Promoting transferability:

Insights from economic evaluations of public health interventions to tackle malaria in central Senegal

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Abstract

Health economic evaluation seeks to guide priority setting by generating evidence on the relative efficiency of alternative policy choices. Yet, the volume and quality of economic evaluations are insufficient to inform the vast array of policy choices, especially in low- and lower-middle-income countries. This thesis aims to inform policy choices regarding strategies to tackle malaria and to improve methods to transfer economic evaluation evidence across contexts.

A bibliometric analysis of the applied economic evaluation literature frames the thesis. Two economic evaluations were conducted sequentially alongside two cluster-randomized controlled trials in approximately the same population of over 500,000 people in four districts of central Senegal. The first evaluation explored the financial and economic costs of equipping community health workers to deliver seasonal malaria chemoprevention (SMC) door-to-door to children under 10 years of age. It revealed substantial economies of scale, with the largest primary healthcare facility catchment areas (by population) incurring the lowest average costs per child treated. The second evaluation assessed the costs and cost-effectiveness of several multi-component, geographically targeted, malaria strategies in a low transmission context. Building on the analysis of SMC, the data collected in the second trial was used to develop and populate a simple, transparent, flexible, and intuitive cost model, which projects how the costs of four interventions may be expected to vary outside the study setting, in other contexts, and with certain changes to the interventions themselves, as well as with input prices and epidemiology.

Drawing on the two economic evaluations and a critical review of wide-ranging literatures relevant to transferability, the thesis concludes by proposing guidance for the design and conduct of economic evaluations alongside trials or pilots in ways that promote transferability. In particular, it recommends efforts from the outset of the evaluation to identify and narrow the “transferability gap” between planned implementation within the trial or pilot and the intended decision contexts.

Declaration

I, Catherine Krown Pitt, 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.

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Contents

Lists of Tables, Figures, and Boxes

NB: These lists do not include the tables, figures, and boxes included within the articles within Chapters 2 and 4, which are presented in their published format.

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Abbreviations

ACT: Artemisinin combination therapy

CEA: Cost-effectiveness analysis

CHW: Community health worker

cRCT: Cluster-randomized controlled trial

DALY: Disability-adjusted life-year

DP: Dihydroartemisinin-piperaquine

FSAT: Focal Screening and Treatment

GBD: Global Burden of Disease

GCEA: Generalized cost-effectiveness analysis

GHCC: Global Health Cost Consortium

HICs: High-income countries

HIV: Human Immunodeficiency Virus

HTA: Health Technology Assessment

iDSI: International Decision Support Initiative

IPT: Intermittent preventive treatment (for malaria)

IRS: Indoor residual spraying (with insecticide)

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

LICs: Low-income countries

LLIN: Long-lasting insecticide-treated bed net

LMICs: Low- and middle-income countries

LLMICs: Low- and lower-middle-income countries

MDA: Mass drug administration

MICs: Middle-income countries

MSAT: Mass screening and treatment

NICE: National Institute for Health and Care Excellence

NTDs: Neglected tropical diseases

ODA: Official Development Assistance

QALY: Quality-adjusted life-year

RCT: Randomized controlled trial

RDT: Rapid diagnostic test

SMC: Seasonal malaria chemoprevention

UK: United Kingdom

UHC: Universal health coverage

USD: United States dollar

WHO: World Health Organization

WHO-CHOICE: World Health Organization Choosing Interventions that are Cost-Effective programme

Chapter 1. Introduction to the thesis

1.1. Background

Achieving universal health coverage (UHC) globally will require explicit priority setting processes informed by evidence on policy choices relevant to each context. Health economic evaluation seeks to guide priority setting by generating evidence on the relative efficiency of alternative policy choices. It has been defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences." (Drummond et al., 2008) The use of health economic evaluations in decision processes for public health systems became institutionalized in Canada, Australia, the United Kingdom (UK) and several other European countries in the 1990s (Hjelmgren et al., 2001, Briggs et al., 2006, Drummond and Banta, 2009). In the last twenty years, the number of economic evaluations conducted globally each year has grown dramatically, as has the number of economic evaluations conducted in low- and middle-income countries (LMICs) (Neumann et al., 2018). More recently, efforts to institutionalize health technology assessment (HTA) in LMICs including Thailand (Tantivess et al., 2009), South Africa, China (Hofman and Tollman, 2010, Butt et al., 2019, MacQuilkan et al., 2018), and Ghana (Hollingworth et al., 2020) as well as in decision-making processes at the World Health Organization (WHO) (Brunetti et al., 2013, Rehfuess et al., 2019), have begun to draw on this growing body of literature and to generate further demand for economic evaluation evidence (Li et al., 2016). This increased focus on the role of economic evaluation in LMICs has led to the development and growth of various international initiatives, including the International Decision Support Initiative (iDSI) and various iterations of the Disease Control Priorities Project.

Yet, despite this increase in interest and in the numbers of economic evaluations produced, scarcity of economic evaluation evidence remains a challenge for decision-making in all contexts. At every level, policy makers face constant decisions about whether to maintain the status quo or to adopt a new course of action. Either choice risks substantial opportunity costs if the alternative turns out to be the more efficient choice. As LMICs have fewer resources for health interventions and higher burdens of ill health than high-income countries (HICs), the opportunity costs they face in terms of both resources and health forgone from inefficient policy choices are even greater.

To inform these myriad choices, decision-makers can only rarely draw on robust evidence from an empirical evaluation conducted to inform the exact decision problem they face in their own decision context. While they may sometimes commission empirical research, such investment is not feasible for every decision in every context and takes time. Instead, especially for new interventions, any potentially relevant evidence is often drawn from small-scale pilots or trials and/or larger-scale implementation in another context of interventions that may not precisely reflect the ones under consideration. Policy makers must then consider whether and to what extent such evidence is relevant to their particular decision problem.

Judgments about the relevance of economic evaluation evidence are challenging because the cost, effectiveness, and cost-effectiveness of a given intervention may vary across contexts; however, both overly wide and overly narrow definitions of "relevant evidence" risk sub-optimal policy choices (Drummond et al., 2009). The degree to which evidence regarding interventions in one context may be appropriately used to inform decisions regarding another context is known as "transferability". Evidence may be considered not transferable to a given decision problem, fully transferable, or transferable with modifications to the analysis or interpretation (Barbieri et al., 2010). As discussed further in Chapter 6, numerous, wide-ranging literature streams have offered insights for how to improve the transferability of economic evaluations conducted alongside trials and pilots, but their solutions have remained piecemeal.

More economic evaluation evidence is therefore needed regarding key health priorities and areas of investment in LMICs, but just producing a greater volume of economic evaluations cannot effectively inform the vast and constantly evolving array of health policy decisions across the diverse range of LMICs. In addition to expanding the empirical evidence base by evaluating more interventions in more LMIC contexts, research is also required to increase the usefulness of those evaluations by facilitating evidence transfer beyond the specific evaluation context.

Prioritizing subjects and contexts for economic evaluation research in LMICs is challenging because so many countries lack relevant evidence to guide their priority-setting decisions across so many areas of health (Neumann et al., 2016, Pratt et al., 2018, Woods et al., 2018). However, there is consensus that malaria control is a priority in many settings. It remains one of the leading causes of death in low- and lower-middle-income countries (LLMICs), especially in children and in Sub-Saharan Africa (GBD Collaborative Network, 2018), and imposes a substantial economic burden on households, health systems, and countries (Gallup and Sachs,

2001, Alonso et al., 2019, Arrow et al., 2004, Azemar and Desbordes, 2009, Fink et al., 2013, Holding and Snow, 2001, Klejnstrup et al., 2018, Onwujekwe et al., 2013, Ameme et al., 2014, Larsen et al., 2017). This burden, in turn, hinders the improvements in living conditions which could reduce malaria's spread and impact (Degarege et al., 2019). The literature on the costs and cost-effectiveness of malaria interventions is relatively large compared with other health issues in LLMICs (except HIV), and has generally found that the main malaria interventions are amongst the "best buys" (Tediosi et al., 2017, White et al., 2011). The economic evidence base remains small, however, relative to the diversity of countries and contexts with ongoing risk of malaria, the wide range of new interventions and possible combinations of interventions now available or emerging, and the global resources invested in tackling malaria (WHO, 2019d).

The epidemiology of malaria has shifted in recent years, with some countries eliminating malaria, others recording dramatic declines in malaria incidence, and a remainder continuing to face a very high and (in some cases) increasing disease burden (WHO, 2019d). Some of the global declines in malaria incidence and deaths have been achieved through substantial global investment in expanding coverage of proven preventive interventions, notably insecticide-treated bed nets, and in expanding access to prompt treatment with artemisinin combination therapies (ACTs) (WHO, 2019d). New products and strategies are at various stages in the development process and aim to "maintain the gains" and to achieve further progress both in countries and regions approaching malaria elimination and in those still facing a high burden. Yet, donor funding for malaria has plateaued, its future is uncertain, and LLMICs, by definition, have especially scarce domestic resources. The push towards UHC may also call into question the global and national prioritization of malaria over the last fifteen years in favour of other health priorities. Evidence on the efficiency of new strategies to tackle malaria is therefore urgently needed to inform decisions regarding their adoption.

Senegal's entire population of nearly 16m is considered at risk of malaria; WHO estimated there were 884,000 cases (618,000 to 1,163,000) and 4,480 malaria deaths (4,260 to 4,780) in 2018 (WHO, 2019d). As with other Sahelian countries, malaria transmission is highly seasonal, which affects the types of malaria interventions that may be appropriate. Seasonal malaria chemoprevention (SMC) emerged more than a decade ago as a highly efficacious strategy in such highly seasonal settings, reducing malaria incidence by up to 75% in children who received it in clinical trials (Wilson, 2011). Informed in part by economic evidence produced within this thesis, SMC has been scaled up in Senegal and across 11 other countries (WHO, 2019d). As described in Chapter 4, the epidemiological context in central Senegal has changed

in the last 20 years from a relatively high transmission setting to one with overall low, but locally heterogenous transmission in which elimination was considered potentially feasible if additional interventions were implemented. This shifting epidemiological and policy context created new evidence gaps, necessitating evidence to inform decision-making on the implementation of geographically targeted interventions in malaria "hotspots".

While more politically stable than many neighbouring countries in West Africa, Senegal's income group classification has switched several times in recent decades between lower-middle-income (1987-1993, 2009-14, 2018) and low-income (1994-2008, 2015-17) status (World Bank, 2020a). In 2018, gross national income averaged $1,410 per capita (Atlas method) (World Bank, 2020b). As of 2011, the most recent year for which estimates are available, 38% of the population lived on less than $1.90 per day (2011 purchasing power parity) and 88% lived on less than $5.50 per day (World Bank, 2020b). Despite rapid urbanization, more than half (53%) of Senegal's population still lived in rural areas in 2018, and 57% of the rural population lived in poverty (based on the national threshold in 2010), compared with 33% of the urban population (World Bank, 2020b). The WHO estimated that international donors provided nearly all financing for Senegal's malaria programme up to 2015, and ten times more than the domestic government in 2018, when a combined total of $52m in expenditure was reported (WHO, 2019d). However, as WHO's malaria financing estimates include only direct expenditure on malaria-specific programmes and commodities, they exclude the substantial contributions of health workers' time and existing health infrastructure to malaria control, and so underestimate both total and domestically-financed expenditure on malaria control.

The priority-setting space regarding malaria interventions in Senegal is therefore complex and evolving. Choices must be made domestically within Senegal and other countries about the relative prioritization of health in general, of malaria in particular, of specific malaria interventions, and regarding how to allocate resources across different areas of the country with heterogeneous needs. Analogous choices must also be made in the donor agencies that provide most of LLMICs' malaria funding, and these choices include prioritization across recipient countries with very different health needs and economic circumstances. Furthermore, WHO plays an important role in issuing policy guidance through formal processes based on reviews of available evidence and is therefore a significant, additional decision-maker. Economic evidence on the relative efficiency of new malaria intervention

strategies is therefore needed to inform these decision-makers both in Senegal and elsewhere so as to contribute to improving health.

1.2. Aim and objectives

This thesis aims to provide evidence to inform policy choices regarding strategies to tackle malaria and to improve methods to facilitate transfer of (economic) evaluation evidence more generally.

The specific objectives are:

1) To examine the size, scope, and distribution (geography, disease burden, authorship) of the recent, applied, economic evaluation literature;
2) To analyse the costs of delivering seasonal malaria chemoprevention (SMC) to children under 10 on a large scale in central Senegal;
3) To assess the costs and cost-effectiveness of various combinations of intensive malaria interventions geographically targeted at a local level using data from a trial in central Senegal;
4) To develop and apply methods for the analysis of cost data in ways that promote evidence transfer, and develop general guidance on designing economic evaluations for transferability.

1.3. Structure

The thesis is composed of seven chapters. In this chapter, Chapter 1, I briefly introduce the thesis as a whole. I provide a short background to the thesis; present its aims, objectives, and structure; detail my specific contributions to each element of the research included within the thesis; and summarize ethical considerations and funding for the thesis.

Chapter 2 responds to the first objective of the thesis. It examines the size, scope, and distribution of the recent economic evaluation literature, with an emphasis on those issues and challenges most salient for LLMICs. It identifies the need for more and better-quality

evidence on key health priorities in LLMICs and for greater focus on improving the methods for transferring economic evaluation findings across contexts.

Chapters 3, 4, and 5 present two economic evaluations conducted alongside cluster-randomized controlled trials of public health interventions to tackle malaria in central Senegal. Chapter 3 provides background to and an overview of the two economic evaluations, which are presented in subsequent chapters. Chapter 4 responds to the second objective of the thesis in presenting an analysis of the costs of SMC. Chapter 5 responds to the third and fourth objectives of the thesis in presenting a cost and cost-effectiveness analysis of geographically targeted strategies in malaria hotspots. Both economic evaluations provide important evidence to inform malaria policy, while demonstrating how data can be collected and analysed alongside a trial in ways that explicitly promote the transfer of findings to real-world settings and across geographies.

Chapter 6 completes the response to the fourth objective of the thesis. It presents a critical review of 10 wide-ranging literature streams, which offer insights for understanding how to improve the transferability of economic evaluations conducted alongside trials and pilots. Drawing on this literature and my experience conducting economic evaluations, I propose a practical "designing for transferability" guide. This guide proposes some initial methodological guidance on how to make economic evaluations conducted alongside trials and pilots more transferable in future.

Chapter 7 concludes the thesis. It summarizes the thesis' empirical and methodological contributions to knowledge and discusses the strengths and limitations of the thesis as a whole.

1.4. Contributions of the candidate

This thesis brings together research from three projects. Three articles are included in full within the thesis, one from each of the three projects. These are articles for which I conceived the idea, collected and analysed the data, wrote the initial draft, and implemented revisions in response to feedback from co-authors, peer reviewers, my thesis supervisors, and attendees at conferences and workshops at which I presented the work. The first two of these articles have been published in *Health Economics* and *Health Policy & Planning,* respectively, while the third

will be submitted for publication in conjunction with a manuscript reporting the trial's effectiveness results.

The first project on which this thesis draws is a supplementary issue of *Health Economics*, entitled *Economic evaluations in low- and middle-income settings: Methodological issues and challenges for priority setting*. I initiated and led this supplementary issue, as highlighted in the editorial by Andrew Briggs and Rachel Nugent (2016). The foreword to the supplement (Pitt et al., 2016b), which I drafted with support from co-authors, outlines the supplement's 12 research articles, including the bibliometric analysis included in full in Chapter 2 (Pitt et al., 2016a) and two further articles (Vassall et al., 2016b, Griffiths et al., 2016), which I co-authored. In Chapter 2, I cite findings regarding variations in methods used in economic evaluations across low-, middle-, and high-income countries from the article I co-authored with Ulla Griffiths and Rosa Legood (Griffiths et al., 2016). In Chapter 6, I locate work on the integration of supply and demand constraints in economic evaluations in an article I co-authored with Anna Vassall and colleagues (Vassall et al., 2016b) within literature streams which have addressed transferability and economic evaluations.

