to organisational structure could increase sustainability. Cost distributions for both case management and vector control indicated personnel as the major cost component. As HNTPO provided technical support in maintaining low malaria endemicity levels, its average costs increased as incidence fell. Thus, staff rationalisation appeared feasible over the long term by strengthening managerial skills and widening the responsibilities of local personnel and broadening the skill base of technical personnel (e.g. training malaria specific diagnosticians and health-workers to take a wider role in public health programmes, such as diagnosis and treatment of other diseases). Excepting insecticide and antimalarials, remaining cost components were minimal and their reduction would have minimal impact on total costs.

Limitations

Calculations were subject to several dataset limitations and assumptions. First, calculation of effectiveness indicators was subject to methodological assumptions. The use of matched unsprayed settlements was the best control group available retrospectively and the limited regional data did not allow for epidemic or other modelling to improve estimates further. Data testing indicated this comparison was valid. However, as data variability is an increasing concern as numbers decrease, cost-effectiveness results for Years 4-5 may be less accurate than those for Years 0-3. Second, use of private providers by refugees could have underestimated case numbers while vivax recrudescence could have caused overestimation of numbers yet underestimation of intervention effectiveness. Sensitivity analysis results demonstrated how increased or reduced estimates of cases prevented would affect cost-effectiveness estimates, improving or worsening them respectively. While programme managers would need to decide whether an ICER of US$79 was still worthwhile, it seems likely that this would be the case unless another prevention option such as ITNs could be shown to be more cost-effective. Third, low numbers of falciparum cases could have reduced accuracy of resulting service-user costs. Fourth, recall bias and reliance on settlement as a proxy indication of household wealth could have affected the accuracy of some cost data, though the proportions of estimated costs that relied on participant recall (e.g. household costs) were relatively minimal overall. Fifth, Woods *et al*'s cost-effectiveness threshold calculations used QALYs rather than DALYs and compared results directly with WHO thresholds, which seems justified for decision-making given the large margins of error likely in both approaches. Woods *et al* themselves call for further research on realistic cost-effectiveness thresholds for low and middle-income countries[299]. Finally, cost per death prevented was most sensitive to CFR, and respective indicators should be interpreted

cautiously.

Conclusions

While the cost-effectiveness of IRS varied depending on indicators used, the fact remains that many cases and deaths were prevented and the prolonged epidemic was controlled over the study period. Though case management remains a key component of malaria control, this study shows how prevention using IRS can be an important and cost-effective component of malaria transmission control even in a moderate endemicity, low mortality setting.

CHAPTER 4 CLINICAL TRIAL OF EXTENDED-DOSE CHLOROQUINE FOR RESISTANT FALCIPARUM MALARIA AMONG AFGHAN REFUGEES IN PAKISTAN (1995)

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Author contributions:
NH registered the study, analysed and interpreted data, and wrote the manuscript.

Abstract

Background

Falciparum malaria is a significant problem for Afghan refugees in Pakistan. At the time of this study, refugee treatment guidelines recommended standard three-day chloroquine treatment (25mg/kg) for first episodes and extended five-day treatment (40mg/kg) for recrudescent infections, based on the assumption that a five-day course would more likely achieve a cure. An *in-vivo* randomized controlled trial was conducted among refugees with uncomplicated falciparum malaria to determine whether five-day treatment (CQ40) was more effective than standard treatment (CQ25).

Methods

142 falciparum patients were recruited into CQ25 or CQ40 treatment arms and followed up to 60 days with regular blood smears. The primary outcome was parasitological cure without recrudescence. Treatment failures were retreated with CQ40. PCR genotyping of 270 samples, from the same and nearby sites, was used to support interpretation of outcomes.

Results

84% of CQ25 versus 51% of CQ40 patients experienced parasite recrudescence during follow-up (adjusted odds ratio 0.17, 95%CI 0.08-0.38). Cure rates were significantly improved with CQ40, particularly among adults. Fever clearance time, parasite clearance time, and proportions gametocytaemic post-treatment were similar between treatment groups. Second-line CQ40 treatment resulted in higher failure rates than first-line CQ40 treatment. CQ-resistance marker *pfcrt* 76T was found in all isolates analysed, while *pfmdr1* 86Y and 184Y were found in 18% and 37% of isolates respectively.

Conclusions

CQ was not suitable for first-line falciparum treatment in Afghan refugee communities. The extended-dose CQ regimen could overcome 39% of resistant infections that would recrudesce under the standard regimen, but the high failure rate after directly observed treatment demonstrated that its use was inappropriate.

Background

During the extended Afghan conflict, waves of refugees totalling almost three million entered northwest Pakistan with more than one million remaining in 2017, despite efforts by the government of Pakistan to repatriate them[157, 275, 276]. Malaria became a major problem in Afghan refugee camps, due to overstretched health infrastructure and some camps being located on marginal land prone to anopheline mosquito breeding[275]. By the 1990s, malaria among refugees increased ten-fold to over 100,000 cases per annum[275]. Approximately 30% of confirmed cases were due to *P. falciparum* and the remainder to *P. vivax*[306]. CQ was Pakistan's first-line treatment for uncomplicated falciparum malaria from 1950 to 2007[306]. It remains first-line treatment for vivax malaria, so is still used for treating unconfirmed malaria and falciparum infections undetected by microscopy or misdiagnosed as vivax[93, 307].

UNHCR, following national guidelines, adopted a three-day CQ treatment course (total 25mg/kg as 10mg/kg on Day 0 and Day 1 and 5mg/kg on Day 2) in refugee settlements. However, it became apparent during the 1990s that CQ was failing[243, 308]. BHU doctors claimed that many refugees stopped taking CQ tablets once clinical symptoms reduced or only took them intermittently. Health policy-makers assumed that refugee patients were more likely to take sufficient CQ to cure infections if given a five-day course. Consequently, MoH Pakistan adopted as policy a five-day extended CQ course (CQ 40mg/kg as 10mg/kg/day on Days 0-2 and 5 mg/kg/day on Days 3-4) for any refugee patient returning to a BHU with parasitaemia within a few weeks of their first episode. When this policy was introduced, no *in vivo* resistance survey had been undertaken in refugee camps, despite CQ-resistant falciparum parasites spreading widely in Pakistan in the 1990s[243, 308, 309].

As there was no evidence to support claims of poor adherence or the efficacy of extended-dose CQ, an open-label randomized clinical trial was conducted to determine whether supervised CQ treatment administered at 40mg/kg over five days (CQ40) was more effective than 25mg/kg over three days (CQ25) for curing infections completely without recrudescence[310]. The trial aim was to provide stronger evidence for the extended-dose CQ (ECQ) treatment or justification for discontinuing the policy.

Methods

Study design

The primary trial outcome was the proportion of individuals in each treatment arm that showed clinical and parasitological cure with no recrudescence. Sample size was calculated to detect a difference of 15% in cure rate between CQ25 and CQ40 treatment arms with 95% confidence

and 90% precision, assuming a 20% loss to follow-up. The surveys were conducted during winter months to select only recrudescent episodes. Mosquito densities and malaria transmission drop during December and January, providing little opportunity for trial participants to receive further infective bites within the 60-day follow-up period [85, 311]. Thus, subsequent falciparum episodes were regarded as recrudescence.

Two trials, completed in 1998, were conducted in Baghicha, Kagan and Adizai refugee camps (Figure 7). In Baghicha and Kagan, 121 patients were recruited into two treatment groups and followed for 60 days. The 60-day duration was deliberate to allow sufficient time for back-to-back 30-day *in vivo* studies (i.e. sufficient time for cases to recrudesce following initial CQ treatment and recrudesce again following second-line CQ treatment). In Adizai camp, 21 patients were recruited per treatment group and followed for only 28 days. CQ25 patients received standard three-day treatment (CQ 25mg/kg as 10mg/kg on Day 0 and 1, and 5mg/kg on Day 2). CQ40 patients received extended 5-day treatment (CQ 40mg/kg as 10mg/kg/day on Days 0-2 and 5 mg/kg/day on Days 3-4). Dosages were measured in ¼ CQ tablets of 37.5mg each to give an average dosage (range) of 26.2 (25.0, 27.8) mg/kg for the CQ25 arm and 42.1 (40.0, 45.3) mg/kg for the CQ40 arm. All treatment was directly observed for 30 minutes post-treatment.

If parasites reappeared during the follow-up period, patients received CQ40 second-line rescue treatment as per MoH and UNHCR guidelines. However, while investigators were required to follow national guidelines for second-line treatment it was anticipated that many would fail[312]. Thus, if parasites reappeared a further time, patients received single-dose sulphadoxine-pyrimethamine (S: 25mg/kg, P: 1.25mg/kg) or mefloquine (25mg base/kg) treatment, which was known to be more effective. CQ was manufactured by Aventis and supplied by the WHO-Special Programme for Research and Training in Tropical Diseases (TDR). SP and mefloquine tablets were manufactured by Roche. Samples of *P. falciparum* for genotyping analysis were taken at baseline from a clinical trial of CQ and SP conducted by the authors in Adizai camp and Jalalabad eastern Afghanistan in 2002 and 2003 (Rowland unpublished).

Patient recruitment and follow-up

Participants were recruited through passive case detection at BHUs and active case detection in communities. Individuals with symptomatic falciparum malaria who met WHO *in vivo* selection criteria for low to moderate transmission settings were randomized to either CQ25 or CQ40 groups using randomized lists [313]. Exclusion criteria were infants under six months, pregnant women, vivax malaria co-infections, cases with other febrile illness, parasitaemia outside the

range of 1,000-100,000 asexual parasites/µl, or severe malaria. All patients gave informed consent. Ethical approval was provided by both UNHCR Health Committee and the LSHTM Ethics Committee. The trial was registered at the Clinical Trials website, reference number NCT01019408[314].

Local health supervisors collected demographic and clinical information at enrolment, including weight, temperature, and symptoms. Supervisors directly observed treatment according to dosing schedules, prepared blood smears, and recorded temperature and clinical symptoms daily for the first five days, then every third day until day 28. Patients in Kagan and Baghicha were additionally observed every four days until day 60.

Thick and thin blood smears were stained with 3.5% Giemsa solution and all slides read on day of collection by a BHU-based microscopist. Trophozoites and gametocytes were counted against 200 white blood cells (WBC) from thick blood smears, assuming a WBC count of 8,000/µl. A smear was declared negative if no parasites were seen after examining 100 fields. Slides were re-examined for accuracy of diagnosis and recounted by an independent senior microscopist, blinded to patient, follow-up day, original result, and outcome. Differences in count were on average no greater than 5%. Finger-prick blood samples (~200 µL) were dried on Whatman filter paper prior to treatment (Day 0) and sent to LSHTM for genetic analysis.

Trial outcomes were treatment failure rates, fever clearance times (FCT), parasite clearance times (PCT), and number of recrudescences. Therapeutic responses were early treatment failure (ETF), late treatment failure (LTF) and adequate clinical and parasitological response (ACPR) using standard WHO *in vivo* criteria[313]. Parasitological responses were classified using the WHO S-RIII scale for comparison with earlier literature from low transmission settings[313, 315]. Trial staff were trained to ask about and record adverse and severe adverse events. However, adverse event data were not available at the time of analysis.

Statistical analysis

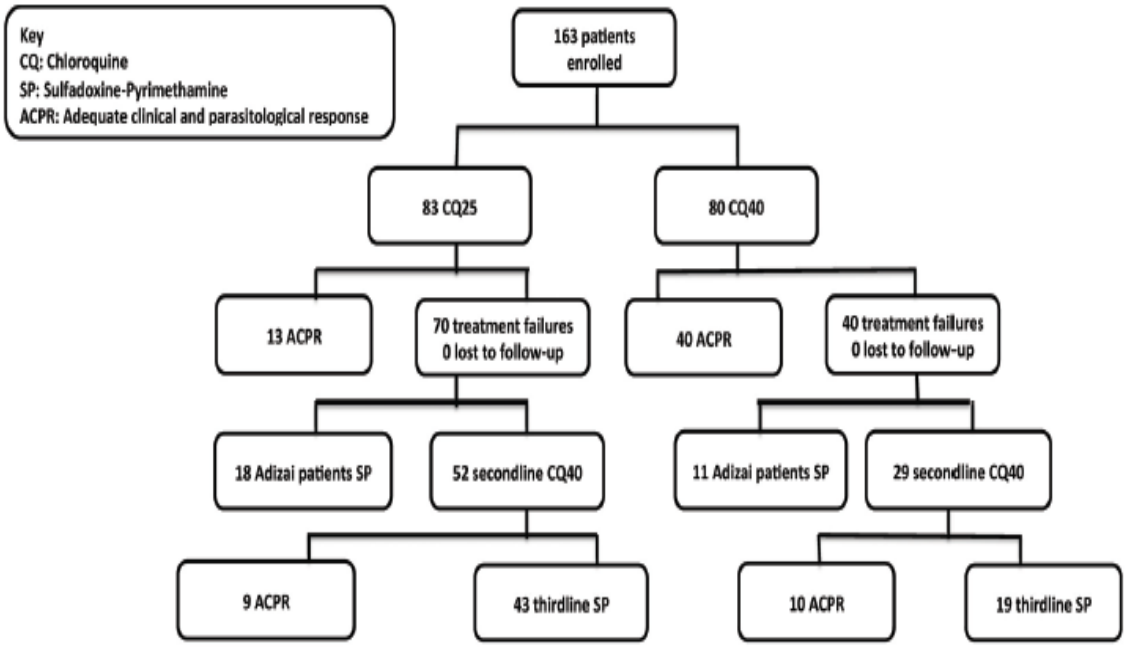
Data were double-entered in Microsoft® Excel, with range and consistency checks to reduce transposition error, and analysed using Stata® 11.0. Analysis was conducted on an intention-to-treat basis. Data from the three study sites were combined for the first 28 days to calculate therapeutic outcomes and analyse subsequent malaria episodes and Kaplan-Meier survival estimates[313]. Data recorded over 60 days from Baghicha and Kaghan were used to estimate second-line therapeutic outcomes. A p-value of <0.05 was considered significant. Univariate analysis used Pearson's chi-square (χ^2) tests for proportions and Mann-Whitney U tests for

continuous data. Logistic regression was used to calculate odds ratios (OR) of treatment success at weekly intervals and differences between treatment outcomes. *A priori* confounders (i.e. camp, gender, weight, age) were adjusted for in multivariate analysis.

Genetic characterisation

PCR genotyping could not be conducted on patient data to determine recrudescences as samples were lost in transit. However, the authors were able to analyse 90 blood samples from falciparum cases in Adizai (the same camp) and 180 from Jalalabad, Afghanistan, collected shortly afterwards for a clinical trial to characterize resistance genotypes (Rowland unpublished). Parasite DNA was extracted from 270 blood spots collected on filter paper pre-treatment (Day 0)[316]. PCR-sequence specific oligonucleotide probe assays were used to analyse genetic polymorphism of *P. falciparum* chloroquine-resistance transporter gene (*pfcrt)* at codons 72-76 and *P. falciparum* multidrug resistance protein-1 (*pfmdr1*) at codons 86 and 184[317]. CQ resistance is associated primarily with point mutations in *pfcrt* leading to a lysine to threonine change at codon 76 (K76T) while *pfmdr1* N86Y and Y184F were thought to have a modulatory effect[318-320]. The *pfcrt* 76T and *pfmdr1* 86Y alleles may serve as predictive markers for CQ resistance in non-immune individuals living in low-transmission areas, while combined *pfcrt* 76T and *pfmdr1* 86Y may be useful molecular markers for resistance to additional drugs, such as amodiaquine (AQ)[320-324].

Figure 7. Trial profile



Results

Enrolment characteristics

Figure 7 shows the trial profile. Of 163 patients recruited, 83 were randomized to CQ25 and 80 to CQ40 treatment groups. Table 7 shows no significant differences in enrolment characteristics between treatment groups on Day 0.

Table 7. Enrolment characteristics on Day 0, by treatment group

Demographic characteristics	**CQ 25 mg/kg**	**CQ 40 mg/kg**
Number enrolled	83	80
Camp		
Adizai	21	21
Baghicha	44	47
Kaghan	18	12
Mean age in years (SD)	12.9 (11.3)	12.9 (11.3)
Age group		
0-5	19	18
6-14	44	44
15+	20	18
Total female	40	48
Mean weight in kg (SD)	30.1 (16.1)	32.2 (18.5)
Clinical characteristics	**CQ 25 mg/kg**	**CQ 40 mg/kg**
Number (%) with temperature >37.5°C	37 (45)	42 (53)
Trophozoite density* (range)	5702 (4297-7566)	6320 (4816-8295)
Number (%) with gametocytes	38 (46)	28 (35)
Gametocyte density* (range)	140 (82-238)	148 (84-260)

NB: *refers to geometric mean. SD is standard deviation.

First-line therapeutic outcomes

No participants were lost to follow up by day 28. Table 8 shows therapeutic and parasitological outcomes using: (i) the WHO *in vivo* system of early and late treatment failure or adequate clinical and parasitological response, and (ii) the parasitological response system of S, RI, RII, RIII [313, 325]. Fever clearance and parasite clearance times were similar in CQ25 and CQ40 arms (Table 8). CQ25 provided adequate clinical and parasitological response in only 13/83 (16%) of patients by day 28, while CQ40 provided 40/80 (50%) ACPR (adjusted OR 0.17; 95%CI 0.08, 0.38). There were few (7%) early treatment failures in either treatment group.

CQ40 patients had fewer recrudescences than did CQ25 patients during the first 28 days. Among CQ40 patients, only one recrudescent episode occurred before Day 7. Among CQ25 patients, 86% of recrudescence occurred between days 7 and 28 post-treatment. The parasitological failure rate was negatively associated with age, with failure highest among under-fives and

lowest among over-fifteens (Table 8). Within each age band, failure rates were consistently lower in the CQ40 group than in the CQ25 group, irrespective of gender or camp.

Table 8. Outcomes on day 28 by treatment group, odds ratios adjusted for age, weight, gender, and camp using logistic regression

Outcomes	CQ 25 mg/kg	CQ 40 mg/kg	OR[1] (95%CI)
Total enrolled	83	80	
Total lost, excluded, or withdrawn	0	0	
Mean days to fever clearance[2] (95% CI)	2.6 (1.9, 3.3)	2.6 (1.9, 3.3)	
Mean days to parasite clearance (95% CI)	2.9 (2.6, 3.1)	3.1 (2.8, 3.3)	
Treatment outcomes: n=163 (%)			
Adequate clinical and parasitological response	13 (16)	40 (50)	1
Early treatment failure	6 (7)	6 (7)	0.28 (0.07, 1.09)
Late treatment failure***	64 (77)	34 (43)	0.16 (0.07, 0.35)
Parasitological outcomes: n=163 (%)			
S	13 (16)	39 (49)	
RI	60 (72)	40 (50)	
RII	10 (12)	1 (1)	
First-line treatment success: n=52 (%)			
Complete parasitological cure without recrudescence***	13 (16)	39 (49)	0.17 (0.08, 0.38)
First-line treatment failures: n=111 (%)			
Age group			
0-5	17 (89)	11 (61)	0.18 (0.03, 1.05)
6-14**	38 (86)	24 (55)	0.17 (0.06, 0.50)
15+*	15 (75)	6 (33)	0.17 (0.04, 0.70)
Gender			
Male**	35 (81)	15 (47)	0.17 (0.06, 0.51)
Female**	35 (88)	26 (54)	0.19 (0.07, 0.56)
Camp			
Adizai	17 (81)	11 (52)	0.26 (0.06, 1.12)
Baghicha**	37 (84)	24 (51)	0.16 (0.06, 0.46)
Kagan	16 (89)	6 (50)	0.23 (0.03, 1.63)

NB: [1]OR is odds ratio, comparing CQ40 to CQ25 adjusted for age, weight, gender, and refugee camp using logistic regression. [2]FCT (<37.5C) excludes those without fever on admission. *<0.05,**p<0.01,***p<0.001

Figure 8 shows the proportion of patients found positive during the first seven days of treatment and the probability of failure among those still positive on subsequent days. The longer a patient took to clear parasites the greater the probability of eventual recrudescence. All cases treated with CQ25 who were still positive on Day 3 ultimately recrudesced, while all cases treated with CQ40 still positive on Day 4 ultimately recrudesced.

Figure 8. Parasite clearance rates and probability of treatment failure among cases still positive on daily intervals after treatment start

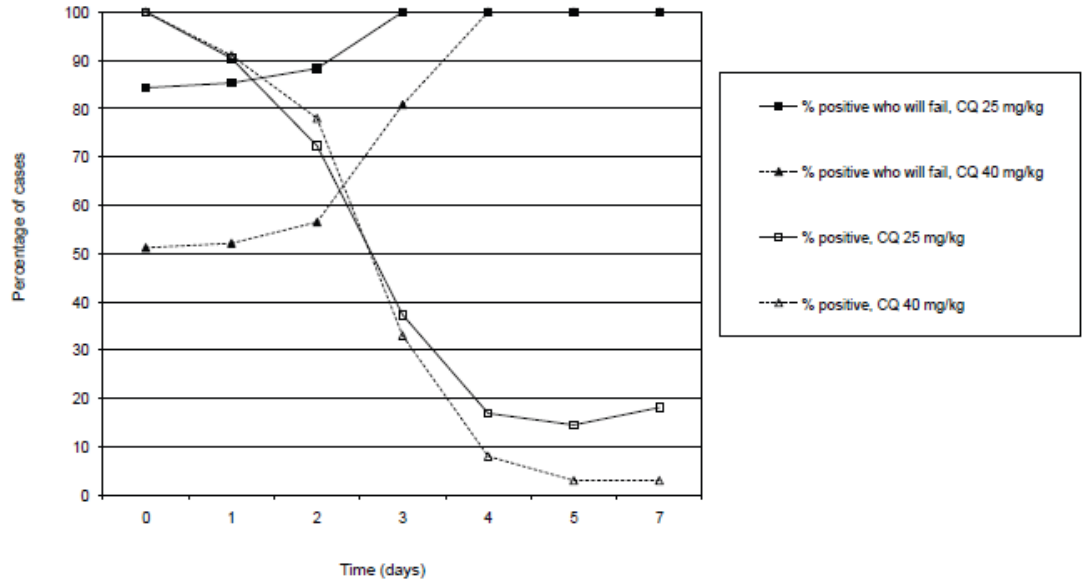


Figure 9 shows cumulative incidence of failure during each week of follow up.

Figure 9. Cumulative incidence of treatment failure for each treatment group

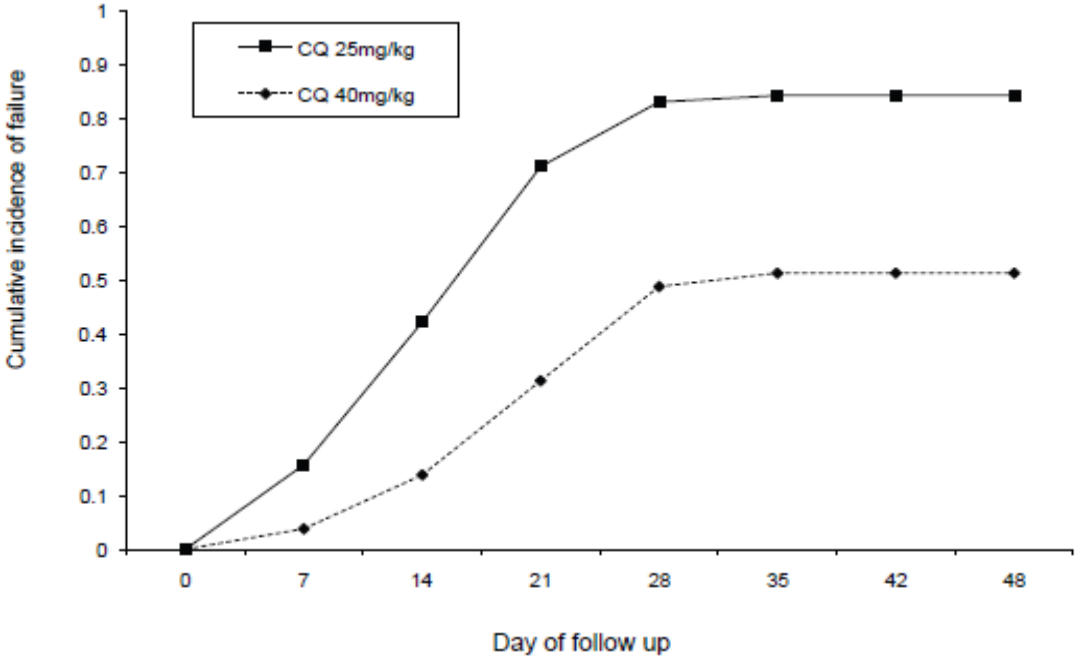


Table 9 shows that adjusted odds of treatment failure remained consistent between CQ40 and CQ25 groups at each 7-day interval. After Day 30 there was no further recrudescence in either group (Figure 9).

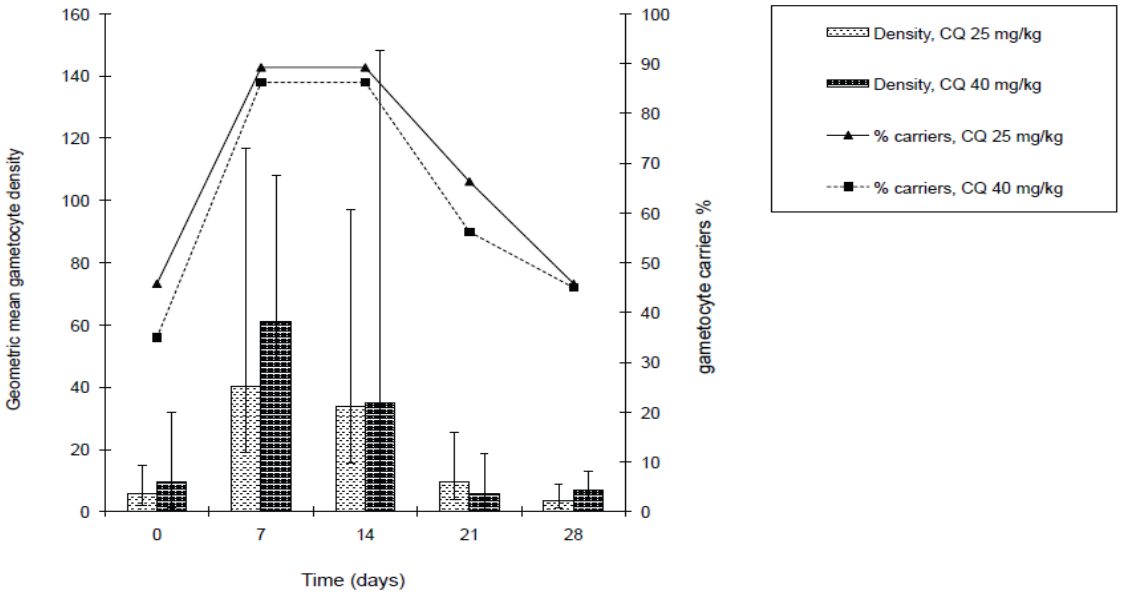
Table 9. Odds ratios of treatment success at weekly intervals post-treatment, comparing CQ 40 mg/kg with CQ 25 mg/kg, adjusted for age, weight, gender, and camp using logistic regression

Days after treatment start	Odds ratio (95% CI)	p-value
7	0.20 (0.05, 0.73)	0.02
14	0.18 (0.08, 0.40)	<0.0001
21	0.15 (0.07, 0.31)	<0.0001
28	0.18 (0.09-0.38)	<0.0001
35	0.18 (0.08, 0.39)	<0.0001

NB: OR compares CQ40 to CQ25, adjusted for age, weight, refugee camp, and gender using logistic regression.

Figure 10 shows the proportion of cases gametocytaemic and average gametocyte densities at weekly intervals. There were no significant differences in the proportion gametocytaemic or geometric mean gametocyte densities between the two treatment groups at any stage after treatment.

Figure 10. Percentage of cases gametocytaemic and geometric mean gametocyte density (95%CI) at weekly intervals post-treatment



Second and third-line therapeutic outcomes

Table 10 provides therapeutic results for second-line treatment. CQ 40mg/kg administered as second-line was less effective than as first-line treatment, regardless of whether first-line treatment was CQ25 or CQ40. Second-line CQ40 cured a higher proportion in the former CQ40 group than in the former CQ25 group, but this difference was not significant (adjusted OR 0.41; 95%CI 0.14, 1.19; p=0.10). SP administered as third-line provided 88% (44/50) parasitological cure before the trial ended at 60 days.

Table 10. Parasitological outcomes among 81 treatment failures receiving second-line CQ40mg/kg categorized by initial treatment group

Outcomes	CQ 25mg/kg	CQ 40mg/kg	Odds Ratio (95%CI)
Total receiving CQ40 second-line treatment	52	29	
Lost , excluded	0	0	
Treatment outcomes: n=81 (%)			
Adequate response	9 (17)	10 (34)	1
Early failure (0-3 days)	6 (12)	3 (10)	0.46 (0.09, 2.40)
Late failure (4-28 days)	37 (71)	16 (55)	0.41 (0.13, 1.20)
Second-line treatment success: n=19 (%)			
Complete parasitological cure (0-28 days)	9 (17)	10 (34)	0.41 (0.14, 1.19)
Second-line treatment failures: n=62 (%)			
Age group			
0-5	14 (93)	5 (62)	0.12 (0.01, 1.50)
6-14	21 (84)	12 (75)	0.77 (0.14, 4.21)
15+	8 (67)	2 (33)	0.27 (0.03, 2.45)
Gender			
Male	18 (82)	8 (67)	0.44 (0.09, 2.24)
Female	25 (83)	11 (64)	0.37 (0.09, 1.46)
Camp			
Baghicha	29 (78)	15 (65)	0.52 (0.16, 1.66)
Kagan	14 (93)	4 (67)	0.14 (0.01 2.05)

NB: Odds ratios adjusted for age, weight, gender, and camp using logistic regression and 29 first-line failures from Adizai excluded from analysis as these were treated with SP.

PCR analysis of genetic markers

Table 11 shows the frequency of *pfcrt* and *pfmdr1* point mutations among isolates from Adizai and Jalalabad. The CQ resistance-associated *pfcrt* codon 72-76 haplotype SVMNT (Ser-Val-Met-Asn-Thr) was present in 100% of samples successfully analysed from Adizai (63) and Jalabad (179). *Pfmdr1* 86Y was found in 14% (12/88) of Adizai and 22% (33/151) of Jalalabad samples. The *pfmdr1* 184Y allele was found in 27% (22/82) of Adizai samples and 46% (69/151) of Jalalabad samples.

Table 11. PCR results for refugee isolates collected at baseline in Adizai and Jalalabad sites

Gene	Allele	Adizai isolates		Jalalabad isolates	
		n= 90	(%)	n=180	(%)
Pfcrt	76 K	0	(0)	0	(0)
	76 T	63/63	(100)	179/179	(100)
Pfmdr1	86 N	76/88	(86.4)	118/151	(78.1)
	86 Y	12/88	(13.6)	33/151	(21.9)
	184 Y	22/82	(26.8)	69/151	(45.7)
	184 F	60/82	(73.2)		

NB: Denominators are all readable isolates. The Jalalabad isolates of 184F could not be read.

Discussion

CQ failure rates were higher than anticipated, and since administration was directly observed, failure was due to resistance rather than poor adherence. Analysis showed that with 51% failure in CQ40 and 84% failure in CQ25, CQ was no longer suitable for falciparum malaria treatment among Afghan refugees, either as first or second-line with short or extended regimens, and usage needed to stop. Second-line CQ40 achieved a higher failure rate than did first-line, demonstrating lack of suitability for this purpose as well[312]. Study investigators were expected, as part of UNHCR ethics approval, to follow national guidelines for second-line treatment as it was not the intervention. However, this trial demonstrated the ethical inadequacy of using a failing treatment drug for both intervention and second-line treatment for one of the trial arms. Fortunately, resistance was expected, so suitable third-line drugs were available and demonstrated resistance could then be used to advocate for policy change[223]. Clinical trials must adhere to clear ethical standards, including Good Clinical Practice (ICH-GCP) international ethical and scientific standard guidelines, the Helsinki Declaration, and International Ethical Guidelines for Biomedical Research Involving Human Subjects (e.g. about involving potentially vulnerable subjects, including those under-age and low-income refugees)[326-328]. These have progressed significantly since this trial was implemented, and it is less likely that usage of the same first-line and second-line treatment would now be approved by an ethics committee, as patient need and welfare would need to be demonstrated.

While the authors were unable to make use of PCR genotyping to distinguish recrudescent from new infections, other *in vivo* trials conducted in the area that did include genotyping indicated fewer than 5% would be new infections[329]. The most compelling evidence for subsequent infections being therapeutic failures is the very high failure rates by Day 28 and apparent absence of any new parasitaemias over 60 days of follow up.

The finding of the *pfcrt* 76T mutation in 100% of isolates analysed was consistent with a low degree of heterogeneity in the parasite population, as also shown by Khatoon *et al* in isolates from nearby Bannu district[318]. The *pfcrt* 76T allele has been strongly associated with CQ and amodiaquine (AQ) resistance in falciparum isolates from Asia, Papua New Guinea, Africa, and South America[311, 318, 330, 331]. *Pfmdr1* 86Y and 184Y alleles, which were also associated with CQ and AQ resistance, were present in only a minority of isolates from Adizai camp or from Bannu district[318]. In a clinical trial of AQ in nearby Afghanistan, which also resulted in high rates of recrudescence, *pfmdr1* alleles were not strongly selected among treatment failures[161]. These findings indicated that the *pfcrt* codon 72-76 haplotype SVMNT present in Pakistan was sufficient by itself (i.e. without *pfmdr1* 86Y and 184Y) to cause high-level CQ and AQ

resistance[161, 311, 330]. By contrast, in Africa where the CQ-resistant variant *pfcrt* codon 72-76 CVIET appeared to be the predominant haplotype, AQ remained relatively effective[311]. In a clinical trial in East Africa in which AQ did demonstrate high levels of *in vivo* resistance, the CQ-resistant variant CVIET haplotype was present with *pfmdr1* 86Y and 184Y alleles, which presumably added to the resistance there[311, 324, 332-335].

The rate of parasitological failure was higher after second-line than after first-line CQ40 treatment. Recrudescent infections presumably started with higher proportions of resistant parasites than did initial infections. However, this could not explain why the initial CQ40 course seemed to eliminate around 39% of resistant infections, as indicated by the improved cure rates over 60 days following initial five-day (51% recrudescence) as compared to three-day treatment (84% recrudescence). Among this 39%, any resistant parasites must have been removed by the additional two days of treatment and did not reappear over the subsequent 60 days. Ursing *et al* had, in parallel, undertaken clinical studies with high-dose CQ in Guinea-Bissau[336, 337]. They found that high-dose CQ (75mg/kg as split-dose over five days) was well-tolerated (as was the 40mg/kg administered in this trial) and 78% of infections carrying *pfcrt* 76T were successfully treated compared to only 34% with 25mg/kg[336]. This was a higher treatment success rate than in Pakistan.