The second project on which this thesis draws is an evaluation of SMC in Senegal. I joined at the start of the final implementation year, when I took over from Lesong Conteh, who continued to provide advisory support after taking up a new role at Imperial College London. I designed data collection tools; supervised data collection in collaboration with Mouhamed Ndiaye, a physician working as part of the trial team; supervised data entry and management; and conducted the economic evaluation. As part of this work, I drafted sections of a technical report on the economics of SMC for WHO's Technical Expert Group, which subsequently recommended SMC for implementation. I conducted the analysis and wrote the economic evaluation of SMC (Pitt et al., 2017), which is presented in full in this thesis in Chapter 4. I also contributed substantially (as second author) through both analysis and writing to an article on the coverage, equity, and delivery of SMC (Ba et al., 2018), and contributed as a co-author on the trial's main effectiveness paper (Cissé et al., 2016).

The third project on which this thesis draws is an evaluation of geographically targeted strategies in malaria hotspots in Senegal. I contributed to the original grant proposal and the protocol for this trial, including drafting the economic evaluation component and contributing to the wider framing and communication of the study. I worked with a Senegalese research assistant in epidemiology, Fassia Tairou. She supervised data collection in the field with my guidance as part of her wider duties on the trial. I conceived and conducted the economic

analyses, including the development of a mechanistic cost model, which are presented in the article included in full in Chapter 5 of this thesis. I also contributed to the analysis and framing of the overall trial results, which are in preparation (Diallo et al., 2020).

1.5. Ethics

Ethical approval was obtained for the thesis as a whole (**Appendix 1**) and for two of the three empirical components within it (**Appendix 2**). For the bibliometric analysis in Chapter 2, ethics approval was neither sought nor required because only publicly available data were analysed and there were no human subjects involved. The two economic evaluations in Chapters 4 and 5 were listed amongst the objectives and methods in the approved protocols for each of their respective trials and were covered in the ethical approvals obtained for each trial. A sub-group of LSHTM's Research Governance Committee reviewed the plans for this thesis and the ethics approvals in place and were satisfied that appropriate ethical approvals had been obtained for the individual components of the thesis. Further information on ethical considerations is included within each of the economic evaluations and in **Appendix 2**.

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1.7. References for Chapter 1

ALONSO, S., CHACCOUR, C. J., ELOBOLOBO, E., NACIMA, A., CANDRINHO, B., SAIFODINE, A., SAUTE, F., ROBERTSON, M. & ZULLIGER, R. 2019. The economic burden of malaria on households and the health system in a high transmission district of Mozambique. *Malar J,* 18**,** 360.

AMEME, D. K., AFARI, E. A., NYARKO, K. M., MALM, K. L., SACKEY, S. & WURAPA, F. 2014. Direct observation of outpatient management of malaria in a rural Ghanaian district. *Pan Afr Med J,* 19**,** 367.

ARROW, K. J., PANOSIAN, C. & GELBAND, H. 2004. Chapter 7. The Human and Economic Burden of Malaria. *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance.* Washington (DC): National Academies Press.

AZEMAR, C. & DESBORDES, R. 2009. Public Governance, Health and Foreign Direct Investment in Sub-Saharan Africa. *Journal of African Economies,* 18**,** 667-709.

BA, E. H., PITT, C., DIAL, Y., FAYE, S. L., CAIRNS, M., FAYE, E., NDIAYE, M., GOMIS, J. F., FAYE, B., NDIAYE, J. L., SOKHNA, C., GAYE, O., CISSE, B. & MILLIGAN, P. 2018. Implementation, coverage and equity of large-scale door-to-door delivery of Seasonal Malaria Chemoprevention (SMC) to children under 10 in Senegal. *Sci Rep,* 8**,** 5489.

BARBIERI, M., DRUMMOND, M., RUTTEN, F., COOK, J., GLICK, H. A., LIS, J., REED, S. D., SCULPHER, M., SEVERENS, J. L. & ISPOR GOOD RESEARCH PRACTICES ECONOMIC DATA TRANSFERABILITY TASK FORCE 2010. What do international pharmacoeconomic guidelines say about economic data transferability? *Value Health,* 13**,** 1028-37.

BRIGGS, A. & NUGENT, R. 2016. Editorial. *Health Econ,* 25 Suppl 1**,** 6-8.

BRIGGS, A. H., CLAXTON, K. & SCULPHER, M. J. 2006. *Decision modelling for health economic evaluation,* Oxford, Oxford University Press.

BRUNETTI, M., SHEMILT, I., PREGNO, S., VALE, L., OXMAN, A. D., LORD, J., SISK, J., RUIZ, F., HILL, S., GUYATT, G. H., JAESCHKE, R., HELFAND, M., HARBOUR, R., DAVOLI, M., AMATO, L., LIBERATI, A. & SCHUNEMANN, H. J. 2013. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol,* 66**,** 140-50.

BUTT, T., LIU, G. G., KIM, D. D. & NEUMANN, P. J. 2019. Taking stock of cost-effectiveness analysis of healthcare in China. *BMJ Glob Health,* 4**,** e001418.

CISSÉ, B., BA, E. H., SOKHNA, C., JL, N. D., GOMIS, J. F., DIAL, Y., PITT, C., M, N. D., CAIRNS, M., FAYE, E., M, N. D., LO, A., TINE, R., FAYE, S., FAYE, B., SY, O., KONATE, L., KOUEVIJDIN, E., FLACH, C., FAYE, O., TRAPE, J. F., SUTHERLAND, C., FALL, F. B., THIOR, P. M., FAYE, O. K., GREENWOOD, B., GAYE, O. & MILLIGAN, P. 2016. Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial. *PLoS Med,* 13**,** e1002175.

DEGAREGE, A., FENNIE, K., DEGAREGE, D., CHENNUPATI, S. & MADHIVANAN, P. 2019. Improving socioeconomic status may reduce the burden of malaria in sub Saharan Africa: A systematic review and meta-analysis. *PloS one,* 14**,** e0211205-e0211205.

DIALLO, A., CISSE, B., BA EL, H., TAIROU, F., FLACH, C., PITT, C., SY, O., FAYE, O., GAUDART, J., GOMIS, J. F., WANG, D., NDOYE, T., BA, M., BA-FALL, F., NDIOP, M., NDIAYE, J. L., TINE, R., FAYE, B., SOKHNA, C., GAYE, O. & MILLIGAN, P. 2020. Accelerating malaria transmission reduction in Senegal: a cluster-randomized trial of the effectiveness of targeted control in hotspots using Indoor Residual Spraying (IRS) combined with either Mass Screening and Treatment (MSAT) or Mass Drug Administration (MDA). *[Working Paper]*.

DRUMMOND, M. & BANTA, D. 2009. Health technology assessment in the United Kingdom. *Int J Technol Assess Health Care,* 25 Suppl 1**,** 178-81.

DRUMMOND, M., BARBIERI, M., COOK, J., GLICK, H. A., LIS, J., MALIK, F., REED, S. D., RUTTEN, F., SCULPHER, M. & SEVERENS, J. 2009. Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report. *Value in Health,* 12**,** 409-418.

DRUMMOND, M., WEATHERLY, H. & FERGUSON, B. 2008. Economic evaluation of health interventions. *BMJ,* 337**,** a1204.

FINK, G., OLGIATI, A., HAWELA, M., MILLER, J. M. & MATAFWALI, B. 2013. Association between early childhood exposure to malaria and children's pre-school development: evidence from the Zambia early childhood development project. *Malar J,* 12**,** 12.

GALLUP, J. L. & SACHS, J. D. 2001. The economic burden of malaria. *Am J Trop Med Hyg,* 64(1-2 Suppl)**,** 85-96.

GBD COLLABORATIVE NETWORK 2018. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME).

GRIFFITHS, U. K., LEGOOD, R. & PITT, C. 2016. Comparison of Economic Evaluation Methods Across Low-income, Middle-income and High-income Countries: What are the Differences and Why? *Health Econ,* 25 Suppl 1**,** 29-41.

HJELMGREN, J., BERGGREN, F. & ANDERSSON, F. 2001. Health economic guidelines--similarities, differences and some implications. *Value Health,* 4**,** 225-50.

HOFMAN, K. J. & TOLLMAN, S. M. 2010. Setting priorities for health in 21st century South Africa. *S Afr Med J,* 100**,** 798-800.

HOLDING, P. A. & SNOW, R. W. 2001. Impact of Plasmodium falciparum malaria on performance and learning: review of the evidence. *Am J Trop Med Hyg,* 64**,** 68-75.

HOLLINGWORTH, S. A., DOWNEY, L., RUIZ, F. J., ODAME, E., DSANE-SELBY, L., GYANSA-LUTTERODT, M., NONVIGNON, J. & CHALKIDOU, K. 2020. What do we need to know? Data sources to support evidence-based decisions using health technology assessment in Ghana. *Health Res Policy Syst,* 18**,** 41.

KLEJNSTRUP, N. R., BUHL-WIGGERS, J., JONES, S. & RAND, J. 2018. Early life malaria exposure and academic performance. *PLoS One,* 13**,** e0199542.

LARSEN, D. A., WINTERS, A., CHEELO, S., HAMAINZA, B., KAMULIWO, M., MILLER, J. M. & BRIDGES, D. J. 2017. Shifting the burden or expanding access to care? Assessing malaria trends following scale-up of community health worker malaria case management and reactive case detection. *Malar J,* 16**,** 441.

LI, R., HERNANDEZ-VILLAFUERTE, K., TOWSE, A., VLAD, I. & CHALKIDOU, K. 2016. Mapping Priority Setting in Health in 17 Countries Across Asia, Latin America, and sub-Saharan Africa. *Health Syst Reform,* 2**,** 71-83.

MACQUILKAN, K., BAKER, P., DOWNEY, L., RUIZ, F., CHALKIDOU, K., PRINJA, S., ZHAO, K., WILKINSON, T., GLASSMAN, A. & HOFMAN, K. 2018. Strengthening health technology

assessment systems in the global south: a comparative analysis of the HTA journeys of China, India and South Africa. *Glob Health Action,* 11**,** 1527556.

NEUMANN, P. J., ANDERSON, J. E., PANZER, A. D., POPE, E. F., D'CRUZ, B. N., KIM, D. D. & COHEN, J. T. 2018. Comparing the cost-per-QALYs gained and cost-per-DALYs averted literatures. *Gates Open Res,* 2**,** 5.

NEUMANN, P. J., THORAT, T., ZHONG, Y., ANDERSON, J., FARQUHAR, M., SALEM, M., SANDBERG, E., SARET, C. J., WILKINSON, C. & COHEN, J. T. 2016. A Systematic Review of Cost-Effectiveness Studies Reporting Cost-per-DALY Averted. *PLoS One,* 11**,** e0168512.

ONWUJEKWE, O., UGURU, N., ETIABA, E., CHIKEZIE, I., UZOCHUKWU, B. & ADJAGBA, A. 2013. The economic burden of malaria on households and the health system in Enugu State southeast Nigeria. *PLoS One,* 8**,** e78362.

PITT, C., GOODMAN, C. & HANSON, K. 2016a. Economic Evaluation in Global Perspective: A Bibliometric Analysis of the Recent Literature. *Health Econ,* 25 Suppl 1**,** 9-28.

PITT, C., NDIAYE, M., CONTEH, L., SY, O., HADJ BA, E., CISSE, B., GOMIS, J. F., GAYE, O., NDIAYE, J. L. & MILLIGAN, P. J. 2017. Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis. *Health Policy Plan,* 32**,** 1256-1266.

PITT, C., VASSALL, A., TEERAWATTANANON, Y., GRIFFITHS, U. K., GUINNESS, L., WALKER, D., FOSTER, N. & HANSON, K. 2016b. Foreword: Health Economic Evaluations in Low- and Middle-income Countries: Methodological Issues and Challenges for Priority Setting. *Health Econ,* 25 Suppl 1**,** 1-5.

PRATT, B., SHEEHAN, M., BARSDORF, N. & HYDER, A. A. 2018. Exploring the ethics of global health research priority-setting. *BMC Med Ethics,* 19**,** 94.

REHFUESS, E. A., STRATIL, J. M., SCHEEL, I. B., PORTELA, A., NORRIS, S. L. & BALTUSSEN, R. 2019. The WHO-INTEGRATE evidence to decision framework version 1.0: integrating WHO norms and values and a complexity perspective. *BMJ Glob Health,* 4**,** e000844.

TANTIVESS, S., TEERAWATTANANON, Y. & MILLS, A. 2009. Strengthening cost-effectiveness analysis in Thailand through the establishment of the health intervention and technology assessment program. *Pharmacoeconomics,* 27**,** 931-45.

TEDIOSI, F., LENGELER, C., CASTRO, M., SHRETTA, R., LEVIN, C., WELLS, T. & TANNER, M. 2017. Malaria Control. *In:* HOLMES, K. K., BERTOZZI, S., BLOOM, B. R. & JHA, P. (eds.) *Disease Control Priorities (third edition): Volume 6, Major Infectious Diseases.* Washington (DC).

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016b. Incorporating Demand and Supply Constraints into Economic Evaluations in Low-Income and Middle-Income Countries. *Health Econ,* 25 Suppl 1**,** 95-115.

WHITE, M. T., CONTEH, L., CIBULSKIS, R. & GHANI, A. C. 2011. Costs and cost-effectiveness of malaria control interventions - a systematic review. *Malar J,* 10**,** 337.

WHO 2019d. World malaria report 2019. Geneva, Switzerland: World Health Organization.

WILSON, A. L. 2011. A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment of malaria in children (IPTc). *PLoS ONE,* 6**,** e16976.

WOODS, B. S., ROTHERY, C., REVILL, P., HALLETT, T. & PHILLIPS, A. 2018. Setting research priorities in Global Health. *appraising the value of evidence generation activities to support decision-making in health care.* York: Centre for Health Economics, University of York.

WORLD BANK 2020a. Country and Lending Groups. 2 January 2020 [accessed] ed. Washington, D.C.: World Bank Group.

WORLD BANK 2020b. World Development Indicators 2020. 3 January 2020 [accessed] ed. Washington, D.C.

Chapter 2. Analysis of the applied economic evaluation literature

2.1. Introduction to Chapter 2

In this second part of the thesis, I systematically analyse the recent, applied economic evaluation literature and identify key gaps and challenges for this growing research field. My overall objective was to examine the size, scope, and distribution (geography, disease burden, authorship) of the recent, applied economic evaluation literature. Specific research questions were as follows:

- What is the size and scope of published, full, applied economic evaluations globally?
- How does the distribution of economic evaluations across health areas and country income groups relate to disease burden and resources for health?
- Who is producing this research in terms of institutional and geographic affiliations and where is it being published, and how does this relate to where the countries are being done?
- What are the implications for using economic evaluations to inform decision-making, especially in LLMICs?

I present an article published in *Health Economics*, in which I report a bibliometric analysis of all cost-effectiveness, cost-utility, and cost-benefit analyses of health interventions published globally over a recent 28-month period. The bibliometric analysis evaluates what is studied, where, and by whom in economic evaluations, as well as where they are published and how to develop sensitive and specific search strategies. These analyses highlight, amongst other challenges, the dearth of economic evaluation evidence in LLMICs to which subsequent chapters of the thesis seek to respond.

2.2. Economic Evaluation in Global Perspective: A Bibliometric Analysis of the Recent Literature

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First Name(s)	Catherine Krown		
Surname/Family Name	Pitt		
Thesis Title	Promoting transferability: Insights from economic evaluations of public health interventions to tackle malaria in central Senegal		
Primary Supervisor	Kara Hanson		

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SECTION E

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ECONOMIC EVALUATION IN GLOBAL PERSPECTIVE: A BIBLIOMETRIC ANALYSIS OF THE RECENT LITERATURE

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ABSTRACT

We present a bibliometric analysis of recently published full economic evaluations of health interventions and reflect critically on the implications of our findings for this growing field. We created a database drawing on 14 health, economic, and/or general literature databases for articles published between 1 January 2012 and 3 May 2014 and identified 2844 economic evaluations meeting our criteria. We present findings regarding the sensitivity, specificity, and added value of searches in the different databases. We examine the distribution of publications between countries, regions, and health areas studied and compare the relative volume of research with disease burden. We analyse authors' country and institutional affiliations, journals and journal type, language, and type of economic evaluation conducted. More than 1200 economic evaluations were published annually, of which 4% addressed low-income countries, 4% lower-middle-income countries, 14% upper-middle-income countries, and 83% high-income countries. Across country income levels, 53, 54, 86, and 100% of articles, respectively, included an author based in a country within the income level studied. Biomedical journals published 74% of economic evaluations. The volume of research across health areas correlates more closely with disease burden in high-income than in low-income and middle-income countries. Our findings provide an empirical basis for further study on methods, research prioritization, and capacity development in health economic evaluation.