While *pfcrt* 76T was highly prevalent in the Pakistan samples, *pfcrt* 76T prevalence in the Guinea-Bissau population, discussed above, remained stable at a much lower 25% between 1990 and 2005[336, 338]. These contrasts in *pfcrt* 76T between continents were likely due to differences in the fitness of resistance alleles, as the *pfcrt* 72-76 SVMNT resistance haplotype dominant in India, Iran, Pakistan and Afghanistan was not associated with re-emergence of CQ sensitivity or fluctuations in seasonal prevalence shown by the CVIET haplotype in some parts of Africa[332, 336, 337, 339-341]. Drug pressure may also have affected stability. If most infections were treated with a quinoline, *pfcrt* 76T frequency would remain high. In the African settings, sensitive parasites may have found a niche in the many untreated infections, where their greater fitness would allow them to compete better than any co-infecting resistant parasites. It was more difficult for CVIET-carrying parasites to gain the same high prevalence in Africa as SVMNT-carrying parasites have achieved in parts of Asia.

This trial did not measure adherence, as it was designed to assess efficacy rather than effectiveness. Consequently, it could not challenge the initial assumption that refugees failed to adhere to either three-day or five-day courses. However, later research demonstrated that with appropriate instructions - as in a trial of unsupervised 14-day primaquine treatment - Afghan

refugees did adhere to much longer treatment regimens than the five-day course described here[161, 342]. What was clear from directly-observed treatment was that neither CQ25 nor CQ40 regimens could continue to be justified, as neither could provide acceptable cure rates given the high prevalence of CQ-resistant falciparum malaria in Pakistan[93, 243, 308].

In Afghanistan, where many refugees have returned, numerous malaria cases are still treated with CQ, without parasitological diagnosis by either microscopy or RDT[92, 343, 344]. This makes this study, though conducted more than fifteen years ago, still highly relevant. About 80-95% of cases in Afghanistan are due to vivax and will respond to CQ[273]. However, most of the falciparum cases treated with CQ - whether for three days or longer - are likely to fail[91, 92, 342]. While the total number of falciparum cases will be small, without effective treatment these risk developing into severe malaria. As up to one-fifth of suspected malaria cases arrive at government clinics with detectable CQ present in their urine, irregular or intermittent treatment with CQ might be common[91, 344, 345]. The need for routine parasitological diagnosis by microscopy or RDT to allow differential and, most importantly, effective treatment for both falciparum and vivax malaria remains paramount in Pakistan and Afghanistan.

Although combination therapy using artesunate-SP was adopted as policy for treatment of confirmed falciparum malaria in both Pakistan and Afghanistan, implementation remains patchy[273, 329, 344, 346]. While follow-up and numbers of SP patients were too few in this trial to determine significance, the 12% SP failure rate raised questions about SP's long-term efficacy. While SP has a role as combination partner in Pakistan and Afghanistan, if administered without artesunate, resistance to SP may select rapidly[94, 347].

CHAPTER 5 MALARIA CONTROL UNDER THE TALIBAN REGIME: INSECTICIDE-TREATED NET PURCHASING, COVERAGE, AND USAGE AMONG MEN AND WOMEN IN EASTERN AFGHANISTAN (2000)

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Author contributions:
NH designed the study, conducted interviews and supervised survey data collection, conducted analysis, and wrote the manuscript.

Abstract

Background

Scaling up ITN coverage is a key malaria control strategy even in conflict-affected countries. Socioeconomic factors influence access to ITNs whether subsidized or provided free to users. This study examines reported ITN purchasing, coverage, and usage in eastern Afghanistan and explores women's access to health information during the Taliban regime (1996-2001). This strengthens the knowledge base on household-level health choices in complex-emergency settings.

Methods

Fifteen focus group discussions (FGDs) and thirty in-depth interviews (IDIs) were conducted with men and women from ITN-owning and non-owning households. FGDs included rank ordering, pile sorting and focused discussion of malaria knowledge and ITN purchasing. Interviews explored general health issues, prevention and treatment practices, and women's malaria knowledge and concerns. Seven key informant interviews with health-related workers and a concurrent survey of 200 ITN-owning and 214 non-owning households were used to clarify or quantify findings.

Results

Malaria knowledge was similar among men and women and ITN owners and non-owners. Women reported obtaining health information through a variety of sources including clinic staff, their husbands who had easier access to information, and particularly female peers. Most participants considered ITNs very desirable, though not usually household necessities. ITN owners reported more household assets than non-owners. Male ITN owners and non-owners ranked rugs and ITNs as most desired, while women ranked personal assets such as jewellery highest. While men were primarily responsible for household decision-making and purchasing, older women exerted considerable influence. Widow-led and landless households reported most difficulties purchasing ITNs. Most participants wanted to buy ITNs only if they could cover all household members. When not possible, preferential usage was given to women and children.

Conclusions

Despite restricted access to health facilities and formal education, Afghan women were surprisingly knowledgeable about the causes of malaria and the value of ITNs in prevention. Inequities in ITN usage were noted between rather than within households, with some unable to afford even one ITN and others not wanting ITNs unless all household members could be

protected. Malaria knowledge thus appears a lesser barrier to ITN purchasing and coverage in eastern Afghanistan than are pricing and distribution strategies.

Background

Scaling up coverage of ITNs has become a global malaria-control strategy[10, 13, 30]. Many countries, striving to reach malaria-related SDG and RBM targets, rely on ITN implementation[51, 268, 348, 349]. However, socioeconomic factors can heavily influence success, even with free ITN or LLIN distribution[350-353]. ITN purchasing can depend on cost and availability, perceived value and safety, ideas of disease causation, risk conceptions, and peer acceptance[115, 353-355]. Regular usage can depend on amount of insect nuisance biting, perceived malaria danger, sleeping patterns, comfort, and convenience considerations[38, 352, 355, 356]. This study examines aspects of reported ITN purchasing, coverage and usage in eastern Afghanistan during Taliban control. By disaggregating women's malaria knowledge and reported behaviour from that of men, it builds on limited knowledge of household-level health choices in socially conservative complex-emergency settings[186, 350-352, 357-360].

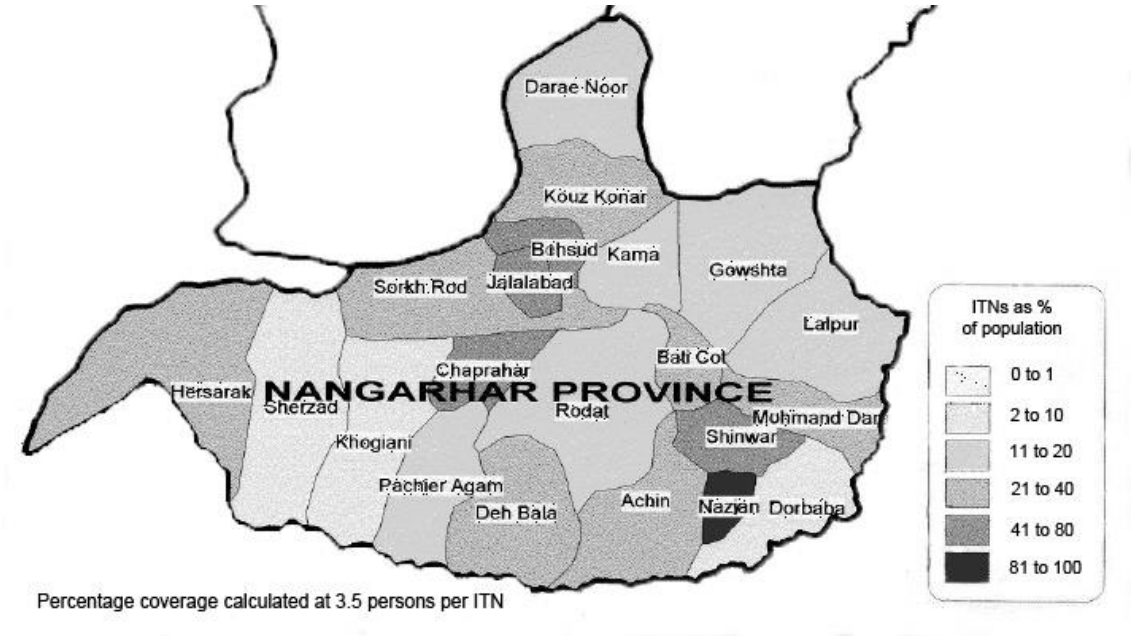
Before Afghanistan's extended conflict, malaria was almost eliminated as a public health issue through vertical governmental IRS and CQ treatment [52, 152, 246]. As control infrastructure deteriorated malaria rates increased, peaking during the mid-1990s [152, 246]. From 1992, eastern Afghanistan became stable enough to establish a network of NGO-supported clinics, standardize training and monitoring of microscopists and clinical staff, and distribute ITNs and insecticide retreatment. Malaria control was coordinated by technical agency HNTPO[152]. During the mujahedeen and Taliban eras (1992-96 and 1996-2001), HNTPO developed a package of interventions shown through operational research to be effective, popular and not requiring significant government input[52, 151, 153, 188, 246, 251, 361]. Government infrastructure and support remained minimal [248].

HNTPO coordinated wide promotion and subsidized sales of ITNs in eastern Afghanistan and refugee communities in Pakistan since 1992 [152]. Endemicity was seasonal and health infrastructure weak, making household-level interventions more practicable and cheaper for implementing agencies[246]. Using several distribution strategies, HNTPO disseminated sufficient family-size ITNs to cover approximately one million Afghans by the time the Taliban first gained power. ITNs were available both in BHCs and through mobile teams. Strategies included mobile teams of ITN salesmen, health educators and logisticians for remote areas, community-based ITN implementers, and BHC-based health education, sales and insecticide treatment provided

by trained BHC staff. By 2000, HNTPO was attempting cost recovery to create a revolving fund that could extend the limited resources then available for malaria control[51, 152, 362, 363].

Investigators were not convinced that coverage achieved by these strategies could provide sufficient community-wide protection, and wanted to find ways to increase ITN purchasing. As part of this, social research was undertaken in 2000 among men and women from ITN-owning and non-owning households in Nangarhar Province, Eastern Afghanistan. A concurrent socioeconomic analysis showed that the wealthiest 25% of households surveyed were 4.5 times more likely to own ITNs than the poorest 25%[115]. Objectives of qualitative data collection were to deepen understanding of factors affecting ITN purchasing, coverage, and usage patterns in the area.

Figure 11. Nangarhar Province and districts, showing percentage ITN coverage



Source: HNTPO, Jalalabad office 2000

Methods

Study design and target population

A mixed-methods study design was chosen, incorporating FGDs, IDIs, and a quantitative household survey, which allowed for collection of measurable data and more in-depth personal data on socioeconomic and cultural contexts of reported behaviour. The target population was men and women in ITN-owning and non-owning households from an estimated population of 500,000 in Nangarhar Province exposed to HNTPO's ITN programme (Figure 11). The population around Jalalabad had been exposed to almost a decade of HNTPO health education and ITN

social-marketing, through static BHCs and mobile sales teams, and differences in geographical access were expected to be minimal. Study components were conducted during February-April 2000, as the low transmission season was intended to help reduce overestimation of malaria risk and ITN usage. 'Household' was defined as a family group sharing a compound and cooking facilities. 'ITN ownership' was defined as having one or more ITNs. 'ITN usage' was defined as 'sleeping under an ITN,' rather than the narrower 'sleeping under an ITN the previous night' sometimes used in the literature, as ITN usage reflected mosquito and malaria seasonality and research indicated owners actually used their ITNs[52, 151]. Interviews and household survey were conducted following initial analysis of FGDs.

Sampling and recruitment

FGD sampling and recruitment were purposive, with the main aim to determine the feasibility of conducting community-level social research in this setting. Three districts (i.e. Achin, Muhmand-Dara, Shinwar) were selected purposively for accessibility, security, and ITN ownership of less than 40%. FGD participants were recruited purposively, by either HNTPO or BHC staff, to provide a sufficient range of men and women from ITN-owning and non-owning households.

Survey sampling was multi-stage. Survey sample size was calculated to detect a difference of 10% versus 20% between strata of equal size with 80% power and 95% confidence interval. First, eight districts were purposefully selected to include those regularly targeted by ITN sales campaigns and those further from Jalalabad, the provincial capital, that had been targeted less frequently. Second, approximately twenty villages were randomly selected from those previously exposed to HNTPO's ITN campaigns. Third, households in these villages were randomly selected using a directional numbering system in which the interviewers, on leaving the house of the village head, asked any child to choose a number between 1 and 4 and proceeded to the second house in the direction thus selected and conducted an interview if the household was eligible. To be eligible a household had to consist minimally of husband, wife and a child under 12 years of age. Interviewers were given a daily target of eight to 24 households depending on village size, and instructed to select approximately equal numbers of net-owning and non-owning households. Once half his daily target had been interviewed (e.g. if six ITN owner questionnaires had been filled), he continued the four directional selection method until the other half of the day's target had been completed (e.g. six non-owners interviewed). Thus, approximately even numbers of owners and non-owners where randomly selected and interviewed each day. This method was chosen because it was relatively simple, required no

equipment, allowed community participation, and no village census data or maps were available.

Interviews were conducted concurrently with the household survey. Interview sampling was a mix of theoretical and convenience, as described by Green and Thorogood. Participants were recruited purposively, so as to interview two man and two woman from different ITN-owning and non-owning households (i.e. approximately four interviews) per district[364, 365]. Additional key informant interviews were completed with clinic staff, informal health providers, and ITN implementers on a convenience basis to clarify findings.

Data collection

FGDs were conducted during February, separately with men and women from ITN-owning and non-owning households. See Annex 1.1-1.2 for FGD topic guides. Each group was moderated in Pashtu or Dari by a trained local researcher of the same gender as participants and supervised by an experienced LSHTM-based qualitative researcher. FGDs took place in locations selected by participants and were tape-recorded, with participants' verbal consent, for later transcription and translation. FGDs included formal pile-sorting and rank-ordering exercises and targeted discussion of malaria knowledge and perceptions, ITNs and retreatment, and gender and cultural attitudes.

Interviews were conducted in March-April in Achin, Bati Kote, Bihsood, Lalpur, Muhmand-Dara, Nazyan, Shinwar, and Surkhrod districts, by an Afghan male and foreign female researcher using a sub-headed topic guide (Annex 2.1). Interviews investigated FGD topics plus perceptions of malaria's relative importance, prevention and treatment practices, and women's malaria-related health information and access. All, except three with doctors in English, were interpreted directly between English and Pashtu or Dari. Researchers were constrained by the lack of an experienced female interpreter, but recruited a male researcher who appeared youthful enough to be considered culturally acceptable. Researchers chose not to tape interviews because several male family members refused consent for women to be recorded and researchers wanted to interview as many women as possible and remain methodologically consistent[366, 367]. To minimize data loss, both researchers took notes under simple topic codes in English or Dari/Pashtu. Notes and observations were discussed by researchers after each interview and written up each evening[367]. Interviews were conducted by the DrPH candidate and AS, the lead translator and an experienced local researcher. Most lasted 35 minutes to an hour.

The household survey was conducted in March-April, with structured questionnaire interviews conducted in Pashtu or Dari by five trained male data-collectors. Five Pashto-speaking interviewers were hired in Jalalabad and trained for three days on survey techniques, malaria control issues, and health education. Continuous field monitoring and feedback sessions were conducted throughout the study. The questionnaire was developed from similar instruments and FGD results, and piloted in three villages not included in the study. The questionnaire included demographics, socioeconomics, health knowledge, malaria, mosquitoes, and ITNs (Annex 2.2). Household assets and socioeconomic indicators, identified in a preliminary survey and from published literature[368-370], formed the basis for a structured questionnaire that was developed in English, translated into Pashtu, checked by two translators, and back-translated into English by a third to validate accuracy. The questionnaire was field tested over a 3-day period, and some questions changed or removed (e.g. "How many wives in the household?" was removed as sensitive and not culturally useful, while questions on direct monetary amounts such as "salary level", were changed to a binary "is part of your income from salaries" format to encourage accurate reporting). Gold jewellery ownership, though a potential indicator, was removed due to sensitivity and inaccurate reporting. As houses were almost universally unscreened mud-brick, questions on housing materials were excluded. Some categorical responses, such as "what causes malaria?" were partially precoded, while others, such as "job of household head" were coded at data entry.

Analysis

Data were transcribed and translated in Peshawar and analysed in London. Qualitative data were analysed descriptively and thematically. The full range of responses and views expressed by FGD and interview participants was assessed and shared responses grouped using thematic coding[365]. Survey data were analysed in Stata® and outcomes assessed for associations with ITN ownership using logistic regression.

Ethics

The LSHTM Research Ethics Committee provided ethics approval. Local ethics approval for operational research was not required, nor was any research ethics body available within the Taliban government, during the time of the study. Informed consent was obtained from all participants and data were anonymized.

Results

Fifteen FGDs were conducted in six villages: five with male ITN owners, one with female ITN-owners, five with male non-owners, and four with female non-owners. Eighty-two men and 40

women participated. Rank-ordering and pile-sorting exercises were successfully completed in men's but not women's FGDs owing to moderator inexperience. Thus, pile-sorting and ranking analysis is restricted to data from men's FGDs.

Thirty IDIs were conducted in eight districts: eight with men and six with women from ITN-owning households, and seven with men and eight with women from non-owning households. Most women chose to be interviewed with female relatives or friends present, due to the absence of a female interpreter. Seven key informant interviews, completed with health-related workers (i.e. three doctors, one laboratory technician, one traditional healer, and two ITN implementers), were analysed separately.

Two-hundred ITN-owning and 214 non-owning households completed survey interviews. The response rate was 95%, with non-participation reported as due to ongoing poppy harvesting. All but five household heads were male, and only 48 (11.6%) respondents were female. Most self-identified as Pashtun, while 36% in Bihsood district were of Tajik ethnicity. Half of households (58%) relied on agriculture. Main crops were wheat, opium poppy, corn, and cotton. Most (83%) came to the area in 1993, when security improved in eastern Afghanistan.

Table 12. Percentage reported malaria knowledge and practices, comparing ITN-owning to non-owning households

	% ITN Non-owners (n=214)	% ITN Owners (n=200)
What causes malaria?		
Mosquitoes	77	73
Water	18	20
Other/Don't know	6	8
Where do mosquitoes breed?		
Water	58	69
Grass	23	20
Other/Don't know	19	12
Malaria season		
Summer	46	40
Spring/Summer	33	39
Autumn	11	11
Other/All	10	10
Who is at most risk from malaria?		
Children	50	48
Women and children	25	19
Everyone	21	17
Pregnant women and under-fives*	1	10
Women	3	4
Aged	1	2
*What is the best malaria protection?**		
ITNs	74	86
IRS	12	7
Other (e.g. electric fans)	7	5

Traditional	3	1
Don't know	4	1
What current malaria protection do you use?[1]*		
ITNs	4	95
Other (e.g. smoke, chadors)	92	1
Insecticide spray	4	3
Traditional	0	1
Who in your household was seriously ill this year?		
All	57	54
Children	35	32
None	4	8
Aged	3	3
Women	1	3
*What is the best treatment for malaria?**		
Chloroquine	68	79
Don't know	21	11
Traditional/Other	7	7
Paracetamol	4	3
Who makes treatment-seeking decisions?		
Household head	92	90
Other	8	10
Where do you go for malaria treatment?		
Get treatment at NGO clinic	42	48
Private doctor (unregulated)	35	24
Other/Combination	22	28
Private drug seller (unregulated)	2	1
Average reported costs for malaria treatment[2]	*(US$15)*	*(US$15)*
Adult visit	0.64	0.48
Adult drugs	9.02	6.58
Child visit	0.62	0.46
Child drugs	5.78	4.28
Average costs per ITN[2]	*(US$15)*	*(US$15)*
ITN (insecticide added at point-of-purchase)	7.16	7.16
ITN retreatment (annual)	0.08	0.08

NB: Sample size is 414. Logistic regression *p-value<0.05 or [1]p<0.001. [2]Costs were not disaggregated by provider. Pakistani rupee 2000 prices have been converted to US dollar 2015 constant equivalents (US$15).

Pile sorting and ranking exercises

Information generated by pile sorting indicated differences in household asset ownership between participating ITN owners and non-owners. Non-owners generally reported fewer possessions than ITN owners. This was particularly noticeable for rugs (59% versus 27%), radios (54% versus 29%), jewellery (54% versus 29%) and pressure cookers (54% versus 29%). Some non-owners reported very few household possessions. For example, 16% reported no kettle and 12% no lamps, whereas all ITN owners had these items. Approximately 15% of non-owners reported similar quantities of household assets as ITN owners (i.e. radio plus at least two - rug, pressure cooker, or jewellery). This reinforced quantitative survey findings, that households with at least one ITN were likely to have more assets than those without ITNs[115].

FGD participants were asked to rank household assets in the order in which they would most likely procure them if they had extra cash or goods for bartering. Rugs and ITNs ranked highest

among both ITN owners and non-owners. Items deemed essential, such as clothes and a lamp, ranked in the top three for non-owners. Bicycles and pressure cookers, reported as luxury items, were ranked in the top three by ITN owners. In discussing ranking, non-owners explained that they ranked clothing highly because it was essential for wives to keep covered when going outside due to Taliban restrictions. They also revealed that rugs, topping the list for both groups, were seen as status items. Even men who already owned rugs said they would, as a first choice, purchase more. ITN ownership was also described as reflecting status, though data needs caution as FGD participants were aware that researchers were associated with HNTPO's malaria control programme. However, both ITN owners and non-owners ranked IRS highly, suggesting that mosquitoes and other insects were problematic.

Women were eager to participate in FGD discussions, but appeared so determined to talk that they generally did not complete formal exercises. Discussions clarified that women ranked clothing and jewellery, assets Afghan women own personally, as the two most important household assets.

Knowledge and reported behaviour

Interview, survey, and remaining FGD results are reported under key themes: malaria knowledge and perceptions; malaria prevention and treatment; ITN knowledge and perceptions; reported ITN purchasing; reported ITN coverage and usage; and health-related workers' perceptions.

Malaria knowledge and perceptions. There appeared to be little difference in knowledge of malaria transmission between genders or between ITN owners and non-owners. Table 12 shows approximately 75% of survey respondents said mosquitoes caused malaria, though 19% said it was caused by water. Unsurprisingly, participants could not distinguish between vector and nuisance mosquitoes.

> *"When mosquitoes bite healthy people they catch malaria." (Female non-owner, Ghazgay, Muhmand-Dara)*

Approximately one-third of interviewees suggested mosquito bites were only one way of catching malaria with the main contributor reported as drinking dirty water. Most survey respondents (64%) knew that mosquitoes breed in water, but most participants did not know how mosquitoes transmit malaria, often describing faecal-oral routes (e.g. mosquitoes breed in dirty water and garbage, and this dirt infects people when they are bitten).

"Malaria is caused by mosquitoes who get parasites from dirty water" (Male ITN owner, Muhmand-Dara)

Another belief reported in each district was that malaria, if it continues or increases in severity, becomes *moriqa* (typhoid).

"Malaria comes from mosquitoes and dirty water. Mosquitoes breed in dirty ponds, cow dung and refuse... malaria becomes typhoid if it is not cured" (Male non-owner, Bati Kote)

"The clinic doctors told us typhoid is from malaria." (Female ITN owner, Ghani Khel, Shinwar)

Participants reported that malaria was a serious illness. In interviews, researchers attempted to estimate its perceived importance by asking participants the three greatest health concerns in their community. The top three concerns reported were diarrhoea, 'maternal problems,' and tuberculosis.

While not directly related to this research, it is interesting that as early as 2000, maternal ill health was reported as a major concern by both genders in all districts. It was described as a particular concern due to female travel restrictions, and lack of female health staff or culturally acceptable facilities. Several women mentioned the lack of confidential contraception as their main health concern.

"It's not appropriate for our women to give birth publicly in the clinic. Many women have serious problems during childbirth... We can't afford when the lady doctor comes to the house and anyway she usually doesn't because she can't come alone. There is no one around who knows how to birth the baby properly and so many die." (Male non-owner, Bati Kote)

Health messages, aimed at men for cultural reasons, did appear to reach women. Women interviewees reported getting most of their health and ITN information from clinics, their husbands, or most commonly from each other.

"When one of us learns something, then she tells it to the others." (Female non-owner, Shinwar)

"Our husbands don't let us listen to radio because it uses up the batteries. We are encouraged to listen to religious programmes. I learned about ITNs from my husband and the clinic doctors." (Female ITN owner, Nazyan)

Malaria prevention and treatment. Eighty percent of survey respondents said ITNs were the best means of malaria prevention. Interviewees reported that other common forms of protection against mosquitoes were burning grass, rubbing lamp or motor oil on the skin, and sleeping wrapped in wet *chadors* (traditional outer garments).

> *"Preventive measures are good against malaria, but there are no effective ones; sprays wash off, ITNs only protect part of the time. Burning straw is very effective against mosquitoes, but there is some problem with coughing and TB. Electricity is better because we can use fans." (Female non-owner, Shinwar)*

Many participants said previous government IRS campaigns had been very effective against mosquitoes, though only 9% of survey respondents considered IRS to be the best means of malaria prevention. These IRS campaigns were generally described as intrusive, but most said they favoured a return to spraying. IRS provision had been free and sprayers reportedly paid for information on households with malaria cases. Now households needed to spend their own money on ITNs.

> *"We are talking about 20 years ago when the government authorities were spraying houses by force. We didn't know the benefits of spraying and now we know how effective it was!" (Male ITN owner, Pakhail, Achin)*

> *"Spraying should be done by the government, because if we spray individually or have ITNs, mosquitoes will keep coming from our neighbours' houses." (Female non-owner, Bihsood)*

Most participants, including 73% of survey respondents, named CQ as the best treatment for malaria. Some interviewees, though only 7% of survey respondents, favoured traditional treatments The main reason reported was cost, though a minor percentage were concerned about safety (e.g. for pregnant women). Traditional treatments included cooling drinks, such as *dogh* or *lassie* (from yoghurt), or various plants, the most common of which was a tea from *shamaki* roots. *Shamaki* is a Pashtu term for a plant used locally in traditional medicine, said by some respondents to contain quinine.

> *"We usually resort to traditional treatment rather than clinical treatment unless the traditional treatment doesn't work. It is due to poverty and people can't afford to cover doctor's and transportation costs." (Male ITN owner, Gharzay, Muhmand-Dara)*

Some interviewees said they would only buy half the recommended tablets to reduce treatment costs, while others reported they could be treated on credit.

> *"…sometimes we borrow from doctors for treating our patient. For instance, doctors in the clinic treat our patient and we will pay them later in the harvest time or as soon as we get cash. The other way is to pay them with wheat or corn." (Male non-owner, Gharzay, Muhmand-Dara)*

While participants agreed it was less costly to prevent than to treat malaria, emergency funds for treatment could be borrowed from relatives or neighbours, while funds for protective goods, such as ITNs, could not be readily mobilised.

> *"I saved money for four years to buy ITNs. I can borrow money from my neighbours and relatives to pay for treatment, but they're not willing to lend for something like a bednet." (Widow, ITN owner, Bihsood)*

ITN knowledge and perceptions. All participants could accurately describe ITNs and how they should be used. Authors found no differences between genders or ITN-owners and non-owners in recall of health messages about the benefits of sleeping under ITNs.

> *"Using ITNs has two benefits. One is that it protects you from malaria and the second is that you sleep well." (Male non-owner, Achin)*

> *"We need ITNs for protection against malaria, not for having fun!" (Male non-owner, Achin)*

While ITNs were frequently mentioned as playing an important role in the prevention of both nuisance biting and malaria, some participants said they did not want to make the initial investment.

> *"Malaria is not something that much can be done about, just to endure. ITNs are out of reach and not useful enough to buy." (Male non-owner, Shinwar)*

Participants in a women's FGD, asked their views on possible inclusion of ITNs as part of a dowry, responded with laughter. As this differed from men's pile-sorting and ranking results, it indicates that either women valued ITNs less than did men or that ITNs were affordable for many households and thus not of sufficient monetary value to feature in a dowry.

> *"That is totally absurd! How should we let this stupid boy get married with our daughters by providing us with nets rather than paying?" (Female non-owner, Meydanak, Achin)*

"We work hard to bring up our daughter and then to give her for ITNs? It is an absolutely silly thing to do! We are not stupid." (Female non-owner, Meydanak, Achin)

Reported ITN purchasing. Table 13 shows 84% of survey respondents said they were planning to buy ITNs. While 57% wanted them to reduce mosquito nuisance, 38% wanted them for malaria protection. Of those not planning to buy ITNs, the primary reasons given were cost (39%) and already having enough (30%). Responsibility for purchasing decisions rested with the household head, almost invariably an adult male - husband, father, or grandfather.

Table 13. Percentage reported purchasing intentions, comparing ITN-owning to non-owning households

	% Non-owners (n=214)	% ITN owners (n=200)
Planning to buy ITNs*	89	78
Not planning to buy ITNs	9	19
Not sure about buying ITNs	2	3
We'll buy ITNs when they're available	81	83
We'll buy ITNs this month	12	12
We'll buy this year/Unknown	7	5
Want ITNs to prevent mosquito bites*	51	62
Want ITNs to prevent malaria	42	35
Other/Unsure	7	3
Don't want ITNs due to cost*	46	35
Don't want ITNs due to having enough already	0	47
Other/Unknown*	54	19

NB: Sample size is 414. *Logistic regression p-value <0.05 to <0.01.

"Head of the family - father or grandfather - is responsible for making the decision to buy something like nets and protection of the family." (Male ITN owner, Hazar Naw, Muhmand-Dara)

Heads of ITN-owning households were significantly better educated. Comparing ITN-owning to non-owning households, household heads with above secondary-school education were 1.85 times more likely to own ITNs than were those with no education (95% confidence interval 1.2-2.8).

Women participants said they had little decision-making power or opportunity to make purchases, but some said their husbands could be persuaded to buy items that they requested. Young women, even if married, were not able to go outside without accompaniment by their husband or parent-in-law.

"We don't go ourselves. Our husbands don't allow us to go for shopping. They usually provide us with what we want them to buy." (Female non-owner, Sunduq, Achin)

"No woman can go anywhere without asking the permission of her husband." (Female ITN owner, Meydanak, Achin)

A common perception of HNTPO among interviewees was as an ITN sales company rather than a humanitarian organization. This was despite several local clinics being sign-posted as run by HNTPO. However, it was not clear whether this perception was likely to help or hinder HNTPO's activities.

Four main purchasing constraints were reported. The first was cost. ITNs were sold for the average equivalent of US$7.16 in 2015 constant prices, with insecticide retreatment costing the US$15 equivalent of US$0.08. Poorest people said they had more urgent problems for daily survival than mosquitoes and fever.

Cost was the most frequently mentioned ITN purchasing constraint among non-owners. Some participants appeared unable to afford an ITN at prevailing prices. Poorest households appeared to be those headed by widows, women whose husbands were disabled or working in Pakistan, and those who did not own enough land to support their household. Women whose husbands were in Pakistan could purchase some supplies from local shops on credit. Credit limits were unclear, though several women said that making ITNs available on credit would increase their ability to buy them.

"ITNs are the best way to protect against malaria, but we can't afford to buy them because we barely have enough to get food every day, and if we have enough for food, we have to buy clothes to cover our bodies. We can't go around naked!" (Female non-owner, Bati Kote)

"We know everything about ITNs but don't have the money to buy." (Male non-owner, Muhmand-Dara)

A second purchasing constraint reported was that participants did not have sufficient money for enough ITNs to cover everyone in their households. Some non-owners expressed reluctance to buy ITNs unless they could provide for the whole household.

"Fifteen people in my family and we have only one net! I don't have any money in hand to buy more nets." (Male ITN owner, Gerday-Ghous, Muhmand-Dara)

"The other problem is that there are 20-30 people in each household and to cover them all with ITNs we need at least 8-10 ITNs that we can't afford to provide." (Male non-owner, Ghazgay, Muhmand-Dara)

A third purchasing constraint, mentioned by both non-owners and owners purchasing additional ITNs, was that seasonal income did not match ITN availability. Several participants complained that ITNs were made available at the beginning of malaria season when they did not have enough cash to purchase them, and when they did ITNs were no longer available.

"ITNs are available in this village only for a couple of weeks and that's usually the time which doesn't match harvest time (March/April) or when we don't have money" (Male ITN owner, lower Meydanak, Achin)

This lack of consistent availability led some non-owners to speculate that ITN sellers were favouring certain families and health staff were selling ITNs in Pakistan or charging more than they should. However, recent purchasers reported paying the price recommended by HNTPO.

"We had money last year, but ITNs were not available. Only relatives and friends of the sellers were able to buy them." (Male, non-owner, Bati Kote)

"Clinic staff sell the ITNs and drugs in the bazaar to make money. If you don't know someone in the clinic, you won't get help." (Female, non-owner, Bihsood)

The final purchasing constraint reported was that perceptions of poor-quality ITN retreatment were discouraging ITN purchasing. Several non-owners reported as a strong purchasing disincentive ITN-owning neighbours telling them ITNs were not as useful as previously. HNTPO had recently switched from *permethrin* to *deltamethrin*, and complaints about retreatment with watered down or expired insecticide may have affected ITN sales and retreatment uptake.

"Retreatment is good, but not like it was. Salesmen add more water now, but they say they know what they are doing." (Female ITN owner, Bihsood)

"There has been a gradual decrease in effectiveness since 1994. Maybe the insecticide is not good quality or they're mixing it with too much water. There have been many complaints and many surveys, but nothing ever changes" (Male ITN owner, Bihsood)

"Poor quality retreatment stops people buying ITNs." (Male ITN owner, Pakhail, Shinwar)

Reported ITN coverage and usage

Table 14 shows most owners (69%) paid for ITNs from savings. ITN-owning households had an average of three ITNs and four occupants per ITN. Where ITNs were limited, 70% of survey respondents said children and women were given preference. Participants said available ITNs were used by children and women, because they were the weakest and most vulnerable household members and keeping children covered by blankets to protect them from mosquitoes was very difficult. These practices may result from effective health messages, which emphasize the need to cover the most vulnerable (i.e. young children and pregnant women), but also reflect beliefs that women and children are weak, uninformed and unable to protect themselves.

Table 14. Percentage reported ITN usage among ITN-owning households

	% ITN owners (n=200)
No. of ITNs per household	Mean=2.9 (SD=2.4)
Who sleeps under ITNs in your household?	
Children	36
Women/Children	31
Everyone (sufficient ITNs for all)	29
Women	3
Aged/Other	1
Are your mosquito nets insecticide treated?	
Yes	61
No/Unknown	39
How often are your ITNs retreated?	
Yearly	78
Bi-annually	12
Don't know/Never	10
After cleaning	1
Where did you get funds to pay for your ITNs?	
Savings	69
Loan	17
Gift	8
Crop sales	4
Other	4

NB: Sample size is 200.