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KEY WORDS: bibliometrics; economic evaluation; cost-effectiveness analysis; low-income countries; middle-income countries; high-income countries

1. INTRODUCTION

In 2012, Wagstaff and Culyer published a high-profile bibliometric analysis that set out to characterise the entirety of the health economics field, updating and extending prior work by Rubin and Chang (2003). Their ambitious work examined publications across 42 years (1969–2010) and generated much discussed rankings of the leading authors, institutions, and topics of health economics research over time. By restricting their analyses to journals indexed in EconLit, however, they omitted the substantial body of health economics research published in the medical literature, including many economic evaluations of health interventions. This important and growing area of health economics examines the relative efficiency of alternative courses of action in improving health (Drummond *et al*., 2005).

To address this gap, we present a bibliometric analysis of recently published, full health economic evaluations (Drummond *et al*., 2005) and reflect critically on the implications of our findings. Bibliometric analysis is defined as the quantitative study of written communication in forms such as journal articles and books (Pritchard, 1969). It sets out to characterise a literature, rather than examine the findings of that literature, which

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is the approach of a systematic review. We stratify our analyses of the economic evaluation literature by the income group classification of the countries studied (World Bank, 2015). This stratification ensures that findings regarding low-income and middle-income countries (LMICs) receive due attention, given that they are home to 84% of the world's population and bear 89% of the global burden of disease (GBD) (World Health Organization (WHO), 2014). In light of the growing interest in global health and priority setting, this contribution to the evidence base is also timely.

A previous bibliometric analysis of cost-effectiveness analyses (CEAs) was limited to studies reporting outcomes as cost per quality-adjusted life-year (QALY) up to 2006 published in English in journals indexed in Medline (Greenberg *et al*., 2010). As QALYs were infrequently used in LMICs up to 2006, this restriction biased Greenberg *et al*.'s findings towards studies undertaken in HICs and omitted nearly half of full economic evaluations (as we will show). Much has also changed since 2006, with a rapid expansion in the literature, including in LMICs.

By 1984, just a handful of economic evaluations of health interventions had been conducted in LMICs (Mills and Thomas, 1984) and even in 2000, Walker and Fox-Rushby (2000) were still able to review critically the 107 economic evaluations of interventions to address communicable diseases in LMICs published between 1984 and 1997. In the past decade, however, the body of work has expanded such that it has been possible for reviews to focus on specific disease areas, for example non-communicable diseases (Mulligan *et al*., 2006); road traffic injuries (Waters *et al*., 2004); malaria (Goodman and Mills, 1999, White *et al*., 2011); various aspects of HIV/AIDS (Creese *et al*., 2002, Galarraga *et al*., 2009, Walensky *et al*., 2010, Johri and Ako-Arrey, 2011) and tuberculosis (Fitzpatrick and Floyd, 2012, Chavan *et al*., 2011); vaccination for Haemophilus influenzae type b (Griffiths and Miners, 2009), seasonal (Ott *et al*., 2013) and pandemic influenza (Perez Velasco *et al*., 2012); human papilloma virus (Natunen *et al*., 2013, Fesenfeld *et al*., 2013); cardiovascular diseases (Suhrcke *et al*., 2012); surgery (Chao *et al*., 2014); and strategies to improve the demand and supply of maternal and neonatal care (Mangham-Jefferies *et al*., 2014). Reviews of economic evaluations in LMICs have also narrowed their focus by geography, for example to Meso-America (Valencia-Mendoza *et al*., 2011), Latin America and the Caribbean (Augustovski *et al*., 2009), Thailand (Teerawattananon *et al*., 2007), Nigeria (Gavaza *et al*., 2010), Tanzania (Mori and Robberstad, 2012), and Ghana (Odame, 2013). In adopting a more constrained perspective, these reviews have allowed important insights into the economic evidence for specific disease areas or geographies, but have not provided a wider perspective on the overall economic evaluation literature in LMICs, nor been able to compare this literature with the far larger body of economic evaluations in high-income countries (HICs).

We aim to provide a recent snapshot of the state of the economic evaluation field. In the following sections, we describe the methods for generating and analysing our data, present our results, and reflect on the state of the field and the implications of our findings for research priority setting and capacity development.

2. METHODS

We began by developing a comprehensive database of peer-reviewed research articles reporting a primary, full economic evaluation. Following Drummond *et al*. (2008), we defined 'full economic evaluation' as studies which evaluate the efficiency of alternative interventions or courses of action by combining data on the costs and effects on human health of the alternatives in CEA, cost-utility analysis (CUA), or cost-benefit analysis (CBA). Further, we aimed to restrict our database to articles which went beyond simple reporting of some cost and effect data, and instead included only articles which either (i) produced a summary measure of efficiency, such as a ratio (e.g. incremental cost-effectiveness ratio), probability (e.g. that an intervention is cost-effective given a defined threshold), difference (e.g. incremental net benefit), and/or graph, such as a cost-effectiveness plane or cost-effectiveness acceptability curve as recommended in International Society for Pharmacoeconomics and Outcomes Research guidelines (Ramsey *et al*., 2005), or (ii) which demonstrated strict dominance (i.e. that one intervention is both more costly and less effective than the other). We defined 'primary research' to include

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the production of a novel estimate (i.e. to include modelling studies) and to exclude reviews which only cite previously published estimates.

Our analysis was restricted to articles published from 1 January 2012 to the date of our searches, 3 May 2014, comprising a period of 28 months. This restriction reflects both our aim to provide a recent snapshot of a rapidly changing field and also practical considerations, since even this restricted timeframe required screening, cleaning, and coding large volumes of data. In the following sections we describe the process of constructing the database and our analytical methods.

2.1. Data

Search strategies. Figure S1 illustrates our search strategy in a flow diagram adapted from the PRISMA guidelines for systematic reviews.(Liberati *et al*., 2009) We identified 17 potential databases for our search by consulting recent systematic reviews of economic evaluations and a health sciences librarian to identify databases which seemed, *prima facie*, to be potentially useful or used by researchers.

Based on preliminary searches in all databases and a review of their content and functionality, we selected 14 databases for our final search: two health economics databases (the National Health Service Economic Evaluations Database (NHS EED) and the Health Economic Evaluations Database (HEED)), one economics database (EconLit), one general literature database (Scopus), two broad databases (the Science Citation Index Extended (SCI), and the Social Science Citation Index, which were searched simultaneously), and eight health sciences databases (Embase, Medline including in-process, Latin American Health Sciences Literature (LILACS), Global Health, PsycInfo, Scielo, Biosis, and Cinahl). We excluded Google Scholar because Google prohibits bulk downloading of citations; Pubmed because we were able to obtain the same set of articles (Medline, Medline-in-process, and Pubmed-not-Medline) in our search using the Ovid SP interface, which we also used to access EconLit, Embase, Global Health, and PsycInfo, and the Tufts Cost-Effectiveness Analysis Registry because its coverage was limited to articles published in English which report outcomes as QALYs and it charges substantial access fees.

Search strategies were optimised individually for each database, taking into account the scope of each database and the features of its user interface. Careful checks were performed to ensure that the initial search was as sensitive as possible and that any restrictions increased specificity without compromising sensitivity. Each time we considered an additional restriction to increase the specificity of the search, such as excluding all articles with the word 'protocol' in the title, we first reviewed the first 100 excluded records, and revised the search strategy if any excluded records were found to meet our inclusion criteria. Full details of the final search strategy employed in each database are provided in Table S1 and further discussion of the reasons for not using controlled vocabulary indexing terms (e.g. MeSH terms) is available in Text S1.

Merging and screening. Search results were exported to Excel. We identified duplicate records to produce a set of unique records linked to the bibliographic data in all of the databases in which they were found. By comparing multiple databases and carefully reviewing data, we corrected many of the errors within the bibliographic data. Titles and, if necessary, abstracts and in some cases full text were screened by one author (CP) to determine whether they met our inclusion criteria. Although only English-language search terms were used, no language restrictions were applied. Keyword searches of all text fields were used to facilitate identification of articles for exclusion (using terms such as 'review' and 'protocol') and inclusion (using terms such as 'dominant' and 'cost-utility').

We excluded articles which described themselves as CEA, CUA, or CBA but did not meet our inclusion criteria. For example, self-proclaimed 'cost-benefit analyses' which only compared the costs of interventions with cost savings resulting from reduced subsequent health care use were excluded as they did not measure health benefits. Cost-minimization analyses were similarly excluded (Dakin and Wordsworth, 2013), as were the many articles declaring an intervention 'cost-effective' which did not analyse both costs and effects.

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2.2. Analyses

All analyses are disaggregated by country income group and were conducted in Microsoft Excel.

Databases. For each of the 14 databases, we provide estimates of the sensitivity[1] and specificity[2] of our search. Given the substantial overlap between databases and to allow us to identify the minimum number of databases required to achieve a given overall sensitivity, we also assessed the added value of each database firstly, by identifying the database yielding the greatest number of economic evaluations, and secondly, by ranking the remaining databases in descending order according to the number of *additional* economic evaluations they identified beyond those already identified by a more highly ranked database.

Geographical areas studied. Key term searches were developed to classify articles by country (or countries) studied, which were then mapped onto World Bank income groups and regions (World Bank, 2015).[3] All potentially ambiguous country names were reviewed,[4] as were all articles not classified by any search term or classified as analysing multiple income groups. Articles which described themselves as studying a region or set of countries (such as 'malaria endemic countries' (WHO Global Malaria Programme, 2014)) were classified according to all the countries within that region. A single article could be classified as belonging to multiple income levels or regions.

Health areas. We developed a classification of 25 health areas so as to allow comparability with the global burden of disease (GBD) estimates (WHO, 2014), to be implementable with an electronic key term search, and to permit meaningful analysis. In Table S2, we show how our 25 health areas map onto the GBD and onto the WHO's International Classification of Disease, version 10 (WHO, 2011). A set of up to 49 search terms was developed for each of our health areas through an iterative process.

As with countries studied, a single article could be classified as belonging to multiple health areas. For example, we counted economic evaluations of interventions for gestational diabetes as both 'maternal and newborn health' and 'diabetes', and interventions to address HIV and tuberculosis co-infection (Pawlowski *et al*., 2012) as addressing each disease. While this could be considered double-counting, we argue that interventions addressing multiple areas do not contribute any less to each area than those interventions addressing only one disease. Further information is available in Text S2.

We then compared the distribution of health areas studied in economic evaluations to the GBD. Comparisons are presented graphically with scatter plots comparing the volume of economic evaluations and burden of disease by (i) ranking and (ii) proportion of total, disaggregated by income group and in total, which allows us both to assess the correlation and to identify health areas which are outliers meriting deeper exploration.

Languages and journals. Journals were classified as follows: (i) biomedical; (ii) health economics, services, policy, and/or social sciences; or (iii) other (Table S3). We analysed the proportion of health economic evaluations published in each journal type, the top 20 journals, and the concentration of economic evaluations by income group and in total.

The language of the full text was also analysed. Where the full text was available in English and another language, the article was categorised as English to permit analysis of what would be missed if only

[1]Sensitivity = (number of economic evaluations identified by our search of the given database) / (total number of economic evaluations identified in our final economic evaluation database).
[2]Specificity = (number of economic evaluations identified by our search of the given database) / (total number of records identified by our search of the given database).
[3]Macao, Hong Kong, and Taiwan, which are all classified as high-income countries by the World Bank, were analysed separately from the mainland of the People's Republic of China, an upper-middle-income country.
[4]Potentially ambiguous country names included for example, 'Congo', 'Korea', 'Niger', and 'Guinea', each of which is contained within more than one country name; 'China', which is often used in reference to Taiwan, Hong Kong, and Macao; 'Japan', which appears within the bibliographic data of studies of Japanese encephalitis; and 'England', which may refer to the United Kingdom, to New England in the USA, or to studies published in the New England Journal of Medicine.

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English-language publications were considered. As there were many errors in the language data in the bibliographic databases, these data were also compared with the journal name and country studied, and in some cases the full text or journal website examined, to arrive at a final language classification.

Types of economic evaluation. We used key term searches to disaggregate studies by self-reported type: CBA, CUA, and other CEAs. We further disaggregated cost-utility studies between those employing disability-adjusted life-years (DALYs) and those employing QALYs. Search terms are listed in Table S4.

Institutional and geographical affiliations of authors. We analysed data on the institutional affiliation of all authors to develop a comprehensive picture of the institutions and countries contributing to health economic evaluations.

We identified the top 10 institutions within each income group by volume of economic evaluations produced. As in previous work (Wagstaff and Culyer, 2012, Rubin and Chang, 2003), schools, colleges, and institutes were aggregated with the university to which they belonged, with the exception of the highly federal Universities of London, California, Texas, and other similar university systems, whose constituent members were analysed separately.

We considered a number of possible approaches for analysing articles with more than one institutional affiliation, including assigning a fractional value (and even weighted fractional values reflecting author order) to each institution based on the number of authors or institutions represented on a given article (Aksnes *et al*., 2012, Hagen, 2013, Retzer and Jurasinski, 2009). However, we rejected such approaches because using zero-sum metrics, in general, establishes a perverse incentive against collaboration between institutions and against the crediting of collaborators. We therefore assigned one point per institution per article, regardless of the number of institutions or authors on a given article. This has the disadvantage of weighting the analysis towards articles from multiple institutions, as these articles are counted multiple times in the analyses of institutional and country affiliations. More information on how we classified health areas and institutional affiliations is available in Text S2.

3. RESULTS

3.1. Search results

In total, our searches of the 14 databases identified 47 407 records (Figure S1). After duplicate removal, 15 057 unique records remained, and after screening, a total of 2844 unique, full economic evaluations were retained for analysis.

3.2. Databases

Our search of Scopus identified the largest number of economic evaluations ($n = 2409$), 85% of our total, followed by NHS EED, which identified 80% of the articles we identified (Table S5). Together, these two databases identified 96% of articles, and adding the Medline search increased this to 98%. With each additional database, the incremental gains were diminishingly small, and one database, Lilacs, failed to identify any additional articles beyond those identified by other databases. Econlit identified just 42 economic evaluations, 1% of the total. If we exclude NHS EED from consideration as it ceased to update records from March 2015 and exclude Wiley HEED as it ceased to be available from the end of 2014, our searches of a combination of Scopus, Medline, and Global Health would identify 91% of the economic evaluations, but a remaining 7% of economic evaluations in our database were only identified by NHS EED and Wiley HEED and not by our searches of other databases (Table S6). If we restrict the analysis to articles studying LMICs and exclude NHS EED and Wiley HEED, our searches of Scopus, Medline, and Global Health would together identify 93% of economic evaluations in LMIC settings, while 4% were only identified in NHS EED and Wiley HEED (Table S7).

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3.3. Subjects studied

Geographical areas studied. At least one country, region, and income group studied was assigned to all economic evaluations identified. Of these, 83% studied HICs, 14% upper-MICs, 4% lower-MICs and 4% LICs. These sum to more than 100% because 2% of articles reported studies set in multiple countries in more than one of the four income groups. As expected, most articles reported findings from Europe and Central Asia (44%) and/or North America (34%) (Table I).

Table II and Figure 1 present the individual countries most frequently studied. The United States (USA) was the subject of 813 studies, followed by the United Kingdom (UK) ($n = 478$) and six further countries which were each studied in at least 100 articles. While China, South Africa, and Brazil were studied in a relatively large number of articles, only 10 upper-MICs were studied in at least 20 articles each. Led by Uganda, India, Kenya, and Zambia, all of the top 20 LICs and lower-MICs were studied in more than 20 economic evaluations, in part because 61 of the 184 articles (33%) studying at least one LIC or lower MIC examined more than one country

Table I. Number of economic evaluations by income group and region of study

	Income group(s) of countries studied						
Region(s) studied	Low	Lower-middle	Upper-middle	High	Multiple[a]	Total	% of total
East Asia and Pacific	22	43	165	229	25	405	14%
Europe and Central Asia	11	16	44	1210	20	1243	44%
Latin America and Caribbean	13	18	116	16	19	129	5%
Middle East and North Africa	14	20	43	27	20	62	2%
North America	1	1	1	960	1	960	34%
South Asia	27	49	20	15	25	56	2%
Sub-Saharan Africa	92	64	78	22	46	158	6%
Multiple[a]	27	35	31	85	38	102	4%
Total	104	121	391	2350	63	2844	100%
% of total	4%	4%	14%	83%	2%	100%	

[a]Articles studying at least two countries of differing income levels or regions are categorised as 'Multiple'.