> *"They (women and children) are weak in nature and also we men keep covered the exposed parts of our body, though children don't care about this." (Male ITN owner, Meydanak, Achin)*

> *"If malaria mosquitoes bite children they will immediately get ill and can't resist against fever either, and the same applies to women. It is OK with men; they can go to the clinic on foot." (Male ITN owner, Gerday Ghaus)*

The average number of children under five per ITN was 1.6 (±SD 1.4), though the number of children under five per household was not associated with ITN ownership (logistic regression

p=0.86). Only one man reported using the household ITN for himself, since as the family bread-winner he wanted to stay healthy. However, a few respondents (1%) said they gave preferential ITN use to the weak old men.

Interviewees reported that most ITN users did not sleep under them throughout the year. The primary reasons given for ITN use were to prevent both nuisance biting and malaria. Malaria was reported to be a more serious but less frequent problem, while nuisance biting was an everyday frustration. Many owners said that they used ITNs only in summer when mosquito densities and nuisance biting were highest and perceptions of malaria risk increased. However, some participants were aware that malaria could be transmitted in other seasons.

> *"We use ITNs only during the nights and particularly in the summer – only in summer." (Female ITN owner, Ghazai)*

> *"There is (malaria) in winter but not as high as in the summer." (Male ITN owner, Ghazai)*

While there was still some risk of both nuisance biting and malaria in winter, several participants said that people slept under blankets in winter so the likelihood of mosquito bites was reduced.

Health-related workers' perceptions

Interviews with health workers and ITN implementers supported general findings and sometimes provided additional insight.

Those doctors interviewed considered malaria an important contributor to morbidity and lost productivity, though not the primary disease priority in communities.

> *"The most dangerous (disease) is TB because it's transmissible easily and also if a person is diseased by this microbe and doesn't take care of himself he will die. But in malaria death is not essential, and the treatment of TB requires more time, at least 6 months, and the drugs are very expensive." (Doctor, Bati Kote)*

Almost half of participants reported first going to public/NGO clinics for treatment, because they were cheapest. However, if treatment results were unsatisfactory many also went to private doctors. Several health workers described this type of treatment seeking negatively.

> *"If the clinic technician says it's not malaria she will think he's no good and go to a private lab where they will tell her it's malaria. There's a lot of overprescribing of chloroquine to make people happy." (Laboratory technician, Bihsood)*

While most participants favoured the idea of credit schemes, and said that purchasing ITNs through small weekly or monthly sums would be beneficial, ITN implementers were not so eager.

> *"I'm only working seven months a year. It would take at least nine months to collect money from credit. We (ITN implementers) know who needs and deserves credit and could take responsibility for monitoring, but they would need to pay us all year round." (ITN implementer, Bihsood)*

Discussion

Many aspects of ITN purchasing are similar for countries during conflict or peace, under despotic or benign authority. The Taliban, espousing a strict anti-modern antifeminist ideology adapted from Sunni Muslim sharia and Pashtun tribal codes, governed Afghanistan from 1996 to late 2001[152, 371, 372]. While the presence of the Taliban placed profound restrictions on mobility, access and acquisition of information, their influence was far from all-pervasive and householders – women in particular – adopted a number of coping strategies to access information and influence health-related family decision-making.

ITN purchasing

Two key issues influencing purchasing were availability and pricing, constraints also found in several African studies of the same period[373-376]. Afghan men and women were aware of the link between mosquitoes and disease and of the protective effects of ITNs. Knowledge did not appear to be the main factor influencing ITN purchase and usage, as there was little difference in knowledge between ITN owners and non-owners[377, 378]. This is attributable to successful transmission of health information from sources such as health facility staff, HNTPO implementers, and radio programmes (e.g. BBC Pashtu Service news and dramas). HNTPO's ITN coverage reached 60% in some trial areas where no limits were placed on the numbers of ITNs individuals purchased. Overall coverage was around 30% (Figure 11). Among participants who did not have ITNs, most said they wanted but could not afford them. Despite successful transmission of health messages, ITNs were not yet seen as household necessities. Rather, they were one of the first 'extras' families with greater financial stability felt able to afford. Household decision-makers appeared to understand the reasons for having ITNs, but make purchasing decisions based on overall risk perceptions [379, 380]. More research is needed to explore this.

Lack of ITN availability when participants said they were ready to purchase suggests delivery strategies could have benefited from restructuring[41, 381, 382]. ITNs were usually available during summer when mosquito nuisance was severe, but spare cash from harvests was already spent.

Making ITNs available when people were likely to have cash (e.g. harvest or crop purchase times) could increase sales[382]. Making ITNs more visible throughout the year (e.g. through mobile salesmen or local shops) could improve awareness of ITNs as household rather than health products and increase availability when cash was available. Strong perceptions existed that clinics and salesmen were preferentially selling ITNs to relatives or for profit. Year-round availability of ITNs, clearer promotion and pricing, and improved staff monitoring could reduce complaints[383, 384].

Some high-risk households (e.g. widow-led) did not have sufficient funds to purchase ITNs at prevailing prices. While free mass distribution is more difficult to justify in this low-transmission area, maintenance of a targeted subsidy to make ITNs affordable for those who truly cannot pay, or free distribution to most-at-risk groups is probably necessary to improve coverage rates[373, 385, 386]. Additional distribution through local shops, where poorer women could get credit, might also increase access[381, 386].

Table 12 shows the price of an ITN was only slightly more than the average cost of treating one malaria episode. However, participants noted that emergency funds were easier than prevention funds to mobilise. It is also worth noting that non-owners reported slightly higher average malaria treatment prices (Table 12). This might indicate either the operation of informal credit mechanisms or respondent bias. As reported ITN prices were the same for both groups, more research on informal financing mechanisms may be warranted. However, authors found that money was as sensitive an issue as gender in rural areas. Since this study was conducted, foreign funding for malaria control in Afghanistan has increased dramatically. Mass distribution of LLINs is coordinated by HNTPO through a greatly expanded BHC-based system[235]. ITNs continue to be subsidized rather than provided free to users and findings reported here are still applicable.

ITN coverage and usage

Three key issues raised by ITN owners were seasonality, sleeper prioritization, and poor quality re-treatment. Most participants used ITNs in summer. This corroborates an earlier clinic-based case-control study of ITN effectiveness against malaria in Nangarhar, showing that despite high summer and autumn temperatures this was when people used nets most[52]. Fortunately, this is the peak malaria transmission season[246]. Many who did not use ITNs reported sleeping wrapped in their water-soaked *chadors* to keep cool. In emergencies, *chadors* treated with the repellent insecticide *permethrin* have provided some malaria protection[251]. Soaking in water could limit

the effectiveness of insecticide-treated *chadors* unless rendered wash-resistant through newer formulations.

Prioritisation of women and children under ITNs was a key health message emphasized by ITN implementers in Afghanistan[152]. Most families automatically prioritised children, and to a lesser extent women, so messages could focus on youngest children and pregnant women as those at greatest potential risk. With current donor focus on gender issues and women's capacity-building in Afghanistan, there is more scope for improvement in this area than when this study was conducted.

A widely held perception that the quality of insecticides used to re-treat ITNs had deteriorated was attributed to implementers over-diluting insecticide. In reality, the type of insecticide used had changed. Initially HNTPO used *permethrin*, but as this became harder to obtain the agency switched to *lambda-cyhalothrin* and *deltamethrin*. These alphacyanopyrethroids are more toxic but less repellent than *permethrin*, possibly giving the impression implementers had tampered with insecticide[387-389]. If people continued to perceive that the retreatment insecticide did not work, they would be less likely to have ITNs retreated or recommend that others buy ITNs. Fortunately, with the transition to long-lasting technologies this is less of an issue, as only LLINs are now sold in Afghanistan.

During the malaria eradication era of the 1950s and 1960s, IRS was widely and successfully applied in Afghanistan[390, 391]. IRS and effective treatment drugs, as parasites were not yet resistant to chloroquine, led to low malaria prevalence in most parts of the country[176]. Effective IRS campaigns require infrastructure and planning that was not feasible during the Soviet and civil wars[248]. Participants indicated they would favour reintroducing an IRS programme, as it protected all household members, reduced overall mosquito numbers, and was free-of-cost to households. However, additional technical and coordination requirements often make it more costly than ITNs for implementers[10, 47, 392]. As sentinel surveillance data indicates malaria in Afghanistan is declining, coinciding with the scale-up of LLINs and wider use of more effective anti-malarial drugs, a return to IRS appears unwarranted.

Gender

Three gender-related issues could be further addressed. First, the authors found it possible to conduct research among Afghan women, even in Taliban-controlled areas. Teaming a foreign female and Afghan male researcher was a relatively novel approach in these isolated areas. Women wanted to meet 'the foreign lady,' and allowing curiosity to overcome suspicion enabled access to women in their home environment that might not otherwise have been allowed. Such

direct engagement could increase bias if not handled sensitively, but worked effectively when combined with findings from other data sources. More could be done to adapt social research methods for conservative, conflict-affected, and insecure environments.

Second, while men had the primary role in household decision-making, information access and purchasing, older women particularly mothers-in-law exerted considerable influence. Efforts could be made to mobilize these women more effectively in health promotion campaigns.

Third, male-focused health education did appear to filter through to women, making this a potential approach for socially-segregated environments. Interviews and FGD results with women corresponded well with quantitative survey findings, even though most survey participants were men.

Implications and further research

Issues for further investigation include equality of access to ITNs and the status of widow-led families in post-war Afghanistan, women whose husbands are economic migrants, and landless households. Work has been done on this in Africa, but more research is required to identify how best to target and support these high-risk households in Afghanistan[41, 375, 383, 393, 394]. Additional research could explore delivery strategies and cost-effectiveness of ITNs in areas of relatively low malaria endemicity or whether ITNs should form the basis of a malaria elimination strategy – important issues that were not addressed in this study[394].

Limitations

Several potential limitations should be considered. First, due to security and access concerns for foreign researchers, sampling and recruitment of FGD and IDI participants was a combination of purposive and convenience. This may have affected responses received. Second, social acceptability bias may have been worsened by the relative inexperience of field interviewers. However, IDIs gave the opportunity to probe more carefully into both predictable and more unusual issues. Third, variations in ITN ownership by socioeconomic status may have been due to barriers other than cost that were not identified in principal components analysis, for example undisclosed socio-cultural influences or hierarchies, tribal issues, or unidentified geographical constraints.

Conclusion

Conditions in parts of rural Afghanistan have not changed greatly since this research was conducted. The south and east of the country have become, if anything, more insecure since

allied occupation and as a result, INGOs have less freedom to operate than did the researchers in 2000. Health funding and infrastructure have greatly improved over the decade since the Taliban last held power. However, availability of health services in remote communities remains variable. While women have greater freedom of movement and better access to health care and information than under the Taliban, they still face many financial and social barriers. This paper provides an indication of health-related constraints and potential approaches should support for the Afghan government deteriorate or a group such as the Taliban once again gain control in Afghanistan.

CHAPTER 6 TOWARDS A MALARIA IN PREGNANCY STRATEGY IN AFGHANISTAN: PERCEPTIONS AND REALITIES OF MALARIA AND ANAEMIA (2004-2005)

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NH co-designed the study, supervised clinical data collection, analysed data, and wrote the manuscript.

Abstract

Background

Afghanistan has some of the worst maternal and infant mortality indicators in the world and malaria is a significant public health concern. Study objectives were to assess prevalence of malaria and anaemia, related knowledge and practices, and malaria prevention barriers among pregnant women in eastern Afghanistan.

Methods

Three studies were conducted: (i) a clinical survey of maternal malaria, maternal anaemia, and neonatal birthweight in a rural district hospital delivery-ward; (ii) a case-control study of malaria risk among reproductive-age women attending primary-level clinics; and (iii) community surveys of malaria and anaemia prevalence, socioeconomic status, malaria knowledge and reported behaviour among pregnant women.

Findings

Among 517 delivery-ward participants (i), one malaria case (prevalence 1.9/1,000), 179 anaemia cases (prevalence 346/1,000), and 59 low-birthweight deliveries (prevalence 107/1,000) were detected. Anaemia was not associated with age, gravidity, intestinal parasite prevalence, or low-birthweight at delivery. Among 141 malaria cases and 1,010 controls (ii), no association was found between malaria infection and pregnancy (AOR 0.89; 95%CI 0.57-1.39), parity (AOR 0.95; 95%CI 0.85-1.05), age (AOR 1.02; 95%CI 1.00-1.04), or anaemia (AOR 1.00; 95%CI 0.65-1.54). Those reporting ITN usage had 40% reduced odds of malaria infection (AOR 0.60; 95%CI 0.40-0.91). Among 530 community survey participants (iii), malaria and anaemia prevalence were 3.9/1,000 and 277/1,000 respectively, with 34/1,000 experiencing severe anaemia. Despite most women having no formal education, malaria knowledge was high. Most expressed reluctance to take malaria preventive medication during pregnancy, deeming it potentially unsafe.

Conclusions

Given the low malaria risk and reported avoidance of medication during pregnancy, IPT in pregnancy is hard to justify or implement. Preventive strategy should instead focus on LLINs for all pregnant women.

Background

Infection with *P. falciparum* or *P.* vivax can be dangerous in pregnancy, increasing risks of severe anaemia, premature delivery, low-birthweight (LBW), and foetal, neonatal and maternal death[395-397]. Falciparum infection in pregnancy causes up to approximately 10,000 maternal deaths, 3-8% infant deaths, and 8-14% LBW deliveries annually, and pregnant women are often prioritised for preventive interventions including LLINs and IPT[397-399]. In unstable transmission settings, such as much of South Asia, pregnant women experience 2-3 times higher risk than non-pregnant women of developing severe malaria or malaria-related severe anaemia[396, 399-401].

Malaria in pregnancy is most studied for falciparum infection in sub-Saharan Africa and Southeast Asia[397, 398, 402, 403]. Though less documented, growing literature on vivax infection in pregnancy indicates considerable risk and approximately 71 million pregnancies in vivax-endemic areas globally[395, 399, 401, 404-411]. *P. vivax* is the most geographically widespread human malaria parasite - endemic in much of Asia, including Afghanistan, with approximately 2.9 billion people at risk globally[410-415]. It has been associated with severe clinical manifestations in pregnancy, including severe anaemia, thrombocytopenia, miscarriage, low-birthweight, and preterm delivery[395, 399, 415, 416]. Though *in vivo P. vivax* placental sequestration has not been identified, *in vitro* evidence exists of cytoadherence to placental glycosaminoglycans[417]. Relapsing infections from hypnozoite reservoirs cannot be treated effectively, as primaquine is contraindicated in pregnancy, making prevention preferable[418].

Afghanistan has received considerable international attention and support since the Taliban government ended in 2001, but remains a fragile country[419, 420]. The estimated maternal mortality ratio reduced from 1,300/100,000 in 2000 to 460/100,000 in 2010, but disparities between urban and rural areas remain stark (e.g. maternal mortality ratio of 166/100,000 in Kabul versus 713/100,000 in Badakhshan)[421, 422]. Similarly, the infant mortality rate reduced from 153/1,000 to 74/1,000 in 2011[423-425]. However, indicators remain poor. An estimated 16 million people are at risk of malaria in Afghanistan and it remains a public health concern[160, 235, 426]. Transmission is unstable and seasonal, and a significant cause of morbidity in lowland and rice irrigation areas [426].

No publications were found on malaria epidemiology in pregnancy in Afghanistan. This study aimed to assess the contribution of malaria to maternal anaemia and birth outcomes in eastern Afghanistan. Objectives were to assess: (i) prevalence of malaria and anaemia among pregnant

women, (ii) risks of malaria in pregnancy, and (iii) malaria awareness and reported behaviours during pregnancy.

Methods

Study site and population

Studies were conducted in Ghani Khel District Hospital, a secondary-level facility in rural Nangarhar province, and primary-level facilities (i.e. BHCs) and communities within its catchment area. The target population was women of reproductive age (WRA; aged 15-49) from among an estimated population of 500,000 women accessing health services subcontracted to an NGO provider, HNTPO, through Afghanistan's Basic Package of Health Services[186, 235]. Malaria transmission is moderate and seasonal, vivax peaking May-August and causing 70-95% of malaria, and falciparum predominantly in October-November[246]. Main vectors are *Anopheles stephensi, An. superpictus*, and *An. culicifacies*[246, 426]. At the time of this study, the National Malaria and Leishmaniasis Control Programme worked to prevent malaria through insecticide-treated nets (e.g. ITNs/LLINs) - targeted preferentially to pregnant women - distributed at subsidised prices through primary-level BHCs[52, 115, 236]. Antenatal services during the four recommended visits followed WHO guidelines[427]. Unicef supported prevention of maternal anaemia by providing iron/folate tablets during antenatal care visits[428].

Study design and data collection

Three complementary studies were conducted: (i) a clinical survey of maternal malaria, maternal anaemia, and neonatal birthweight in the district hospital (ii) a case-control study of malaria risk factors among WRA attending nearby primary-level facilities, and (iii) a two-round community survey of malaria and anaemia prevalence, socioeconomic status and related knowledge, attitudes and practices among pregnant women in four nearby districts.

Delivery-ward survey: Women delivering between February and December were enrolled and examined on giving informed consent: (i) thick and thin Giemsa-stained blood smears of peripheral, cord and placental blood were tested for malaria; (ii) maternal blood tested for haemoglobin; (iii) stool tested for intestinal parasites; and (iv) neonate and placenta weighed at delivery. Blood slides were collected by a trained midwife, stained and examined the same day by a trained microscopist at 100x magnification, with 200 fields checked before recording a negative result. All slides were re-read by an experienced microscopist, blinded to original diagnosis. Haemoglobin was measured by attending midwife using a HemoCue point-of-care test (Ängelholm, Sweden). Stool was examined for helminths and intestinal protozoa by trained microscopists, using duplicate Kato-Katz thick smears prepared shortly after collection and

allowed to clear for 45-60 minutes before examination[429]. Participants found positive were treated according to national guidelines, e.g. Albendazole 400mg PO for helminths; CQ 25mg/kg x 3 days for uncomplicated malaria; quinine IV 20mg/kg loading dose, then 10mg/kg t.i.d x 7 days for severe malaria; daily iron (120mg of elemental iron) and folic acid (400µg) supplementation until haemoglobin concentration rises to normal for mild-moderate anaemia; whole blood or packed red cells 10 ml/kg over 3 hours for severe anaemia[343, 430, 431]. Birthweight was measured by attending midwife for all births within one hour of delivery, using an electronic scale (Salter, Birmingham UK) accurate to ±10g and calibrated weekly[432]. Fresh placentas were weighed by attending midwife, untrimmed and without blood expressed, using the same procedure[433]. Data were double-entered into Microsoft® Access 2000, with range and consistency checks to reduce transposition errors.

Case-control study: All reproductive-age female outpatients presenting with suspected malaria (i.e. fever or history of fever suspected to be malaria) and providing informed consent, were enrolled between September and January at basic health facilities with malaria diagnostics and staff willing to participate in a study. All patients were examined by clinic doctors and clinical diagnosis, age, marital status, number of children, and number of previous pregnancies recorded on standardised forms. Controls were defined as WRA with clinically-suspected malaria, negative blood slides and no recent history of malaria (i.e. to exclude recently treated patients). Cases were defined as WRA with microscopically confirmed malaria and categorised according to malaria species and severity. Severe cases were defined as parasitaemic, with one or more WHO indicators for severe malaria and absence of identified alternative causes[434]. Microscopy, treatment, and data entry replicated delivery survey protocols.

Community survey: Multi-stage sampling was used: (i) four districts were selected with functioning community health infrastructure (i.e. Shinwar, Mohmand Dara, Batikot, Nazian); (ii) villages were identified within each district that were malaria-endemic, with antenatal services, and accessible by four-wheel drive vehicle; (iii) all pregnant women in each village were invited to participate. Sample size was calculated to detect a malaria prevalence of 5% with 80% power and 95% confidence. Two collection periods, May-June and December, incorporated seasonal peaks of vivax and falciparum transmission respectively. Those providing informed consent were tested for malaria and anaemia and answered a structured questionnaire (Annex 3). Adapted from previous research[115], the questionnaire was back-translated in Pashtu and piloted in a non-participating district. Literate female interviewers were recruited from local communities and trained over three days on privacy, prompting, and questionnaire completion. Microscopy, treatment, and data entry replicated delivery survey protocols.

Analysis

Data were analysed using Stata/IC13.1.

Delivery-ward survey: Malaria infection was categorised as negative (i.e. negative peripheral, umbilical, and placental slide result) or positive (i.e. any positive result). Anaemia was categorised as non-anaemic (i.e. 110g/l or above) or anaemic (i.e. below 110g/l) if anaemia was mild (100-109g/l), moderate (70-99g/l), or severe (<70g/l)[435, 436]. Birthweight was categorised as non-LBW (i.e. 2,500g or above) or LBW (i.e. below 2,500g). Intestinal parasites were categorised as absent (i.e. none detected) or present (i.e. detection of any helminth or protozoa). Logistic regression was used to calculate odds ratios of anaemia or LBW outcomes, with univariate regression providing crude estimates and multivariate regression adjusting for *a priori* confounders (i.e. age, gravidity, presence of intestinal parasites). Cell sizes below 30 prompted exact logistic methods. Effect modifiers (i.e. significant likelihood ratio test) were reported individually.

Case-control study: Categorisation and analysis replicated delivery survey protocols. Additionally, ITN usage was defined as reporting sleeping under ITNs the previous night. Logistic regression calculated odds ratios of exposures. *A priori* confounders were district, facility, age, and parity.

Community survey: Categorisation and analysis replicated delivery survey protocols. Additionally, participant age, education, housing, and household asset variables were weighted and scored within a socioeconomic status (SES) index using principal components analysis [115, 210]. Logistic regression calculated odds ratios of anaemia. *A priori* confounders were SES, district, age, parity, trimester, and season.

Ethics

Approval was provided by the Ministry of Public Health in Afghanistan and the LSHTM Research Ethics Committee in the United Kingdom (reference 5508). All participants were informed about the study purpose, content and potential publication and written or verbal informed consent was recorded. Data were coded anonymously and stored in password-protected hard-drives.

Results

Delivery-ward survey

In total, 517 patients agreed to participate. Average age was 25 years (range 16-40). Approximately 35% were primigravida, 31% multigravida (2-4 pregnancies) and 33% grand-multigravida (5+ pregnancies). Among 38 women with intestinal parasites (prevalence 74/1,000, 95%CI 54-99), most frequent were *Entamoeba histolytica* (47%), *Giardia lamblia* (26%) and *Ascaris lumbricoides* (16%). One malaria case, asymptomatic at delivery and detected in peripheral blood only (prevalence 1.9/1,000, 95%CI 0.3-13.7); 179 anaemia cases (prevalence 346/1,000, 95%CI 306-388), 12 of them severely anaemic (23/1,000, 95%CI 20-25); and 59 LBW deliveries (114/1,000, 95%CI 89-115) were recorded.

As only one malaria case was detected, further analysis only compared factors associated with anaemia and LBW (Table 15). Anaemia presence was not associated with age, gravidity, presence of intestinal parasites, or LBW delivery. LBW delivery was not associated with intestinal parasite or anaemia presence, though it was associated with gravidity in multivariate analysis.

Table 15. Associations of demographic and clinical variables with maternal anaemia and low-birthweight delivery among 517 delivery-ward patients in eastern Afghanistan

Associations with anaemia	Anaemic, n (%) (N=179)	Non-anaemic, n (%) (N=338)	OR (95%CI)	AOR (95%CI)
Age group				
15-20	66 (36.9)	143 (42.3)	Ref.	Ref.
21-30	84 (46.9)	154 (45.6)	1.18 (0.80-1.75)	1.00 (0.63-1.60)
31-49	29 (16.2)	41 (12.1)	1.53 (0.88-2.68)	1.20 (0.59-2.44)
Gravidity				
Primigravidous	54 (30.2)	129 (38.2)	Ref.	Ref.
Multigravidous (2-4)	58 (32.4)	104 (30.8)	1.33 (0.85-2.09)	1.32 (0.81-2.17)
Grand-multigravidous (5+)	67 (37.4)	105 (31.1)	1.52 (0.98-2.37)	1.42 (0.80-2.53)
Intestinal parasites				
No	167 (93.3)	312 (92.3)	Ref.	Ref.
Yes	12 (6.7)	26 (7.7)	0.86 (0.42-1.75)	0.82 (0.40-1.67)
LBW				
No	159 (88.8)	229 (88.5)	Ref.	Ref.
Yes	20 (11.2)	39 (11.5)	0.96 (0.54-1.71)	1.09 (0.60-1.97)
Associations with LBW	**LBW, n (%) (N=59)**	**Non-LBW, n (%) (N=458)**	**OR (95%CI)**	**AOR (95%CI)**
Age				
15-20	33 (55.9)	176 (38.4)	Ref.	Ref.
21-30	21 (35.6)	217 (47.4)	0.52 (0.29-0.92)*	1.13 (0.57-2.22)
31-49	5 (8.5)	65 (14.2)	0.41 (0.15-1.10)	2.17 (0.55-8.49)
Gravidity				
Primigravidous	38 (64.4)	145 (31.7)	Ref.	Ref.
Multigravidous (2-4)	13 (22.0)	149 (32.5)	0.33 (0.17-0.64)**	0.31 (0.15-0.64)**
Grand-multigravidous (5+)	8 (13.6)	164 (35.8)	0.19 (0.08-0.41)**	0.13 (0.04-0.39)**
Intestinal parasites				
No	55 (93.2)	424 (92.6)	Ref.	Ref.
Yes	4 (6.8)	34 (7.4)	0.90 (0.31-2.65)	1.04 (0.34-3.14)
Anaemia				
No	39 (66.1)	299 (65.3)	Ref.	Ref.
Yes	20 (33.9)	159 (34.7)	0.96 (0.54-1.70)	1.09 (0.60-1.96)

NB: *p<0.05; **p<0.001; AOR adjusted for age, gravidity, intestinal parasite presence. Cell sizes below 30 use exact logistic methods.

Case-control study

In total, 141 malaria cases and 1,010 controls were enrolled from reproductive-age women attending eight district clinics (Table 16). Most were resident in Jalalabad (40%), Shinwar (23%) and Momand Dara (15%) districts. Average age was 28 (range 15-45). Most (81%) were married. Approximately 25% were nulliparous, 38% had delivered 1-5 times, and 36% more than five times. Parous women averaged 4.6 children (range 1-13). Approximately 25% of women were pregnant and 23% anaemic. *P. falciparum* infection accounted for 37% (52/141) of malaria cases, 25% (13/52) of which were assessed as severe. Among pregnant women, 11% (31/286) had malaria infection compared to 15% (110/755) of non-pregnant women. Among pregnant women with malaria, 35% (11/31) were infected with *P. falciparum*, of which 1 was severe.

Reported ITN usage was 32% (45/141) among cases and 43% (431/1,010) among controls, giving a protective 40% lower odds of malaria infection (AOR 0.60; 95%CI 0.40-0.91). None of age, pregnancy status, parity, or anaemia were associated with malaria infection in univariate or multivariate analyses (Table 16).

Table 16. Associations between demographic and clinical exposures and malaria, among 1,150 case-control study participants in eastern Afghanistan

Variables	Cases, n (%) (N=141)	Controls, n (%) (N=1,010)	OR (95%CI)	AOR (95%CI)
Age group				
15-20	32 (22.7)	286 (28.3)	Ref.	Ref.
21-30	62 (44.0)	437 (43.3)	1.27 (0.81-1.99)	1.36 (0.74-2.49)
31-49	47 (33.3)	287 (28.4)	1.46 (0.91-2.36)	1.49 (0.75-2.97)
Pregnant	31 (22.0)	255 (25.3)	0.83 (0.55-1.27)	0.89 (0.56-1.42)
Parity				
Nulliparous (no births)	36 (25.5)	256 (25.4)	Ref.	Ref.
Parous (1-5 births)	55 (39.0)	389 (38.5)	1.01 (0.64-1.57)	0.84 (0.47-1.52)
Grand-multiparous (6+ births)	50 (35.5)	365 (36.1)	0.97 (0.62-1.54)	0.68 (0.35-1.31)
Anaemic	33 (23.4)	230 (22.8)	1.04 (0.68-1.57)	1.00 (0.65-1.54)
ITN usage	45 (32.0)	431 (42.7)	0.63 (0.43-0.92)*	0.60 (0.40-0.91)*

NB: *p<0.05; **p<0.001; AOR adjusted for district, facility, age, parity.

Community survey

Socioeconomic and clinical variables: In total, 530 pregnant women participated. Mean age was 28 (range 15-45) and 80% had no formal education. Most households averaged 9.8 members (range 1-39), 2.6 under age five (range 0-18), living in three rooms (range 1-12). Most had no electricity (73%; 387/530), while 48% owned land (255/530).

Table 17 shows education, employment and household assets used for principle components analysis, disaggregated by socioeconomic quartile.

Table 17. Factors used in principle components analysis to define socioeconomic quartiles among 530 community survey participants in eastern Afghanistan

Socioeconomic variables	Socioeconomic quartile, n (%)			
	1. Poorest (N=133)	2. Poor (N=132)	3. Less poor (N=133)	4. Least poor (N=132)
Education				
None	128 (30.2)	109 (25.8)	100 (23.6)	87 (20.5)
Religious/Informal	3 (5.4)	15 (26.8)	18 (32.1)	20 (35.8)
Primary-school	2 (9.1)	6 (27.3)	3 (13.6)	11 (50.0)
Middle-school	0 (0)	1 (8.3)	4 (33.3)	7 (58.3)
High-school	0 (0)	1 (6.7)	8 (53.3)	6 (40.0)
University/Technical	0 (0)	0 (0)	0 (0)	1 (100)
Primary earner's employment				
Not working	2 (40.0)	2 (40.0)	1 (20.0)	0 (0)
Manual labour	70 (37.6)	46 (24.7)	43 (23.1)	27 (14.5)
Farming	35 (22.0)	48 (30.2)	34 (21.4)	42 (26.4)
Trade/Market	14 (18.0)	22 (28.2)	20 (25.6)	22 (28.2)
Driver	8 (18.1)	10 (22.7)	11 (25.0)	15 (34.1)
Office/Similar	4 (7.0)	4 (7.0)	24 (41.4)	26 (44.9)
Household assets				
Guestroom	28 (9.3)	70 (23.3)	91 (30.2)	112 (37.2)
Electricity	11 (7.4)	29 (19.7)	43 (29.3)	64 (43.5)
Land ownership	33 (13.0)	64 (25.1)	61 (24.0)	97 (38.0)
Car/Truck	0 (0)	2 (4.0)	12 (24.0)	36 (72.0)
Radio/Music-player	5 (4.2)	15 (12.7)	30 (25.4)	68 (57.6)
Rug	12 (6.6)	33 (18.2)	60 (33.2)	76 (42.0)
Curtains	18 (7.1)	57 (22.4)	71 (28.0)	108 (42.5)
Bicycle	25 (12.1)	38 (18.4)	60 (29.0)	84 (40.6)
Pressure-cooker	27 (8.3)	79 (24.2)	101 (31.0)	119 (36.5)
ITNs	9 (4.5)	31 (15.6)	65 (32.7)	94 (47.2)

Malaria point prevalence was 3.8/1,000 (95%CI 0.9-15.0), anaemia was 277/1,000 (95%CI 241-317), and severe anaemia 34/1,000 (95%CI 21-53), similar to delivery-ward survey findings. As only two malaria cases were detected, analysis of effects on maternal haemoglobin concentration was conducted for anaemia instead. Table 18 shows none of age, parity, trimester, malaria infection, iron/folate usage, antenatal attendance, ITN usage, or SES were associated with anaemia in multivariate analysis.

Table 18. Associations of socioeconomic, clinical and behavioural responses with anaemia among 530 community survey participants in eastern Afghanistan

Variables	Hb	Anaemic, n (%)	Non-anaemic, n (%)	OR (95%CI)	AOR (95%CI)
	mean±SD (range)	(N=147)	(N=383)		
Age					
15-20	11.4±1.9 (7.3-19.3)	22 (15.0)	78 (20.4)	Ref.	Ref.
21-30	11.0±1.7 (6.5-17.5)	81 (55.1)	223 (58.2)	1.29 (0.75-2.20)	1.35 (0.71-2.57)
31-45	10.7±1.7 (6.5-15.5)	44 (29.9)	82 (21.4)	1.90 (1.05-3.46)*	1.89 (0.85-4.20)
Parity					
Nulli/Primiparous (0-1 births)	11.1±1.8 (6.8-17.5)	35 (23.8)	103 (27.0)	Ref.	Ref.
Multiparous (2-5 births)	10.9±1.7 (6.5-19.3)	76 (51.7)	187 (48.8)	1.20 (0.75-1.90)	0.99 (0.57-1.72)
Grand-multiparous (6+ births)	10.9±1.7 (6.5-14.7)	36 (24.5)	93 (24.3)	1.14 (0.67-1.96)	0.76 (0.38-1.52)
Trimester					

1st	10.9±2.1 (8.0-14.0)	3 (2.0)	6 (1.58)	Ref.	Ref.
2nd	11.3±1.7 (7.0-17.5)	57 (38.8)	188 (49.1)	0.61 (0.15-2.50)	0.53 (0.12-2.41)
3rd	10.7±1.7 (6.5-19.3)	87 (59.2)	189 (49.4)	0.92 (0.22-3.77)	0.76 (0.17-3.41)
Malaria infection					
No	11.0±1.7 (6.5-19.3)	147 (100)	381 (99.5)	..	..
Yes	12.5±1.4 (11.5-14)	0 (0)	2 (0.5)	..	..
Iron/Folate usage					
No	10.9±1.7 (6.5-19.3)	108 (73.5)	277 (72.3)	Ref.	Ref.
Yes	11.1±1.7 (6.7-15.5)	39 (26.5)	106 (27.7)	0.94 (0.61-1.44)	1.16 (0.73-1.84)
Antenatal attendance (at least once)					
No	11.0±1.4 (6.9-17.5)	20 (13.6)	54 (14.1)	Ref.	Ref.
Yes	11.0±1.7 (6.5-19.3)	127 (86.4)	329 (85.9)	1.04 (0.60-1.81)	1.03 (0.57-1.87)
Household ITN ownership					
No	11.0±1.8 (6.5-19.3)	91 (61.9)	240 (62.7)	Ref.	Ref.
Yes	11.1±1.7 (6.5-15.5)	56 (38.1)	143 (37.3)	1.03 (0.70-1.53)	1.74 (0.99-2.90)
Slept under ITN last night					
No	11.0±1.4 (6.5-19.3)	134 (91.2)	357 (93.2)	Ref.	Ref.
Yes	10.8±1.4 (8.6-14.2)	13 (8.8)	26 (6.8)	1.33 (0.66-2.67)	1.71 (0.82-3.64)
Socioeconomic status					
1.Poorest	10.8±1.9 (6.5-17.5)	47 (32.0)	86 (22.5)	Ref.	Ref.
2.Poor	10.9±1.8 (6.8-19.3)	35 (23.8)	97 (25.3)	0.66 (0.39-1.12)	0.72 (0.41-1.26)
3.Less poor	10.9±1.7 (6.5-14.3)	39 (26.5)	94 (24.5)	0.76 (0.45-1.27)	0.95 (0.53-1.71)
4.Least poor	11.4±1.6 (7.5-15.5)	26 (17.7)	106 (27.7)	0.45 (0.26-0.78)*	0.57 (0.29-1.10)

NB: *p<0.05; **p<0.001; AOR adjusted for survey, age, parity, trimester, SES, district; Cell sizes below 30 use exact logistic methods.