Table II. Top 20 countries most frequently studied in economic evaluations by income group

	High income			Upper-middle-income			Low and lower-middle-income		
Rank	Country	N	%	Country	N	%	Country	N	%
1	USA	813	35%	China	116	30%	Uganda	49	27%
2	UK	478	20%	South Africa	71	18%	India[a]	41	22%
3	Netherlands	183	8%	Brazil	56	14%	Kenya[a]	41	22%
4	Canada	162	7%	Thailand	36	9%	Zambia	39	21%
5	Spain	136	6%	Iran	31	8%	Malawi	35	19%
6	Germany	109	5%	Colombia[a]	28	7%	Nigeria[a]	34	18%
7	Australia	100	4%	Mexico[a]	28	7%	Tanzania[a]	34	18%
8	Italy	98	4%	Turkey	24	6%	Zimbabwe	33	18%
9	Sweden	74	3%	Botswana[a]	23	6%	Congo, Dem. Rep.	30	16%
10	France	57	2%	Namibia[a]	23	6%	Ethiopia	29	16%
11	Japan	45	2%	Angola	18	5%	Lesotho[a]	28	15%
12	Belgium	42	2%	Gabon	17	4%	Mozambique[a]	28	15%
13	Denmark	33	2%	Mauritius[a]	14	4%	Rwanda[a]	28	15%
14	Korea, Rep.[a]	31	1%	Peru[a]	14	4%	Vietnam[a]	28	15%
15	Norway[a]	31	1%	Seychelles[a]	14	4%	Ghana	27	15%
16	Greece	29	1%	Bulgaria	13	3%	Central African Republic	26	14%
17	Ireland	27	1%	Argentina[a]	12	3%	Burundi[a]	25	14%
18	Switzerland[a]	24	1%	Hungary[a]	12	3%	Cameroon[a]	25	14%
19	Finland[a]	24	1%	Maldives	11	3%	Eritrea[a]	25	14%
20	Taiwan	23	1%	Serbia	10	3%	Burkina Faso	24	13%
High-income countries		2350	100%	Upper-middle-income countries	391	100%	Low- and lower-middle-income countries	184	100%

[a]Equal ranking with country above and/or below.

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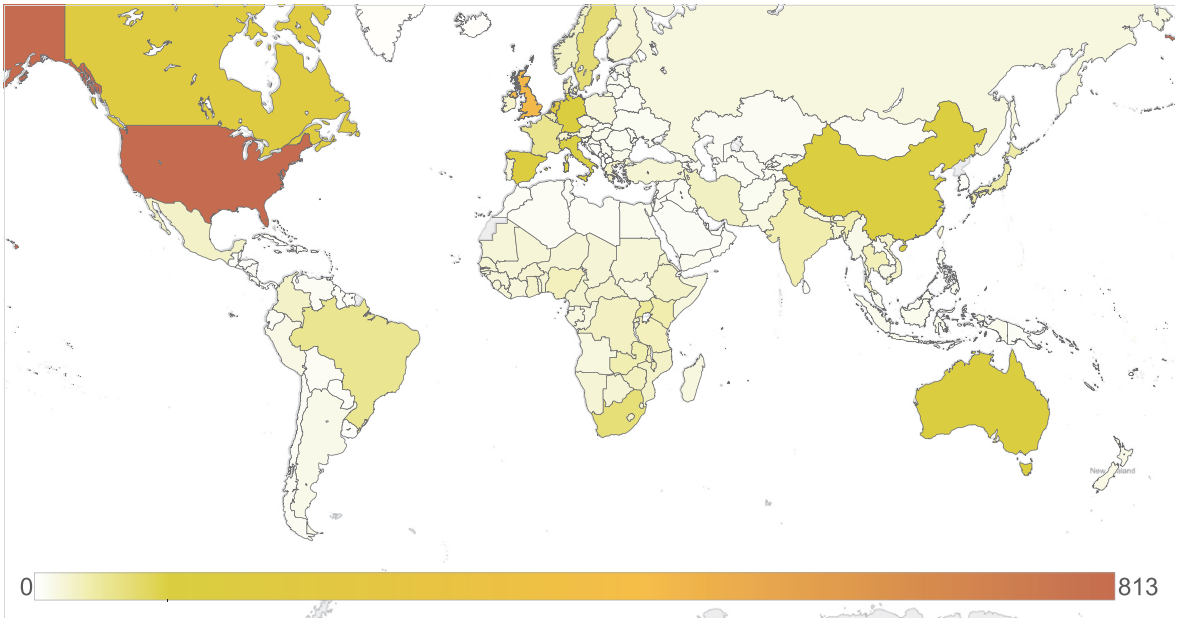

Figure 1. Number of economic evaluations set in each country. The intensity of shading reflects the number of economic evaluations analyzing each country over the 28-month period from 1 January 2012 to 3 May 2014

and 33 LIC and lower MIC articles (18%) studied more than 10 countries. In upper-MICs and HICs, only 14% ($n = 54$) and 7% ($n = 169$) of studies, respectively, examined more than one country and 8% ($n = 32$) and 1% ($n = 27$) examined more than 10 countries.

Health areas studied and the global burden of disease. At least one health area was assigned to 2829 (99.5%) articles. The mean number of health areas per article was 1.4 and the maximum 7. Whereas 71% of articles were assigned a single health area, 21% addressed two health areas and 8% addressed three or more. In LICs, three health areas dominate: HIV/AIDS (30% of classified LIC articles), neonatal and maternal conditions (16%), and malaria (15%) (Table III). In lower-MICs, HIV/AIDS again dominates (23%), but the remaining health areas are more evenly distributed; malaria comes second (11%), and is followed by other infectious diseases (8%) and mental health (8%); half of the latter focused on HIV treatment and prevention amongst injection drug users. In upper-MICs, HIV/AIDS (12%) falls to second place, while cancer and other neoplasms (19%) occupy the top spot with cardiovascular (11%) and respiratory diseases (10%) in third and fourth respectively. As HICs are studied in 83% of economic evaluations, the disease areas addressed in economic evaluations in HICs drive the distribution of all economic evaluations conducted worldwide, with cardiovascular diseases (19% in HICs), cancer and other neoplasms (18%), mental health (10%), and musculoskeletal diseases (10%), the leading areas of study in HICs and overall (Table III).

The distribution of articles across health areas corresponds substantially but by no means perfectly with the global disease burden. The degree of correlation varies by income level, but also depends on whether rankings or proportions are compared. By either metric, the health areas studied in HICs correlate surprisingly well with disease burden and substantially better than economic evaluations in other income groups, which feature more numerous and extreme outliers (Figure 2). The correlation between the health focus of economic evaluations and disease burden is also substantially stronger in studies of HICs than globally, because most economic evaluations (83%) address HICs and are well correlated with HICs' disease burden, whereas most of the GBD (89%) affects LMICs.

HIV/AIDS is studied in a greater proportion of economic evaluations at every income level than its share of the disease burden; however, the gap is much smaller in HICs than in LICs and lower-MICs, where it is an

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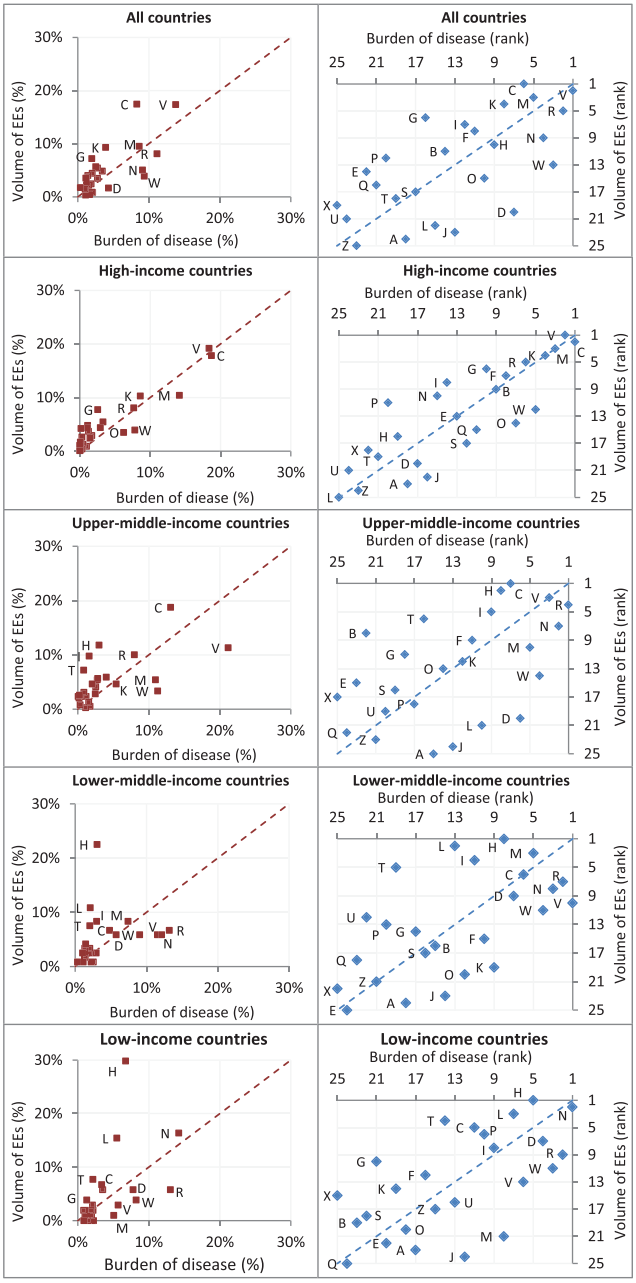

Legend

- **A** Anaemia
- **B** Diabetes
- **C** Cancer and other neoplasms
- **D** Diarrhoeal diseases
- **E** Endocrine, blood, and immune disorders (other than diabetes or HIV)
- **F** Digestive disorders
- **G** Genitourinary diseases, contraception & fertility
- **H** HIV/AIDS
- **I** Other infectious diseases (including encephalitis, hepatitis, other parasitic and vector-borne diseases, and nematode infections)
- **J** Congenital anomalies
- **K** Musculoskeletal diseases (including back pain)
- **L** Malaria
- **M** Mental health, cognition, and developmental and behavioural disorders (including self-harm and substance disorders)
- **N** Neonatal and maternal conditions
- **O** Neurological conditions
- **P** Malnutrition (including obesity and exercise)
- **Q** Skin and oral conditions
- **R** Respiratory diseases
- **S** Sense organ diseases
- **T** Tuberculosis
- **U** Communicable childhood diseases
- **V** Cardiovascular diseases
- **W** Wounds and injuries (including violence)
- **X** Sexually transmited diseases (other than HIV)
- **Z** Meningitis

Figure 2. Economic evaluations versus burden of disease by income group. Results are presented in two ways: the lefthand column compares the proportion of the total number of economic evaluations examining each of the 25 health area with the proportion of the total burden of disease accounted for by each health area and the righthand column compares the ranking of the health areas by the volume of economic evaluations and by burden of disease

extreme outlier. Other such 'winners' across all income levels include 'other infectious diseases'; 'genitourinary diseases, contraception, and fertility'; and 'sexually transmitted diseases (excluding HIV)'. By contrast, interventions to address wounds and injuries and, to a somewhat lesser extent, neurological conditions, appear to be substantially under-researched relative to disease burden at every income level.

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Table III. Number of economic evaluations by health area and income group

	Income group studied				
Health area	Low	Lower-middle	Upper-middle	High	World
Cancer and other neoplasms	7	8	73	416	492
Cardiovascular diseases	3	7	44	448	490
Mental health, cognition, and developmental and behavioural disorders (including self-harm and substance disorders)	1	10	21	243	268
Musculoskeletal diseases (including back pain)	2	3	18	240	262
Respiratory diseases	6	8	39	188	228
Genitourinary diseases, contraception & fertility	4	4	18	180	203
Other infectious diseases (including encephalitis, hepatitis, other parasitic and vector-borne diseases, and nematode infections)	6	10	38	111	159
Digestive disorders	3	3	21	127	152
Neonatal and maternal conditions	17	7	23	102	142
HIV/AIDS	31	27	46	61	136
Diabetes	1	3	22	102	125
Malnutrition (including obesity and exercise)	6	4	9	98	113
Wounds and injuries (including violence)	4	7	13	91	109
Endocrine, blood, and immune disorders (excluding diabetes or HIV)	0	1	12	86	99
Neurological conditions	1	3	16	81	98
Skin and oral conditions	0	3	5	67	75
Sense organ diseases	2	3	11	56	68
Tuberculosis	8	9	28	34	62
Sexually transmitted diseases (excluding HIV)	2	1	10	39	49
Diarrhoeal diseases	6	7	9	29	46
Communicable childhood diseases	2	5	9	24	40
Malaria	16	13	8	1	24
Congenital anomalies	0	1	2	20	23
Anaemia	0	1	1	9	11
Meningitis	2	2	3	3	9
TOTAL	104	120	390	2337	2829

A single economic evaluation may address more than one health area in countries of more than one income group. The totals exclude the 15 articles (0.5%) in our data set which could not be classified by health area.

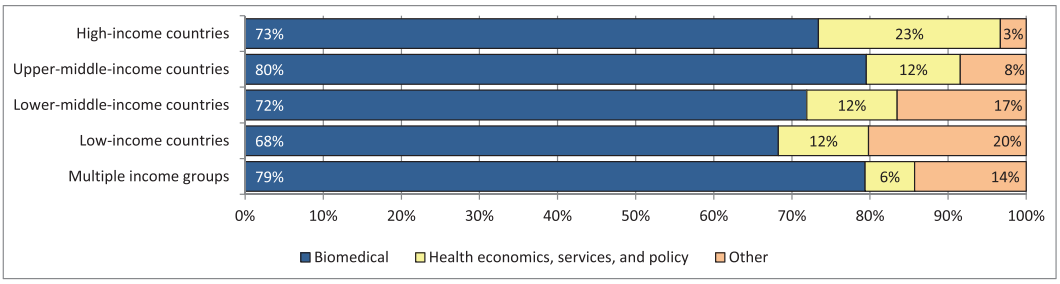

Figure 3. Proportion of economic evaluations by journal type and income group. The classification of journals by type is provided in Web appendix 6. Articles are disaggregated by the income group(s) of the country or countries studied

3.4. Journals and languages

Economic evaluations were published in a total of 967 different journals (Table S8). Five hundred fifty-nine journals published only one economic evaluation each in the entire 28-month period we analysed and 165 journals published only two. Whereas 802 different journals published HIC articles, only 44 published LIC articles. The proportion of articles published in the top 20 journals for each income group increased

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Table IV. Journals publishing the greatest number of economic evaluations by income group of countries studied

	Low and lower-middle			Upper-middle			High			All		
Rank	Journal	Type	N	Journal	Type	N	Journal	Type	N	Journal	Type	N
1	PLoS One	Other	30	PLoS One	Other	31	Journal of Medical Economics	HEPS	100	PLoS One	Other	121
2	Vaccine	BM	13	Vaccine	Other	17	Health Technology Assessment	HEPS	82	Journal of Medical Economics	HEPS	101
3	Malaria Journal	BM	9	Value in Health Regional Issues	BM	11	PLoS One	Other	70	Health Technology Assessment	HEPS	82
4	Journal of Acquired Immune Deficiency Syndromes	BM	8	Value in Health	HEPS	8	Value in Health	HEPS	54	Vaccine	BM	66
5	Health Policy and Planning	HEPS	8	BMJ	HEPS	7	Vaccine	BM	44	Value in Health	HEPS	63
6	BMJ	BM	6	AIDS	BM	7	ClinicoEconomics and Outcomes Research	HEPS	36	ClinicoEconomics and Outcomes Research	HEPS	37
7	Value in Health Regional Issues	HEPS	6	Cadernos de Saúde Pública	BM	7	European Journal of Health Economics	HEPS	35	European Journal of Health Economics	HEPS	36
8	Cost Effectiveness and Resource Allocation	HEPS	5	BMC Public Health	BM	6	PharmacoEconomics	HEPS	33	PharmacoEconomics	HEPS	34
9	PLoS Medicine	BM	5	BMC Health Services Research	BM	6	Clinical Therapeutics	BM	28	Clinical Therapeutics	BM	32
10	AIDS	BM	4	PLoS Medicine	HEPS	5	BMJ Open	BM	26	Value in Health Regional Issues	HEPS	28
11	PloS Neglected Tropical Diseases	BM	4	International Journal of Tuberculosis and Lung Disease	BM	5	Applied Health Economics and Health Policy	HEPS	26	BMJ Open	BM	26
12	BMC Public Health	BM	3	Journal of the Medical Association of Thailand	BM	5	International Journal of Technology Assessment in Health Care	HEPS	22	Applied Health Economics and Health Policy	HEPS	26
13	International Journal of Tuberculosis and Lung Disease	BM	3	Malaria Journal	BM	4	Cancer	BM	21	International Journal of Technology Assessment in Health Care	HEPS	25
14	World Journal of Surgery	BM	3	Journal of Acquired Immune Deficiency Syndromes	BM	4	BMJ	BM	19	BMC Health Services Research	HEPS	23
15	Bulletin of the World Health Organization	HEPS	3	Cost Effectiveness and Resource Allocation	BM	4	BMC Health Services Research	HEPS	17	Cancer	BM	21
16	Tropical Medicine and International Health	BM	3	Clinical Therapeutics	HEPS	4	American Journal of Managed Care	BM	16	BMJ	BM	20
17	Clinical Infectious Diseases	BM	2	BMC Infectious Diseases	BM	4	Osteoporosis International	BM	14	BMC Public Health	BM	20
18	Lancet	BM	2	Revista Panamericana de Salud Pública	BM	4	Gynecologic Oncology	BM	14	Cost Effectiveness and Resource Allocation	HEPS	20
19	Biosystems	BM	2	Modern Preventive Medicine	BM	4	BMC Public Health	BM	13	American Journal of Managed Care	BM	16
20	Journal of Pediatrics	BM	2	Biomedica	BM	4	Cost Effectiveness and Resource Allocation	HEPS	13	AIDS	BM	16
	Lancet Global Health	BM	2	Chinese Journal of New Drugs	BM	4	BJU International	BM	13			
	Proceedings of the National Academy of Sciences of the USA	BM	2	Zhonghua liu xing bing xue za zhi	BM	4	Heart	BM	13			
	Journal of the Pakistan Medical Association	BM	2									
	Disasters	Other	2									

BM: Biomedical; HEPS: Health economics, policy, and services; OTH: Other.

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steeply down the income groups: 29% of articles studying HICs were published in the top 20 journals publishing HIC evaluations, while 38, 66, and 77% of articles studying upper-MICs, lower-MICs, and LICs, respectively, were published in the top 20 journals publishing evaluations set in each of the respective income groups.

Overall, 74% of articles were published in biomedical rather than health economics, systems, and policy journals (22%) or other journal types (5%) (Figure 3). In HICs, 6 of the top 10 journals were health economics, systems, or policy journals, compared with only 3 of the top 10 journals publishing articles about LICs and lower-MICs (Table IV). The top outlet for economic evaluations across all income levels was *PLoS ONE*, an open-access journal publishing 'primary research from any scientific discipline', which ranked amongst the top three journals for all income groups. *Vaccine* ranked fourth overall ($n=66$) and in the top five for all income groups. Yet overall, journals tended towards segregation by income group; 6 of the top 10 journals publishing economic evaluations about HICs did not publish a single LIC or lower MIC study and two of the remaining published only one each.

All articles addressing LICs and lower-MICs were published in English, while 4% of HIC articles ($n=89$) were published in other languages, as was a striking 22% ($n=87$) of all articles addressing upper-MICs. In upper-MICs, Chinese was the leading non-English language ($n=48$, 12%), followed by Spanish (23, 6%), Portuguese ($n=13$, 3%), Turkish ($n=2$, 1%), and Farsi ($n=1$, 0%), while in HICs, Spanish was the language of full-text for 46 articles (2%), followed by German ($n=13$, 1%), and 10 other languages.

3.5. Types of economic evaluation

Although the term is widely (mis)used in the literature, genuine cost-benefit analyses are very rare; we excluded many articles from our database which described themselves as CBAs of health interventions but did not value health or welfare outcomes. Of the 147 (5%) articles in our database which described themselves as CBAs, some do not in fact place a monetary value on health outcomes and should probably be described as CEAs or CUAs; however, for consistency and feasibility, our analysis of evaluation type is based on key term searches, and therefore reflect the authors' classification (Table S4). Cost-utility analyses accounted for at least half of economic evaluations across all income levels, ranging from 50% ($n=52$) in LICs to 62% ($n=1448$) in HICs. The proportion of CUAs employing DALYs decreases from 87% ($n=45$) in LICs to 2% ($n=35$) in HICs, while the proportion employing QALYs increases from 13% ($n=7$) in LICs to 35% ($n=23$) in lower-MICs, 68% ($n=123$) in upper-MICs, and 96% ($n=1385$) in HICs. A very small proportion of studies described themselves as CUAs but did not contain any search terms for DALYs or QALYs (Figure 4 and Table S9).

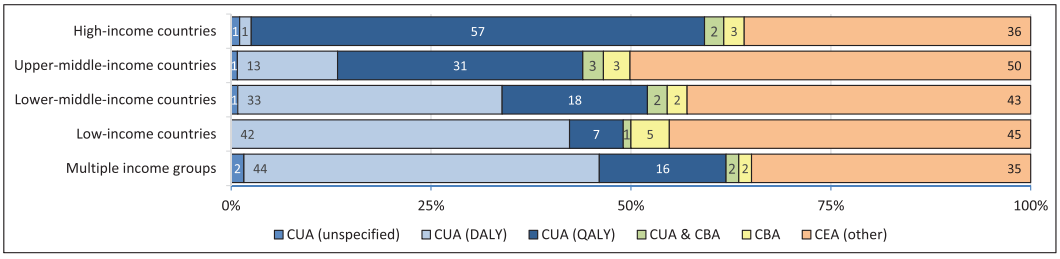

Figure 4. Proportion of economic evaluations by analytical type and income group studied. In this figure, 'cost-effectiveness analysis' refers to articles meeting our definition of a full economic evaluation but not containing any keywords to define it more specifically as a cost-utility or cost-benefit analysis. Articles can be classified as both cost-utility and cost-benefit analyses if they contain keywords for both. Articles are disaggregated by the income group(s) of the country or countries studied. CBA: cost-benefit analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis, DALY: disability-adjusted life-year, QALY: quality-adjusted life-year

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Table V. Most frequent countries of institutional affiliation of authors

	High-income		Upper-middle-income		Low-income and lower-middle-income	
Rank	Country	N	Country	N	Country	N
1	USA	1145	China	116	India	22
2	UK	619	Brazil	51	Uganda	20
3	Netherlands	267	South Africa	49	Kenya	13
4	Canada	238	Thailand	37	Vietnam	11
5	Australia	191	Colombia	32	Ghana[a]	9
6	Germany	151	Mexico	26	Zambia[a]	9
7	Spain	147	Iran	25	Nigeria	8
8	Switzerland	104	Turkey	18	Indonesia[a]	5
9	France	103	Argentina	14	Burkina Faso[a]	5
10	Italy	99	Malaysia	12	Bangladesh[a]	4
11	Sweden	98	Peru	9	Pakistan[a]	4
12	Belgium	78	Bulgaria[a]	7	Tanzania[a]	4
13	Japan	53	Serbia[a]	7	Philippines[a]	4
14	Denmark	45	Hungary	5	Egypt[a]	4
15	Ireland	39	Venezuela	3	Ethiopia[a]	2
16	Norway	32	Romania[a]	2	Malawi[a]	2
17	Taiwan	28	Lebanon[a]	2	Congo, Dem. Rep.[a]	2
18	Finland	27	Costa Rica[a]	2	Benin[a]	2
19	Korea, Rep.[a]	25	Jordan[a]	2	Myanmar[a]	2
20	Austria[a]	25	Tunisia[a]	2	Zimbabwe[a]	2
21	Greece	23	Iraq[a]	1	Cameroon[a]	2
22	Hong Kong	21	Botswana[a]	1	Senegal[a]	2
23	Singapore	21	Cuba[a]	1	Sri Lanka[a]	1
24	New Zealand[a]	19	Kazakhstan[a]	1	Cambodia[a]	1
25	Poland[a]	19	Panama[a]	1	Niger[a]	1
26	Portugal	15	Jamaica[a]	1	Afghanistan[a]	1
27	Israel	12	Dominican Republic[a]	1	Nepal[a]	1
28	Russia	9			Rwanda[a]	1
29	Chile	8			Sierra Leone[a]	1
30	Czech Republic	7			Somalia[a]	1
31	Slovenia[a]	5			Syria[a]	1
32	Qatar[a]	5			Bolivia[a]	1
33	Croatia[a]	2			Guyana[a]	1
34	Saudi Arabia[a]	2			Uzbekistan[a]	1
35	Estonia[a]	2			West Bank and Gaza[a]	1
36	Iceland[a], Liechtenstein[a], Lithuania[a], Macao[a], Malta[a], Puerto Rico[a], Trinidad and Tobago[a]	1				

The table ranks countries of institutional affiliations of authors by the number of economic evaluations including at least one author affiliated with that country. All countries affiliated with at least one author of at least one economic evaluation are listed.
[a]Equal ranking with country above and/or below.

Table VI. Income group studied versus income group of author affiliations

	Income group of authors' country affiliation(s)									
Income group of countries studied	Low		Lower-middle		Upper-middle		High		Total	
Low	55	(53%)	7	(7%)	16	(15%)	98	(94%)	104	(100%)
Lower-middle	8	(7%)	65	(54%)	15	(12%)	99	(82%)	121	(100%)
Upper-middle	11	(3%)	11	(3%)	338	(86%)	175	(45%)	391	(100%)
High	4	(0%)	12	(1%)	51	(2%)	2345	(100%)	2350	(100%)
Total	59	(2%)	80	(3%)	394	(14%)	2601	(91%)	2844	(100%)

Row percentages are presented and reflect the proportion of articles addressing a given income level, which include authors affiliated with institutions based in a country of the given income level.

3.6. Authors' geographical and institutional affiliations

Author affiliation data were obtained for all articles. At least one author was affiliated with an institution in the USA or the UK on 1145 (40%) and 619 (22%) of articles respectively (Table V). China-based authors

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Table VII. Most frequent institutional affiliation of authors

Income group of authors' institutions									
Rank	High Institution	Country	N	Upper-middle Institution	Country	N	Low and lower-middle Institution	Country	N
1	Harvard University	USA	152	University of Cape Town	South Africa	19	Makerere University	Uganda	14
2	Johns Hopkins University	USA	74	Tehran University of Medical Sciences	Iran	17	Kenya Medical Research Institute	Kenya	9
3	London School of Hygiene and Tropical Medicine	UK	70	Shanghai Jiao Tong University[a]	China	15	Ministry of Health	Vietnam	6
4	University of Toronto	Canada	65	Universidade de Sao Paulo[a]	Brazil	15	All India Institute of Medical Sciences[a]	India	5
5	University of Amsterdam	Netherlands	62	University of the Witwatersrand[a]	South Africa	15	Hanoi Medical University[a]	Vietnam	5
6	University College London	UK	61	Chinese Center for Disease Control and Prevention[a]	China	11	Ghana Health Service[a]	Ghana	4
7	University of York	UK	57	Mahidol University[a]	Thailand	11	Ministry of Health[a]	Zambia	4
8	Pfizer, inc.	Multinational private company	51	Instituto Mexicano del Seguro Social[a]	Mexico	10	University of Nigeria[a]	Nigeria	4
9	Centers for Disease Control and Prevention[a]	USA	46	Universidad Nacional de Colombia[a]	Colombia	10	Centre Muraz[a]	Burkina Faso	3
10	Duke University[a]	USA	46	Health Intervention and Technology Assessment Program	Thailand	8	Family Health[a] International	Vietnam	3
							INDEPTH Network[a]	Ghana	3
							Kenya Government Medical Research Center[a]	Kenya	3
							Mbarara University of Science and Technology[a]	Uganda	3
							Ministry of Health[a]	Kenya	3
							Universitas Padjadjaran[a]	Indonesia	3
							University of Ghana[a]	Ghana	3
							YR Gaitonde Centre for AIDS Research and Education[a]	India	3

The table ranks institutional affiliations of authors by the number of economic evaluations including at least one author affiliated with that institution. The top 10 institutions located in each income level are listed. To the extent possible, institutions' totals include their affiliated hospitals, centres, and groups even if the parent institution was not specifically cited in the affiliation data.

[a]Equal ranking with country above and/or below.

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contributed to 4% ($n = 116$) of all articles, making it the ninth largest contributor to economic evaluations, while Brazil (51, 2%) and South Africa (49, 2%) also ranked within the top 20 country affiliations. With 22 articles (1%), India was the highest ranking lower MIC and ranked 29th overall, just ahead of Hong Kong and Singapore. Uganda was the largest contributor to economic evaluations amongst LICs with 20 articles (1%) and ranked 32nd overall just ahead of New Zealand. In general, the lists of leading country affiliations of authors within each income group strongly resemble the leading countries studied. Even for Uganda, however, the largest LIC contributor, 30 of the 49 articles about the country did not include any Uganda-based authors; of these, 25 were studies set in at least 15 countries each, but 5 articles focused on 3 or fewer countries.

On 91% of articles, at least one author was based in a HIC (Table VI). All but 5 of the 2350 articles studying HICs included at least one author based in a HIC and most articles studying upper-MICs included at least one upper MIC-based author ($n = 338$, 86%). By contrast, only 53 and 54% of articles studying LICs and lower-MICs, respectively, included any author based in an institution in the respective income group. Authors based in upper-MICs contributed to a relatively small proportion of articles analyzing LICs ($n = 16$, 15%) or lower-MICs ($n = 15$, 12%), and in nearly half of these articles, upper-MICs were also studied. Authors based in HIC institutions contributed to 94% ($n = 98$) of articles analyzing LICs and 82% ($n = 99$) analyzing lower-MICs, compared with fewer than half of evaluations in upper-MICs ($n = 175$, 45%). Of the 65 articles studying LIC and lower-MIC which did not include an author from those income levels, 44 articles included at least one author based in the USA (68%). At least one author listed a major pharmaceutical company amongst the institutional affiliations on 9% of articles ($n = 246$) overall, varying from 9% ($n = 221$) of articles studying HICs, to 12% ($n = 46$) studying an upper-MIC, 7% ($n = 8$) studying a lower-MIC and 4% ($n = 4$) studying a LIC. English is an official language in four of the top five HICs and LICs and lower-MICs contributing to economic evaluations, compared with just one of the top five upper-MICs (Table VII).

Harvard University, including its affiliated hospitals, was by some distance the institution contributing to the largest number of economic evaluations ($n = 152$). The top institutions producing economic evaluations in LICs and lower-MICs are notable for their low individual and collective output, as well as for including many ministries of health or (semi-)autonomous research institutes (Table VII). The leading LIC or lower MIC institution, Makerere University, was listed amongst the author affiliations of 14 economic evaluations over the 2.3 years we studied. The WHO was listed amongst the author affiliations on 25 articles, while the World Bank and United Nations' Children's Fund contributed to only four economic evaluations each.

4. DISCUSSION

Our analysis provides an evidence base from which to discuss the current state of the economic evaluation field and has generated many questions which warrant further investigation. Some of these issues are examined in other papers in this special issue. For example, Griffiths *et al*. (2016) compare the methods used in economic evaluations in countries of differing income groups in a representative sample of articles from the database we created, while other authors examine costing methods (Sweeney *et al*., 2016, Cunnama *et al*., 2016), outcome metrics (Greco *et al*., 2016), and issues around capacity to produce and to use economic evaluations (Kaló *et al*., 2016). Our analysis also offers insights to strengthen the process of prioritising, conducting, publishing, and developing capacity for economic evaluation research. Here, we discuss the state of the field and the implications of our findings for research priority setting and capacity development.