Knowledge/perceptions: Malaria knowledge was high, with 99% reporting fever, shivering/chills, headache, weakness or joint pain as symptoms, 97% reporting mosquito bites transmit malaria, 70% reporting diagnosis by blood test, and 81% reporting ITN usage as the best available prevention. Risk perception was also high, with 85% identifying malaria as their community's 'worst health problem,' 90% as common in their community, and 38% reporting they had experienced 'malaria' during their present pregnancy. In contrast, only 6% identified either diarrhoeal disease or acute respiratory tract infections as concerns, despite high frequency of both (Table 19).

Table 19. Associations of knowledge and behavioural responses with socioeconomic status among 530 community survey participants in eastern Afghanistan

Response variables	Poorer# (N=265)	Wealthier# (N=265)	OR (95%CI)	AOR (95%CI)
Primary source of healthcare				
NGO/government health facility	217 (81.9)	184 (69.4)	Ref.	Ref.
Private health facility	43 (16.2)	67 (25.3)	1.84 (1.19-2.82)*	1.30 (0.77-2.21)
Traditional/Self-treat	5 (1.9)	14 (5.3)	..	..
Attended antenatal services at least once	228 (86.0)	228 (86.0)	1.00 (0.61-1.63)	1.38 (0.75-2.54)
Uses iron/folate supplements	54 (20.45)	91 (34.3)	2.34 (1.55-3.53)*	1.90 (1.17-3.09)*
Greatest health concern				
Other	3 (1.1)	10 (3.8)	..	..
Diarrhoea	18 (6.8)	14 (5.3)	Ref.	Ref.
ARI	12 (4.5)	21 (7.9)	0.53 (0.12-2.29)	0.53 (0.09-3.03)
Malaria	232 (87.6)	220 (83.0)	0.28 (0.77-1.05)	0.43 (0.91-2.00)
How common is malaria				
No malaria/Infrequent	22 (8.3)	29 (10.9)	Ref.	Ref.
Common	243 (91.7)	236 (89.1)	0.74 (0.41-1.32)	0.73 (0.36-1.48)
Best malaria prevention in pregnancy				
Nothing works	29 (10.9)	24 (9.1)	Ref.	Ref.

ITNs	212 (80.0)	219 (82.6)	1.25 (0.70-2.21)	1.26 (0.64-2.46)
Rapid diagnosis/treatment	1 (0.4)	1 (0.4)	..	..
Burning/Smoke	8 (3.0)	9 (3.4)	..	..
Clean house/area	15 (5.7)	12 (4.5)	0.97 (0.38-2.46)	0.53 (0.17-1.64)
Preferred malaria diagnosis				
Self/Informal	31 (11.7)	48 (18.1)	Ref.	Ref.
Facility (clinical)	50 (18.9)	29 (10.9)	0.37 (0.20-0.71)*	0.43 (0.19-0.96)*
Facility (blood test)	184 (69.4)	188 (70.9)	0.66 (0.40-1.08)	0.91 (0.48-1.72)
Preferred malaria treatment				
NGO/government health facility	214 (80.8)	198 (74.2)	Ref.	Ref.
Private health facility/Other	51 (19.2)	67 (25.3)	1.42 (0.94-2.14)	0.86 (0.51-1.44)
Would use malaria-preventive drugs in pregnancy				
Never	232 (87.6)	204 (77.0)	Ref.	Ref.
Yes/Maybe	33 (12.5)	61 (23.0)	2.10 (1.32-3.34)*	1.69 (0.98-2.91)
Why use ITNs				
Avoid mosquitoes	169 (63.8)	167 (63.0)	Ref.	Ref.
Prevent insect bites	49 (18.5)	43 (16.2)	0.89 (0.56-1.41)	1.15 (0.65-2.02)
Prevent malaria	40 (15.1)	51 (19.3)	1.29 (0.81-2.06)	1.92 (1.07-3.43)*
Other/Don't know	7 (2.6)	4 (1.5)	..	..
ITN-owners only	**n=40 (%)**	**n=159 (%)**		
Which family members use ITNs				
Nobody/Unknown	11 (27.5)	41 (25.8)	Ref.	Ref.
All	9 (22.5)	61 (38.4)	1.82 (0.69-4.78)	1.23 (0.37-4.04)
Children	20 (50.0)	43 (27.0)	0.58 (0.24-1.35)	0.48 (0.16-1.40)
Women	0 (0)	11 (6.9)	..	..
Men/Elderly	0 (0)	3 (1.9)	..	..
Participant used ITN last night	7 (17.5)	32 (20.1)	1.19 (0.48-2.93)	3.09 (1.01-9.51)*
Reasons for not using ITN last night	**n=33 (%)**	**n=127 (%)**		
No mosquito nuisance	11 (33.3)	35 (27.6)	Ref.	Ref.
ITN used by others	12 (36.4)	26 (20.5)	0.68 (0.26-1.78)	2.87 (0.42-19.8)
No reason provided	10 (30.3)	66 (52.0)	2.07 (0.80-5.36)	4.65 (1.09-19.8)*

NB: *p<0.05; **p<0.001; AOR adjusted for survey, age, parity, trimester, district; #Poorer merges SEQ 1 and 2, Wealthier merges SEQ 3 and 4.

Reported practices: Most (76%) reported NGO-run public-sector facilities as their primary source of healthcare and 86% reported attending antenatal services at least once during pregnancy. Only 27% reported taking iron/folate during pregnancy, with 55% reporting no use of dietary supplements. However, this differed by SES, with wealthier women having almost double the odds of taking iron/folate (AOR 1.90; 95%CI 1.17-3.09).

Most (78%) reported using public facilities for malaria treatment, primarily due to affordability (45%) and effectiveness (40%), with no differences by SES. Most (82%) reported they would never take drugs to prevent malaria during pregnancy. Of almost half (43%) reporting avoiding all medicines during pregnancy, 55% reported doing so because they might feel sick and 32% because drugs - including antimalarials - might be dangerous during pregnancy. Although most (81%) recommended ITNs for malaria prevention, only 17% reported this as their major advantage and most (81%) identified avoiding nuisance biting as most important. Approximately 38% reported household ownership of at least one ITN. Most women in ITN-owning households reported that everyone (35%) or children (32%) usually slept under ITNs. While 80% reported not using an ITN the previous night, wealthier women had three times higher odds of having slept under one (AOR 3.09; 95%CI 1.01-9.51).

Discussion

Prevalence and perceptions

This study design, by using three distinct data sources to examine the scope of the problem in Afghanistan, provides a broad view of malaria and anaemia in pregnancy. Malaria prevalence of only 3.9/1,000 among pregnant women in communities and 1.9/1,000 in a delivery-ward appears to reflect a genuine reduction in malaria transmission rates in Afghanistan[246]. A decade previously, community surveys among all age groups in this province typically recorded a prevalence of 7-10% for vivax and 2-5% for falciparum malaria[52]. Reasons for this reduction could include expansion of health services[186, 419], increased availability of malaria diagnosis and treatment[91], enhanced control activities[12, 152], improved political stability and socioeconomic development[186], and/or changing environmental conditions and improved agricultural practices[160].

While recorded malaria prevalence was low, the high prevalence of maternal anaemia - consistent with a reported national prevalence of 40.3% among WRA - is a concern[428]. Associations between anaemia and malaria were not observed, and it is clear that factors other than malaria are chiefly responsible for the high prevalence of maternal anaemia detected in delivery-ward and cross-sectional surveys. More likely contributors were poor diet, lack of access to nutritional supplements during pregnancy, poor spacing and high frequency of pregnancies, and possible genetic traits[11, 428, 437]. South Asia generally has high anaemia levels, accounting for 37.5% of the entire global anaemia years lost to disability in 2010, down from 39.8% in 1990[438]. Over 50% of this was iron-deficiency anaemia, which was higher in females than males, and compared to rates of less than 25% in sub-Saharan Africa and all high-income countries[438]. South Asia also has the highest anaemia prevalence among pregnant women, which has changed little since 1995[437]. Anaemia prevalence among pregnant women aged 15-49 in South Asia reduced marginally from 53% in 1995 to 52% in 2011, while severe anaemia in this group reduced from 2.9% to 1.3%[437]. This compared with global rates of 48% in 1995 and 33% in 2011 (2% and 0.9% severe anaemia) and high-income region rates of 23% and 22% (0.5% and 0.2% severe anaemia)[437]. Low haemoglobin concentrations can be caused by a range of factors, including genetic traits, e.g. sickle-cell anaemia and thalassaemia; inadequate bioavailability of dietary iron, folate, or vitamin B12; infectious diseases, e.g. malaria, schistosomiasis, and HIV; hookworm infection; and some non-communicable diseases[437]. It was beyond the scope of this study to identify the reasons for the high anaemia and severe anaemia prevalence detected. Research indicates that sickle-cell traits and thalassaemias may be important contributors in parts of South Asia[439]. However, it was apparent that anaemia results

(i.e. 34% at hospital, 28% in communities) were not unusually high regionally, while severe anaemia results (i.e. 2.3% at hospital and 3.4% in communities) appeared high even for the region. Intestinal parasite prevalence was higher than the 3.8% reported among pregnant women in the 2013 National Nutrition Survey, but did not appear to be associated with anaemia (OR 0.82; 95%CI 0.40-1.67)[428]. LBW prevalence was lower than the Unicef estimate of 28% for the South Asia region, though comparable data were unavailable for Afghanistan[440].

Perceptions of malaria risk appeared higher than warranted by a prevalence of 1.9-3.8/1,000. These perhaps predated health system strengthening and/or were encouraged by popular misconceptions that non-specific febrile illness was often malaria[91, 344]. Despite minimal educational attainment, women were knowledgeable about malaria, probably reflecting long-running health education efforts by NGOs since the 1990s[441]. Growing evidence indicates messages have been effective, despite low literacy and cultural constraints targeting most efforts at men[115, 441].

Policy and practice implications

This study demonstrated that the risk of malaria in pregnancy is low among Afghan women. However, the malaria burden among pregnant women in Afghanistan remains sufficient to warrant specific action. *P. vivax* treatment is particularly challenging in pregnancy. While blood-borne parasites respond to CQ or SP, both safe in pregnancy [158], vivax infections often relapse without radical primaquine treatment[442]. Pregnant and lactating women cannot receive primaquine, due to risks of haemolytic anaemia in glucose-6-phosphate dehydrogenase (G6PD) deficient foetuses[418]. Pregnant women thus risk repeated clinical episodes throughout pregnancy and lactation, as well as pre-term, miscarried, and LBW deliveries[395, 399, 401, 405-410, 415, 416]. Given the challenges of infection in pregnancy, prevention is clearly preferable. The two prevention approaches advocated by WHO in pregnancy are (i) ITN/LLINs, and (ii) IPTp, providing a full therapeutic antimalarial course during antenatal visits.

Which approach would be most effective and acceptable for Afghanistan? ITN/LLINs demonstrated 40% malaria protection in the case-control study, similar to protection demonstrated for Afghan refugee populations in neighbouring Pakistan[151]. Additionally, the community survey confirmed ITN/LLINs were popular and used by all family members[52, 115]. Conversely, persuading pregnant women to take IPTp could be challenging given the perceived risks of taking medication during pregnancy. Weighing the limited risk of malaria in pregnancy, demonstrable protection and popularity of LLINs, reported avoidance of drugs during pregnancy, and still relatively limited data on IPTp for vivax malaria, there seems no real

justification to initiate an IPTp strategy in Afghanistan. ITNs/LLINs are a proven preventive strategy, which along with rapid diagnosis and treatment, can help protect pregnant women in low-endemicity countries such as Afghanistan[52]. Universal coverage with ITNs/LLINs, such as the Global Fund supported initiative providing free LLINs to pregnant women and immunised children, should be the preventive strategy of choice for pregnant women in Afghanistan.

Less than half of community survey participants reported household ownership of any ITNs and only 20% reported using ITNs the previous night, irrespective of season or socioeconomic status. Since this study universal LLIN coverage campaigns have increased coverage to approximately 80% of high-risk populations[12]. LLINs can be used for an average 3-5 year lifespan without retreatment, and since 2005 WHO has recommended programmes only purchase and distribute LLINs[443]. Health messages should emphasise that LLINs be used by all family members, particularly those at greatest risk from malaria. That over 80% of women cited prevention of nuisance biting as more relevant than malaria prevention is not necessarily negative, as families do use ITNs appropriately when given access[246].

Anaemia prevention and treatment policies are already in place in Afghanistan[235, 236, 343]. Unicef is particularly active in nutrition, and nutritional anaemia can be addressed through dietary diversification, improved access to foods with high iron bioavailability, and/or staple foods fortification[438]. Approximately 50% of anaemia and 60% of severe anaemia in pregnancy in the region appears amenable to iron[438], suggesting increased coverage of such programmes should help to reduce anaemia in pregnancy. However, more research is needed to determine the reasons for the high rates of severe anaemia in pregnancy in this population to provide better guidance on other possible prevention and treatment measures.

Limitations

Low malaria prevalence limited analysis of associations. Community sampling may have underestimated malaria prevalence if those ill at home did not participate. However, comparison of facility and community samples produced no evidence of bias, indicating surveys reflected transmission. Use of febrile outpatient rather than community controls is a limitation, as controls may have been previously parasitaemic. A population control, though preferable, was not feasible.

Conclusions

Malaria did not appear responsible for the high prevalence of maternal anaemia detected. While malaria prevalence was low, the risk of severe malaria among pregnant women is sufficient in Afghanistan to justify specific preventive interventions. Given women's perceptions of drug

usage in pregnancy and the limited transmission risk, an IPTp implementation strategy is not justified. Scaling-up LLINs, with increased MOPH emphasis on usage in pregnancy, is likely to be more successful in Afghanistan.

CHAPTER 7 DISCUSSION

Overview

This chapter synthesises and discusses the main research findings from the four studies included in this DrPH thesis. The first section synthesises primary findings under the four evaluation framework dimensions of: (i) effectiveness, (ii) efficiency, (iii) equity, and (iv) humanity. It draws from relevant literature to discuss how findings fit within the broader knowledge base, what insights may be possible from bringing together these studies on disparate malaria control topics, and how well the framework served to support analysis. The second section discusses implications for malaria control, focusing on potential research. The third section describes research limitations. The final section provides concluding reflections.

Primary findings

Results chapters 3 to 6 include four individual studies using different methods and covering different topics of programme cost-effectiveness (economic analysis), antimalarial regimen effectiveness (clinical epidemiology), malaria prevention and health education (qualitative analysis), and malaria in pregnancy needs and responses (clinical and social epidemiology). To synthesise key lessons, common themes in these studies are considered below using the 'four-dimensional' framework introduced in Chapter 1 (Figure 1).

Effectiveness

Effectiveness involves the extent to which identified objectives can be shown to have been met. A major question asked about any disease control programme is 'Are the interventions it provides effective, meaning do they achieve programmatic aims and objectives?' Relatedly, what other interventions might be equally or more effective? These questions are primarily addressed through epidemiological analyses of statistical associations and causality. Chapters 3, 4 and 6 included epidemiological analyses of associations between programme interventions and outcome indicators. Additionally, qualitative social science analyses can address questions about how and why programme objectives may or may not have been met, including context, motivations, and politics[444]. Chapter 5 included qualitative analysis of people's understanding of health and usage of protective measures including ITNs. Thus, the majority of study data were related to effectiveness of interventions and all studies included effectiveness measures. This is perhaps unsurprising, given study data were originally operational research datasets. This also means it is perhaps easiest to answer whether HNTPO's malaria control initiatives were effective.

In Chapter 3, the study aim was to determine whether adding malaria prevention using targeted IRS to case management using quality-assured microscopy and national first-line treatment was a better use of limited resources than case management alone during a prolonged epidemic in Afghan refugee settlements in Pakistan. Epidemiological analysis showed that targeted IRS averted an estimated additional average of 13,598 vivax cases, 3,716 falciparum cases, 26 deaths, and 2,545 DALYs annually.

Adding IRS thus clearly appeared effective. However, it is first necessary to consider whether another preventive intervention (e.g. ITNs) might have been more effective[165, 445]. While it was not possible to determine this with the data available, further analysis of existing operational datasets within Afghan refugee and returnee populations could help (e.g. Dataset 2, on the cost-effectiveness of adding ITNs to IRS, which was not included in this thesis). However, it remains difficult to answer specific queries through secondary analysis of operational datasets and further research is warranted. For example, a Cochrane review found limited data from two studies in unstable transmission settings, suggesting ITNs gave better protection than IRS in India (i.e. malaria incidence risk ratio was 1.48) and South Africa (risk ratio was 1.34 but not significant at 0.05)[87]. Due to increasing resistance globally to the pyrethroids used in ITNs, research on both ITNs and IRS is still needed to address efficacy questions. For example, Fullman and others have demonstrated additional benefits from combining ITNs with IRS using non-pyrethroid insecticides[445-447]. Further research is thus needed on ITN and IRS effectiveness in the context of potential insecticide resistance in Afghanistan and Pakistan[93, 448-450]. Secondly, findings assumed no protective effect of prompt and effective malaria treatment due to lack of data. This assumption may be incorrect, in which case IRS results would become comparably less effective (e.g. as shown in the sensitivity analysis in Table 6). Further research is needed on the protective effect of case management in South Asia and elsewhere. Finally, effectiveness findings alone do not give any indication of the costs of IRS or comparable preventive intervention and cost-effectiveness analysis is necessary.

In Chapter 4, the study aim was to determine whether extended five-day CQ treatment was more effective than standard three-day CQ treatment for uncomplicated falciparum malaria among Afghan refugees in Pakistan. The study was justified because national treatment guidelines recommended extended treatment for all refugee patients returning with symptoms within a few weeks of initial three-day treatment, despite increasing CQ resistance in Pakistan and a lack of *in vivo* testing. Thus, HNTPO staff were required to provide a treatment regimen that lacked any research evidence to support its usage. Epidemiological analysis showed that 84% of patients receiving three-day treatment versus 51% of patients receiving five-day

treatment experienced parasite recrudescence during follow-up (AOR 0.17, 95%CI 0.08-0.38). Thus, cure rates were significantly improved with the five-day regimen, particularly among adults, though fever and parasite clearance times and proportions gametocytaemic post-treatment were similar between treatment groups. As second-line, the five-day regimen resulted in higher failure rates than as first-line. Finding the CQ-resistance marker pfcrt 76T in all isolates analysed, and pfmdr1 86Y and 184Y in 18% and 37% of isolates respectively, indicated that CQ resistance would worsen[321, 331].

Implementing the extended-dose regimen was thus demonstrated to be ineffective, indicating an urgent need to consider and potentially revise national malaria treatment policy. In this case, HNTPO took on the role of advocating for changes in first-line treatment policy, which occurred regionally around 2006, and for improvements in policy uptake, which has been slower and is still ongoing in South Asia[91, 451-453].

In Chapter 6, the study aim was to determine whether malaria in pregnancy was a significant enough concern for Unicef and WHO, the study funders, to recommend chemoprevention for pregnant women in Afghanistan in addition to prioritised ITN usage. Clinical and social epidemiological analyses of data in the three chapter sub-studies provided a coherent picture. First, among 517 delivery-ward participants, one malaria case (prevalence 1.9/1,000), 179 anaemia cases (prevalence 346/1,000), with 12 severely anaemic (prevalence 23/1,000), and 59 LBW deliveries (prevalence 107/1,000) were detected. Second, among 141 malaria cases and 1,010 controls, no association was found between malaria infection and pregnancy (AOR 0.89; 95%CI 0.57-1.39), parity (AOR 0.95; 95%CI 0.85-1.05), age (AOR 1.02; 95%CI 1.00–1.04), or anaemia (AOR 1.00; 95%CI 0.65-1.54). However, 45/141 (32%) cases and 431/1,010 (43%) controls reporting ITN usage indicated ITNs provided 40% reduced odds of malaria infection (AOR 0.60; 95%CI 0.40-0.91). Third, among 530 community survey participants, malaria and anaemia prevalence were 3.9/1,000 and 277/1,000 respectively, with 34/1,000 experiencing severe anaemia. While RDTs may have detected sub-microscopic infections, it is not clear, given the low levels of malaria detected overall and lack of malaria immunity in study areas, whether using RDTs would have increased numbers significantly. However, Leslie *et al* showed that RDTs could improve malaria diagnosis in low transmission areas in Afghanistan[92]. Despite most women having no formal education, malaria knowledge was high, but most expressed reluctance to take malaria preventive medication during pregnancy as they considered it potentially unsafe.

Implementing chemoprevention was thus demonstrated to be unnecessary and therefore ineffective. In this case, HNTPO control programme staff advocated for a nuanced and contextually-appropriate approach to IPT roll-out globally and that IPTp not be implemented in Afghanistan. WHO now only recommends chemoprevention in areas of moderate-to-high malaria transmission in sub-Saharan Africa[10]. Less progress has been apparent in anaemia prevention, which remains 'one of the most intractable public health challenges in South Asia'[454]. Anaemia is typically due to nutritional deficiencies, infectious diseases, or genetic haemoglobin disorders. While relatively little of the anaemia detected in Chapter 6 appeared to be due to common infections (i.e. malaria, worms), it seemed probable that a significant proportion was due to undernutrition or genetic disorders, which were not normally diagnosed in these remote and resource poor areas[454]. While both countries have made progress with iron supplementation programmes, the minimal improvements demonstrated suggest that these have either been insufficiently implemented or that genetic causes are a more significant contributor[454]. For example, β-thalassemia is one of the most common haemoglobin disorders in Pakistan, with a carrier rate of 5-8%[455, 456].

Generally, research questions related to how and why interventions succeed or fail draw from social science approaches. Chapter 5 included social science analysis that allowed for qualitative assessment of the effectiveness of programme interventions[225]. The study was conducted as part of efforts to identify and explore socioeconomic determinants of ITN purchasing and usage so as to help increase ITN coverage, as ITN social-marketing was the primary malaria prevention intervention in Afghan communities[115]. Qualitative analysis indicated that health education interventions had increased malaria knowledge and motivation to purchase ITNs, though there remained some confusion about different prevention initiatives (e.g. the common perception that the reason for boiling water was to kill the mosquitoes breeding in it and thus prevent malaria and typhoid).

Implementing behaviour-change communication, through health education sessions and social-marketing of ITNs, was thus shown to be effective in improving malaria-related knowledge and the desire to own ITNs among targeted communities. It is worth noting, that while Chapter 6 included social epidemiology – which quantitatively analyses social determinants and the dynamics between social context and health[457] – only one of the four studies (Chapter 5) included data that allowed for qualitative social science analysis. HNTPO set-up a social research unit in 2001, though organisational expertise was generally stronger in quantitative research. This may have had implications for other interventions. For example, a qualitative component

could have helped determine the value of women's unpaid work in Chapter 3 or explore reasons for the fear of chemoprevention reported by women in Chapter 6.

Efficiency

The second question usually asked about a programme is 'Do the interventions provide value-for-money?' Such questions are addressed through economic analysis of intervention costs per outcome of interest. As with qualitative analysis, only one of the four studies (Chapter 3) included data that allowed for economic analysis. However, in this case it was not due to the lack of other economic datasets but rather a pragmatic decision to include only the largest and most relevant economic dataset.

Chapter 3 included economic assessment of the cost-effectiveness, or economic efficiency, of a programme intervention[224]. Economic analysis showed that the additional cost of including IRS over five years per case averted was US$39; US$50 for vivax (US$43 in years 1-3, US$80 in years 4-5) and US$182 for falciparum (US$139 in years 1-3 and US$680 in years 4-5). Per DALY averted this was US$266 (US$220 in years 1-3 and US$486 in years 4-5). Cost-effectiveness thresholds used were the somewhat aspirational WHO threshold of 1 and 3 times GDP per capita and the lower but less well-known threshold proposed by Woods *et al* of US$87-669 for Pakistan[296, 299].

Adding targeted IRS to routine case management was thus shown to be cost-effective using both WHO and comparison thresholds. The intervention was 'highly cost-effective' using the WHO threshold of 1xGDP per capita (i.e. US$479 for Pakistan in year 0) per DALY averted when averaged over five years and in years 1-3. This reduced in years 4-5, as the epidemic came to an end, but remained cost-effective at the WHO threshold of 3xGDP per capita (i.e. US$1,436 for Pakistan) per DALY averted[296]. The intervention remained cost-effective over all time-periods using Woods et al's threshold[299]. However, as noted in the *Effectiveness* sub-section above, it is necessary to consider whether another preventive intervention (e.g. ITNs) might have been more cost-effective. For example, in a systematic review White *et al* found the median incremental cost effectiveness ratio per DALY averted was $27 (range $8.15-$110) for ITNs versus $143 (range$135-$150) for IRS, indicating ITNs are more cost-effective in some contexts[303]. Secondly, findings assumed no protective effect of prompt and effective malaria treatment, which may have overestimated IRS cost-effectiveness. Sensitivity analysis showed that increasing cases averted by case management from zero to 30% and 50% increased ICER costs from US$39 to US$56 and US$78 respectively, while reducing cases prevented by 50% increased ICER costs to US$79, which were notable reductions in cost-effectiveness.

Equity

A third question that is often asked about an intervention is 'Is it equitable?', or more specifically, 'How well does the intervention address principles of equality, fairness, and distributive justice?' The principle of fairness is sometimes explained in terms of *equality* (i.e. uniform distribution), in which everyone has equal access to healthcare resources, but is more accurately explained in terms of equity, in which socially marginalised individuals are provided with additional opportunities to help redress chronic disparities[458]. Cromwell notes that while equality is a descriptive concept (i.e. two or more groups are equivalent when compared by one or more measure), equity is a moral concept that requires adoption of an explicitly ethical framework for its evaluation[459]. Thus, Braveman and Gruskin consider equity inherently normative[120, 460]. Distributive or social justice, the principle that costs and benefits are allocated fairly according to either contribution or need, is increasingly important in the bioethics and healthcare literature[125, 461-463]. It is commonly referred to in terms of horizontal equity, i.e. people in equivalent circumstances are treated equally, and vertical equity, i.e. people in different circumstances are treated differently to improve fairness[125].

Arguably, the two most common measures used in assessing equity of health interventions are *equality of access* (e.g. equal access to an intervention among groups) and *equality of usage* (i.e. equal provision and usage of an intervention among groups). The social variable that was both considered relevant and with data available from which to consider equality of access was socioeconomic status. Chapters 5 and 6 included some examination of equality of access to programme interventions.

Quantitative data analysis, conducted previously by the investigator, demonstrated that Afghan households in the richest socioeconomic quartile had 4.5 times higher odds of owning ITNs than those in the lowest quartile[115]. Qualitative analysis in Chapter 5 supported quantitative findings that the poorest struggled to afford ITNs, even at subsidised prices. Thus, findings demonstrated that equality of access to ITNs through social-marketing was not sufficient to enable distributive justice for the poorest and that alternative or additional distribution strategies that contributed to vertical equity in relation to socioeconomic status (e.g. additional targeted subsidy) were needed. Alternatively, free mass distribution of ITNs - as a means of increasing horizontal equity - would also likely improve access for the poorest.

Chapter 6 used a similar asset index to show that women from poorer and wealthier households had similar malaria knowledge and reported behaviours (Table 19). This suggested that equality of access and usage in relation to socioeconomic status were sufficient for health education and

case management interventions, both of which were free to service-users. Thus, these horizontal equity initiatives (i.e. in that all had access to free health education and case management, regardless of socioeconomic status) appeared effective, in that they appeared to work as intended and not exclude any of the socioeconomically marginalised groups included in assessment.

It is perhaps worth noting that Table 19 shows children were prioritised for sleeping under ITNs among lower-income households where ITNs were insufficient to cover everyone, while other age groups were not. This may indicate that children were considered most vulnerable and/or most valued in households. Health education messages encouraged prioritisation of under-five children and pregnant women to sleep under ITNs. However, though numbers were too small to determine significance, Table 19 gives no indication that women were prioritised to sleep under available ITNs in poorer households when ITNs were insufficient to cover everyone (i.e. no women, or 0%, in poorer households versus 11 women, or 6.9%, in wealthier households). Therefore, though data were insufficient to be definitive, it appears that health education interventions contributed to age-related vertical equality of ITN usage in relation to children, though not necessarily to gender-related equality of usage.

ITN social-marketing was thus not equitable according to the equality of access measure, as poorest households were less likely to have enough ITNs to cover all household members. Conversely, health education and case management appeared to contribute to horizontal equity using the same equality of access measure. HNTPO had initially selected a social-marketing approach for ITNs, as a means of maximising coverage due to low funding levels[115]. On finding that social-marketing did not reach the poorest, HNTPO began experimenting with targeted subsidies. However, national policy has since changed to free mass distribution of ITNs in both Afghanistan and Pakistan, primarily enabled by significantly increased international funding due to the launch of GFATM. Thus, there was no opportunity to test the effectiveness of these subsidies and research is needed to determine whether mass interventions intended to improve horizontal equity (e.g. free IRS and ITN distribution) are able to sufficiently improve equality of access and usage of malaria control interventions among the most marginalised Afghan refugees and returnees or whether additional vertical approaches are needed.

As the global universal health coverage movement gains momentum and countries work to achieve the SDG3 target on 'universal health coverage, financial risk protection, and access to quality essential healthcare services, safe, effective, quality, and affordable essential medicines and vaccines'[464] greater efforts will be required to address health equity in redistributive rather

than merely equivalent ways[113, 122-124]. For example, this might require more engagement between health and non-health sectors (e.g. education, labour) to address the root causes of the income inequities that contribute to health inequities.

Humanity

A fourth question is 'Are interventions humane (e.g. do they support the humanity of participants)?', or more specifically, 'How well does the intervention address the principles of autonomy, justice, beneficence, and dignity?' Smith *et al* noted that exploring humanity in public health interventions involves assessing the "social, psychological, and ethical acceptability of the way people are treated"[198]. As described in Chapter 1, the five generally agreed principles of humanity are *autonomy*, the right to informed choice; *beneficence*, choosing to do good; *non-maleficence,* avoiding harm; *dignity*, the right to respect; and *justice*, the right to fair treatment[138, 217, 465]. Humanity principles are not routinely measured in public health interventions in low and middle-income countries, which is unfortunate given their importance[142, 466]. As Smith *et al* noted, the humanity of programme interventions is most obvious in its absence[198].

One reason humanity principles are seldom included explicitly may be that their assessment still requires further development. Early assessments of humanity relied on satisfaction surveys, but these were criticised both methodologically (because survey instruments had poor psychometric properties and satisfaction correlated poorly with humane treatment) and theoretically (because satisfaction is poorly defined)[465]. Humanity is now most commonly assessed through data on service-user perspectives and experiences, using surveys, in-depth or semi-structured interviews, and observation. A second reason may be that the role of humanity still lacks consensus among public health practitioners, particularly individual autonomy versus communal health benefit[467, 468]. As Kass indicated, autonomy cannot be assumed as a priority for public health in the same way that it is for biomedical practice[467]. For example, interventions that require sufficient coverage to provide communal benefit (e.g. vaccination, ITNs) work best when all those at risk access and use them. However, while compulsory vaccination has been debated, and enacted in some countries (e.g. in the UK against smallpox in 1853), no similar debate on enforcing ITN usage seems likely[469, 470]. Malaria control interventions are not generally conducive to legal mandate and rely on informed choice among community members to be implemented effectively. Additionally, malaria control and research generally occurs in low-income settings, often conducted or overseen by those from very different socioeconomic and cultural backgrounds, which could allow opportunities for mistakes or even exploitation if providers were given powers to enforce usage. Therefore, autonomy and other humanity

considerations remain relevant to malaria control programmes. Malaria control, as a public health intervention, should '*minimise unnecessary burdens on the population while fulfilling the mandate to improve population health and reduce social health inequalities'*[471].

As assessment of the humanity of interventions is not routinely or explicitly included in research, it was more challenging to examine retrospectively than other dimensions and findings were more ambiguous. The investigator did not have the opportunity to include humanity assessment measures in survey questionnaires and interview guides. Additionally, and perhaps more relevantly, the literature provided limited guidance on how to correlate service-user experience with humanity principles or determine thresholds of humanity in health interventions[465]. Based on available guidance, the investigator correlated humanity principles with the following measures: (i) *autonomy* with measurements of perceived independence and informed choice; (ii) *beneficence* with provision of the best available interventions; (iii) *non-maleficence* with service-user safety; (iv) *dignity* with perceived respectful treatment; and (v) *justice* with equality of access or usage, as described above under *Equity*, and reciprocity in providing benefits to those being studied[125, 466]. Chapters 5 and 6 included elements of the humanity of programme interventions[223, 472].

Consideration of autonomy was most feasible in terms of gender and socioeconomic status, and consisted of determining whether men and women of all socioeconomic levels perceived themselves able to make informed choices about accessing and using prevention and treatment interventions. Quantitative analysis of survey data in Chapter 6 showed most women service-users (78%) said they preferred malaria treatment at 'NGO/government' facilities run by HNTPO and preferred a malaria blood test (70%), as opposed to the clinical diagnoses often provided at private facilities (Table 19). Another indication of malaria services at HNTPO-supported facilities being valued was that wealthier women were somewhat less likely to seek treatment for non-malaria issues at these facilities (e.g. 69% of wealthier versus 82% of poorer women). Most (81%) also identified ITNs as the best malaria prevention intervention during pregnancy. This suggested that both lower-income and higher-income women considered themselves able to choose appropriate case management and prevention interventions, though not necessarily to access or use them. Qualitative analysis of interview data in Chapter 5 showed that men and older women often made access and usage decisions for other household members. Thus, younger women had less autonomy than men and some older women in terms of choosing how to prevent or treat malaria. However, data were insufficient for further interpretation or to suggest any action that HNTPO might have taken to mitigate this.

Beneficence and non-maleficence related to HNTPO policy and practices and could not be considered through the available data on service-user perspectives. Consideration of beneficence consisted of determining whether HNTPO ensured provision of the best available interventions. Critical comparison of WHO global and regional guidelines and HNTPO research outputs indicated that operational research had been conducted on all major and some relatively obscure (e.g. cattle sponging) malaria control interventions to determine the most effective interventions for populations served. Assessment of non-maleficence consisted of determining that HNTPO only implemented prevention and treatment interventions that were deemed safe according to national and international standards. Economic analysis of HNTPO costs indicated that routine procurement of prevention, diagnostic, and treatment equipment and supplies adhered to standard practice and nothing was deemed to be unusual or worthy of particular concern.