4.1. The state of health economic evaluation

We identified a large volume of economic evaluations—2844 over 28 months—including 1273 in 2013 alone. The principal economics database, EconLit, contains 5483 publications with 'Health' JEL codes for 2012 and 2013, but captured just 1% of economic evaluations published in those years. A large majority of economic evaluations were published in biomedical journals and even many of the journals we categorised as 'health economics, services, and policy' are not indexed in EconLit. Adding the 2413 economic evaluations we identified

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for 2012 and 2013 to the EconLit health records would increase the volume of 'health economics' research by 44%. Further, these publications still do not include the many other health economic analyses of, for example equity, demand, markets, and incentives, which are published in journals outside the economics literature as defined by the EconLit database.

Despite important analytical differences and the lack of overlap between the body of literature addressed in our analysis and Wagstaff and Culyer's analysis of health economics within the EconLit database, our findings share some commonalities. Both our analyses (along with Greenberg *et al*. (2010)) identified Harvard as the leading institution and the USA as by far the most prolific contributor to health economic (evaluation) research, followed by the UK, and then the Netherlands, Canada, and Australia. China and South Africa also rank highly in both our analyses. Nonetheless, our findings also differ in important ways. As expected, our lists of leading journals share very little in common, as economic evaluations are predominantly published in biomedical journals, which are not indexed in EconLit. Some contributors, such as the World Bank and Taiwan, which ranked very highly in Wagstaff and Culyer's analysis, contribute far less to economic evaluations, while institutions with a stronger focus on health (rather than only economics) tend to rank more highly in our analysis. There are also substantial differences with respect to our estimates of the volume of research. Whereas Wagstaff and Culyer find that 'economic evaluation . . .[shows] no clear trend', our analysis has highlighted the substantial size of the applied health economic evaluation literature relative to the health economics literature within EconLit and indicates that with just 1% of the applied economic evaluation literature, the EconLit database is unlikely to provide a representative indication of trends over time in the size or relative importance of health economic evaluation.

As previously highlighted (Wagstaff and Culyer, 2012), identifying health economic literature in the biomedical databases was not straightforward. We found the use of economic vocabulary and article classifications in biomedical journals and databases to be so poor and inconsistent as to render simultaneously sensitive and specific searching impossible (Text S1). The NHS EED database, while incomplete, was by far the most sensitive and specific source of economic evaluations, which makes the decision to cease to update it from March 2015 particularly lamentable. The ongoing work to add DALY-based cost-utility analyses to the existing QALY-based Tufts Economic Evaluation Registry is a welcome development; however, it will still omit half of economic evaluations conducted in LMICs and currently charges for access.

Our findings paint a picture of a research community that is simultaneously highly concentrated in a few countries and institutions and highly fragmented. A very small number of journals publish economic evaluations from both high-income and low-income settings and a large proportion of articles appear in journals which only very rarely publish economic evaluations. The fact that so many biomedical journals now publish economic evaluations (if only rarely) is a positive sign of the acceptance and integration of economic evaluation within health research. It is also perhaps unsurprising, as economic evaluations are usually oriented towards health sector decision makers. This fragmentation may, however, also explain some of the problems of quality highlighted elsewhere (Griffiths *et al*., 2016), as biomedical journal editors may not only lack specialist knowledge of economic evaluation methods but also lack familiarity with pools of suitably qualified reviewers. In this way, the small number of journals publishing economic evaluations about LMICs may present an opportunity to engage with the editors of these journals to help improve standards where necessary, whereas the vast array of authors, institutions, and journals associated with economic evaluations set in HICs presents a greater challenge. In any case, the lack of scholarly dialogue between those focusing on countries of differing income levels seems likely to be detrimental to all.

We hope that recognition of the size, importance, and fundamental interdisciplinarity of health economic evaluation will lead to an evolution in research culture within the field, and also, on a practical level, to improvements in existing databases or creation of a new one that will better reflect and serve the needs of health economics researchers. Of course, authors themselves, reviewers, and editors could already do far more to facilitate the efficient identification of health economic evaluations. For example, an initial step could include ensuring that all articles include the study design in their title, as is already required by *Plos Medicine*, and that those that are not economic evaluations avoid economic terminology, such as 'cost-effective' in their titles, abstracts, and keywords.

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4.2. Research priority setting

Our findings also raise a number of questions about the health and geographical areas that are and are not prioritised for health economic evaluation. Burden of disease is not and should not be the sole determinant of the volume of economic evaluation research. It seems difficult to argue, however, that the differences between the number of economic evaluations conducted across LICs, MICs, and HICs are equitable or efficient. HICs account for 16% of the world's population, 11% of the GBD (WHO, 2014), and 83% of all economic evaluations conducted, while LICs account for 12% of the world's population, 19% of the GBD, and 4% of economic evaluations. There are 139 different LMICs (World Bank, 2015), which have very diverse epidemiological and economic characteristics, and also, in many cases, weak(er) health systems with substantial and diverse constraints on the supply and demand for health care; this diversity likely contributes to greater heterogeneity in the cost-effectiveness of interventions and necessitates more, not less, research (Vassall *et al*., 2016). Further, the health benefits foregone by incorrect priority setting decisions may be substantially higher in low-income settings than in high-income settings.

One of our most surprising findings is how well the health areas studied in HICs correlate with the burden of disease in those settings. In LMICs, however, the picture is much more mixed, with many more economic evaluations conducted about health areas accounting for lower proportions of the burden of disease. There are several reasons why such discrepancies may not be inequitable or inefficient. First, the GBD estimates themselves are highly contested (Nord, 2013, Byass *et al*., 2013); intended to reflect only a very narrow definition of health, the newest disability weights used in the GBD estimates exclude wider individual or social welfare consequences (Salomon *et al*., 2012). In the case of HIV/AIDS, for example, the many and varied stakeholders could therefore conclude that it is right that HIV should be studied more than health areas accounting for a larger burden of disease because of its wider social and economic consequences or because its health consequences are only lower than other diseases because of ongoing and expensive control efforts. Second, some health areas may have a low value of additional information relative to the costs of generating the information, especially if extensive research has already been conducted in that area. Third, so little may be understood about some health problems at a clinical level that economic evaluation of interventions may be premature. Fourth, economic evaluations may be conducted not to consider adding another more effective and more costly intervention, but rather to consider divestment from costly interventions, and therefore economic evaluations in health areas that contribute very little to the disease burden may be warranted. Finally, as economic evaluations are conceptualised around a (package of) interventions, which may not map neatly onto specific conditions, categorization of economic evaluations by health areas also has some conceptual limitations, which could weaken their correlation with disease burden; we found this to be particularly true for surgical procedures, pain management and palliative care, and health systems and intersectoral interventions.

On the other hand, the four health areas accounting for the largest burden of disease in LICs are as follows: (i) neonatal and maternal conditions; (ii) respiratory diseases; (iii) wounds and injuries; and (iv) diarrhoeal diseases. While further biomedical advances, such as a point-of-care test for bacterial infections would help (Zumla *et al*., 2014), the bulk of the impact of all four of these health areas needs to be addressed through health systems, multi-sectoral, and/or social interventions such as prompt access to high-quality health facilities (Kerber *et al*., 2007), road safety measures (WHO, 2013), and improved water and sanitation (Bartram *et al*., 2005). Such solutions offer little potential for pharmaceutical company profits and instead require complex interventions. Recent systematic reviews of economic evaluations of cardiovascular disease interventions in LMICs similarly found that evaluations of pharmacological interventions dominated and a greater focus on evaluation of non-clinical strategies were needed (Shroufi *et al*., 2013, Suhrcke *et al*., 2012). Financing such evaluations is unlikely to appeal to private for-profit companies, and so domestic and international research funders, as well as researchers themselves, should concentrate on producing research in these areas, and thereby correct this market failure.

4.3. Capacity development

Several of our findings have important implications for thinking about how to increase capacity to produce and to use high-quality and policy-relevant health economic evaluations. Large upper-MICs, especially China but

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also South Africa, Brazil, and Iran, produce substantial numbers of economic evaluations and far more than many smaller HICs. This is in some ways unsurprising, as the costs of research are independent of the size of a country's population or economy and so the relative costs of research are lower in large economies. Capacity development is important for all countries, but particularly challenging for LMICs and for small HICs as well (Kaló *et al*., 2016). A large gap between the numbers of economic evaluations conducted and what is needed for priority setting persists in all but a few countries (Geroy, 2012, Odame, 2013, Mori and Robberstad, 2012).

Our analysis has identified some clear institutional leaders in LMICs, but also highlighted that many countries produce few, if any, economic evaluations. We propose the development of strong regional or sub-regional networks, which bring together existing capacity in health economic evaluation and build on centres of strength in health intervention research, even where substantial economic evaluation capacity may not yet exist. A multi-stakeholder report on how to strengthen health economics more generally in Africa highlighted the importance of international networks as well as local institutional support (McIntyre *et al*., 2008). In addition to training and ongoing technical support, a well-funded regional network could also offer scope for deeper collaboration in producing multi-country evaluations and assessing transferability of findings across the region. Such a regional approach could be more efficient in generating economic evidence and assessing its relevance to a wider range of settings more systematically.

The leading contributors to economic evaluations from LICs and lower-MICs tend to be research institutions, often within or associated with ministries of health, rather than universities. Such embeddedness should be an advantage in ensuring that research both reflects and informs a country's health priorities. It also means, however, that there may be no pre-existing link between those who conduct health economic evaluation research and those who teach and train undergraduate and postgraduate students in these countries. This marked difference from HICs and even upper-MICs may require new approaches to capacity development, rather than replication of strategies that have achieved successes in upper-MICs and HICs.

At the same time, further work is needed to generate demand for economic evaluation both at national level, through the institutionalization of priority setting (Odame, 2013, Mori and Robberstad, 2012), and globally, through transparent priority-setting initiatives at global funding bodies and continuing efforts to strengthen the role of economic evaluation in policy making at the WHO (Wiseman *et al.,* 2016), whose policy recommendations play a particularly large role in LICs and lower-MICs (WHO, 2012).

Finally, nearly half of economic evaluations studying LICs and lower-MICs do not include any authors from LMIC institutions. Some of these were desk-based modelling studies; however, many involved data collection in LMICs. Some may have included authors from LMICs affiliated with a HIC institution, for example as doctoral students; however, such cases cannot explain the full magnitude of the discrepancy. It is unclear whether this discrepancy reflects a lack of opportunities for participation from fellow researchers or funders, lack of skills or incentives, or some combination of these and other factors, but the results are clearly inequitable (Chu *et al*., 2014). The situation also suggests a failure to recognise the wider potential of research capacity development to improve health in LMICs and the more immediate impact that real partnership with LMIC researchers and policy makers can have in ensuring that the research is policy-relevant and informs policy decisions. Both funders and researchers in all countries must examine and address these inequities.

We hope that the findings of this analysis will be useful for those conducting (systematic) reviews of the economic evaluation literature and that they will encourage and provide an empirical grounding for debate on the current state and future directions for this growing field.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

ETHICS STATEMENT

As the analysis is based entirely on publicly available data, specific ethical approval was not required.

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REFERENCES

Aksnes DW, Schneider JW, Gunnarsson M. 2012. Ranking national research systems by citation indicators: a comparative analysis using whole and fractionalised counting methods. *Journal of Informetrics* **6**: 36–43.

Augustovski F, Iglesias C, Manca A, Drummond M, Rubinstein A, Marti SG. 2009. Barriers to generalizability of health economic evaluations in Latin America and the Caribbean region. *PharmacoEconomics* **27**: 919–29.

Bartram J, Lewis K, Lenton R, Wright A. 2005. Focusing on improved water and sanitation for health. *Lancet* **365**: 810–2.

Byass P, De Courten M, Graham WJ, Laflamme L, Mccaw-Binns A, Sankoh OA, Tollman SM, Zaba B. 2013. Reflections on the global burden of disease 2010 estimates. *PLoS Medicine* **10**: e1001477.

Chao TE, Sharma K, Mandigo M, Hagander L, Resch SC, Weiser TG, Meara JG. 2014. Cost-effectiveness of surgery and its policy implications for global health: a systematic review and analysis. *The Lancet Global Health* **2**: e334–e345.

Chavan S, Newlands D, Smith C. 2011. A Systematic Review of Economic Evaluations of Chemoprophylaxis for Tuberculosis, Journal of Tropical Medicine.

Chu KM, Jayaraman S, Kyamanywa P, Ntakiyiruta G. 2014. Building research capacity in Africa: equity and global health collaborations. *PLoS Medicine* **11**: e1001612.

Creese A, Floyd K, Alban A, Guinness L. 2002. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet* **359**: 1635–43.

Cunnama, L., Sinanovic, E., Ramma, L., Foster, N., Berrie, L., Stevens, W., Molapo, S., Marokane, P., Mccarthy, K., Churchyard, G. & Vassall, A. 2016. Using top-down and bottom-up costing approaches in LMICs: The case for using both to assess the incremental costs of new technologies at scale. *Health Economics* **25:**S1, DOI: 10.1002/hec.3295.

Dakin H, Wordsworth S. 2013. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. *Health Economics* **22**: 22–34.

Drummond M, Weatherly H, Ferguson B. 2008. Economic evaluation of health interventions. *BMJ* **337**: a1204.

Drummond MF, Sculpher MJ, Torrance GW, O'brien BJ, Stoddart GL. 2005. Methods for the economic evaluation of health care programmes, Oxford, Oxford University Press.

Fesenfeld M, Hutubessy R, JIT M. 2013. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. *Vaccine* **31**: 3786–3804.

Fitzpatrick C, Floyd K. 2012. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. *PharmacoEconomics* **30**: 63–80.

Galarraga O, Colchero MA, Wamai RG, Bertozzi SM. 2009. HIV prevention cost-effectiveness: a systematic review. *BMC Public Health* **9**(1)Suppl: S5.

Gavaza P, Rascati KL, Oladapo AO, Khoza S. 2010. The state of health economic evaluation research in Nigeria: a systematic review. *PharmacoEconomics* **28**: 539–53.

Geroy LSA. 2012. Economic evaluation for first-line anti-hypertensive medicines: Applications for the Philippines. *Cost Effectiveness and Resource Allocation* **10**.

Goodman CA, Mills AJ. 1999. The evidence base on the cost-effectiveness of malaria control measures in Africa. *Health Policy and Planning* **14**: 301–12.

Greco, G., Lorgelly, P. & Yamabhai, I. 2016. Outcomes in economic evaluations of public health interventions in low- and middle-income countries: health, capabilities and subjective wellbeing. *Health Economics* **25:**S1, DOI: 10.1002/hec.3302.

Greenberg D, Rosen AB, Wacht O, Palmer J, Neumann PJ. 2010. A bibliometric review of cost-effectiveness analyses in the economic and medical literature: 1976–2006. *Medical Decision Making* **30**: 320–327.

Griffiths U, Legood R, Pitt C. 2016. Comparison of Economic Evaluation Methods Across Low-income, Middle-income, and High-Income Countries: What Are the Differences and Why?. *Health Economics* **25:**S1, DOI: 10.1002/hec.3312.

Griffiths UK, Miners A. 2009. Economic evaluations of Haemophilus influenzae type b vaccine: systematic review of the literature. *Expert Review of Pharmacoeconomics and Outcomes Research* **9**: 333–346.

Hagen NT. 2013. Harmonic coauthor credit: a parsimonious quantification of the byline hierarchy. *Journal of Informetrics* **7**: 784–791.

Johri M, Ako-Arrey D. 2011. The cost-effectiveness of preventing mother-to-child transmission of HIV in low- and middle-income countries: systematic review. *Cost Effectiveness and Resource Allocation* **9**.

Kaló Z, Gheorghe A, Huic M, Csanadi M, Boerlum Kristensen F. 2016. HTA Implementation Roadmap in Central and Eastern European Countries. *Health Economics* **25:**S1, DOI: 10.1002/hec.3298.

Kerber KJ, De Graft-Johnson JE, Bhutta ZA, Okong P, Starrs A, Lawn JE. 2007. Continuum of care for maternal, newborn, and child health: from slogan to service delivery. *Lancet* **370**: 1358–69.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, GOTZSCHE PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology* **62**: e1–34.

Mangham-Jefferies L, Pitt C, Cousens S, Mills A, Schellenberg J. 2014. Cost-effectiveness of strategies to improve the utilization and provision of maternal and newborn health care in low-income and lower-middle-income countries: a systematic review. *BMC Pregnancy and Childbirth* **14**: 243.

Mcintyre D, Wayling S, WORLD HEALTH ORGANIZATION & SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES. 2008. Strengthening health-economics capability in Africa : summary and outcomes of a regional consultation of experts and policy-makers, Geneva, World Health Organization/Special Programme for Research & Training in Tropical Diseases.

Mills AJ, Thomas M. 1984. Economic Evaluation of Health Programmes in Developing Countries: A review and selected annotated bibliography, London: London School of Hygiene & Tropical Medicine.

Mori AT, Robberstad B. 2012. Pharmacoeconomics and its implication on priority-setting for essential medicines in Tanzania: a systematic review. *BMC Medical Informatics and Decision Making* **12**.

Mulligan JA, Walker D, Fox-Rushby J. 2006. Economic evaluations of non-communicable disease interventions in developing countries: a critical review of the evidence base. *Cost Eff Resour Alloc* **4**: 7.

Natunen K, Lehtinen TA, Torvinen S, Lehtinen M. 2013. Cost-effectiveness of HPV-vaccination in medium or low income countries with high cervical cancer incidence - a systematic review. *Journal of Vaccines and Vaccination* **4**: 172.

Nord E. 2013. Disability weights in the Global Burden of Disease 2010: unclear meaning and overstatement of international agreement. *Health Policy* **111**: 99–104.

Odame EA. 2013. Systematic review of economic evaluation literature in Ghana: is health technology assessment the future? *Value in Health Regional Issues* **2**: 279–283.

Ott JJ, Breteler JK, Tam JS, Hutubessy RCW, Jit M, De Boer MR. 2013. Influenza vaccines in low and middle income countries: a systematic review of economic evaluations. *Human Vaccines and Immunotherapeutics* **9**: 1500–1511.

Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. 2012. Tuberculosis and HIV co-infection. *PLoS Pathogens* **8**.

Perez Velasco R, Praditsitthikorn N, Wichmann K, Mohara A, Kotirum S, Tantivess S, Vallenas C, Harmanci H, Teerawattananon Y. 2012. Systematic review of economic evaluations of preparedness strategies and interventions against influenza pandemics. *PLoS One* **7**: e30333.

Pritchard A. 1969. Statistical bibliography or bibliometrics. *Journal of Documentation* **25**: 348–349.

Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, Cook J, Glick H, Liljas B, Petitti D, Reed S. 2005. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value in Health* **8**: 521–33.

Retzer V, Jurasinski G. 2009. Towards objectivity in research evaluation using bibliometric indicators – a protocol for incorporating complexity. *Basic and Applied Ecology* **10**: 393–400.

Rubin RM, Chang CF. 2003. A bibliometric analysis of health economics articles in the economics literature: 1991–2000. *Health Economics* **12**: 403–414.

Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A, Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Abdulhak AB, Blyth F, Bourne R, Braithwaite T, Brooks P, Brugha TS, Bryan-Hancock C, Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Díaz-Torné C, Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, JARVIS D, Jonas JB, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, Mcgill N, Mcgrath J, Mensah GA, Meyer AC, Michaud C, Moran A, Mori R, Murdoch ME, Naldi L, Newton CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT, Remuzzi G, *et al*. 2012. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *The Lancet* **380**: 2129–2143.

Shroufi A, Chowdhury R, Anchala R, Stevens S, Blanco P, Han T, Niessen L, Franco OH. 2013. Cost effective interventions for the prevention of cardiovascular disease in low and middle income countries: a systematic review. *BMC Public Health* **13**: 285.

Suhrcke M, Boluarte TA, Niessen L. 2012. A systematic review of economic evaluations of interventions to tackle cardiovascular disease in low- and middle-income countries. *BMC Public Health* **12**: 2.

Sweeney, S., Vassall, A., Foster, N., Simms, V., Ilboudo, P., Kimaro, G., Mudzengi, D. & Guinness, L. 2016. Methodological Issues to Consider When Collecting Data to Estimate Poverty Impact in Economic Evaluations in Low-income and Middle-income Countries. *Health Economics* **25:**S1, DOI: 10.1002/hec.3304.

Teerawattananon Y, Russell S, Mugford M. 2007. A systematic review of economic evaluation literature in Thailand: are the data good enough to be used by policy-makers? *PharmacoEconomics* **25**: 467–479.
Valencia-Mendoza A, Danese-dlSantos LG, Sosa-Rubi SG, Aracena-Genao B. 2011. Cost-effectiveness of public health practices: a literature review of public health interventions from the Mesoamerican Health Initiative. *Salud Pública de México* **53**(3)Suppl: S375–85.
Vassall A, Mangham-Jefferies L, Gomez GB, Pitt C, Foster N. 2016. Incorporating Demand and Supply Constraints into Economic Evaluation in Low-Income and Middle-Income countries. *Health Economics* **25:**S1, DOI: 10.1002/hec.3306.
Wagstaff A, Culyer AJ. 2012. Four decades of health economics through a bibliometric lens. *Journal of Health Economics* **31**: 406–439.
Walensky RP, Ciaranello AL, Park JE, Freedberg KA. 2010. Cost-effectiveness of laboratory monitoring in sub-Saharan Africa: a review of the current literature. *Clinical Infectious Diseases* **51**: 85–92.
Walker D, Fox-Rushby JA. 2000. Economic evaluation of communicable disease interventions in developing countries: a critical review of the published literature. *Health Economics* **9**: 681–98.
Waters HR, Hyder AA, PHILLIPS TL. 2004. Economic evaluation of interventions to reduce road traffic injuries--a review of the literature with applications to low and middle-income countries. *Asia-Pacific Journal of Public Health* **16**: 23–31.
White MT, Conteh L, Cibulskis R, Ghani AC. 2011. Costs and cost-effectiveness of malaria control interventions - a systematic review. *Malaria Journal* **10**: 337.
WHO GLOBAL MALARIA PROGRAMME. 2014. World malaria report 2014, Geneva, Switzerland: World Health Organization.
Wiseman V, Mitton C, Doyle-Waters M, Drake T, Conteh L, Newall AT, Onwujekwe O, Stephen J. 2016. Using Economic Evidence to Set Healthcare Priorities in Low-Income and Lower-Middle Income Countries: A Systematic Review of Methodological Frameworks. *Health Economics* **25:**S1, DOI: 10.1002/hec.3299.
WORLD BANK. 2015. Country and Lending Groups, World Bank Group: Washington, D.C.: World Bank Group.
WORLD HEALTH ORGANIZATION. 2011. International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Edition 2010, Geneva: World Health Organization.
WORLD HEALTH ORGANIZATION. 2012. Strategy on Health Policy and Systems Research: Changing Mindsets, Geneva, World Health Organization.
WORLD HEALTH ORGANIZATION. 2013. Global Status Report on Road Safety 2013 : Supporting a Decade of Action, Geneva: World Health Organization.
WORLD HEALTH ORGANIZATION. 2014. Global Health Estimates 2014 Summary Tables: DALY by Cause, Age and Sex, by World Bank Income Group Category, 2000–2012, Geneva: World Health Organization.
Zumla A, Al-Tawfiq JA, Enne VI, Kidd M, Drosten C, Breuer J, Muller MA, Hui D, Maeurer M, Bates M, Mwaba P, Al-Hakeem R, Gray G, GAUTRET P, Al-Rabeeah AA, Memish ZA, Gant V. 2014. Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections--needs, advances, and future prospects. *Lancet Infectious Diseases* **14**: 1123–35.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

2.3. Evidence gaps and challenges

While the bibliometric analysis highlighted numerous research gaps and challenges, the most salient issue that emerged was the lack of economic evaluations on which to base priority-setting decisions in LLMICs. This evidence gap is not unique to LLMICs, but data scarcity, the disproportionately high burden of disease, and scarcity of resources for health research and interventions make the challenge more acute (Pitt et al., 2016b). Nearly six years have passed since the period covered by the bibliometric analysis; however, it is unlikely that that an updated analysis would reach substantially different conclusions. To respond to the evidence gap, more economic evaluations are needed in LLMICs and these economic evaluations need to inform decision-making across a wide range of contexts.

The bibliometric analysis indicated some of the most neglected countries and health areas within LLMICs. While malaria emerged as the second- and third-most-studied health area in economic evaluations in lower-middle-income and low-income countries, respectively, francophone Africa and West Africa emerged as regions in which economic evaluations were particularly scarce. This gap is especially problematic because malaria was estimated to be the leading cause of death in francophone Africa in 2017, the historical development of francophone countries' health systems differed from that of anglophone countries, and malaria epidemiology in West Africa differs from other regions (El Bcheraoui et al., 2020, Boum and Mburu, 2020). In the following chapters, I respond to this research gap by presenting two new economic evaluations of malaria interventions in Senegal, which I conducted in ways that seek to maximize the transferability and thus usefulness of the evidence generated for other settings.

The bibliometric analysis also demonstrated that a substantial proportion of economic evaluations in LLMICs already explicitly seek to guide decision-making across many countries. While vastly fewer economic evaluations addressed LLMICs (n=184) than UMICs (n=390) or especially HICs (n=2337), the numbers of economic evaluations examining more than 10 countries were highest in LLMICs (n=33), followed by UMICs (n=32) and HICs (n=27). Yet, other research in the same *Health Economics* supplement raised important questions about the degree to which large, multi-country modelling studies – which most of these were – appropriately account for contextual variation, including health system constraints, which may lead to sub-optimal decision recommendations (Vassall et al., 2016a). In Chapter 6, I identify and respond to gaps in the methodological literature on transferability of economic

evaluations and offer guidance on how to conduct economic evaluations alongside trials and pilots in ways that allow them to inform decision-making across a range of contexts, especially in LLMICs, where economic evaluation evidence is so scarce.

2.4. References for Chapter 2

BOUM, Y. & MBURU, Y. 2020. Burden of disease in francophone Africa 1990-2017: the triple penalty? *The Lancet Global Health,* 8**,** e306-e307.

EL BCHERAOUI, C., MIMCHE, H., MIANGOTAR, Y., KRISH, V. S., ZIEGEWEID, F., KROHN, K. J., EKAT, M. H., NANSSEU, J. R., DIMBUENE, Z. T., OLSEN, H. E., TINE, R. C. K., ODELL, C. M., TROEGER, C. E., KASSEBAUM, N. J., FARAG, T., HAY, S. I. & MOKDAD, A. H. 2020. Burden of disease in francophone Africa, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Global Health,* 8**,** e341-e351.

PITT, C., VASSALL, A., TEERAWATTANANON, Y., GRIFFITHS, U. K., GUINNESS, L., WALKER, D., FOSTER, N. & HANSON, K. 2016b. Foreword: Health Economic Evaluations in Low- and Middle-income Countries: Methodological Issues and Challenges for Priority Setting. *Health Econ,* 25 Suppl 1**,** 1-5.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016a. Incorporating demand and supply constraints in economic evaluation in low- and middle-income countries. *Health Econ,* 25.

Chapter 3. Introduction to the economic evaluations

3.1. Overview

In this third chapter, I respond to some of the key evidence gaps identified in Chapter 2 with two economic evaluations, both of which examine malaria interventions in central Senegal. These economic evaluations make important contributions to a scarce evidence base in an area of major public health importance and investment in many LLMICs. In recognition of the need to make potentially far-reaching policy decisions with relatively scarce evidence on these topics, I sought to facilitate evidence transfer and make the economic evaluations as informative as possible for a wide range of settings and decision-makers. To do this, I began by exploring cost variation in the first economic evaluation using econometric techniques (Sculpher et al., 2004, Drummond et al., 2005) and found that the scale of delivery at the level of the health post – rather than a wide range of other variables considered – accounted for most of the cost variation observed. In that first economic evaluation, I also developed a simple approach to disaggregating costs and thinking about how costs might be expected to vary outside the trial context. In the second evaluation, I extend and implement more fully this mechanistic approach to cost modelling and demonstrate the value of this approach in enhancing the transferability of economic evaluation findings from the trial to real-world settings, across geographies, and with changes to the interventions. Before presenting the economic evaluations in Chapters 4 and 5, I first summarize in this chapter the global burden of and investments in tackling malaria, the interventions evaluated and their contexts, and give a brief overview of the methods used in the two economic evaluations, with a focus on the links between them.

3.2. Malaria epidemiology and burden

Malaria remains one of the leading causes of death in LLMICs, especially in children and in Sub-Saharan Africa (WHO, 2018a). In francophone Africa, malaria is the leading cause of death (El

Bcheraoui et al., 2020). Usually presenting initially as a fever, it can result in permanent disability or death without prompt treatment. A parasitic infection transmitted by female anopheles mosquitoes, it disproportionately affects the poorest people in the poorest countries (Degarege et al., 2019, de Glanville et al., 2019, Barat et al., 2004). The WHO estimated that there were 228 (95% confidence interval, CI: 206 to 258) million malaria cases and 405,000 (384,000 to 452,000) deaths from malaria in 2018, of which 93% and 94%, respectively, occurred in the WHO Africa region (WHO, 2019d). Children under 5 accounted for 67% of global malaria deaths in 2018 (WHO, 2019d), while malaria accounted for 6.9% of deaths in children under 5 in Africa in 2017 (WHO and MCEE, 2018). Globally, 84 countries experienced malaria cases in 2018, of which 43 were in the WHO African region (WHO, 2019d). Across Africa, malaria remained the fifth largest cause of death in all ages (WHO, 2018b) and in children under 5 (WHO and MCEE, 2018).

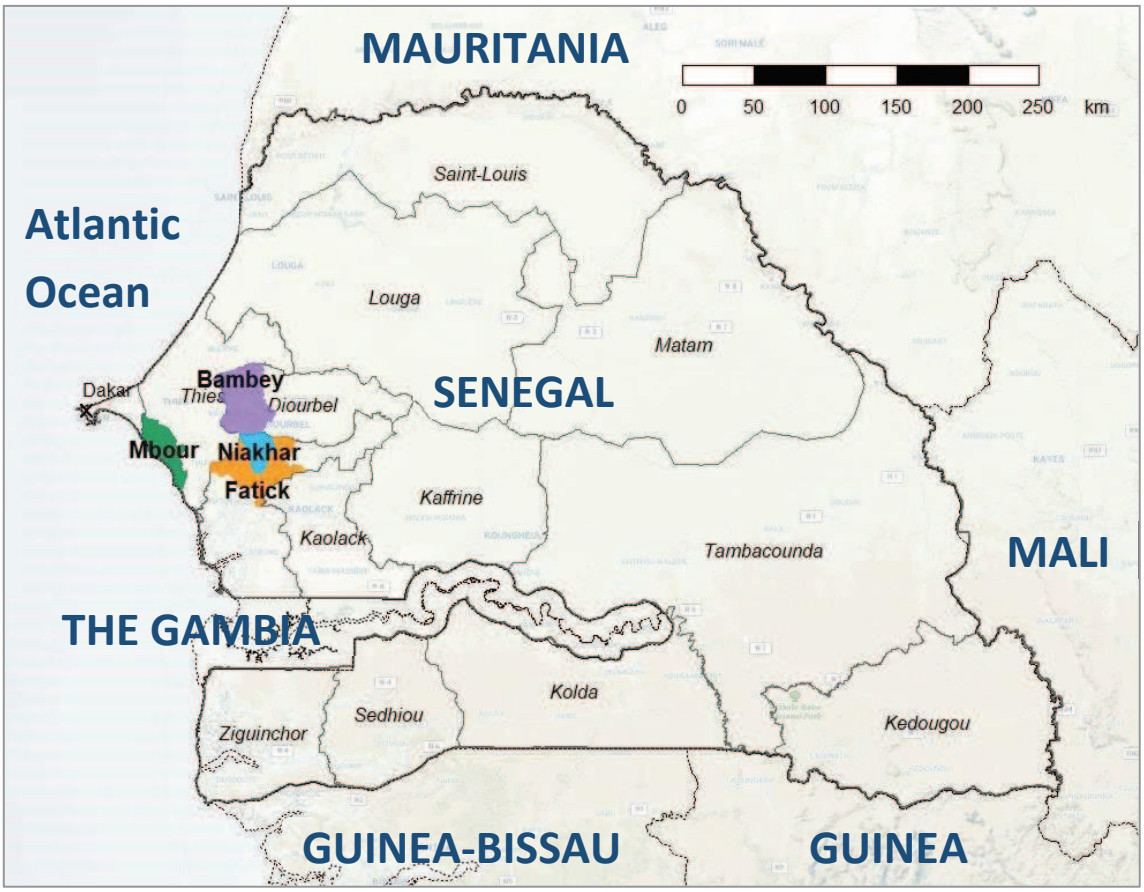
Malaria imposes a substantial economic burden on households, health systems, and countries. Households in endemic areas bear the direct costs of any preventive tools they purchase and of seeking treatment when ill, as well as the indirect costs of lost income and productivity when a member of the household falls ill or dies. Public health services – often with donor support – bear the costs of publicly-provided preventive activities, such as bed net distribution or indoor residual spraying (IRS) campaigns, as well as the costs of providing treatment through public facilities with health service staff and other resources. Malaria has been shown to have negative effects on child development (Fink et al., 2013, Holding and Snow, 2001, Klejnstrup et al., 2018), the quality of the labour force (Arrow et al., 2004, Cole and Neumayer, 2006), and foreign investment (Azemar and Desbordes, 2009), all of which are thought to contribute to reductions in overall economic growth – once estimated at 1% per year (Gallup and Sachs, 2001) – and in turn reduce the tax base for public services.