Consideration of dignity consisted of determining whether men and women perceived that their choices about whether and how to engage with malaria control interventions were respected. Data were insufficient and qualitative analysis did not provide any findings in relation to perceived dignity. However, it additionally did not raise any concerns around this issue.

Consideration of justice first consisted of determining whether men and women of all socioeconomic levels experienced equality of access to prevention and treatment interventions. Thus, qualitative analysis of interview data suggested concerns around justice, due to difficulties expressed by the poorest in affording ITNs (discussed above under *Equity*), though no similar concerns were expressed by participants about IRS, which was free to service-users. Both qualitative and quantitative data indicated that participants were satisfied with malaria prevention, whether using IRS or ITNs, if the costs of ITNs were to be addressed. No data were available related to the justice of case management interventions. Second, consideration of justice consisted of determining whether reciprocity for study participants (e.g. non-financial tokens of appreciation for their contributions) was discussed or practiced. This did not seem to be HNTPO policy, which instead appeared to favour an 'ethic of the common good' (e.g. participant cooperation and short-term sacrifice so as to increase community health benefits in the longer-term)[473, 474]. However, to avoid any accusations of paternalism or lack of pluralism and increase opportunities for community ownership and perceived justice, this is something that could be debated explicitly in future[475, 476].

Available data thus indicated that interventions partially addressed humanity and appeared generally humane, though more data were needed to allow explicit assessment of one or more humanity principle.

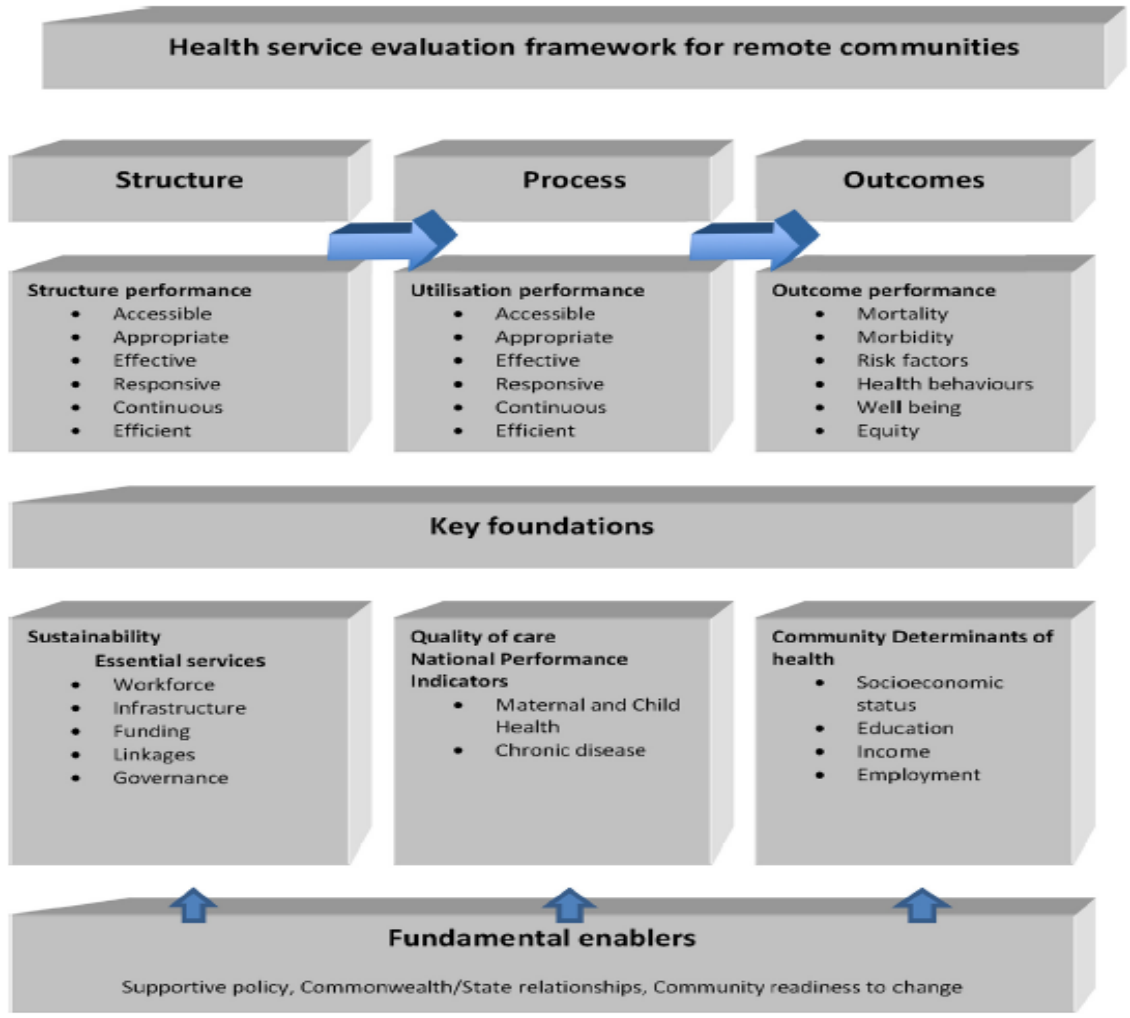
HNTPO interventions and the evaluation framework

Synthesising results from the four studies and relevant literature raised three issues. First, it indicated that HNTPO interventions could be related to and potentially score well on all dimensions of the evaluation framework. Second, it suggested that while the framework was useful, further development of tools and consensus on measurement and thresholds would make it more useful for use by implementing agencies. Third, it demonstrated that operational research could be used to address academic research questions.

Considering each dimension of the framework appeared to be a useful exercise in that it helped delineate and provide greater depth to evaluation aspects such as equity and humanity that were not explicitly considered within individual studies. However, the framework did not provide guidance on measurement methods or achievement thresholds and therefore analysis remained overly subjective. While this framework is not new, further research is clearly needed for the framework to be useful and useable. First, only the efficiency dimension includes a measurable threshold and even these widely used cost-effectiveness thresholds are the subject of ongoing debate[299]. Second, more evidence is needed on evaluating the five aspects of humanity in terms of: (i) whether these can be ranked/prioritised or should always be included and weighted equally; (ii) measurable thresholds; and (iii) systematic and more easily replicable methods to gauge relevant participant experiences and correlate them with the different elements of humanity. The principles of humanity are not new either[198]. However, no articles were found that included the five principles explicitly in a low or middle-income country healthcare intervention evaluation context.

Other evaluation frameworks were considered, as discussed in Chapter 2, particularly that of Reeve *et al*, which looks promising for adaptation in future research (Figure 12). An strength of Reeve *et al*'s framework over Black and Gruen's used here, is that it explicitly considers external factors affecting the programme such as donor interest and funding availability, national policy, and global priorities (e.g. Key Foundations, Fundamental Enablers in Figure 12).

Figure 12. Reeve *et al*'s health service evaluation framework



Source: Reeve *et al*[261]

External factors affected the malaria control programme significantly, including the chronic conflict in Afghanistan, governance issues, constrained donor funding during the study period, and competing health priorities (e.g. maternal health, leishmaniasis). While these effects could not easily be measured, they could be considered qualitatively. However, while interesting for future research, Reeve *et al*'s framework was deemed overly complex and possibly inflexible for secondary analysis of operational datasets and did not explicitly include either equity or humanity. Both equity and humanity seem particularly important evaluation concerns when working with vulnerable populations in conflict-affected and resource-constrained settings, such as Afghan refugee camps and returnee villages. None of the other frameworks considered appeared better (Table 2).

Black and Gruen's framework, despite its overall simplicity, enabled deeper analysis of these old operational datasets and discussion of equity and humanity issues not routinely considered in

public health interventions. This supports the potential for even relatively simple evaluation frameworks to guide and support secondary analyses of operational data.

A number of public health ethics frameworks and guidance questions (e.g. Table 20) have been developed to support equity and humanity considerations within public health[467, 468, 471, 477]. These can be used to guide future malaria control programme development, and thus improve implementation and evaluation of equity and humanity considerations. Table 20, for example, provides a list of ethics questions for public health interventions – including autonomy, justice, beneficence, and non-maleficence - to help ensure they are equitable and humane.

Table 20. Public Health Ontario public health ethics questions

No	Question
1	**What are the objectives of the initiative? How are they linked to potential improvements in public health?**
	− A clear link must be provided between the initiative and potential public health improvements; potential benefits may be immediate or future. Collection of data where public health value is more speculative may be permissible with justification.
	− This question serves as an anchor for review, as many of the questions below relate back to the original objectives.
2	**Can the objectives be achieved using the proposed methods?**
	− Initiatives lacking sufficient methodological rigour may lead to data that is of poor quality or invalid, wasting resources and potentially causing potential harm through misinformation.
	− Requirements for scientific rigour must be balanced with sensitivity to the context in which an activity is implemented.
	− Judgment regarding the design of an initiative requires relevant methodological expertise as well as some knowledge about the participating populations and other contextual details, as relevant.
3	**Who are the expected beneficiaries of the knowledge gained or other benefits?**
	− Beneficiaries may include individuals and/or communities, whether or not they are directly participating in the proposed initiative.
	− Individual and collective interests may be shared or competing, or both, depending on the circumstance.
4	**What are the burdens and potential harms associated with the proposed initiative? Who bears them?**
	− Harms associated with evidence generation in public health frequently arise from collection, use or disclosure of information; potential consequences include stigmatization, discrimination, psychological distress or economic loss. Other harms, such as threats to health, may also occur.
	− Burdens generally are borne by those participating in an initiative. Harms may affect individuals and/or communities, whether or not they are directly participating in the proposed initiative.
	− Potential harm to relationships should be considered.
	− Where possible, an effort must be made to mitigate or minimize risks and burdens, balancing against any loss in potential benefit.
5	**Are burdens and potential harms justified in light of the potential benefits to participants and/or to society?**
	− Burdens and potential harms should be weighed against not only potential benefit from conducting an inquiry, but the harm in not carrying out that inquiry.
	− Burdens or harms may accrue to different individuals/groups than those receiving the benefit but, where this is the case, there should be some justification.
	− "Fair procedures" such as transparency and stakeholder participation should be used to guide decision making regarding balancing of burdens, harms and benefits.
6	**Is selection of participants fair and appropriate?**
	− Fair distribution of burdens, risks and potential benefits includes paying special attention to vulnerable or disadvantaged populations, to be included where there is potential benefit, excluded where certain groups face greater burden or risk, or preferentially included because of increased probability or magnitude of benefit.
	− The principle of reciprocity requires finding ways to give back to individuals or communities that bear a disproportionate share of burden or risk for the benefit of others.
7	**Is individual informed consent warranted? Is it feasible? Is it appropriate? Is it sufficient?**

	− While important, individual autonomy does not always take priority over other ethical concerns, such as welfare of populations.
	− For many public health initiatives, obtaining individual consent may not be required, feasible or appropriate. Where departure from individual informed consent is proposed, consider alternatives such as broad consent, notice with opt out, and consultation with a representative sample of the population of interest.
	− In certain cases, such as examination of illegal behaviour, alternative approaches such as use of verbal consent or pseudonyms may be appropriate.
8	**Is community engagement warranted? Is it feasible? What level of engagement is appropriate?**
	− Community engagement is encouraged where feasible and might be used in lieu of, or in addition to individual consent.
	− Engagement may range from informing to consultation, collaboration and empowerment.
	− Community engagement may include some form of collective consent or consensus process authorizing the initiative in the community.
	− Challenges include determining what level of engagement is appropriate, what counts as a community, and who the appropriate representatives are.
9	**What are the social justice implications of this initiative?**
	− Projects that reinforce existing inequities should be avoided and opportunities to promote social justice should be considered where possible.
	− Extra resources or special measures may be needed to promote social justice, for example to ensure that disadvantaged groups are appropriately considered in the development of project objectives, or to remove barriers to their participation in public health initiatives.
10	**What are the potential longer-term consequences?**
	− Where possible, potential negative long-term consequences of an initiative should be considered and plans for mitigating these risks should be developed prior to implementation.
	− Community engagement can be helpful both in identifying potential long-term harms, and in devising methods to address them.

Source: Willison *et al*[466]

Operational research was shown here to have considerable value, as even these old datasets maintained relevance for today. Operational research needs to demonstrate relevance and value by improving policy and practice[221]. It is particularly useful in settings often considered too challenging for academic research, e.g. Afghanistan, which was affected by ongoing conflict at the time of data collection[220]. Good quality operational research is not only relevant to public health but can support academic enquiry, by: (i) improving the quality and effectiveness of existing treatment or prevention outcomes, (ii) assessing the feasibility of new approaches or interventions in specific settings or populations, and (iii) advocating for policy change based on findings[218]. HNTPO malaria research was robust enough to be able to do these three things.

Implications and recommendations

While the studies in this thesis covered disparate topics, all were conducted as part of operational research for HNTPO's malaria control programme for Afghans living in northwest Pakistan and Eastern Afghanistan and contribute to a coherent body of research on malaria control in the two countries. Specific implications for policy and practice have already been discussed within each study chapter. Therefore, this section focuses on research implications in relation to the four evaluation dimensions.

Effectiveness

Findings contribute to the knowledge base on effectiveness of targeted IRS, ineffectiveness of a five-day treatment regimen against *pfcrt* 76T allele-related CQ resistance, and the effectiveness of locally relevant health education and behaviour change communication. Implications of these findings for both policy-makers and practitioners include the importance of relying on data rather than assumptions (e.g. that refugees would not take the correct antimalarial dosages) when determining treatment policy, the need to ensure effective drug resistance surveillance, and the potential benefits of long-term health education initiatives. The diversity of implications related to effectiveness, that cannot all be included here, is partially an indication of the prominence of effectiveness research in comparison to other dimensions. While more research can certainly be recommended, it appears particularly relevant to recommend a balance of research efforts between the four dimensions.

Efficiency

Findings contribute to the knowledge base on cost-effectiveness of targeted IRS in low-endemicity vivax-dominant settings in South Asia. As national policy already includes the usage of targeted IRS, the main implications of these findings involve the need for additional research, particularly to determine whether ITNs might provide more cost-effective prevention than IRS does in these countries. Analysis of existing HNTPO economic datasets comparing ITNs to IRS and different insecticide formulations in Pakistan, and static versus mobile distribution of ITNs in Afghanistan, is needed to provide a more comprehensive understanding of programme efficiency.

Equity

Findings contribute to the knowledge base on equality of access to ITNs, case management, and health education. These findings supported earlier socioeconomic findings[115] in implying that the primary barrier to ITN purchasing and usage in these Afghan communities was price, indicating that social-marketing could not effectively distribute ITNs to the poorest and free or more affordable targeted mechanisms were likely necessary to increase coverage. Since the time of the study, mass distribution of ITNs free to high-risk service-users has become national policy. Therefore, instead of recommending increased access it would be worthwhile to evaluate the equity of existing ITN distribution initiatives to ensure that all those in need at all socioeconomic levels can access effective malaria prevention under existing policies[121]. Additionally, it would be useful to collect and analyse data on Mooney's other measures of equity, for example: (i) equality of expenditure per capita, (ii) equality of inputs per capita, (iii) equality of input for equal need, (iv) equality of marginal met need, and (v) equality of health[212].

All, except perhaps the last of these, would require economic data, which supports the need for explicitly considering equity in economic analyses of malaria control interventions.

Humanity

Findings contribute to the knowledge base on the humanity of malaria control interventions through an initial attempt to correlate five principles of humanity with measurable aspects of service-user experience and provider action. These include: (i) *autonomy* with perceived independence and informed choice; (ii) *beneficence* with provision of the best available interventions; (iii) *non-maleficence* with service-user safety; (iv) *dignity* with perceived respectful treatment; and (v) *justice* with equality of access and usage[125]. Further research is needed to test and improve upon this initial attempt. The main recommendation is that individuals and organisations engaged in research, particularly in low-income and conflict-affected countries where issues of humanity can be particularly crucial, strengthen the knowledge base by incorporating measurement and analysis of humanity and equity indicators within their studies.

Limitations

General limitations

A major limitation of using secondary data was that data did not always answer specific research questions directly[478]. Since the DrPH investigator did not collect data for all of the studies included (i.e. studies in Chapters 3,4, components of Chapter 6), she had minimal control over variables included in the datasets or how these were initially categorised. Thus, there were gaps in some datasets (e.g. particularly those used in Chapter 3) that could not be reconstructed retrospectively. This limitation was mitigated by adjusting analytical approaches where necessary and excluding variables or categorisations that could not be interpreted or replicated.

A second major limitation was that the DrPH investigator could not always determine how or how well data had been collected[478]. For example, it was not always apparent how quantitative socioeconomic data might have been affected by observer or responder biases, such as participant misunderstanding of interview questions or assumptions about what interviewers were looking for (e.g. expenditure and mortality surveys in Chapter 3, community survey in Chapter 6). To address clarity issues, the investigator checked with field supervisors and data collectors where possible and made assumptions or estimations when data collectors were not available or did not remember. To help mitigate issues around potential information bias, results on perspectives and reported behaviours from studies in which the investigator did not supervise data collection were compared with those for which she did, and no notable

differences were found using this approach[115, 225]. Assumptions and estimations drew from the investigator's own experience in Afghanistan and working with the HNTPO malaria control programme and discussion with senior HNTPO researchers, including Professor Mark Rowland, Dr Toby Leslie, and Naeem Durrani.

A third general limitation was that data on equity and humanity dimensions were relatively minimal. As data included in this thesis had not been published previously, it was thus deemed requisite to focus sub-study analysis and write-up on publishing each study as a stand-alone article addressing original or adapted research objectives. Primarily, this meant that effectiveness received much greater focus than efficiency, equity, or humanity, both because the data were able to address this dimension most clearly and because findings that may have informed equity or humanity dimensions were generally less comprehensive or clear and therefore not included in the final versions for publication provided here as chapters. This limitation was mitigated somewhat through the data synthesis and interpretation included in this discussion chapter. However, the general lack of data that could be used to analyse equity and particularly humanity remains a limitation.

A final general limitation is that study chapters were published in different years and therefore grounded in the knowledge and literature of their respective publication years. For example, Chapter 5 was published in 2010, Chapter 4 was published in 2011, Chapter 6 was published in 2015, and Chapter 3 was published in 2017. This limitation was mitigated by updating the literature included in study chapters and inclusion of recent literature and changes in policy and practice in the introduction and discussion chapters.

Specific sub-study limitations

The main limitations in the economic study (Chapter 3) were the need to rely on unsprayed settlements as the best control available retrospectively and lack of suitable control for case management, which meant cases prevented by diagnosis and treatment had to be estimated at zero; low numbers of falciparum cases and lack of reliable mortality data, which could have reduced the accuracy of estimations for deaths and DALYs averted; lack of disaggregated age and sex data for calculating women's time and life-years directly; and lack of agreed cost-effectiveness thresholds[299]. This was the oldest data, from 1997, so it is perhaps unsurprising that there were several important limitations to consider. Limitation were mitigated by considering each in a univariate sensitivity analysis, to identify how sensitive results were to uncertainty and how they would be affected by changes in specified assumption or data parameters[479, 480].

The main limitations in the clinical trial (Chapter 4) were relatively small sample size, lack of PCR genotyping to distinguish between recrudescent and new infections, and lack of adherence measurement. Limitations were mitigated through drawing on supportive findings from similar research (e.g. Leslie *et al*'s findings that fewer than 5% of infections were new[329] and that Afghan's adhered to much longer fourteen-day regimens[342]).

The main limitations in the qualitative study (Chapter 5) were time constraints limiting the number of possible interviews; access restrictions (e.g. geographical, security), as roads were very poor and Taliban commanders had to approve travel to avoid unwanted killing or detention; and sensitivities around certain topics (e.g. gender, finances). Limitations were mitigated through meetings with commanders to discuss the study and research aims, training and close supervision of data collectors and interpreters, and discussing interpretations of interview data and socio-cultural issues with the research team.

The main limitations in the epidemiological study (Chapter 6) were the low malaria incidence in pregnant women that restricted the type and depth of analysis that could be conducted; usage of febrile outpatients as controls in the case-control sub-study, as controls may have been previously parasitaemic; and the need to rely on prevalence rather than incidence data. Limitations were mitigated primarily through comparative 'triangulation' of results between the three different sub-studies included in Chapter 6.

Conclusions

First, HNTPO has supported, implemented and researched malaria control for Afghans in refugee settlements in Pakistan and villages in Afghanistan for over 25 years. During that time, staff have conducted operational research and provided evidence-informed prevention and treatment services to people in desperate need. The four studies included here reflect some of the diversity of this body of research. While this thesis cannot, and did not aim to, draw overall conclusions on the effectiveness, efficiency, equity, and humanity of HNTPO's overall programme, consideration within the four-dimensional framework suggests that the interventions included here can be considered generally successful in terms of all dimensions of effectiveness, efficiency, equity, and humanity. While more analysis of economic data and more research on aspects of equity and humanity is required, available evidence indicates solid achievement.

Second, findings clearly demonstrate that operational research, including secondary analysis of datasets collected by implementing organizations, can be a valuable addition to the knowledge-base and despite limitations robust and academically-relevant findings can be made.

Third, effectiveness, efficiency, equity and humanity appear to be worthwhile dimensions of public health intervention evaluation. However, more research is needed to make this framework practical and more measurable as an evaluation tool. For example, HNTPO and other organisations engaged in operational research in low and middle-income countries particularly, could further strengthen both their research and the knowledge base by incorporating measurement and analysis of all of these dimensions, rather than just one or two, within each research study.

REFERENCES

1. Carneiro I, Howard N. Introduction to Epidemiology, Second Edition: Open University Press; 2011.
2. Howard N, Sondorp E, ter Veen A, editors. Conflict and Health: Open University Press; 2012.
3. South A, Howard N. Financing Mechanisms for Malaria: Report of the All Party Parliamentary Malaria Group (APPMG). London: APPMG, 2007.
4. Yin R. Case Study Research: Design and Methods (3rd edition). Bickman L, Rog D, editors: Sage Publications; 2003.
5. Coffman J. Foundations and Public Policy Grantmaking. Irvine CA: The James Irvine Foundation, 2008.
6. Reisman J, Gienapp A, Stachowiak S. A Guide to Measuring Advocacy and Policy. Organizational Research Services, 2007.
7. Guthrie K, Louie J, David T, Chrystal-Foster C. The Challenge of Assessing Policy and Advocacy Activities: Strategies for a Prospective Evaluation Approach. Woodland Hills: the California Endowment, 2005.
8. Trigg PI, Kondrachine AV. Commentary: malaria control in the 1990s. Bull World Health Organ. 1998;76(1):11-6
9. Fairhurst RM, Dondorp AM. Artemisinin-Resistant Plasmodium falciparum Malaria. Microbiol Spectr. 2016 Jun;4(3)
10. WHO. Global technical strategy for malaria 2016-2030. Geneva: World Health Organization; 2015.
11. WHO. World Malaria Report 2016. Geneva: World Health Organization, 2016.
12. WHO. World Malaria Report 2015. Geneva: World Health Organization; 2015.
13. RBM Partnership. Action and Investment to defeat Malaria 2016–2030: for a malaria-free world. Geneva: World Health Organization; 2015.
14. White NJ. Plasmodium knowlesi: the fifth human malaria parasite. Clin Infect Dis. 2008 Jan 15;46(2):172-3
15. Agyepong IA, Kangeya-Kayonda J. Providing practical estimates of malaria burden for health planners in resource-poor countries. Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):162-7
16. O'Meara WP, Mangeni JN, Steketee R, Greenwood B. Changes in the burden of malaria in sub-Saharan Africa. Lancet Infect Dis. 2010 Aug;10(8):545-55
17. RBM Partnership Secretariat. RBM Global Strategy 2005 - 2015. Geneva: 2005.
18. Baird JK. Neglect of Plasmodium vivax malaria. Trends Parasitol. 2007 Nov;23(11):533-9
19. Hay SI, Guerra CA, Tatem AJ, Atkinson PM, Snow RW. Urbanization, malaria transmission and disease burden in Africa. Nat Rev Microbiol. 2005 Jan;3(1):81-90
20. Guerra CA, Howes RE, Patil AP, Gething PW, Van Boeckel TP, Temperley WH, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. PLoS Negl Trop Dis. 2010;4(8):e774
21. Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL, et al. Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. Lancet Infect Dis. 2009 Sep;9(9):555-66
22. Price RN, Douglas NM, Anstey NM. New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. Curr Opin Infect Dis. 2009 Oct;22(5):430-5
23. Rogerson SJ, Carter R. Severe vivax malaria: newly recognised or rediscovered. PLoS Med. 2008 Jun 17;5(6):e136
24. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, et al. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med. 2008 Jun 17;5(6):e128
25. Genton B, D'Acremont V, Rare L, Baea K, Reeder JC, Alpers MP, et al. Plasmodium vivax and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. PLoS Med. 2008 Jun 17;5(6):e127
26. White MT, Yeung S, Patouillard E, Cibulskis R. Costs and Cost-Effectiveness of Plasmodium vivax Control. Am J Trop Med Hyg. 2016 Dec 28;95(6 Suppl):52-61

27. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. Am J Trop Med Hyg. 2007 Dec;77(6 Suppl):79-87
28. Raykar N, Laxminarayan R. Benefits and Costs of the Malaria Targets for the Post-2015 Development Agenda: Consensus Project. Copenhagen: Copenhagen Consensus Center, 2014.
29. Smith DL, Cohen JM, Chiyaka C, Johnston G, Gething PW, Gosling R, et al. A sticky situation: the unexpected stability of malaria elimination. Philos Trans R Soc Lond B Biol Sci. 2013 Aug 05;368(1623):20120145
30. RBM Partnership. Defeating malaria in Asia, the Pacific, Americas, Middle East and Europe. WHO, 2012.
31. RBM Partnership Secretariat, editor The Abuja Declaration and the Plan of Action. The African Summit on Roll Back Malaria; 2000; Abuja: WHO.
32. WHO. Millennium Development Declaration Goals. 2003
33. WHO GMP. Indoor residual spraying: Use of indoor residual spraying for scaling up global malaria control and elimination. Geneva: 2006.
34. Coleman PG, Goodman CA, Mills A. Rebound mortality and the cost-effectiveness of malaria control: potential impact of increased mortality in late childhood following the introduction of insecticide treated nets. Trop Med Int Health. 1999;4(3):175-86
35. Guyatt HL, Snow RW, Evans DB. Malaria epidemiology and economics: the effect of delayed immune acquisition on the cost-effectiveness of insecticide-treated bednets. Philos Trans R Soc Lond B Biol Sci. 1999;354(1384):827-35
36. Kolaczinski J, Hanson K. Costing the distribution of insecticide-treated nets: a review of cost and cost-effectiveness studies to provide guidance on standardization of costing methodology. Malar J. 2006;5:37
37. Stevens W, Wiseman V, Ortiz J, Chavasse D. The costs and effects of a nationwide insecticide-treated net programme: the case of Malawi. Malar J. 2005 May 10;4(1):22
38. Breman JG, Alilio MS, Mills A. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):1-15
39. Bhatia MR, Fox-Rushby J, Mills A. Cost-effectiveness of malaria control interventions when malaria mortality is low: insecticide-treated nets versus in-house residual spraying in India. Soc Sci Med. 2004 Aug;59(3):525-39
40. Wiseman V, Hawley WA, ter Kuile FO, Phillips-Howard PA, Vulule JM, Nahlen BL, et al. The cost-effectiveness of permethrin-treated bed nets in an area of intense malaria transmission in western Kenya. Am J Trop Med Hyg. 2003 Apr;68(4 Suppl):161-7
41. Webster J, Hill J, Lines J, Hanson K. Delivery systems for insecticide treated and untreated mosquito nets in Africa: categorization and outcomes achieved. Health Policy Plan. 2007 Jun 28
42. Guyatt HL, Corlett SK, Robinson TP, Ochola SA, Snow RW. Malaria prevention in highland Kenya: indoor residual house-spraying vs. insecticide-treated bednets. Trop Med Int Health. 2002 Apr;7(4):298-303
43. Cost-effectiveness of insecticide-treated nets (ITNs). TDR News. 1996 Jun(50):2
44. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004 (2):CD000363
45. Lengeler C, Snow RW. From efficacy to effectiveness: insecticide-treated bednets in Africa. Bull World Health Organ. 1996;74(3):325-32
46. Lengeler C, Cattani J, de Savigny D, editors. Net Gain: A new method for preventing malaria deaths. Geneva and Ottawa: WHO and International Development Research Centre; 1996.
47. Yukich JO, Lengeler C, Tediosi F, Brown N, Mulligan JA, Chavasse D, et al. Costs and consequences of large-scale vector control for malaria. Malar J. 2008;7:258
48. Yukich JO, Zerom M, Ghebremeskel T, Tediosi F, Lengeler C. Costs and cost-effectiveness of vector control in Eritrea using insecticide-treated bed nets. Malar J. 2009;8:51
49. Morel CM, Lauer JA, Evans DB. Cost effectiveness analysis of strategies to combat malaria in developing countries. BMJ. 2005 Dec 3;331(7528):1299

50. Bockarie MJ, Dagoro H. Are insecticide-treated bednets more protective against Plasmodium falciparum than Plasmodium vivax-infected mosquitoes? Malar J. 2006;5:15
51. Hill J, Lines J, Rowland M. Insecticide-treated nets. Adv Parasitol. 2006;61:77-128
52. Rowland M, Webster J, Saleh P, Chandramohan D, Freeman T, Pearcy B, et al. Prevention of malaria in Afghanistan through social marketing of insecticide-treated nets: evaluation of coverage and effectiveness by cross-sectional surveys and passive surveillance. Trop Med Int Health. 2002 Oct;7(10):813-22
53. Worrall E, Rietveld A, Delacollette C. The burden of malaria epidemics and cost-effectiveness of interventions in epidemic situations in Africa. Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):136-40
54. White MT, Shirreff G, Karl S, Ghani AC, Mueller I. Variation in relapse frequency and the transmission potential of Plasmodium vivax malaria. Proc Biol Sci. 2016 Mar 30;283(1827):20160048
55. Yukich J, Tediosi F, Lengeler C. Operations, costs and cost-effectiveness of five insecticide-treated net programmes (Eritrea, Malawi, Tanzania, Togo, Senegal) and two indoor residual spraying programmes (Kwa-Zulu-Natal, Mozambique). Basel: Swiss Tropical Institute, 2007.
56. Menendez C, D'Alessandro U, ter Kuile FO. Reducing the burden of malaria in pregnancy by preventive strategies. Lancet Infect Dis. 2007 Feb;7(2):126-35
57. Chanda P, Masiye F, Chitah BM, Sipilanyambe N, Hawela M, Banda P, et al. A cost-effectiveness analysis of artemether lumefantrine for treatment of uncomplicated malaria in Zambia. Malar J. 2007;6:21
58. Tediosi F, Maire N, Smith T, Hutton G, Utzinger J, Ross A, et al. An approach to model the costs and effects of case management of Plasmodium falciparum malaria in sub-saharan Africa. Am J Trop Med Hyg. 2006 Aug;75(2 Suppl):90-103
59. Goodman CA, Mutemi WM, Baya EK, Willetts A, Marsh V. The cost-effectiveness of improving malaria home management: shopkeeper training in rural Kenya. Health Policy Plan. 2006 Jul;21(4):275-88
60. Scott JA, Mlacha Z, Nyiro J, Njenga S, Lewa P, Obiero J, et al. Diagnosis of invasive pneumococcal disease among children in Kenya with enzyme-linked immunosorbent assay for immunoglobulin G antibodies to pneumococcal surface adhesin A. Clin Diagn Lab Immunol. 2005 Oct;12(10):1195-201
61. Mubyazi GM, Gonzalez-Block MA. Research influence on antimalarial drug policy change in Tanzania: case study of replacing chloroquine with sulfadoxine-pyrimethamine as the first-line drug. Malar J. 2005;4:51
62. Conteh L, Sharp BL, Streat E, Barreto A, Konar S. The cost and cost-effectiveness of malaria vector control by residual insecticide house-spraying in southern Mozambique: a rural and urban analysis. Trop Med Int Health. 2004 Jan;9(1):125-32
63. Gogtay NJ, Kadam VS, Desai S, Kamtekar KD, Dalvi SS, Kshirsagar NA. A cost-effectiveness analysis of three antimalarial treatments for acute, uncomplicated Plasmodium falciparum malaria in Mumbai, India. J Assoc Physicians India. 2003 Sep;51:877-9
64. Wilkins JJ, Folb PI, Valentine N, Barnes KI. An economic comparison of chloroquine and sulfadoxine-pyrimethamine as first-line treatment for malaria in South Africa: development of a model for estimating recurrent direct costs. Trans R Soc Trop Med Hyg. 2002 Jan-Feb;96(1):85-90
65. Kamya MR, Bakyaita NN, Talisuna AO, Were WM, Staedke SG. Increasing antimalarial drug resistance in Uganda and revision of the national drug policy. Trop Med Int Health. 2002 Dec;7(12):1031-41
66. Garg R, Lee LA, Beach MJ, Wamae CN, Ramakrishnan U, Deming MS. Evaluation of the Integrated Management of Childhood Illness guidelines for treatment of intestinal helminth infections among sick children aged 2-4 years in western Kenya. Trans R Soc Trop Med Hyg. 2002 Sep-Oct;96(5):543-8
67. Wolfe EB, Parise ME, Haddix AC, Nahlen BL, Ayisi JG, Misore A, et al. Cost-effectiveness of sulfadoxine-pyrimethamine for the prevention of malaria-associated low birth weight. Am J Trop Med Hyg. 2001 Mar-Apr;64(3-4):178-86

68. Utzinger J, Tozan Y, Singer BH. Efficacy and cost-effectiveness of environmental management for malaria control. Trop Med Int Health. 2001 Sep;6(9):677-87
69. Hutubessy RC, Bendib LM, Evans DB. Critical issues in the economic evaluation of interventions against communicable diseases. Acta Trop. 2001 Mar 30;78(3):191-206
70. Goodman CA, Coleman PG, Mills AJ. Changing the first line drug for malaria treatment--cost-effectiveness analysis with highly uncertain inter-temporal trade-offs. Health Econ. 2001 Dec;10(8):731-49
71. Duhl L. Guide to Community Preventive Services: a commentary. Am J Prev Med. 2000 Jan;18(1 Suppl):10-1
72. Carter R, Mendis KN, Roberts D. Spatial targeting of interventions against malaria. Bull World Health Organ. 2000;78(12):1401-11
73. Konradsen F, Steele P, Perera D, van der Hoek W, Amerasinghe PH, Amerasinghe FP. Cost of malaria control in Sri Lanka. Bull World Health Organ. 1999;77(4):301-9
74. Goodman CA, Mills AJ. The evidence base on the cost-effectiveness of malaria control measures in Africa. Health Policy Plan. 1999 Dec;14(4):301-12
75. Goodman CA, Coleman PG, Mills AJ. Cost-effectiveness of malaria control in sub-Saharan Africa. Lancet. 1999 Jul 31;354(9176):378-85
76. Jha P, Bangoura O, Ranson K. The cost-effectiveness of forty health interventions in Guinea. Health Policy Plan. 1998 Sep;13(3):249-62
77. Graves PM. Comparison of the cost-effectiveness of vaccines and insecticide impregnation of mosquito nets for the prevention of malaria. Ann Trop Med Parasitol. 1998 Jun;92(4):399-410
78. Schultz LJ, Steketee RW, Chitsulo L, Macheso A, Kazembe P, Wirima JJ. Evaluation of maternal practices, efficacy, and cost-effectiveness of alternative antimalarial regimens for use in pregnancy: chloroquine and sulfadoxine-pyrimethamine. Am J Trop Med Hyg. 1996;55(1 Suppl):87-94
79. Snow RW, Lengeler C, de Savigny D, Cattani J. Insecticide-treated bed nets in control of malaria in Africa [letter]. Lancet. 1995;345(8956):1056-7
80. Schultz LJ, Steketee RW, Chitsulo L, Wirima JJ. Antimalarials during pregnancy: a cost-effectiveness analysis. Bull World Health Organ. 1995;73(2):207-14
81. Murray CJ, Kreuser J, Whang W. Cost-effectiveness analysis and policy choices: investing in health systems. Bull World Health Organ. 1994;72(4):663-74
82. Nicholls PJ, Malcolm AD. Nucleic acid analysis by sandwich hybridization. J Clin Lab Anal. 1989;3(2):122-35
83. Mills A. Vertical vs horizontal health programmes in Africa: idealism, pragmatism, resources and efficiency. Soc Sci Med. 1983;17(24):1971-81
84. Attaran A, Maharaj R. Ethical debate: doctoring malaria, badly: the global campaign to ban DDT. BMJ. 2000 Dec 2;321(7273):1403-5
85. Rowland M, Hewitt S, Durrani N, Bano N, Wirtz R. Transmission and control of vivax malaria in Afghan refugee settlements in Pakistan. Trans R Soc Trop Med Hyg. 1997 May-Jun;91(3):252-5
86. Shretta R, Avancena AL, Hatefi A. The economics of malaria control and elimination: a systematic review. Malar J. 2016 Dec 12;15(1):593
87. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev. 2010;4:CD006657
88. Worrall E, Connor SJ, Thomson MC. Improving the cost-effectiveness of IRS with climate informed health surveillance systems. Malar J. 2008;7:263
89. Howard N, Enayatullah S, Mohammad N, Mayan I, Shamszai Z, Rowland M, et al. Towards a strategy for malaria in pregnancy in Afghanistan: analysis of clinical realities and women's perceptions of malaria and anaemia. Malar J. 2015 Nov 04;14:431
90. Fernandes S, Sicuri E, Kayentao K, van Eijk AM, Hill J, Webster J, et al. Cost-effectiveness of two versus three or more doses of intermittent preventive treatment for malaria during pregnancy in sub-Saharan Africa: a modelling study of meta-analysis and cost data. Lancet Glob Health. 2015 Mar;3(3):e143-53

91. Leslie T, Mikhail A, Mayan I, Anwar M, Bakhtash S, Nader M, et al. Overdiagnosis and mistreatment of malaria among febrile patients at primary healthcare level in Afghanistan: observational study. BMJ. 2012;345:e4389
92. Leslie T, Mikhail A, Mayan I, Cundill B, Anwar M, Bakhtash SH, et al. Rapid diagnostic tests to improve treatment of malaria and other febrile illnesses: patient randomised effectiveness trial in primary care clinics in Afghanistan. BMJ. 2014 Jun 19;348:g3730
93. Ghanchi NK, Shakoor S, Thaver AM, Khan MS, Janjua A, Beg MA. Current situation and challenges in implementing Malaria control strategies in Pakistan. Crit Rev Microbiol. 2016 Aug;42(4):588-93
94. Awab GR, Imwong M, Pukrittayakamee S, Alim F, Hanpithakpong W, Tarning J, et al. Clinical trials of artesunate plus sulfadoxine-pyrimethamine for Plasmodium falciparum malaria in Afghanistan: maintained efficacy a decade after introduction. Malar J. 2016 Feb 25;15:121
95. Nosten F, McGready R, Ashley E, White NJ. Malaria misconceptions. Lancet. 2005 Feb 19-25;365(9460):653
96. Lubell Y, Yeung S, Dondorp AM, Day NP, Nosten F, Tjitra E, et al. Cost-effectiveness of artesunate for the treatment of severe malaria. Trop Med Int Health. 2009 Mar;14(3):332-7
97. Wiseman V, Kim M, Mutabingwa TK, Whitty CJ. Cost-Effectiveness Study of Three Antimalarial Drug Combinations in Tanzania. PLoS Med. 2006 Oct 10;3(10)
98. Bukirwa H, Yeka A, Kamya MR, Talisuna A, Banek K, Bakyaita N, et al. Artemisinin combination therapies for treatment of uncomplicated malaria in Uganda. PLoS Clin Trials. 2006 May;1(1):e7
99. Hanson K. Public and private roles in malaria control: the contributions of economic analysis. Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):168-73
100. Coleman PG, Morel C, Shillcutt S, Goodman C, Mills AJ. A threshold analysis of the cost-effectiveness of artemisinin-based combination therapies in sub-saharan Africa. Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):196-204
101. Rolland E, Checchi F, Pinoges L, Balkan S, Guthmann JP, Guerin PJ. Operational response to malaria epidemics: are rapid diagnostic tests cost-effective? Trop Med Int Health. 2006 Apr;11(4):398-408
102. Bualombai P, Prajakwong S, Aussawatheerakul N, Congpoung K, Sudathip S, Thimasarn K, et al. Determining cost-effectiveness and cost component of three malaria diagnostic models being used in remote non-microscope areas. Southeast Asian J Trop Med Public Health. 2003 Jun;34(2):322-33
103. Pfeil J, Borrmann S, Tozan Y. Dihydroartemisinin-piperaquine vs. artemether-lumefantrine for first-line treatment of uncomplicated malaria in African children: a cost-effectiveness analysis. PLoS One. 2014;9(4):e95681
104. Silumbe K, Yukich JO, Hamainza B, Bennett A, Earle D, Kamuliwo M, et al. Costs and cost-effectiveness of a large-scale mass testing and treatment intervention for malaria in Southern Province, Zambia. Malar J. 2015 May 20;14:211
105. Tawiah T, Hansen KS, Baiden F, Bruce J, Tivura M, Delimini R, et al. Cost-Effectiveness Analysis of Test-Based versus Presumptive Treatment of Uncomplicated Malaria in Children under Five Years in an Area of High Transmission in Central Ghana. PLoS One. 2016;11(10):e0164055
106. Maka DE, Chiabi A, Obadeyi B, Mah E, Nguefack S, Nana P, et al. Economic evaluation of artesunate and three quinine regimens in the treatment of severe malaria in children at the Ebolowa Regional Hospital-Cameroon: a cost analysis. Malar J. 2016 Dec 07;15(1):587
107. Sicuri E, Fernandes S, Macete E, Gonzalez R, Mombo-Ngoma G, Massougbodgi A, et al. Economic evaluation of an alternative drug to sulfadoxine-pyrimethamine as intermittent preventive treatment of malaria in pregnancy. PLoS One. 2015;10(4):e0125072
108. Hansen KS, Ndyomugyenyi R, Magnussen P, Lal S, Clarke SE. Cost-effectiveness analysis of malaria rapid diagnostic tests for appropriate treatment of malaria at the community level in Uganda. Health Policy Plan. 2017 Feb 15

109. Lemma H, San Sebastian M, Lofgren C, Barnabas G. Cost-effectiveness of three malaria treatment strategies in rural Tigray, Ethiopia where both Plasmodium falciparum and Plasmodium vivax co-dominate. Cost Eff Resour Alloc. 2011 Feb 08;9:2
110. Xia S, Ma JX, Wang DQ, Li SZ, Rollinson D, Zhou SS, et al. Economic cost analysis of malaria case management at the household level during the malaria elimination phase in The People's Republic of China. Infect Dis Poverty. 2016 Jun 03;5(1):50
111. Okell LC, Cairns M, Griffin JT, Ferguson NM, Tarning J, Jagoe G, et al. Contrasting benefits of different artemisinin combination therapies as first-line malaria treatments using model-based cost-effectiveness analysis. Nat Commun. 2014 Nov 26;5:5606
112. Tusting LS, Rek J, Arinaitwe E, Staedke SG, Kamya MR, Cano J, et al. Why is malaria associated with poverty? Findings from a cohort study in rural Uganda. Infect Dis Poverty. 2016 Aug 04;5(1):78
113. Steketee RW, Eisele TP. Is the scale up of malaria intervention coverage also achieving equity? PLoS One. 2009;4(12):e8409
114. Barat LM, Palmer N, Basu S, Worrall E, Hanson K, Mills A. Do malaria control interventions reach the poor? A view through the equity lens. Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):174-8
115. Howard N, Chandramohan D, Freeman T, Shafi A, Rafi M, Enayatullah S, et al. Socio-economic factors associated with the purchasing of insecticide-treated nets in Afghanistan and their implications for social marketing. Trop Med Int Health. 2003 Dec;8(12):1043-50
116. Lengeler C. From Rio to Iragua--sustainability versus efficiency and equity for preventive health interventions. Trop Med Int Health. 1999 Jun;4(6):409-11
117. Lengeler C, Grabowsky M, McGuire D, deSavigny D. Quick wins versus sustainability: options for the upscaling of insecticide-treated nets. Am J Trop Med Hyg. 2007 Dec;77(6 Suppl):222-6
118. Onwujekwe O, Uzochukwu B, Eze S, Obikeze E, Okoli C, Ochonma O. Improving equity in malaria treatment: relationship of socio-economic status with health seeking as well as with perceptions of ease of using the services of different providers for the treatment of malaria in Nigeria. Malar J. 2008;7:5
119. Etiaba E, Onwujekwe O, Uzochukwu B, Adjagba A. Investigating payment coping mechanisms used for the treatment of uncomplicated malaria to different socio-economic groups in Nigeria. Afr Health Sci. 2015 Mar;15(1):42-8
120. Braveman P. What are health disparities and health equity? We need to be clear. Public health reports. 2014 Jan-Feb;129 Suppl 2:5-8
121. Hailu A, Lindtjorn B, Deressa W, Gari T, Loha E, Robberstad B. Equity in long-lasting insecticidal nets and indoor residual spraying for malaria prevention in a rural South Central Ethiopia. Malar J. 2016 Jul 16;15:366
122. Chakraborty NM, Firestone R, Bellows N. Equity monitoring for social marketing: use of wealth quintiles and the concentration index for decision making in HIV prevention, family planning, and malaria programs. BMC Public Health. 2013;13 Suppl 2:S6
123. Snow RW, Okiro EA, Gething PW, Atun R, Hay SI. Equity and adequacy of international donor assistance for global malaria control: an analysis of populations at risk and external funding commitments. Lancet. 2010 Oct 23;376(9750):1409-16
124. Shah NK. Assessing strategy and equity in the elimination of malaria. PLoS Med. 2010 Aug 03;7(8):e1000312
125. Tsang C, Cromwell D, editors. Health Care Evaluation. Second ed. London: Open University Press; 2017.
126. Davis SL. Human rights and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Health and human rights. 2014 Jun 14;16(1):134-47
127. Mamotte N, Wassenaar D, Koen J, Essack Z. Convergent ethical issues in HIV/AIDS, tuberculosis and malaria vaccine trials in Africa: Report from the WHO/UNAIDS African AIDS Vaccine Programme's Ethics, Law and Human Rights Collaborating Centre consultation, 10-11 February 2009, Durban, South Africa. BMC Med Ethics. 2010 Mar 09;11:3

128. Noor AM, Zurovac D, Hay SI, Ochola SA, Snow RW. Defining equity in physical access to clinical services using geographical information systems as part of malaria planning and monitoring in Kenya. Trop Med Int Health. 2003 Oct;8(10):917-26
129. Yeung S, Van Damme W, Socheat D, White NJ, Mills A. Access to artemisinin combination therapy for malaria in remote areas of Cambodia. Malar J. 2008;7:96
130. Hetzel M, Alba S, Fankhauser M, Mayumana I, Lengeler C, Obrist B, et al. Malaria risk and access to prevention and treatment in the paddies of the Kilombero Valley, Tanzania. Malaria J. 2008;7(1):7
131. Hetzel MW, Obrist B, Lengeler C, Msechu JJ, Nathan R, Dillip A, et al. Obstacles to prompt and effective malaria treatment lead to low community-coverage in two rural districts of Tanzania. BMC Public Health. 2008;8:317
132. Guthmann JP. [Clinical research and humanitarian work: the role of Medecins sans Frontieres in the fight against malaria]. Med Sci (Paris). 2009 Mar;25(3):301-6
133. Baird JK, Surjadjaja C. Consideration of ethics in primaquine therapy against malaria transmission. Trends Parasitol. 2011 Jan;27(1):11-6
134. Nathan R, Masanja H, Mshinda H, Schellenberg JA, de Savigny D, Lengeler C, et al. Mosquito nets and the poor: can social marketing redress inequities in access? Trop Med Int Health. 2004 Oct;9(10):1121-6
135. Onwujekwe O, Hanson K, Uzochukwu B, Ichoku H, Ike E, Onwughalu B. Are malaria treatment expenditures catastrophic to different socio-economic and geographic groups and how do they cope with payment? A study in southeast Nigeria. Trop Med Int Health. 2010 Jan;15(1):18-25
136. Uguru NP, Onwujekwe OE, Tasie NG, Uzochukwu BS, Ezeoke UE. Do consumers' preferences for improved provision of malaria treatment services differ by their socio-economic status and geographic location? A study in southeast Nigeria. BMC Public Health. 2010 Jan 05;10:7
137. Brentlinger PE. Health, human rights, and malaria control: historical background and current challenges. Health and human rights. 2006;9(2):10-38
138. Beauchamp T, Childress J, editors. Principles of Biomedical Ethics. 1st ed: Oxford University Press; 1979.
139. Ledermann W, Valle G. [Ethics and research in the history of malaria]. Rev Chilena Infectol. 2009 Oct;26(5):466-71
140. Kilama WL. Health research ethics in public health: trials and implementation of malaria mosquito control strategies. Acta Trop. 2009 Nov;112 Suppl 1:S37-47
141. Spielman A. Ethical dilemmas in malaria control. J Vector Ecol. 2006 Jun;31(1):1-8
142. Adams P, Prakobtham S, Limphattharacharoen C, Vutikes P, Khusmith S, Pengsaa K, et al. Ethical considerations in malaria research proposal review: empirical evidence from 114 proposals submitted to an Ethics Committee in Thailand. Malar J. 2015 Sep 14;14:342
143. Kilama WL. Ethical perspective on malaria research for Africa. Acta Trop. 2005 Sep;95(3):276-84
144. Kilama WL. Health research ethics in malaria vector trials in Africa. Malar J. 2010 Dec 13;9 Suppl 3:S3
145. Lubell Y, White L, Varadan S, Drake T, Yeung S, Cheah PY, et al. Ethics, economics, and the use of primaquine to reduce falciparum malaria transmission in asymptomatic populations. PLoS Med. 2014 Aug;11(8):e1001704
146. Arnot DE, Jepsen S, Kilama W. Health research ethics in Africa. Parasitol Today. 2000 Apr;16(4):136-7
147. Chippaux JP. [Defining an ethics for preventive trials]. Bull Soc Pathol Exot. 2008 Apr;101(2):85-9
148. Dieudonne DA. [Research ethics and developing countries]. J Int Bioethique. 2007 Dec;18(4):69-73, 8-9
149. Farmer P, Campos NG. Rethinking medical ethics: a view from below. Dev World Bioeth. 2004 May;4(1):17-41

150. Rowland M, Hewitt S, Durrani N. Prevalence of malaria in Afghan refugee villages in Pakistan sprayed with lambdacyhalothrin or malathion. Trans R Soc Trop Med Hyg. 1994 Jul-Aug;88(4):378-9
151. Rowland M, Hewitt S, Durrani N, Saleh P, Bouma M, Sondorp E. Sustainability of pyrethroid-impregnated bednets for malaria control in Afghan communities. Bull World Health Organ. 1997;75(1):23-9
152. Kolaczinski J, Graham K, Fahim A, Brooker S, Rowland M. Malaria control in Afghanistan: progress and challenges. Lancet. 2005 Apr 23-29;365(9469):1506-12
153. Rowland M, Nosten F. Malaria epidemiology and control in refugee camps and complex emergencies. Ann Trop Med Parasitol. 2001 Dec;95(8):741-54
154. Rowland M, Mahmood P, Iqbal J, Carneiro I, Chavasse D. Indoor residual spraying with alphacypermethrin controls malaria in Pakistan: a community-randomized trial. Trop Med Int Health. 2000 Jul;5(7):472-81
155. Health Works. Health Works History https://www.health-works.org/en/6/history: Health Works; 2017 [14 Oct 2017].
156. DMC. Pakistan Malaria Programme Review (MPR). Islamabad: Directorate of Malaria Control Pakistan, 2013.
157. UNHCR. UNHCR in Pakistan: An enduring partnership. http://unhcrpk.org/: 2017.
158. Leslie T, Mayan MI, Hasan MA, Safi MH, Klinkenberg E, Whitty CJ, et al. Sulfadoxine-pyrimethamine, chlorproguanil-dapsone, or chloroquine for the treatment of Plasmodium vivax malaria in Afghanistan and Pakistan: a randomized controlled trial. JAMA. 2007 May 23;297(20):2201-9
159. Croft AM, Darbyshire AH, Jackson CJ, van Thiel PP. Malaria prevention measures in coalition troops in Afghanistan. JAMA. 2007 May 23;297(20):2197-200
160. Brooker S, Leslie T, Kolaczinski K, Mohsen E, Mehboob N, Saleheen S, et al. Spatial epidemiology of Plasmodium vivax, Afghanistan. Emerg Infect Dis. 2006 Oct;12(10):1600-2
161. Durrani N, Leslie T, Rahim S, Graham K, Ahmad F, Rowland M. Efficacy of combination therapy with artesunate plus amodiaquine compared to monotherapy with chloroquine, amodiaquine or sulfadoxine-pyrimethamine for treatment of uncomplicated Plasmodium falciparum in Afghanistan. Trop Med Int Health. 2005 Jun;10(6):521-9
162. Rowland M, Freeman T, Downey G, Hadi A, Saeed M. DEET mosquito repellent sold through social marketing provides personal protection against malaria in an area of all-night mosquito biting and partial coverage of insecticide-treated nets: a case-control study of effectiveness. Trop Med Int Health. 2004 Mar;9(3):343-50
163. Abdur Rab M, Freeman TW, Rahim S, Durrani N, Simon-Taha A, Rowland M. High altitude epidemic malaria in Bamian province, central Afghanistan. East Mediterr Health J. 2003 May;9(3):232-9
164. Abdel-Hameed AA. Antimalarial drug resistance in the Eastern Mediterranean Region. East Mediterr Health J. 2003 Jul;9(4):492-508
165. Rowland M. Malaria control: bednets or spraying? Malaria control in the Afghan refugee camps of western Pakistan. Trans R Soc Trop Med Hyg. 1999 Sep-Oct;93(5):458-9
166. Hewitt S, Kamal M, Muhammad N, Rowland M. An entomological investigation of the likely impact of cattle ownership on malaria in an Afghan refugee camp in the North West Frontier Province of Pakistan. Med Vet Entomol. 1994 Apr;8(2):160-4
167. World malaria situation 1990. Division of Control of Tropical Diseases. World Health Organization, Geneva. World Health Stat Q. 1992;45(2-3):257-66
168. World malaria situation, 1988. Division of Control of Tropical Diseases. World Health Stat Q. 1990;43(2):68-79
169. Delfini LF. The first case of Plasmodium falciparum resistant to chloroquine treatment discovered in the Republic of Afghanistan. Trans R Soc Trop Med Hyg. 1989 May-Jun;83(3):316
170. Aboff BM. Febrile illness in an Afghani "freedom fighter". J Tenn Med Assoc. 1989 Nov;82(11):599

171. Suleman M. Malaria in Afghan refugees in Pakistan. Trans R Soc Trop Med Hyg. 1988;82(1):44-7
172. Artem'ev MM, Anufrieva VN, Zharov AA, Flerova OA. [Problem of malaria and the malaria control measures in northern Afghanistan. 3. Anopheles mosquitoes in the rice-growing areas]. Med Parazitol (Mosk). 1977 Jul-Aug;46(4):406-13
173. Polevoi NI, Artem'ev MM, Nushin MK, Iakubi G, Lopukhina NG. [Problem of malaria and antimalarial measures in northern Afghanistan. 2. Topographical malariological districting of northern Afghanistan and the restructuring of the system of antimalarial measures]. Med Parazitol (Mosk). 1975 May-Jun;44(3):338-44
174. Abdul Q. [On eradication of malaria in Afghanistan]. Med Parazitol (Mosk). 1965 Mar-Apr;34(2):194-5
175. Fischer L, Steinhart W. [Malaria & malaria carriers in Sarobie, Afghanistan.]. Z Tropenmed Parasitol. 1957 Mar;8(1-2):69-83
176. Dhir SL, Rahim A. Malaria and its control in Afghanistan (1950-1954). Indian J Malariol. 1957 Mar;11(1):73-126
177. Iyengar MO. Vector of malaria in Kabul, Afghanistan. Trans R Soc Trop Med Hyg. 1954 Jul;48(4):319-24
178. Ramachandra T. Malaria control using indoor residual sprays in the Eastern Province of Afghanistan. Bull World Health Organ. 1951;3(4):639-61
179. Alegana VA, Wright JA, Nahzat SM, Butt W, Sediqi AW, Habib N, et al. Modelling the incidence of Plasmodium vivax and Plasmodium falciparum malaria in Afghanistan 2006-2009. PLoS One. 2014;9(7):e102304
180. Mashal T, Takano T, Nakamura K, Kizuki M, Hemat S, Watanabe M, et al. Factors associated with the health and nutritional status of children under 5 years of age in Afghanistan: family behaviour related to women and past experience of war-related hardships. BMC Public Health. 2008;8:301
181. Hansen PM, Peters DH, Niayesh H, Singh LP, Dwivedi V, Burnham G. Measuring and managing progress in the establishment of basic health services: the Afghanistan health sector balanced scorecard. Int J Health Plann Manage. 2008 Apr-Jun;23(2):107-17
182. Korzeniewski K. [Epidemiological situation of Afghanistan]. Przegl Epidemiol. 2005;59(4):903-13
183. Cook J. Post-conflict reconstruction of the health system of Afghanistan: assisting in the rehabilitation of a provincial hospital--context and experience. Med Confl Surviv. 2003 Apr-Jun;19(2):128-41
184. Newbrander W, Yoder R, Debevoise AB. Rebuilding health systems in post-conflict countries: estimating the costs of basic services. Int J Health Plann Manage. 2007 Apr 23
185. Siddiqi S, Masud TI, Sabri B. Contracting but not without caution: experience with outsourcing of health services in countries of the Eastern Mediterranean Region. Bull World Health Organ. 2006 Nov;84(11):867-75
186. Howard N, Woodward A, Patel D, Shafi A, Oddy L, Ter Veen A, et al. Perspectives on reproductive healthcare delivered through a basic package of health services in Afghanistan: a qualitative study. BMC health services research. 2014 Aug 28;14(1):359
187. Palmer N, Strong L, Wali A, Sondorp E. Contracting out health services in fragile states. BMJ. 2006 Mar 25;332(7543):718-21
188. Hewitt S, Rowland M. Control of zoophilic malaria vectors by applying pyrethroid insecticides to cattle. Trop Med Int Health. 1999 Jul;4(7):481-6
189. Diabate A, Chandre F, Rowland M, N'Guessan R, Duchon S, Dabire KR, et al. The indoor use of plastic sheeting pre-impregnated with insecticide for control of malaria vectors. Trop Med Int Health. 2006 May;11(5):597-603
190. WHO. World Malaria Report 2009. Geneva: 2009.
191. WHO-EMRO. Pakistan malaria profile. http://www.emro.who.int/rbm/CountryProfiles-pak.htm2017.

192. Glaeske G, Augustin M, Abholz H, Banik N, Bruggenjurgen B, Hasford J, et al. [Epidemiological methods for health services research]. Gesundheitswesen. 2009 Oct;71(10):685-93
193. Saldaña J. The Coding Manual for Qualitative Researchers. London: Sage; 2009.
194. Trochim W, editor Developing an evaluation culture for international agricultural research. Assessing the Impact of International Agricultural Research for Sustainable Development: Proceedings from a Symposium at Cornell University, June 16-19; 1991; Ithaca NY: Cornell Institute for Food, Agriculture and Development,.
195. DCD-DAC. DAC Principles for the Evaluation of Development Assistance. 1991.
196. Framework for program evaluation in public health. MMWR Recomm Rep. 1999 Sep 17;48(RR-11):1-40
197. ACF-OPRE. Chapter 2: What is program evaluation? The Program Manager's Guide to Evaluation: US Dept of Health & Human Services.; 2006.
198. Smith S, Sinclair D, Raine R, Reeves B. Health Care Evaluation. Black N, Raine R, editors. Maidenhead: Open University Press; 2005.
199. McNamara C. Field Guide to Nonprofit Program Design, Marketing and Evaluation. 4th ed: Authenticity Consulting; 2006.
200. Hopkins D. Evaluation for School Development. Milton Keynes: Open University Press; 1989.
201. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. BMJ. 2000 Sep 16;321(7262):694-6
202. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655
203. GFATM. Monitoring and Evaluation Toolkit: HIV/AIDS, Tuberculosis, and Malaria. Geneva: GFATM, WHO, WB, UNAIDS, USAID, PMI, RBM, StopTB, HMN, MEASURE, 2009.
204. Bailey L, Vardulaki K, Langham J, Chandramohan D. Introduction to Epidemiology. Maidenhead: Open University Press; 2006.
205. Wensing M. Research methods from social science can contribute much to the health sciences. J Clin Epidemiol. 2008 Jun;61(6):519-20
206. Palmer S, Byford S, Raftery J. Economics notes: types of economic evaluation. BMJ. 1999 May 15;318(7194):1349
207. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G, editors. Methods for the Economic Evaluation of Health Care Programmes. Third Edition ed. Oxford: Oxford University Press; 2006.
208. Macinko JA, Starfield B. Annotated Bibliography on Equity in Health, 1980-2001. Int J Equity Health. 2002 Apr 22;1(1):1
209. Stevens A, Gabbay J. Needs assessment needs assessment. Health Trends. 1991;23(1):20-3
210. Vyas S, Kumaranayake L. Constructing socio-economic status indices: how to use principal components analysis. Health Policy Plan. 2006 Nov;21(6):459-68
211. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83
212. Mooney GH. Equity in health care: confronting the confusion. Eff Health Care. 1983 Dec;1(4):179-85
213. Hodge S. Humanity and equality--will they ever be fully compatible? Perspect Public Health. 2009 Sep;129(5):204
214. de Roodenbeke E. Reconciling technology and humanity in health care. World Hosp Health Serv. 2008;44(3):3
215. Gillon R. Medical ethics: four principles plus attention to scope. BMJ. 1994 Jul 16;309(6948):184-8
216. Smith AF. Reaching the parts that are hard to reach: expanding the scope of professional education in anaesthesia. Br J Anaesth. 2007 Oct;99(4):453-6

217. Block D. Healthcare outcomes management: strategies for planning and evaluation. Sudbury MA: Jones & Bartlett; 2006.
218. Zachariah R, Harries AD, Ishikawa N, Rieder HL, Bissell K, Laserson K, et al. Operational research in low-income countries: what, why, and how? Lancet Infect Dis. 2009 Nov;9(11):711-7
219. MSF. Operational Research Definition, Purpose & Procedures (A Policy Framework): Version 2. Brussels: Médecins Sans Frontières, 2010.
220. Quaglio G, Ramsay A, Harries AD, Karapiperis T, Putoto G, Dye C, et al. Calling on Europe to support operational research in low-income and middle-income countries. Lancet Glob Health. 2014 Jun;2(6):e308-10
221. Zachariah R, Ford N, Maher D, Bissell K, Van den Bergh R, van den Boogaard W, et al. Is operational research delivering the goods? The journey to success in low-income countries. Lancet Infect Dis. 2012 May;12(5):415-21
222. Horstick O, Sommerfeld J, Kroeger A, Ridley R. Operational research in low-income countries. Lancet Infect Dis. 2010 Jun;10(6):369-70
223. Howard N, Durrani N, Sanda S, Beshir K, Hallett R, Rowland M. Clinical trial of extended-dose chloroquine for treatment of resistant falciparum malaria among Afghan refugees in Pakistan. Malar J. 2011;10:171
224. Howard N, Guinness L, Durrani N, Rowland M, Hanson K. Cost-effectiveness of adding indoor residual spraying to case management in Afghan refugee settlements in Northwest Pakistan during a prolonged malaria epidemic. PLoS Negl Trop Dis. 2017;11(10)
225. Howard N, Shafi A, Jones C, Rowland M. Malaria control under the Taliban regime: insecticide-treated net purchasing, coverage, and usage among men and women in eastern Afghanistan. Malar J. 2010 Jan 6;9(1):7
226. CIA. South Asia. The World Factbook. Washington DC: Central Intelligence Agency; 2017.
227. Messner J, Haken N, Taft P, Blyth H, Lawrence K, Graham S, et al. Fragile States Index 2015. Washington DC: The Fund for Peace, 2015.
228. DeSilva-Ranasinghe S. Why South Asia matters in world affairs: an interview with Professor Sandy Gordon. Policy. 2012;28(1)
229. HM Govt. Health is Global: an outcomes framework for global health 2011-15. London: UK Government, 2011.
230. Skolnik R. Chapter 1. The Principles and Goals of Global Health. Global Health 101. Essential Public Health. Second ed. New Haven: Jones and Bartlett; 2011.
231. WHO. EMRO official website http://www.emro.who.int/: World Health Organization; 2017 [07.01.2017].
232. CIA. South Asia: Pakistan. The World Factbook2017.
233. WHO. Mid-level health workers for delivery of essential health services: A global systematic review and country experiences. http://www.who.int/workforcealliance/knowledge/resources/mlp2013/en/: Global Health Workforce Alliance,, 2013.
234. CIA. South Asia: Afghanistan The World Factbook Washington DC: US Central Intelligence Agency; 2017.
235. MoPH. National Health Strategy 2016–2020: Sustaining Progress and Building for Tomorrow and Beyond. Kabul: Ministry of Public Health, Islamic Republic of Afghanistan, 2016.
236. MOPH. A Basic Package of Health Services for Afghanistan, 2005/1384. Kabul: Islamic Republic of Afghanistan Ministry of Public Health, 2005.
237. Shaikh B. Private sector in health care delivery: A reality and a challenge in Pakistan. J Ayub Med Coll Abbottabad. 2015;27(2)
238. Frost A, Wilkinson M, Boyle P, Patel P, Sullivan R. An assessment of the barriers to accessing the Basic Package of Health Services (BPHS) in Afghanistan: was the BPHS a success? Global Health. 2016 Nov 15;12(1):71

239. Cross HE, Sayedi O, Irani L, Archer LC, Sears K, Sharma S. Government stewardship of the for-profit private health sector in Afghanistan. Health Policy Plan. 2017 Apr 01;32(3):338-48
240. ICMC Europe. Afghan refugees in Pakistan and Iran. http://www.resettlement.eu/page/afghan-refugees-iran-pakistan-0: 2013.
241. Colville R. Afghanistan: the unending crisis. Refugees. 1997 (108)
242. Hewitt SE, Farhan M, Urhaman H, Muhammad N, Kamal M, Rowland MW. Self-protection from malaria vectors in Pakistan: an evaluation of popular existing methods and appropriate new techniques in Afghan refugee communities. Ann Trop Med Parasitol. 1996 Jun;90(3):337-44
243. Shah I, Rowland M, Mehmood P, Mujahid C, Razique F, Hewitt S, et al. Chloroquine resistance in Pakistan and the upsurge of falciparum malaria in Pakistani and Afghan refugee populations. Ann Trop Med Parasitol. 1997 Sep;91(6):591-602
244. Rana SM, Khan EA, Yaqoob A, Latif AA, Abbasi MM. Susceptibility and irritability of adult forms of main malaria vectors against insecticides used in the indoor residual sprays in Muzaffargarh District, Pakistan: a field survey. J Med Entomol. 2014 Mar;51(2):387-91
245. Bouma MJ, Parvez SD, Nesbit R, Winkler AM. Malaria control using permethrin applied to tents of nomadic Afghan refugees in northern Pakistan. Bull World Health Organ. 1996;74(4):413-21
246. Rowland M, Mohammed N, Rehman H, Hewitt S, Mendis C, Ahmad M, et al. Anopheline vectors and malaria transmission in eastern Afghanistan. Trans R Soc Trop Med Hyg. 2002 Nov-Dec;96(6):620-6
247. Faulde MK, Hoffmann R, Fazilat KM, Hoerauf A. Epidemiology of Plasmodium falciparum and P. vivax malaria endemic in northern Afghanistan. J Egypt Soc Parasitol. 2008 Dec;38(3):679-92
248. Kolaczinski J. Roll Back Malaria in the aftermath of complex emergencies: the example of Afghanistan. Trop Med Int Health. 2005 Sep;10(9):888-93
249. Faulde MK, Hoffmann R, Fazilat KM, Hoerauf A. Malaria reemergence in northern Afghanistan. Emerg Infect Dis. 2007 Sep;13(9):1402-4
250. Leslie T, Mohammed N, Omar H, Rasheed H, van der Vorst F, Sediqi A. Malaria sentinel surveillance in Afghanistan. Afghanistan Annual Malaria Journal. 2008;1:114-28
251. Rowland M, Durrani N, Hewitt S, Mohammed N, Bouma M, Carneiro I, et al. Permethrin-treated chaddars and top-sheets: appropriate technology for protection against malaria in Afghanistan and other complex emergencies. Trans R Soc Trop Med Hyg. 1999 Sep-Oct;93(5):465-72
252. Kolaczinski J, Muhammad N, Khan Q, Jan Z, Rehman N, Leslie T, et al. Subsidized sales of insecticide-treated nets in Afghan refugee camps demonstrate the feasibility of a transition from humanitarian aid towards sustainability. Malaria J. 2004;3(1):15
253. Mills A. Is malaria control a priority? Evidence from Nepal. Health Econ. 1993 Dec;2(4):333-47
254. Elias M, Maheswary NP, Islam MS, Rahman MK. Susceptibility of the malaria vectors to insecticides in Bangladesh. Bangladesh Med Res Counc Bull. 1998 Apr;24(1):1-5
255. Donabedian A. The quality of care. How can it be assessed? JAMA. 1988 Sep 23-30;260(12):1743-8
256. Donabedian A. Evaluating the quality of medical care. 1966. The Milbank quarterly. 2005;83(4):691-729
257. Logan S, Boutotte J, Wilce M, Etkind S. Using the CDC framework for program evaluation in public health to assess tuberculosis contact investigation programs. Int J Tuberc Lung Dis. 2003 Dec;7(12 Suppl 3):S375-83
258. Black N, Gruen R, editors. Understanding Health Services. Maidenhead: Open University Press; 2005.
259. Kelley E, Hurst J. Health Care Quality Indicators Project Conceptual Framework Paper https://www.oecd.org/els/health-systems/36262363.pdf: Organisation for Economic Co-operation and Development, 2006.

260. Kruk ME, Porignon D, Rockers PC, Van Lerberghe W. The contribution of primary care to health and health systems in low- and middle-income countries: a critical review of major primary care initiatives. Soc Sci Med. 2010 Mar;70(6):904-11
261. Reeve C, Humphreys J, Wakerman J. A comprehensive health service evaluation and monitoring framework. Eval Program Plann. 2015 Dec;53:91-8
262. Howard N, Penfold S. Chapter 6 Experimental studies: randomized controlled trials. In: Tsang C, Cromwell D, editors. Healthcare Evaluation. Second ed: Open University Press; 2017.
263. Kirkwood B. Essentials of Medical Statistics: Blackwell Science Ltd; 2003.
264. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965 May;58:295-300
265. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002 Jan 19;359(9302):248-52
266. Mwenesi HA. Social science research in malaria prevention, management and control in the last two decades: an overview. Acta Trop. 2005 Sep;95(3):292-7
267. Jones C, Williams HA. Social sciences in malaria control. Trends Parasitol. 2002 May;18(5):195-6
268. RBM Partnership. Towards a Malaria-Free World: A Global Case for Investment and Action 2016-2030. Geneva: 2015.
269. WHO. World Malaria Report 2015. Geneva: World Health Organization, 2015.
270. Cotter C, Sturrock HJ, Hsiang MS, Liu J, Phillips AA, Hwang J, et al. The changing epidemiology of malaria elimination: new strategies for new challenges. Lancet. 2013 Sep 7;382(9895):900-11
271. Alonso PL, Brown G, Arevalo-Herrera M, Binka F, Chitnis C, Collins F, et al. A research agenda to underpin malaria eradication. PLoS Med. 2011 Jan 25;8(1):e1000406
272. RBM Partnership. The Global Malaria Action Plan: for a malaria-free world. Geneva: 2008.
273. Leslie T, Nahzat S, Sediqi W. Epidemiology and Control of Plasmodium vivax in Afghanistan. Am J Trop Med Hyg. 2016 Oct 5
274. Ali N, Noreen S, Khan K, Wahid S. Population dynamics of mosquitoes and malaria vector incrimination in district Charsadda, Khyber Pakhtunkhwa (KP) Pakistan. Acta Trop. 2015 Jan;141(Pt A):25-31
275. Rowland M, Rab MA, Freeman T, Durrani N, Rehman N. Afghan refugees and the temporal and spatial distribution of malaria in Pakistan. Soc Sci Med. 2002 Dec;55(11):2061-72
276. Kazmi JH, Pandit K. Disease and dislocation: the impact of refugee movements on the geography of malaria in NWFP, Pakistan. Soc Sci Med. 2001 Apr;52(7):1043-55
277. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013 Mar-Apr;16(2):231-50
278. Neumann P, Kamal-Bahl S. Should Value Frameworks Take A 'Societal Perspective'? : Health Affairs Blog; 2017 [cited 2017 20 Oct]. Available from: http://healthaffairs.org/blog/2017/09/06/should-value-frameworks-take-a-societal-perspective/.
279. Rowland M, Durrani N. Randomized controlled trials of 5- and 14-days primaquine therapy against relapses of vivax malaria in an Afghan refugee settlement in Pakistan. Trans R Soc Trop Med Hyg. 1999 Nov-Dec;93(6):641-3
280. National Malaria and Leishmaniasis Control Program. National Malaria Treatment Guideline. Kabul: Ministry of Public Health Islamic Republic of Afghanistan, 2010.
281. Rowland M, Bouma M, Ducornez D, Durrani N, Rozendaal J, Schapira A, et al. Pyrethroid-impregnated bed nets for personal protection against malaria for Afghan refugees. Trans R Soc Trop Med Hyg. 1996 Jul-Aug;90(4):357-61
282. HNTPO. Technical Report: Malaria and Leishmaniasis Control Programme. Peshawar: HealthNet, 1993.

283. Lopez A, Salomon J, Murray C, Mafat D. Life tables for 191 countries: data, methods and results. EIP/GPE/EBD World Health Organization, 2001.
284. Chao LW, Szrek H, Pereira NS, Pauly MV. Time preference and its relationship with age, health, and survival probability. Judgm Decis Mak. 2009 Feb 01;4(1):1-19
285. Mathers C, Lopez A, Murray C. Chapter 3 The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001. In: Lopez AD MC, Ezzati M, editor. Global Burden of Disease and Risk Factors: World Bank; 2006.
286. Jamison D, Breman J, Measham A, Alleyne G, Claeson M, Evans D, et al., editors. Disease Control Priorities in Developing Countries. Second ed. New York: Oxford University Press and World Bank; 2006.
287. Acharya A, Murray C. Rethinking Discounting of Health Benefits in Cost Effectiveness Analysis. Sussex: Institute of Development Studies, University of Sussex, 2000.
288. Fox-Rushby JA, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. Health Policy Plan. 2001 Sep;16(3):326-31
289. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2129-43
290. HNTPO. Technical Report. 1991
291. IndexMundi. Afghanistan - Life expectancy at birth. http://www.indexmundi.com/facts/afghanistan/life-expectancy-at-birth (accessed 11 July 2015): 2015.
292. Govt of Pakistan. Economic Survey 2007-08. Islamabad: Ministry of Finance, 2008.
293. Government of Pakistan. Economic Survey 1995-96. Islamabad: Economic Adviser's Wing, 1996.
294. International Monetary Fund. International Financial Statistics, May 1996. 1996.
295. Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level priority-setting in the health sector. Cost Eff Resour Alloc. 2003 Dec 19;1(1):8
296. WHO. Cost effectiveness and strategic planning (WHO-CHOICE): Table: Threshold values for intervention cost-effectiveness by Region http://www.who.int/choice/costs/CER_levels/en/2016 [28 Dec 2016].
297. Shillcutt SD, Walker DG, Goodman CA, Mills AJ. Cost effectiveness in low- and middle-income countries: a review of the debates surrounding decision rules. Pharmacoeconomics. 2009;27(11):903-17
298. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ. 2015 Feb 1;93(2):118-24
299. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. York: Centre for Health Economics, University of York, 2015.
300. Rowland M, Durrani N, Kenward M, Mohammed N, Urahman H, Hewitt S. Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial. Lancet. 2001 Jun 9;357(9271):1837-41
301. Tinghog G. Discounting, preferences, and paternalism in cost-effectiveness analysis. Health Care Anal. 2012 Sep;20(3):297-318
302. WHO. World Malaria Report. World Health Organization, 2014.
303. White MT, Conteh L, Cibulskis R, Ghani AC. Costs and cost-effectiveness of malaria control interventions--a systematic review. Malar J. 2011;10:337
304. Stuckey EM, Stevenson J, Galactionova K, Baidjoe AY, Bousema T, Odongo W, et al. Modeling the cost effectiveness of malaria control interventions in the highlands of western Kenya. PLoS One. 2014;9(10):e107700
305. Newby G, Bennett A, Larson E, Cotter C, Shretta R, Phillips AA, et al. The path to eradication: a progress report on the malaria-eliminating countries. Lancet. 2016 Apr 23;387(10029):1775-84
306. Asif SA. Departmental audit of malaria control programme 2001-2005 north west frontier province (NWFP). J Ayub Med Coll Abbottabad. 2008 Jan-Mar;20(1):98-102

307. MoH. Malaria Case Management: Desk Guide for Clinicians and Health Care Providers. Islamabad: Directorate of Malaria Control, 2007.
308. Rowland M, Durrani N, Hewitt S, Sondorp E. Resistance of falciparum malaria to chloroquine and sulfadoxine-pyrimethamine in Afghan refugee settlements in western Pakistan: surveys by the general health services using a simplified in vivo test. Trop Med Int Health. 1997 Nov;2(11):1049-56
309. Rab MA, Freeman TW, Durrani N, de Poerck D, Rowland MW. Resistance of Plasmodium falciparum malaria to chloroquine is widespread in eastern Afghanistan. Ann Trop Med Parasitol. 2001 Jan;95(1):41-6
310. Sexton JD, Deloron P, Bugilimfura L, Ntilivamunda A, Neill M. Parasitologic and clinical efficacy of 25 and 50 mg/kg of chloroquine for treatment of *Plasmodium falciparum* malaria in Rwandan children. Am J Trop Med Hyg. 1988 Mar;38(2):237-43
311. Beshir K, Sutherland CJ, Merinopoulos I, Durrani N, Leslie T, Rowland M, et al. Amodiaquine resistance in *Plasmodium falciparum* malaria is associated with the pfcrt 72-76 SVMNT allele in Afghanistan. Antimicrob Agents Chemother. 2010 Jun 14
312. WHO. Guidelines for the treatment of malaria. Third edition. Geneva: World Health Organization, 2015.
313. WHO. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. Geneva: World Health Organization, 2003.
314. ClinicalTrials.gov. Clinical trials registry and database http://clinicaltrials.gov: US National Institutes of Health; 2009.
315. WHO. Practical chemotherapy of malaria. Geneva: 1990.
316. Plowe CV, Djimde A, Bouare M, Doumbo O, Wellems TE. Pyrimethamine and proguanil resistance-conferring mutations in *Plasmodium falciparum* dihydrofolate reductase: polymerase chain reaction methods for surveillance in Africa. Am J Trop Med Hyg. 1995 Jun;52(6):565-8
317. Humphreys GS, Merinopoulos I, Ahmed J, Whitty CJ, Mutabingwa TK, Sutherland CJ, et al. Amodiaquine and artemether-lumefantrine select distinct alleles of the *Plasmodium falciparum* mdr1 gene in Tanzanian children treated for uncomplicated malaria. Antimicrob Agents Chemother. 2007 Mar;51(3):991-7
318. Khatoon L, Baliraine FN, Bonizzoni M, Malik SA, Yan G. Prevalence of antimalarial drug resistance mutations in *Plasmodium vivax* and *P. falciparum* from a malaria-endemic area of Pakistan. Am J Trop Med Hyg. 2009 Sep;81(3):525-8
319. Picot S, Olliaro P, de Monbrison F, Bienvenu AL, Price RN, Ringwald P. A systematic review and meta-analysis of evidence for correlation between molecular markers of parasite resistance and treatment outcome in falciparum malaria. Malar J. 2009;8:89
320. Shrivastava SK, Gupta RK, Mahanta J, Dubey ML. Correlation of molecular markers, Pfmdr1-N86Y and Pfcrt-K76T, with in vitro chloroquine resistant Plasmodium falciparum, isolated in the malaria endemic states of Assam and Arunachal Pradesh, Northeast India. PLoS One. 2014;9(8):e103848
321. Khalil IF, Alifrangis M, Tarimo DS, Staalso T, Satti GM, Theander TG, et al. The roles of the pfcrt 76T and pfmdr1 86Y mutations, immunity and the initial level of parasitaemia, in predicting the outcome of chloroquine treatment in two areas with different transmission intensities. Ann Trop Med Parasitol. 2005 Jul;99(5):441-8
322. Keen J, Farcas GA, Zhong K, Yohanna S, Dunne MW, Kain KC. Real-time PCR assay for rapid detection and analysis of PfCRT haplotypes of chloroquine-resistant *Plasmodium falciparum* isolates from India. J Clin Microbiol. 2007 Sep;45(9):2889-93
323. Tekete M, Djimde AA, Beavogui AH, Maiga H, Sagara I, Fofana B, et al. Efficacy of chloroquine, amodiaquine and sulphadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria: revisiting molecular markers in an area of emerging AQ and SP resistance in Mali. Malar J. 2009;8:34
324. Berzosa P, Esteban-Cantos A, Garcia L, Gonzalez V, Navarro M, Fernandez T, et al. Profile of molecular mutations in pfdhfr, pfdhps, pfmdr1, and pfcrt genes of Plasmodium falciparum

related to resistance to different anti-malarial drugs in the Bata District (Equatorial Guinea). Malar J. 2017 Jan 13;16(1):28
325. Gilles H, Warrell DA, editors. Bruce-Chwatt's Essential Malariology - International Student Edition. 3rd ed. London: Arnold; 1993.
326. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4
327. CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects: Council for International Organizations of Medical Sciences; 2002.
328. ICH. Integrated Addendum to E6(R1): Guideline for Good Clinical Practice: Current Step 4 version International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016.
329. Leslie T, Kaur H, Mohammed N, Kolaczinski K, Ord RL, Rowland M. Epidemic of *Plasmodium falciparum* malaria involving substandard antimalarial drugs, Pakistan, 2003. Emerg Infect Dis. 2009 Nov;15(11):1753-9
330. Gabryszewski SJ, Modchang C, Musset L, Chookajorn T, Fidock DA. Combinatorial Genetic Modeling of pfcrt-Mediated Drug Resistance Evolution in Plasmodium falciparum. Mol Biol Evol. 2016 Jun;33(6):1554-70
331. Mawili-Mboumba DP, Ndong Ngomo JM, Maboko F, Guiyedi V, Mourou Mbina JR, Kombila M, et al. Pfcrt 76T and pfmdr1 86Y allele frequency in Plasmodium falciparum isolates and use of self-medication in a rural area of Gabon. Trans R Soc Trop Med Hyg. 2014 Nov;108(11):729-34
332. Ghanchi NK, Martensson A, Ursing J, Jafri S, Bereczky S, Hussain R, et al. Genetic diversity among *Plasmodium falciparum* field isolates in Pakistan measured with PCR genotyping of the merozoite surface protein 1 and 2. Malar J. 2010;9:1
333. Ursing J, Kofoed PE, Rodrigues A, Rombo L, Gil JP. *Plasmodium falciparum* genotypes associated with chloroquine and amodiaquine resistance in Guinea-Bissau. Am J Trop Med Hyg. 2007 May;76(5):844-8
334. Sa JM, Twu O, Hayton K, Reyes S, Fay MP, Ringwald P, et al. Geographic patterns of *Plasmodium falciparum* drug resistance distinguished by differential responses to amodiaquine and chloroquine. Proc Natl Acad Sci USA. 2009 Nov 10;106(45):18883-9
335. Alifrangis M, Dalgaard MB, Lusingu JP, Vestergaard LS, Staalsoe T, Jensen AT, et al. Occurrence of the Southeast Asian/South American SVMNT haplotype of the chloroquine-resistance transporter gene in *Plasmodium falciparum* in Tanzania. J Infect Dis. 2006 Jun 15;193(12):1738-41
336. Ursing J, Kofoed PE, Rodrigues A, Bergqvist Y, Rombo L. Chloroquine is grossly overdosed and overused but well tolerated in Guinea-bissau. Antimicrob Agents Chemother. 2009 Jan;53(1):180-5
337. Ursing J, Schmidt BA, Lebbad M, Kofoed PE, Dias F, Gil JP, et al. Chloroquine resistant *P. falciparum* prevalence is low and unchanged between 1990 and 2005 in Guinea-Bissau: an effect of high chloroquine dosage? Infect Genet Evol. 2007 Sep;7(5):555-61
338. Kofoed PE, Ursing J, Poulsen A, Rodrigues A, Bergquist Y, Aaby P, et al. Different doses of amodiaquine and chloroquine for treatment of uncomplicated malaria in children in Guinea-Bissau: implications for future treatment recommendations. Trans R Soc Trop Med Hyg. 2007 Mar;101(3):231-8
339. Laufer MK, Thesing PC, Eddington ND, Masonga R, Dzinjalamala FK, Takala SL, et al. Return of chloroquine antimalarial efficacy in Malawi. N Engl J Med. 2006 Nov 9;355(19):1959-66
340. Ord R, Alexander N, Dunyo S, Hallett R, Jawara M, Targett G, et al. Seasonal carriage of pfcrt and pfmdr1 alleles in Gambian *Plasmodium falciparum* imply reduced fitness of chloroquine-resistant parasites. J Infect Dis. 2007 Dec 1;196(11):1613-9
341. Abdel-Muhsin AM, Mackinnon MJ, Ali E, Nassir el KA, Suleiman S, Ahmed S, et al. Evolution of drug-resistance genes in *Plasmodium falciparum* in an area of seasonal malaria transmission in Eastern Sudan. J Infect Dis. 2004 Apr 1;189(7):1239-44
342. Leslie T, Rab MA, Ahmadzai H, Durrani N, Fayaz M, Kolaczinski J, et al. Compliance with 14-day primaquine therapy for radical cure of vivax malaria--a randomized placebo-controlled

trial comparing unsupervised with supervised treatment. Trans R Soc Trop Med Hyg. 2004 Mar;98(3):168-73
343. MoPH. National Malaria Treatment Guideline. Kabul: Islamic Republic of Afghanistan Ministry of Public Health, General Directorate of Preventive medicine, Control of Communicable Disease Directorate, National Malaria and Leishmaniasis Control Program, 2010.
344. Reynolds J, Wood M, Mikhail A, Ahmad T, Karimullah K, Motahed M, et al. Malaria "diagnosis" and diagnostics in Afghanistan. Qualitative health research. 2013 May;23(5):579-91
345. Webster J, Chandramohan D, Freeman T, Greenwood B, Kamawal AU, Rahim F, et al. A health facility based case-control study of effectiveness of insecticide treated nets: potential for selection bias due to pre-treatment with chloroquine. Trop Med Int Health. 2003 Mar;8(3):196-201
346. Hansen KS, Grieve E, Mikhail A, Mayan I, Mohammed N, Anwar M, et al. Cost-effectiveness of malaria diagnosis using rapid diagnostic tests compared to microscopy or clinical symptoms alone in Afghanistan. Malar J. 2015 May 28;14:217
347. Laufer MK, Djimde AA, Plowe CV. Monitoring and deterring drug-resistant malaria in the era of combination therapy. Am J Trop Med Hyg. 2007 Dec;77(6 Suppl):160-9
348. Killeen GF, Smith TA, Ferguson HM, Mshinda H, Abdulla S, Lengeler C, et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets. PLoS Med. 2007 Jul;4(7):e229
349. Rowe AK. Assessing the Health Impact of Malaria Control Interventions in the MDG/Sustainable Development Goal Era: A New Generation of Impact Evaluations. Am J Trop Med Hyg. 2017 Sep;97(3_Suppl):6-8
350. Jones CO, Williams HA. The social burden of malaria: what are we measuring? Am J Trop Med Hyg. 2004 Aug;71(2 Suppl):156-61
351. Williams HA, Jones C, Alilio M, Zimicki S, Azevedo I, Nyamongo I, et al. The contribution of social science research to malaria prevention and control. Bull World Health Organ. 2002;80(3):251-2
352. Williams HA, Jones CO. A critical review of behavioral issues related to malaria control in sub-Saharan Africa: what contributions have social scientists made? Soc Sci Med. 2004 Aug;59(3):501-23
353. Atkinson JA, Bobogare A, Fitzgerald L, Boaz L, Appleyard B, Toaliu H, et al. A qualitative study on the acceptability and preference of three types of long-lasting insecticide-treated bed nets in Solomon Islands: implications for malaria elimination. Malar J. 2009 Jun 4;8(1):119
354. Onwujekwe O, Uzochukwu B, Ezumah N, Shu E. Increasing coverage of insecticide-treated nets in rural Nigeria: implications of consumer knowledge, preferences and expenditures for malaria prevention. Malar J. 2005;4(1):29
355. Fokam EB, Kindzeka GF, Ngimuh L, Dzi KT, Wanji S. Determination of the predictive factors of long-lasting insecticide-treated net ownership and utilisation in the Bamenda Health District of Cameroon. BMC Public Health. 2017 Mar 16;17(1):263
356. Winch PJ, Lloyd LS, Hoemeke L, Leontsini E. Vector control at the household level: an analysis of its impact on women. Acta Trop. 1994 Apr;56(4):327-39
357. Brennan RJ, Sondorp E. Humanitarian aid: some political realities. BMJ. 2006 Oct 21;333(7573):817-8
358. Sondorp E, Patel P. The role of health services in conflict-ridden countries. J Health Serv Res Policy. 2004 Jan;9(1):4-5
359. Sondorp E, Zwi AB. Complex political emergencies. BMJ. 2002 Feb 9;324(7333):310-1
360. Johnson GA, Vindrola-Padros C. Rapid qualitative research methods during complex health emergencies: A systematic review of the literature. Soc Sci Med. 2017 Sep;189:63-75
361. Rowland M. Refugee health in the tropics. Malaria control in Afghan refugee camps: novel solutions. Trans R Soc Trop Med Hyg. 2001 Mar-Apr;95(2):125-6

362. Lines J, Lengeler C, Cham K, de Savigny D, Chimumbwa J, Langi P, et al. Scaling-up and sustaining insecticide-treated net coverage. Lancet Infect Dis. 2003 Aug;3(8):465-6; discussion 7-8
363. Whitty CJ, Rowland M, Sanderson F, Mutabingwa TK. Malaria. BMJ. 2002 Nov 23;325(7374):1221-4
364. Patton M. Qualitative evaluation and research methods (2nd ed). Newsbury Park, CA: Sage; 1990.
365. Green J, Thorogood N. Qualitative Methods for Health Research. Silverman D, editor. London: Sage Publications; 2004.
366. Rubin H, Rubin I. Qualitative interviewing: The art of hearing data. 2nd ed. Thousand Oaks, CA: Sage Publications; 2004.
367. List D. Know Your Audience: A Practical Guide to Media Research. Wellington, New Zealand: Original Books; 2005.
368. Lariosa TR. Culture, environment and people's perceptions: considerations in malaria control in the Philippines. Southeast Asian J Trop Med Public Health. 1986 Sep;17(3):360-70
369. Ongore D, Kamunvi F, Knight R, Minawa A. A study of knowledge, attitudes and practices (KAP) of a rural community on malaria and the mosquito vector. East Afr Med J. 1989 Feb;66(2):79-90
370. Rashed S, Johnson H, Dongier P, Moreau R, Lee C, Crepeau R, et al. Determinants of the Permethrin Impregnated Bednets (PIB) in the Republic of Benin: the role of women in the acquisition and utilization of PIBs. Soc Sci Med. 1999 Oct;49(8):993-1005
371. Rashid A. Descent into Chaos: The U.S. and the Disaster in Pakistan, Afghanistan, and Central Asia. 2nd ed: Penguin; 2009.
372. Rashid A. Taliban: Militant Islam, Oil and Fundamentalism in Central Asia: Yale University Press; 2001.
373. Matovu F, Goodman C, Wiseman V, Mwengee W. How equitable is bed net ownership and utilisation in Tanzania? A practical application of the principles of horizontal and vertical equity. Malar J. 2009 May 21;8(1):109
374. Bernard J, Mtove G, Mandike R, Mtei F, Maxwell C, Reyburn H. Equity and coverage of insecticide-treated bed nets in an area of intense transmission of *Plasmodium falciparum* in Tanzania. Malar J. 2009;8:65
375. Noor AM, Amin AA, Akhwale WS, Snow RW. Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children. PLoS Med. 2007 Aug;4(8):e255
376. Onwujekwe O, Hanson K, Fox-Rushby J. Inequalities in purchase of mosquito nets and willingness to pay for insecticide-treated nets in Nigeria: challenges for malaria control interventions. Malar J. 2004 Mar 16;3:6
377. Thwing J, Hochberg N, Vanden Eng J, Issifi S, Eliades MJ, Minkoulou E, et al. Insecticide-treated net ownership and usage in Niger after a nationwide integrated campaign. Trop Med Int Health. 2008 Jun;13(6):827-34
378. Prakash A, Bhattacharyya DR, Mohapatra PK, Goswami BK, Mahanta J. Community practices of using bed nets & acceptance & prospects of scaling up insecticide treated nets in north-east India. Indian J Med Res. 2008 Nov;128(5):623-9
379. Dearborn JL, Lewis J, Mino GP. Preventing mother-to-child transmission in Guayaquil, Ecuador: HIV knowledge and risk perception. Glob Public Health. 2009 Dec 2:1-14
380. Jewell NP. Risk interpretation, perception, and communication. Am J Ophthalmol. 2009 Nov;148(5):636-8
381. Webster J, Lines J, Bruce J, Armstrong Schellenberg JR, Hanson K. Which delivery systems reach the poor? A review of equity of coverage of ever-treated nets, never-treated nets, and immunisation to reduce child mortality in Africa. Lancet Infect Dis. 2005 Nov;5(11):709-17
382. Killeen GF, Tami A, Kihonda J, Okumu FO, Kotas ME, Grundmann H, et al. Cost-sharing strategies combining targeted public subsidies with private-sector delivery achieve high

bednet coverage and reduced malaria transmission in Kilombero Valley, southern Tanzania. BMC Infect Dis. 2007;7:121
383. Korenromp EL, Miller J, Cibulskis RE, Kabir Cham M, Alnwick D, Dye C. Monitoring mosquito net coverage for malaria control in Africa: possession vs. use by children under 5 years. Trop Med Int Health. 2003 Aug;8(8):693-703
384. Hanson K, Nathan R, Marchant T, Mponda H, Jones C, Bruce J, et al. Vouchers for scaling up insecticide-treated nets in Tanzania: methods for monitoring and evaluation of a national health system intervention. BMC Public Health. 2008;8:205
385. Worrall E, Basu S, Hanson K. Is malaria a disease of poverty? A review of the literature. Trop Med Int Health. 2005 Oct;10(10):1047-59
386. Onwujekwe O, Malik el FM, Mustafa SH, Mnzava A. Socio-economic inequity in demand for insecticide-treated nets, in-door residual house spraying, larviciding and fogging in Sudan. Malar J. 2005;4:62
387. Mosha FW, Lyimo IN, Oxborough RM, Matowo J, Malima R, Feston E, et al. Comparative efficacies of permethrin-, deltamethrin- and alpha-cypermethrin-treated nets, against Anopheles arabiensis and Culex quinquefasciatus in northern Tanzania. Ann Trop Med Parasitol. 2008 Jun;102(4):367-76
388. Kolaczinski J, Curtis C. Laboratory evaluation of fipronil, a phenylpyrazole insecticide, against adult Anopheles (Diptera: Culicidae) and investigation of its possible cross-resistance with dieldrin in Anopheles stephensi. Pest Manag Sci. 2001 Jan;57(1):41-5
389. Kolaczinski JH, Fanello C, Herve JP, Conway DJ, Carnevale P, Curtis CF. Experimental and molecular genetic analysis of the impact of pyrethroid and non-pyrethroid insecticide impregnated bednets for mosquito control in an area of pyrethroid resistance. Bull Entomol Res. 2000 Apr;90(2):125-32
390. Onori E, Nushin MK, Cullen JE, Yakubi GH, Mohammed K, Christal FA. An epidemiological assessment of the residual effect of DDT on Anopheles hyrcanus sensulato and A. pulcherrimus (Theobold) in the North eastern region of Afghanistan. Trans R Soc Trop Med Hyg. 1975;69(2):236-42
391. Rao VV. A brief note on the breeding habits of A. sundaicus in the Chilka Lake area. Indian J Malariol. 1951 Jun;5(2):163-4
392. Goodman CA, Mnzava AE, Dlamini SS, Sharp BL, Mthembu DJ, Gumede JK. Comparison of the cost and cost-effectiveness of insecticide-treated bednets and residual house-spraying in KwaZulu-Natal, South Africa. Trop Med Int Health. 2001 Apr;6(4):280-95
393. Grabowsky M, Nobiya T, Selanikio J. Sustained high coverage of insecticide-treated bednets through combined Catch-up and Keep-up strategies. Trop Med Int Health. 2007 Jul;12(7):815-22
394. WHO-EMRO. Regional malaria action plan 2016–2020 Towards a malaria free region. Cairo: Regional Office for the Eastern Mediterranean 2017.
395. McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis. 2012 May;12(5):388-96
396. Schantz-Dunn J, Nour NM. Malaria and pregnancy: a global health perspective. Rev Obstet Gynecol. 2009 Summer;2(3):186-92
397. Ruizendaal E. Malaria in pregnancy: In search of tools for improved prevention: University of Amsterdam; 2017.
398. Nosten F, Rogerson SJ, Beeson JG, McGready R, Mutabingwa TK, Brabin B. Malaria in pregnancy and the endemicity spectrum: what can we learn? Trends Parasitol. 2004 Sep;20(9):425-32
399. Rodriguez-Morales AJ, Sanchez E, Vargas M, Piccolo C, Colina R, Arria M, et al. Pregnancy outcomes associated with Plasmodium vivax malaria in northeastern Venezuela. Am J Trop Med Hyg. 2006 May;74(5):755-7
400. Recker M, Bouma MJ, Bamford P, Gupta S, Dobson AP. Assessing the burden of pregnancy-associated malaria under changing transmission settings. Malar J. 2009;8:245

401. Rijken MJ, McGready R, Boel ME, Poespoprodjo R, Singh N, Syafruddin D, et al. Malaria in pregnancy in the Asia-Pacific region. Lancet Infect Dis. 2012 Jan;12(1):75-88
402. McGready R, Davison BB, Stepniewska K, Cho T, Shee H, Brockman A, et al. The effects of Plasmodium falciparum and P. vivax infections on placental histopathology in an area of low malaria transmission. Am J Trop Med Hyg. 2004 Apr;70(4):398-407
403. McGready R, Nosten F. Symptomatic malaria in pregnancy. J Obstet Gynaecol. 2008 May;28(4):463
404. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med. 2010 Jan;7(1):e1000221
405. Nayak KC, Khatri MP, Gupta BK, Sirohi P, Choudhary V, Verma SK, et al. Spectrum of vivax malaria in pregnancy and its outcome: a hospital-based study. J Vector Borne Dis. 2009 Dec;46(4):299-302
406. Villegas L, McGready R, Htway M, Paw MK, Pimanpanarak M, Arunjerdja R, et al. Chloroquine prophylaxis against vivax malaria in pregnancy: a randomized, double-blind, placebo-controlled trial. Trop Med Int Health. 2007 Feb;12(2):209-18
407. Nosten F, McGready R, Simpson JA, Thwai KL, Balkan S, Cho T, et al. Effects of Plasmodium vivax malaria in pregnancy. Lancet. 1999;354(9178):546-9
408. McGready R, Wongsaen K, Chu CS, Tun NW, Chotivanich K, White NJ, et al. Uncomplicated Plasmodium vivax malaria in pregnancy associated with mortality from acute respiratory distress syndrome. Malar J. 2014;13(1):191
409. Brutus L, Santalla J, Schneider D, Avila JC, Deloron P. Plasmodium vivax malaria during pregnancy, Bolivia. Emerg Infect Dis. 2013 Oct;19(10):1605-11
410. Lacerda MV, Mourao MP, Alexandre MA, Siqueira AM, Magalhaes BM, Martinez-Espinosa FE, et al. Understanding the clinical spectrum of complicated Plasmodium vivax malaria: a systematic review on the contributions of the Brazilian literature. Malar J. 2012;11:12
411. Botto-Menezes C, Bardaji A, Dos Santos Campos G, Fernandes S, Hanson K, Martinez-Espinosa FE, et al. Costs Associated with Malaria in Pregnancy in the Brazilian Amazon, a Low Endemic Area Where Plasmodium vivax Predominates. PLoS Negl Trop Dis. 2016 Mar;10(3):e0004494
412. Singh H, Parakh A, Basu S, Rath B. Plasmodium vivax malaria: is it actually benign? Journal of infection and public health. 2011 Jun;4(2):91-5
413. Carlton JM, Sina BJ, Adams JH. Why is Plasmodium vivax a neglected tropical disease? PLoS Negl Trop Dis. 2011 Jun;5(6):e1160
414. Douglas NM, Anstey NM, Buffet PA, Poespoprodjo JR, Yeo TW, White NJ, et al. The anaemia of Plasmodium vivax malaria. Malar J. 2012;11:135
415. Anstey NM, Douglas NM, Poespoprodjo JR, Price RN. Plasmodium vivax: clinical spectrum, risk factors and pathogenesis. Adv Parasitol. 2012;80:151-201
416. Whitty CJ, Edmonds S, Mutabingwa TK. Malaria in pregnancy. BJOG. 2005 Sep;112(9):1189-95
417. Chotivanich K, Udomsangpetch R, Suwanarusk R, Pukrittayakamee S, Wilairatana P, Beeson JG, et al. Plasmodium vivax adherence to placental glycosaminoglycans. PLoS One. 2012;7(4):e34509
418. Fernando D, Rodrigo C, Rajapakse S. Primaquine in vivax malaria: an update and review on management issues. Malar J. 2011;10:351
419. Michael M, Pavignani E, Hill PS. Too good to be true? An assessment of health system progress in Afghanistan, 2002-2012. Med Confl Surviv. 2013 Oct-Dec;29(4):322-45
420. World Bank. Harmonised list of fragile situations FY17 http://pubdocs.worldbank.org/en/154851467143896227/FY17HLFS-Final-6272016.pdf2017 [04.11.17].
421. APHI/MoPH, CSO, ICF Macro, WHO/EMRO. Afghanistan Mortality Survey 2010 Calverton MD: APHI/MoPH, CSO, ICF Macro, IIHMR, WHO/EMRO, 2011.

422. Bartlett L, LeFevre A, Zimmerman L, Saeedzai SA, Turkmani S, Zabih W, et al. Progress and inequities in maternal mortality in Afghanistan (RAMOS-II): a retrospective observational study. Lancet Glob Health. 2017 May;5(5):e545-e55
423. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, et al. Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet. 2010 May 8;375(9726):1609-23
424. CSO, UNICEF. Afghanistan Multiple Indicator Cluster Survey (2010-2011). Kabul: Central Statistics Organisation (CSO) and UNICEF, 2012.
425. GBD EMRO Neonatal Infant Under-5 Mortality Collaborators, Mokdad A. Neonatal, infant, and under-5 mortality and morbidity burden in the Eastern Mediterranean region: findings from the Global Burden of Disease 2015 study. International journal of public health. 2017 Aug 03
426. Zakeri S, Safi N, Afsharpad M, Butt W, Ghasemi F, Mehrizi AA, et al. Genetic structure of Plasmodium vivax isolates from two malaria endemic areas in Afghanistan. Acta Trop. 2010 Jan;113(1):12-9
427. MoPH. National Standards for Reproductive Health Services: ANTENATAL CARE SERVICES. Kabul: Transitional Islamic Government of Afghanistan Ministry of Health, General Directorate for Health Care and Promotion, Women's and Reproductive Health Directorate, Reproductive Health Task Force, 2003.
428. MOPH, Unicef. National Nutrition Survey Afghanistan (2013): Survey Report. Kabul: Ministry of Public Health, 2013.
429. Cheesbrough M. District Laboratory Practice in Tropical Countries, Part 2: Cambridge University Press; 2000.
430. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organization; 2012.
431. Eddleston M, Pierini S. Oxford Handbook of Tropical Medicine. Oxford: Oxford University Press; 2000.
432. Rijken MJ, Rijken JA, Papageorghiou AT, Kennedy SH, Visser GH, Nosten F, et al. Malaria in pregnancy: the difficulties in measuring birthweight. BJOG. 2011 May;118(6):671-8
433. Vance M. The placenta. In: Fraser D, Cooper M, editors. Myles textbook for midwives (15th edition). Edinburgh Churchill Livingstone Elsevier; 2009.
434. WHO. Severe Malaria Trop Med Int Health. 2014;19 Suppl:7-131
435. WHO. The management of nutrition in major emergencies. Geneva: 2000.
436. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity (WHO/NMH/NHD/MNM/11.1). Geneva: World Health Organization, 2011.
437. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health. 2013 Jul;1(1):e16-25
438. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014 Jan 30;123(5):615-24
439. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008 Jun;86(6):480-7
440. Unicef. Low Birthweight: Country, regional and global estimates - See more at: http://data.unicef.org/nutrition/low-birthweight#sthash.ZLIPwz7d.dpuf: Unicef; 2017 [04.11.17].
441. Howard N, Shafi A, Jones C, Rowland M. Malaria control under the Taliban regime: insecticide-treated net purchasing, coverage, and usage among men and women in eastern Afghanistan. Malaria journal. 2010;9:7
442. Leslie T, Mayan I, Mohammed N, Erasmus P, Kolaczinski J, Whitty CJ, et al. A randomised trial of an eight-week, once weekly primaquine regimen to prevent relapse of plasmodium vivax in Northwest Frontier Province, Pakistan. PLoS One. 2008;3(8):e2861

443. WHO/GMP. Insecticide treated mosquito nets: a WHO position statement. Geneva: WHO Global Malaria Programme, 2005.
444. Social science approaches for r, engagement in health p, systems thematic working group of Health Systems Global RNfEiHiE, Southern A, Emerging Voices for Global H, Daniels K, et al. Fair publication of qualitative research in health systems: a call by health policy and systems researchers. Int J Equity Health. 2016;15(1):98
445. Fullman N, Burstein R, Lim SS, Medlin C, Gakidou E. Nets, spray or both? The effectiveness of insecticide-treated nets and indoor residual spraying in reducing malaria morbidity and child mortality in sub-Saharan Africa. Malar J. 2013 Feb 13;12:62
446. Protopopoff N, Wright A, West PA, Tigererwa R, Mosha FW, Kisinza W, et al. Combination of Insecticide Treated Nets and Indoor Residual Spraying in Northern Tanzania Provides Additional Reduction in Vector Population Density and Malaria Transmission Rates Compared to Insecticide Treated Nets Alone: A Randomised Control Trial. PLoS One. 2015;10(11):e0142671
447. Hamainza B, Sikaala CH, Moonga HB, Chanda J, Chinula D, Mwenda M, et al. Incremental impact upon malaria transmission of supplementing pyrethroid-impregnated long-lasting insecticidal nets with indoor residual spraying using pyrethroids or the organophosphate, pirimiphos methyl. Malar J. 2016 Feb 18;15:100
448. Safi NH, Ahmadi AA, Nahzat S, Ziapour SP, Nikookar SH, Fazeli-Dinan M, et al. Evidence of metabolic mechanisms playing a role in multiple insecticides resistance in Anopheles stephensi populations from Afghanistan. Malar J. 2017 Mar 03;16(1):100
449. Ahmad M, Buhler C, Pignatelli P, Ranson H, Nahzat SM, Naseem M, et al. Status of insecticide resistance in high-risk malaria provinces in Afghanistan. Malar J. 2016 Feb 18;15:98
450. Wahid S, Stresman GH, Kamal SS, Sepulveda N, Kleinschmidt I, Bousema T, et al. Heterogeneous malaria transmission in long-term Afghan refugee populations: a cross-sectional study in five refugee camps in northern Pakistan. Malar J. 2016 Apr 27;15:245
451. Kolaczinski K, Leslie T, Ali I, Durrani N, Lee S, Barends M, et al. Defining Plasmodium falciparum treatment in South West Asia: a randomized trial comparing artesunate or primaquine combined with chloroquine or SP. PLoS One. 2012;7(1):e28957
452. Hussain I, Qureshi NA, Afzal M, Shaheen N, Ali A, Ashraf A. Prevalence and distribution of human Plasmodium infection in Federally Administrative Tribal Areas of Pakistan. Acta Parasitol. 2016 Sep 01;61(3):537-43
453. Khattak AA, Venkatesan M, Nadeem MF, Satti HS, Yaqoob A, Strauss K, et al. Prevalence and distribution of human Plasmodium infection in Pakistan. Malar J. 2013 Aug 28;12:297
454. Harding KL, Aguayo VM, Namirembe G, Webb P. Determinants of anemia among women and children in Nepal and Pakistan: An analysis of recent national survey data. Matern Child Nutr. 2017 Aug 31
455. Muhammad R, Shakeel M, Rehman SU, Lodhi MA. Population-Based Genetic Study of beta-Thalassemia Mutations in Mardan Division, Khyber Pakhtunkhwa Province, Pakistan. Hemoglobin. 2017 Mar;41(2):104-9
456. Kandhro AH, Prachayasittikul V, Isarankura Na-Ayudhya C, Nuchnoi P. Prevalence of Thalassemia Traits and Iron Deficiency Anemia in Sindh, Pakistan. Hemoglobin. 2017 May;41(3):157-63
457. Honjo K. Social epidemiology: Definition, history, and research examples. Environ Health Prev Med. 2004 Sep;9(5):193-9
458. Braveman PA, Kumanyika S, Fielding J, Laveist T, Borrell LN, Manderscheid R, et al. Health disparities and health equity: the issue is justice. American journal of public health. 2011 Dec;101 Suppl 1:S149-55
459. Cromwell D. Defining equity in health care. In: Tsang C, Cromwell D, editors. Health Care Evaluation. second ed. London: Open University Press; 2017.
460. Braveman P, Gruskin S. Defining equity in health. Journal of epidemiology and community health. 2003 Apr;57(4):254-8

461. Norheim OF, Asada Y. The ideal of equal health revisited: definitions and measures of inequity in health should be better integrated with theories of distributive justice. Int J Equity Health. 2009;8:40
462. Skedgel C, Wailoo A, Akehurst R. Societal preferences for distributive justice in the allocation of health care resources: a latent class discrete choice experiment. Medical decision making : an international journal of the Society for Medical Decision Making. 2015 Jan;35(1):94-105
463. Buyx AM. [Equity in health? Health inequalities, ethics, and theories of distributive justice]. Gesundheitswesen. 2010 Jan;72(1):48-53
464. Bermejo RA, Xu J, Henao DE, Ho BL, Sieleunou I. What does UHC mean? Lancet. 2014 Mar 15;383(9921):951
465. Tsang C, Cromwell D. Humanity in health care. In: Tsang C, Cromwell D, editors. Health Care Evaluation second ed. London: Open University Press; 2017.
466. Willison DJ, Ondrusek N, Dawson A, Emerson C, Ferris LE, Saginur R, et al. What makes public health studies ethical? Dissolving the boundary between research and practice. BMC Med Ethics. 2014 Aug 08;15:61
467. Kass NE. An ethics framework for public health. American journal of public health. 2001 Nov;91(11):1776-82
468. Tannahill A. Beyond evidence--to ethics: a decision-making framework for health promotion, public health and health improvement. Health Promot Int. 2008 Dec;23(4):380-90
469. Dubov A, Phung C. Nudges or mandates? The ethics of mandatory flu vaccination. Vaccine. 2015 May 21;33(22):2530-5
470. El-Amin A, Parra M, Kim-Farley R, Fielding J. Ethical issues concerning vaccination requirements. Public Health Reviews. 2012;1(34)
471. Turcotte-Tremblay AM, Ridde V. A friendly critical analysis of Kass's ethics framework for public health. Can J Public Health. 2016 Aug 15;107(2):e209-11
472. Howard N, Enayatullah S, Mohammad N, Mayan I, Shamszai Z, Rowland M, et al. Towards a strategy for malaria in pregnancy in Afghanistan: assessments of clinical realities and women's perceptions of malaria and anaemia. Malar J. in press
473. Velasquez M, Andre C, Shanks T, Meyer M. The Common Good. Issues in Ethics. 2014;5(1)
474. Rawls J. A Theory of Justice: Belknap; 1999.
475. Vineis P. Public health and the common good. Journal of epidemiology and community health. 2014 Feb;68(2):97-100
476. Royo-Bordonada M, Román-Maestre B. Towards public health ethics. Public Health Reviews. 2015;36(3)
477. Marckmann G, Schmidt H, Sofaer N, Strech D. Putting public health ethics into practice: a systematic framework. Front Public Health. 2015;3:23
478. Boslaugh S. Secondary Data Sources for Public Health: A Practical Guide. Cambridge: Cambridge University Press; 2007.
479. Morris S, Devlin N, Parkin D, Spencer A. Economic Analysis in Health Care. Second ed. Chichester: John Wiley & Sons; 2012.
480. Briggs A. Handling uncertainty in economic evaluation and presenting the results. In: Drummond M, McGuire A, editors. Economic evaluation in health care. Oxford: Oxford University Press; 2001.

ANNEXES

Annex 1.1. Chapter 5: FGD guide for people WITH mosquito nets

Functional Questions (to each participant)
Names of Participants
What is the education level of each participant?

Pile Sort Exercises
Give each of the participants a pile of the cards.
1. Ownership: Ask each participant to make two piles, one pile of the things that they own or have and one pile of the things that they do not have.

When they have each made their piles then ask them to bring them up and get the recorder to record the items from each pile on their record sheet.

2. Ranking: Now ask the participants to put the cards together into one pile again and to sort the pile into the order of the things that they would be most likely to buy if they had extra money (or goods to barter and exchange).

When they have done this get the recorder to record the ranking of the items on the "rank order" record sheet.

3. General Discussion of ranking: Ask the participants why they have ranked the items in the order that they have, what are the reasons behind that order?

General Discussion
Points to Discuss:
Are mosquitoes a problem in this area? If yes, then at what times of the year?
What do you do to protect yourself and family from mosquitoes?
What are the most important health problems in this area?
Is malaria a problem? If, yes then where does it rank (i.e., how important is it compared to the other common diseases)? Why?
How do you catch malaria ? (probe for all the possible ways)
Who is the most vulnerable to malaria? Why?
How do you protect yourself from malaria?

Ask each participant:
How many nets do you own? (ask each participant individually)
How long have you had your nets? (ask each participant)
Who sleeps under the nets in your family? (ask each participant)
Why is the net given to those people?
Are the nets used every night? If no, then when are they used and why?
Have you retreated your net?
If yes, then how often and why did you decide to retreat? (probe to see if own decision or if prompted by other family members).
If no, then why not?

General Discussion:
So you all own nets – How did you hear about nets?
What made you decided to buy the nets? (probe to see if they heard about the nets or if some other family member heard and told them about it)
Who made the decision to buy the nets? (probe to see if only they decided or if another family member asked them to buy the nets)

Show the health education messages and ask: Have you seen these?
What do they say? What do you think of them?

Do you believe them?
In your opinion what type of people own nets? (if say rich people then ask what they mean by rich)
In your opinion what sort of people won't buy nets?

Thank you very much for your time and co-operation, your answers will be very useful to us in helping to design better health programmes.
Do you have any questions for us?

Annex 1.2. Chapter 5: FGD guide for people WITHOUT mosquito nets

Functional Questions (to each participant)
Names of Participants
What is the education level of each participant?

Pile Sort Exercises
Give each of the participants a pile of the cards.
1. Ownership: Ask each participant to make two piles, one pile of the things that they own or have and one pile of the things that they do not have.

When they have each made their piles, ask them to bring them up and get the recorder to record the items from each pile on their record sheet.

2. Ranking: Now ask the participants to put the cards together into one pile again and to sort the pile into the order of the things that they would be most likely to buy if they had extra money (or goods to barter and exchange).

When they have done this, get the recorder to record the ranking of the items on the "rank order" record sheet.

3. General Discussion of ranking: Ask the participants why they have ranked the items in the order that they have, what are the reasons behind that order? Why is a net in the position that it is in?

General Discussion
Points to Discuss:
Are mosquitoes a problem in this area? If yes, then at what times of the year?
What do you do to protect yourself and family from mosquitoes?
What are the most important health problems in this area?
Is malaria a problem? If, yes then where does it rank (i.e., how important is it compared to the other common diseases)? Why?
How do you catch malaria? (probe for all the possible ways)
Who is the most vulnerable to malaria? Why?
How do you protect yourself from malaria?

Ask each participant
What do you do if someone in your household gets sick with malaria?
Where do you go for treatment?
What do you buy?
How much does it cost?

General Discussion: So if treatment for malaria costs this much, how do you pay for it? If it costs so much to pay for treatment wouldn't it be cheaper to buy a net for 180,000 afghanis to help prevent you and your families from getting sick?
Show the health education messages and ask: Have you seen these?
What do they say? What do you think of them?

Do you believe them?
In your opinion what type of people own nets? (if say rich people then ask what they mean by rich. Try to probe to find out what it is that makes these people so different from them)
In your opinion, what sort of people won't buy nets?
In your opinion, is there anything (apart from making them cheaper) that would make people buy more nets?
Thank you very much for your time and co-operation, your answers will be very useful to us in helping to design better health programmes.
Do you have any questions for us?

Annex 2.1. Chapter 5: Interview guide, Jalalabad

Need: tape recorder, translator, driver
1. Net Purchasers (if possible one of each). Reasons for purchasing (how able).

a) **non-landowner**
b) **husband in Pakistan**

2. Net Non-purchasers (at least one of each). Reasons for not purchasing (unwilling, or willing but can't)

a) **widow**
b) **husband in Pakistan**
c) **husband disabled**

3. Salespeople - who purchases, how?

4. Clinic sales staff - Who are they selling to?

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1. Net Purchasers
Why did you decide to buy bednets?
How often do you use the bednets you purchased?
How helpful do you consider them?
Would you like to buy more if you could?
If yes, what is currently stopping you?
Do you think that bednets can protect your family's health? Why or why not?
What do you think is the more important problem for your family, mosquito bites or malaria?

When someone in your family is sick, what do you do?
What are the most significant health problems your family faces?
How significant a problem is malaria for you and your family?
Who has had malaria in your household in the past year?
Was this before or after you purchased bednets?
If after, where they sleeping regularly under a net?
What causes malaria?
What are the ways that you protect your family from malaria?
What is your main occupation/source of income?
Do you have other income sources?
If so, what are they?

*****From whom did you buy your nets (clinic, shop, HNI team, etc)
What was the selling procedure?
Did everyone get a chance to buy nets that wanted one?
How did the sellers choose whom to sell to?
Was there any favouritism?
Who got the nets?

Where did you learn about the programme?
Do you listen to radio?
    Did you learn anything about it from radio?
    What can you remember about malaria or nets from the radio programme?
        Health messages?
        Story line?
How would you improve the sales system?
Did you receive any health messages from sellers?
    Can you remember them?
Did you retreat your nets?
    If not, why not?
Any problems with the nets or the programme?
How would you improve the programme/retreatment programme?

2. Net Non-purchasers
When someone in your family is sick, what do you do?
What are the most significant health problems your family faces?
Do you consider malaria to be a significant problem for you and your family?
Who has had malaria in your household in the past year?
What causes malaria?
How do you protect your family from malaria?
*If you were able to purchase malaria protection for your family, would you do so?
*What would you like to purchase and why?
Are mosquitoes a problem for your family?
How do you protect yourselves against biting insects?
Do you think bednets are useful? In what way?

What is your main occupation/source of income?
Do you have other income sources?
If so, what are they?

3. Salesmen
How many bednets have you sold in the past month?
Who usually buys bednets (what kind of people)?
What do you think are the main reasons people buy bednets?
What do you think about the prices that are being charged for bednets?
Do you own any bednets?
What do you think is the best reason to have a bednet?
Do you think that bednets help in malaria prevention? Why / why not?
Do you think it makes a significant difference to the bednet if it has been treated with insecticide? Why/ why not?
What sorts of information if any do you give people when they buy bednets?
How many people do you think retreat their nets regularly?
Do you let people purchase items from your store on credit?
If so, who and what type of items?
Would someone be able to purchase a bednet on credit?

4. Clinic sales staff
How many bednets have you sold in the past month?
Who do you usually sell bednets to?
What do you think are the main reasons people buy bednets?
What do you think about the prices that are being charged for bednets?
Do you own any bednets?

What do you think is the best reason to have a bednet?
Do you think that bednets help significantly in malaria prevention? Why / why not?
Are there more effective or cheaper ways to prevent malaria?
What are the advantages/disadvantages of bednets?
How much information/explanation do you usually give when someone comes to buy a net?
How many people do you think retreat their nets regularly?
Do you think people prefer to buy a net from the clinic or from a private shop? Why/why not?

What do you tell buyers of nets?
    What are the health messages?
    What are the essential messages?
    How do you deliver these messages?
Did you receive instructions about how to implement net sales?
    From whom?
    When (what year)?
Who do you sell nets to?
Do you always have enough nets to satisfy demand?
How do you prioritise net sales-who is included, who is left out?
How do you retreat nets-how do you notify people?
    When-which month?
Do you have enough insecticide to satisfy demand?
What comments/ideas do you have about treatment and net sales?

Health Ed:
Where did you learn about the net programme?
What messages where given to you?
Have you seen this health education material before?
    Was it explained to you?
Can you understand what is being explained in the leaflets?
Can you explain the leaflets to me?

Annex 2.2. Chapter 5: Mosquito net questionnaire, Jalalabad

**NB: formatting and font size have been adjusted.*

Coding: (yes =1, no = 0, I don't know = 9)

Questionnaire number: _________
Date: __/___/___
Interviewer initials: _________

Village: _________
Compound: _________
ITN Purchaser / Non-purchaser
Male / Female head of household
Name of HH: _________
Respondent initials/sex: ____/____
Respondent relationship to HH: ________

1. SOCIO-DEMOGRAPHIC VARIABLES:

1.1 Age of head of household: _______
1.2 Education level of head of household: _______
Number of years of primary school? _______
Number of years of secondary school? _______
Number of years of university or additional technical training? _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _______
1.3 What is the number of occupants in the house? _______
1.4 How many children under age 5 in the house? _______
1.5 Has your family emigrated, and if so when? -
____

2. SOCIO-ECONOMIC VARIABLES

2.1 How many rooms in the house? _______
2.2 Does it have a guestroom? ____
If yes, is it carpeted? ____
2.3 Is your house owned or rented? _______
2.4 Does the house have electricity? ____
If yes, do you have a fan? ____
2.5 Does the compound have a well? ____
2.6 How many members of the household work? ____
2.7 Does anyone in the house own (and if yes, how many?): ____
Bicycle____ / Motorcycle____ / Carpet____ / Radio____
Gold Jewellery____ / Teapot____ / Lamp____ / Pressure cooker____
2.8 Do you support any family members beyond your parents, spouse and children? ____
If yes, how many? _______
2.9 Do you employ staff? ____
If yes, how many? ____
How many months of the year do they work for you? _______
2.10 Do you own land? ____
If yes, how many jerebs? _______
2.11 Do you rent any land? ____
If yes, how many jerebs? _______
2.12 Do you lease land to others? ____
If yes, how many jerebs? _______
2.13 Does any family member work on someone else's land? ____
Never / Sometimes (seasonal) / Always
2.14 What are the three main crops that you grow?

1. __________________
2. __________________
3. __________________

2. 15 Is the food you grow enough to support your family? ____
2.16 About how much of your harvest do you sell (choose one)?
All / Two thirds / Half / One third / None
2.17 What month do you get money from the sale of crops? _______
2.18 Does your family own any livestock? ____
If yes, how many cattle/ buffalo do you own? _______
How many goats/ sheep do you own? _______

How many horses/ donkeys do you own? _____

3. INCOME & EXPENDITURES

3.1 What part of your family's monthly income (money amount) comes from:
Salaries _____ / Wages_____ / Rents_____ / Crop sales_____
Livestock sales_____ / Donations from others (family members abroad, etc.)_____

3.2 When does the family have spare cash? _____

3.3 How much do you spend per month on:
Food?_____ / Rent?_____ / Clothing? _____ / Educational supplies? _____/ Medicine?_____
Other _____ (what is it_____)?

3.4 Do you ever obtain anything on credit (if yes, specify)?
Clothing / Food / Medicines / Household goods (furniture, cooking pots, etc.)/Other_____)

3.5 Could you get a bednet on credit? ____

4. HEALTH & MALARIA VARIABLES

4.1 Where do you go for treatment?
Clinic / Pharmacy / Private doctor / Other _____

4.2 When someone in the family gets sick, who decides if they should go to the clinic?
Father / Mother / Other _____

4.3 How many of your children have been vaccinated? (all vaccinations / some) _____
If not, what is the reason? (cost / availability / difficulty / not useful / other _____)

4.4 How is malaria caused?
Dirty water / Mosquito bites / Other _____

4.5 During what season do people catch malaria?
Spring / Summer / Autumn / Winter / All seasons

4.6 Who are at greatest risk from malaria?
Men / Women / Children / Other _____

4.7 Who in your family has had malaria in the past year?
Men ____ / Women ____/ Children ____/ Other _____

4.8 On average, how much does it cost to treat malaria?
Consultation (adult) _____(child) _____
Drugs (adult)_____(child) _____

4.9 What is the best way to treat malaria ***(circle best answer)*** ?
Paracetomol / Antibiotics / Chloroquine / Fansidar / Other _____

4.10 What is the best way to protect yourself from malaria ***(circle best answer)*** ?
Bednets / Traditional method _____ / House insecticide / Other _____

4.11 During what season are mosquitoes a problem ***(circle best answer)*** ?
Spring / Summer / Autumn / Winter

4.12 Where do mosquitoes breed?
Grass / Water / Other _____

4.13 How do you protect yourselves from mosquitoes ***(circle best answer)*** ?
Bednets / Coils / Repellent oil or cream / Aerosol Insecticide / Other _____

5. BEDNETS

5.1 Does your family own any bednets *(if no, go to 5.5)* ____

5.2 If your family owns bednets, how many do you have? _____
Who sleeps under the net/s? (Men / Women / Children / Other _____)
Are the nets treated with insecticide? ____

5.3 What was the source of money for the net/s ***(circle best answer)*** ?
Savings / Loan / Gift / Crop sales / Other (specify): _____

5.4 How often does your family retreat your bednets ***(circle best answer)*** ?
Once a year / Every 6 months / After cleaning / Never / Other _____

5.5 Are you planning to buy any bednets? ____
If yes, when are you planning to buy any? _____
What makes you want to buy bednets ***(list reasons)*** ?

1. _____
2. _____
3. _____
4. _____

5.6 If you are not planning to buy any, what is the main reason ***(circle best answer)*** ?
Already have enough / Too expensive / Not necessary / Don't like them / Other (_____)

Annex 3. Chapter 6: Malaria in pregnancy survey questionnaire, Jalalabad

Yes =1, No = 0, Do Not Know = 99, Other = 7

No.	5 Questions	Responses	Coding
1	Interviewer's ID Number:		/____/____/____/
2	Start/End time:	_____: _____ _____: _____	/__/__/
3	Respondent's Name:		
4	Respondent's Village:		/____/____/
5	Respondent's District:		/____/

100. SOCIO- ECONOMIC VARIABLES

No.	15-16 Questions	Coding		Skips
101	Approximately how old are you?	|__|__|		
102	What is your husband's approximate age?	|__|__|		
103	Who is the head of your household?	Father-in-Law	1	
		Husband	2	
		Brother-in-Law	3	
		Other (_____)	7	
104	What is the highest level of education you have completed?	NONE	0	
		Religious/Informal	1	
		Primary	2	
		Middle	3	
		High School	4	
		University/Technical	5	
105	What is the highest level of education completed by anyone in your household?	NONE	0	
		Religious/Informal	1	
		Primary	2	
		Middle	3	
		High School	4	
		University/Technical	5	
106	How many people in the house, including you, can read?	NONE	0	
		|__|__|	1	
107	How many members of the household work?	NONE	0	
		|__|__|	1	
108	What is the job of your household's primary wage earner?	NONE	0	
		Farmer	1	
		Labourer	2	
		Shop/Market	3	
		Driver	4	
		Office	5	
		Other (_____)	7	
109	How many people normally live in your house?	|__|__|		
110	How many children under age 5 normally live in your house?	NONE	0	
		|__|__|	1	
111	How many rooms in your house?	|__|__|		
112	Do you have a special room or bedding just for guests?	NO	0	
		YES	1	
113	Does your household own land?	NO	0	
		Number of jerebs (|__|__|) YES	1	
114	Does your house have electricity?	NO	0	
		General/Purchased	1	
		Personal Generator/Turbine	2	
115	What is the drinking water source for the house?	Stream	1	
		Well	2	
		Piped	3	
		Other (_____)	7	

No.	15-16 Questions	Coding		Skips
116	Does anyone in your house own *(If yes, how many?):*	Bicycle |__|__| Car/Truck |__|__| Cassette Player |__|__| Rugs (e.g. Afghani, Iranian) |__|__| Curtains |__|__| Pressure Cooker |__|__| *(if no ITN, skip 500)* ITN |__|__|	1 2 3 4 5 6 8	

200. HEALTH VARIABLES

No.	9-10 Questions	Coding		Skips
201	What is the worst health problem in your community? *(Circle nearest answer)*	NOTHING Malaria Diarrhoea ARI Other (_____)	0 1 2 3 7	
202	Where do you usually go first when someone in the family is sick? *(Circle nearest answer)*	Government Clinic Private Doctor Pharmacy/Drug seller Traditional/Self-Treatment Other (_____)	1 2 3 4 7	
203	When a child in your family gets sick, who decides that they should go for treatment? *(Circle nearest answer)*	Child's Father Child's Mother Other (_____)	1 2 7	
204	As far as you know, are all of the vaccinations of the children in your household up-to-date?	NO YES No children	0 1 2	 →206 →206
205	If not, what is the reason? *(Circle all mentioned)*	Not Available Difficult/ Cannot Access No Benefit Dangerous/Do Not Trust Vaccinations Other (_____)	1 2 3 4 7	
206	Have you had one or more tetanus toxoid ("TT") vaccine?	NO YES Yes, but only one Can't remember	0 1 2 99	 →208
207	If not, what is the reason? *(Circle all mentioned)*	Not Available Difficult/ No Access No Benefit Dangerous/Do Not Trust Vaccinations Other (_____)	1 2 3 4 7	
208	How do you protect yourselves from mosquitoes? *(Circle all mentioned)*	NOTHING ITN Repellent Burning Smoke Insect Spray Other (_____)	0 1 2 3 4 7	 →301 →301 →301 →301 →301
209	If you do nothing to protect yourselves from mosquitoes, why not? *(Circle all mentioned)*	Mosquitoes aren't a problem Not enough money Other (_____)	1 2 7	

300. PREGNANCY VARIABLES

No.	18-20 Questions	Coding		Skips
301	How many children, if any, have you had before this pregnancy?	NONE |__|__|	0 1	
302	How many months pregnant do you think you are?	|__|__|		
303	What foods, if any, do you avoid when you are pregnant?	NONE Water Pickled Vegetables Meat Fruit Others (_____)	0 1 2 3 4 7	→305

No.	18-20 Questions	Coding		Skips
304	Why do you avoid these foods?	Make me feel sick	1	
		Dangerous	2	
		Other (_____)	7	
305	What medicines or drugs do you avoid during your pregnancy?	NONE, unless told to by Dr/midwife	0	→307
		ALL	1	
		Others (_____)	7	
306	Why do you avoid these medicines?	Make me feel sick	1	
		Dangerous	2	
		Other (_____)	7	
307	What special foods, supplements, or drugs do you take during your pregnancy?	NONE	0	
		Iron/Folate Supplement	1	
		Malaria Chemoprophylaxis	2	
		Extra Fruits	3	
		Others (_____)	7	
308	What kind of work/activities, if any, do you avoid during your pregnancy?	NONE	0	
		Heavy Lifting	1	
		Travelling	2	
		Others (_____)	7	
309	Where do you get advice about pregnancy and the delivery of your child?	NOWHERE	0	
		Female relative	1	
		TBA	2	
		Midwife	3	
		Clinic/Hospital Staff	4	
		Other (_____)	7	
310	Do you go to the clinic/hospital for routine antenatal care?	NO	0	→312
		YES	1	
311	How often do you try to go to the ANC clinic during pregnancy?	NEVER	0	
		Only when there are problems	1	
		Shortly before delivery	2	
		At least 3-4 times during pregnancy	3	→313
		Other (_____)	7	
312	If you do not regularly use ANC services, why not?	Not useful/necessary	1	
		Too expensive	2	
		Too difficult to travel/wait, etc	3	
		Husband does not allow it	4	
		Other (_____)	7	
313	Where do you expect to deliver your baby?	Home	1	
		Midwife's Home	2	
		Hospital/Clinic Delivery Room	3	
		Other (_____)	7	
314	Why will you deliver your baby there?	Feel comfortable there	1	
		Help is available if something goes wrong	2	
		Husband decided	3	
		Other (_____)	7	
315	Who do you think will help deliver your baby?	Untrained Female Relative	1	
		TBA	2	
		Midwife	3	
		Doctor	4	
		Other (_____)	7	
316	Why do you expect this person to help you deliver your baby?	Feel comfortable with them	1	
		Help is available if something goes wrong	2	
		Husband decided	3	
		Other (_____)	7	
317	What is your greatest worry during this pregnancy?	NO SPECIFIC WORRIES	0	→401
		Congenital abnormalities	1	
		Difficult/High-Risk Delivery	2	
		Malnourished Baby	3	
		Other (_____)	7	
318	Why are you worried about this?	Dr/Midwife has warned me	1	
		I feel something abnormal	2	
		Elders warned me	3	
		Other (_____)	7	

400. MALARIA VARIABLES

No.	15 Questions	Coding		Skips
401	How common is malaria in your community? *(Circle nearest answer)*	NONE/Rare Very common Somewhat common	0 1 2	
402	What one symptom, besides fever, shows that someone has malaria? *(Circle two)*	Shivering/Chills Headache Weakness Joint Pain Other (_____)	1 2 3 4 7	
403	How do you normally diagnose malaria?	Self-diagnose based on symptoms Drug seller tells me Provider gives clinical diagnosis Provider gives blood test Other (_____)	1 2 3 4 7	
404	How do you think people catch malaria? *(Circle all mentioned)*	Mosquito bites Drinking dirty water Food (which? _____) General Weakness Catching a cold or Flu Other (_____)	1 2 3 4 5 7	
405	Who do you think is at greatest risk from malaria? *(Circle nearest answer)*	Children<5yrs Pregnant women Women Men Elderly/Sick Other (_____)	1 2 3 4 5 7	
406	Who in your family has had malaria in the past six months? *(estimated number of each)*	NO ONE Men |__|__| Women |__|__| Older Children |__|__| <5 Children |__|__| Elderly |__|__| Other (_____) |__|__|	0 1 2 3 4 5 7	
407	Have you ever had malaria while you were pregnant? *(Circle nearest answer)*	NEVER This pregnancy Once in previous pregnancy Several times in previous pregnancies	0 1 2 3	
408	Where do you go to treat malaria? (*Circle nearest answer)*	Clinic Private Doctor Drug seller Traditional Other (_____)	1 2 3 4 7	 →411
409	Why do you go there for malaria? (*Circle nearest answer)*	Most Affordable Most accessible Most effective Can get credit Other (_____)	1 2 3 4 7	
410	What drugs do you usually use to treat malaria (*Circle nearest answer)?*	Whatever the Doctor tells me Chloroquine SP Quinine Other (_____)	1 2 3 7	
411	Why do you choose this treatment?	Most affordable Most easily available Most effective Provider recommendation Other (_____)	1 2 3 4 7	

No.	15 Questions	Coding		Skips
412	What is the best way to prevent malaria? *(Circle nearest answer)*	NOTHING	0	
		ITN	1	
		Immediate treatment	2	
		Burn smoke	3	
		Drink clean water	4	
		Keep house/area clean	5	
		Eat clean food	6	
		Prophylactic Drugs (Which? _____)	8	
		Other (_____)	7	
413	Do you think it is necessary to take special precautions against malaria while you are pregnant?	NO	0	
		YES	1	
414	What, if anything, are you doing to protect yourself from malaria while you are pregnant? *(Circle all mentioned)*	NOTHING	0	
		Sleep under ITN	1	
		Immediate diagnosis/treatment	2	
		Burn smoke	3	
		Keep house/area clean	4	
		Clean food/water	5	
		Prophylactic Drugs (Which? _____)	6	→501
		Other (_____)	7	
415	Would you take drugs during your pregnancy if they might help to prevent malaria?	NEVER	0	
		YES	1	
		Maybe, if I knew enough about their safety	2	
		Other (_____)	7	

500. ITN VARIABLES (ITN OWNERS)

No.	5-6 Questions	Coding		Skips
501	Who usually sleeps under ITN in your household? *(Circle all mentioned)*	NO, NOBODY	0	
		All	1	
		Children	2	
		Women	3	
		Elderly	4	
		Men	5	
		Other (_____)	7	
502	If only some members use them, why?	Not enough ITN	1	
		Too hot/Uncomfortable	2	
		Not Effective	3	
		Other (_____)	7	
503	Did you sleep under ITN last night?	NO	0	
		YES	1	
504	If not, why not?	Not bothered by mosquitoes	1	
		Somebody else was using it	2	
		Too hot	3	
		Other (_____)	7	
505	As far as you know, how often does your family retreat your ITN with insecticide?	NEVER/Less than Yearly	0	
		Yearly or more often	1	
506	What do you think are the advantages of sleeping under ITN? *(Note all mentioned)*	Not bothered by mosquitoes	1	→ 2
		Protection from malaria	2	→ 2
		Prevent insect bites	3	→ 2
		Other (_____)	7	→ 2

600. ITN VARIABLES (NON-OWNERS)

No.	1 Question	Coding		Skips
601	Why does your family not own any ITN?	Too Expensive	1	→ 2
		Not Available	2	→ 2
		Not Useful	3	→ 2
		Uncomfortable	4	→ 2
		Other (_____)	7	→ 2

-- END --