The epidemiology of malaria has shifted in recent years, with some countries eliminating malaria, others recording dramatic declines in malaria incidence, and a remainder continuing to face a very high (and in some cases, growing) burden (WHO, 2019d). In Senegal, malaria incidence has decreased dramatically in the last twenty years and malaria now ranks as only the 10th most common cause of death nationally (GBD Collaborative Network, 2018, PNLP., 2018). IHME estimates indicate a monotonic decline from 210 cases per 1,000 person-years at risk in 2000 to 116 in 2005, 99 in 2010, 64 in 2015, and 44 in 2017 (GBD Collaborative Network, 2018). Throughout the country, as in countries across the Sahel, malaria is highly seasonal, with most cases occurring in a three- to four-month period beginning just after the start of the

annual rainy season, and peaking in October or November. As across West Africa, virtually all cases in Senegal are attributable to the plasmodium falciparum species of the parasite (WHO, 2019d).

Within Senegal, malaria transmission is also highly heterogeneous. The north and west of the country, including Dakar, are the driest parts of the country and have consistently had the lowest malaria incidence (PNLP, 2014) (Figure 1). The south of Senegal, which surrounds Gambia and borders Guinea-Bissau, Guinea, and Mali, is the poorest and most remote area of the country and has the highest rainfall and malaria incidence, which has seasonal peaks but is year-round. The centre of the country, where the two economic evaluations were conducted, averages slightly higher malaria incidence and prevalence than the north and west, but with substantial local-level variation, especially in recent years, when overall incidence and prevalence have been generally low. On various social, economic, and other health indicators, the population of the study districts tends to be somewhat worse off than those in the north and west, but better off than the south (ANSD and ICF, 2018). Malaria incidence and

Figure 1 The four health districts involved in both economic evaluations: Mbour, Bambey, Fatick, and Niahkar
The map presents Senegal with its 14 regions (in beige) and the four health districts (in bright colours) in which the evaluations were conducted.



prevalence are lower, on average, in urban areas, while a wide range of socio-demographic variables indicate generally worse living conditions and health status in rural areas (ANSD and ICF, 2018).

Both trials were undertaken in the four health districts of Niakhar, Fatick, Bambey, and Mbour.(Figure 1), where malaria has declined substantially in the last twenty years (Trape et al., 2012). In Niakhar, a demographic surveillance system (DSS) – the oldest in Africa – provides longterm data on morbidity and mortality and has facilitated the conduct of numerous clinical trials (Trape et al., 2012). In a previous clinical trial of the efficacy of SMC in Niakhar in 2002, children under 5 in the reference arm averaged 2.3 malaria episodes each during the 13 weeks of follow-up in the high transmission season (Cissé et al., 2006) (Figure 2). According to DSS estimates, the prevalence of malaria parasitaemia among children under 5 in Niakhar was estimated to have fallen from 31% in December 2003 to just 2% in December 2008. Malaria prevalence in children under 5 was similarly low at 5.1% (2.3% - 7.9%) in December 2008 across the control areas of the SMC study – which included zones of Niakhar and the other three health districts (Cissé et al., 2016). In the Niakhar DSS, the rate of child deaths from malaria fell from 10.5 per 1000 person-years in 2000-3, to 7.6 in 2004-5, 6.6 in 2006-7, and 2.0 in 2008-10, when the SMC effectiveness trial was conducted (Trape et al., 2012). Reasons for the dramatic 81% decline in child malaria mortality are thought to include the mass distribution of long-lasting insecticide-treated bed nets (LLINs), and the introduction of both rapid diagnostic tests (RDTs) and artemisinin combination therapies (ACTs), as well as climatic and other factors (Trape et al., 2012).

3.3. Malaria financing

To respond to the immense global burden of malaria, both endemic country governments and international donors have invested substantially in tackling malaria in recent years. In 2018, their contributions amounted to $0.9b and $1.8b, respectively (WHO, 2019d). While this combined $2.7b investment fell substantially short of the $5.0b estimated to be needed to meet global targets, the $1.8b donor contribution to malaria remained one of the largest areas of global health investment (OECD, 2019). In the decade to 2010, donor funding for malaria increased dramatically (WHO, 2011b, OECD, 2019), but both donor and domestic financing has stagnated since, and future financing is uncertain (WHO, 2019d).

Figure 2 A Series of randomized controlled trials of malaria interventions in central Senegal

IRS: Indoor residual spraying; MDA: Mass drug administration; MSAT: Mass screening and treatment; SMC: Seasonal malaria chemoprevention.

Like many of its neighbours, Senegal's malaria programme is thus highly donor-dependent, which has important implications for policy making in Senegal and for understanding the global context in which resources for new malaria interventions are allocated. In Senegal in 2018, the National Malaria Control Programme reported expenditure of $4.9m from domestic government resources, and nearly ten times as much from donors, including the United States' President's Malaria Initiative (PMI, $24.0m), the Global Fund ($11.6m), and other bilateral donors ($11.6m) (WHO, 2019d). This ratio of (low) domestic government to (substantial) donor expenditure equalled the West African average. Over 2016-18, Senegal's combined donor and domestic malaria funding ranked 11th of the 17 countries in West Africa, at $2.6 per person at risk (WHO, 2019d). More of Senegal's donor funding for the health sector targeted malaria than any other health area over the period 2009-18 (OECD, 2020).

3.4. Economic evaluations of malaria interventions

To maximize the health impact of these investments, decision-makers must understand the relative efficiency of alternative intervention packages and prioritise interventions accordingly. In the period covered in the bibliometric analysis in Chapter 2 (Pitt et al., 2016a), malaria was the second most-frequently studied health area in cost-effectiveness analyses in lower-middle-income countries (behind HIV), and the third most-studied health area in low-income countries (behind HIV and maternal and neonatal conditions). White and colleagues' (2011) comprehensive review of both cost and cost-effectiveness studies of malaria interventions identified 55 and 43 studies, respectively (of which 33 overlapped). The studies evaluated distribution of insecticide-treated bed nets, IRS, intermittent preventive treatment of malaria in infants (IPTi) and in pregnancy (IPTp), seasonal malaria chemoprevention (SMC), diagnosis, and treatment of uncomplicated and complicated cases. An update of White and colleague's review for the Disease Control Priorities project identified 83 cost and 64 cost-effectiveness studies up to 1 April 2015 (Levin and Brouwer, 2015, Brouwer et al., 2015). More recently, a systematic review of cost-effectiveness analyses of malaria interventions that used DALYs as the effectiveness metric identified 40 studies published between 1996 and 1 June 2016 (Gunda and Chimbari, 2017).

These reviews found that "[all] of the major preventive interventions and ACT treatment were consistently cost-effective against a threshold of $150 per DALY averted" (White et al., 2011), and that "most interventions proved cost-effective" (Gunda and Chimbari, 2017). The DCP3

synthesis argued that "[the] cost of malaria control interventions is relatively low in all countries, but varies widely" and that "[most] of the studies available indicate rather low cost-effectiveness ratios" (Tediosi et al., 2017). The reviews criticized the inconsistent methodological quality – as did a methodological review of transmission dynamic economic evaluations (Drake et al., 2016) – to which they attributed some of the variability in estimates.

The malaria cost and cost-effectiveness literature is thus relatively large compared with economic evaluation literatures for other health areas in LLMICs (except HIV), but small relative to the diversity of countries and contexts with ongoing risk of malaria and the global resources invested in tackling malaria. Further, the growing resistance to insecticides (Hancock et al., 2020) and antimalarials (Uwimana et al., 2020), the wide range of new interventions and possible combinations of interventions now available or emerging (Kyrou et al., 2018, Tusting et al., 2017, Protopopoff et al., 2018, Rogier et al., 2019), and the plateau and uncertainty in future funding create new contexts and policy options requiring new economic evidence to inform decision-making.

Within each of the two economic evaluations in this thesis, the most relevant economic evaluation literature is reviewed and used both to inform the analysis and to contextualize the findings. For both economic evaluations, the relevant empirical literature extends beyond malaria to include interventions for other health conditions involving similar delivery systems.

3.5. Two malaria intervention trials in central Senegal

The two economic evaluations presented in Chapters 4 and 5 were conducted alongside consecutive cluster-randomized, controlled trials (Figure 2**Error! Reference source not found.**). Both trials were designed to assess interventions involving door-to-door mass administration of malaria drugs by an existing cadre of community health workers (CHWs). The different strategies evaluated in the two trials reflected the area's changing malaria epidemiology, as well as changes in the policy context. In 2002, an individually-randomized efficacy trial was conducted in 11 villages in central Senegal; it made the breakthrough finding that SMC (called "seasonal intermittent preventive treatment" at the time) led to an 86% (95% Confidence Interval: 80%, 90%) reduction in episodes of clinical malaria (Cissé et al., 2006). This dramatic result spurred further trials elsewhere in West Africa (Wilson, 2011) and efforts to understand the safety, feasibility, and effectiveness of large-scale, routine implementation of SMC. A large-

scale effectiveness trial of SMC evaluated door-to-door administration of a full treatment course of antimalarial drugs to all children in the intervention areas (with a few small exceptions), regardless of parasite burden or symptoms, at monthly intervals for three months. The first economic evaluation included in this thesis (presented in Chapter 4) was conducted alongside the final year of this step-wedge trial in 2010, when SMC was delivered to approximately 180,000 children under 10. In 2012, WHO recommended SMC for children under 5 in areas of highly seasonal transmission in the Sahel (WHO, 2012), informed in part by evidence from the large-scale SMC trial and associated economic evaluation. The evaluation may also inform future deliberations of the WHO Malaria Policy Advisory Committee (WHO, 2020b) on whether to recommend expansion of the age range for SMC, as it remains the only evaluation to date of SMC in children up to age 10.

The second economic evaluation included in this thesis is presented in Chapter 5 (**Error! Reference source not found.**). The economic evaluation was conducted alongside a three-arm cluster-randomized trial which sought to assess the effectiveness of implementing IRS and either mass drug administration (MDA) or mass screening and treatment (MSAT) in higher incidence (or "hotspot") villages in reducing malaria incidence compared to a reference strategy, which very closely resembled standard malaria control measures in the area. Unlike SMC, these interventions encompassed all age groups, but were targeted at hotspot villages within the study area. The intervention packages thus involved combinations of four different main interventions: classification of hotspot and non-hotspot villages; house-to-house visits to spray insecticide on the interior walls of all consenting households in hotspot villages; and either door-to-door delivery of MDA to people of all ages in the hotspot villages or door-to-door delivery of mass screening (with a rapid diagnostic test) and treatment of those with positive test results by CHWs. The hotspot strategies were implemented in a population of approximately 444,000 people of whom approximately 239,000 lived in villages designated as hotspots in 2014 and were therefore targeted to receive IRS and either MDA or MSAT. The hypothesis was that implementing such a combination of chemotherapy and vector control in hotspot villages could reduce malaria incidence both in hotspot and non-hotspot villages, and in doing so, "virtually eliminate" malaria in the intervention arms, across both hotspot and non-hotspot villages.

The decision to conduct the hotspot trial (Figure 2) and associated economic evaluation reflected changes in the local epidemiology and in the wider policy context. In the early 2000s, much of the malaria world was deeply sceptical about MDA for malaria, which for many

recalled the failures of the Global Malaria Eradication Programme of the 1950s and raised fears of resistance to antimalarials (WHO Evidence Review Group, 2015a, Cissé et al., 2006). However, with the intensification of the push to eliminate malaria by "shrinking the malaria map" (Feachem et al., 2010) – i.e. seeking to eliminate malaria first outside of and on the periphery of Africa – new, intensified control efforts were increasingly considered plausible global policy options. By 2015, WHO had convened an evidence review group on MDA, MSAT, and focal screening and treatment (FSAT) (WHO Evidence Review Group, 2015a). Evidence review groups are time-limited expert groups tasked with reviewing a specific area of work and providing "evidence-based information and options for recommendations" to the Malaria Policy Advisory Committee (WHO, 2020a), an "independent advisory group bringing together the world's foremost experts on malaria . . . [to provide] strategic technical guidance to WHO Director-General" (WHO, 2020c). Both MSAT and MDA were thus receiving serious consideration for global policy.

3.6. Methods overview

The economic evaluation of SMC (Figure 2) was designed to respond to the WHO's Global Malaria Program's concerns at the time regarding the affordability of SMC, rather than its cost-effectiveness. A dramatic drop in malaria incidence across the study area in 2009 had also led researchers to expect at the start of the third year of the trial, when the cost data collection was conducted, that the trial would be underpowered to detect an effect of SMC on malaria incidence, and that a cost-effectiveness analysis would not be meaningful or useful. I therefore led in-depth cost data collection and analysis aimed at understanding variation in the cost per course of SMC delivered. Guidelines on improving the transferability of economic evaluation evidence at the time recommended statistical analysis of heterogeneity within a trial as a means of improving transferability of findings outside of a trial (Sculpher et al., 2004, Drummond et al., 2005). Through careful collection and disaggregation of the costs of delivering SMC, I was able to generate a dataset of the costs of SMC delivery for each of the 46 health posts implementing SMC. This dataset was large compared with other such datasets of costs by facility, but small compared with the number of variables that we hypothesized could explain the variation in costs across facilities. Using econometric approaches, as recommended (Sculpher et al., 2004, Drummond et al., 2005), I found that the size of the catchment area alone – i.e. the local scale of delivery – explained most of the variation in average costs across

this set of facilities. This finding led me to explore other approaches to understanding cost variation, which could exploit the in-depth understanding we had gained of cost drivers and how the intervention worked in practice. In this analysis of SMC, I began by simply disaggregating costs by administration round and by whether they could be expected to vary with the number of districts, health posts, CHWs, or children involved in the administration. In the following economic evaluation, described below, I developed this mechanistic approach to understanding and predicting cost variation more fully.

The economic evaluation of geographically targeted strategies in malaria hotspots (Figure 2) built on and extended the analysis of SMC. Firstly, the cost data collection processes and tools from the SMC costing were re-used with minor adaptations for MDA, MSAT, IRS, and the identification of malaria hotspot villages. Secondly, I extended what was done in the SMC analysis by developing a mechanistic cost model, which I used to estimate how intervention costs would vary if the interventions were implemented in the entire study area or with changes to the interventions. The modelled costs were used in a cost-effectiveness analysis in which I modelled the incremental cost-effectiveness of 7 intervention packages relative to one another. Work on the economic evaluations of SMC and of the hotspot strategies informed the development of new guidance to promote the design and analysis of economic evaluations in ways that promote transferability, presented in Chapter 6.

In both economic evaluations, I assess incremental costs – that is, the difference in costs between two clearly defined comparators – and carefully distinguish between financial and economic costs, as recommended by key guidelines (Vassall et al., 2017). Financial costs reflect payments, and are therefore important for assessing affordability or "budget impact". While there are no strict thresholds for assessing affordability, comparing the financial costs of an intervention with the size of relevant budgets can give a useful indication of the extent of additional resource mobilisation that would be required or the proportion of existing activities that would need to be displaced to implement the intervention. Financial costs exclude donated resources, such as volunteers' time, or the repurposing of existing resources – such as infrastructure or staff time – where no additional payments are made. They also reflect the time point at which a cost is incurred, which is important for interventions requiring substantial up-front payments. Economic costs reflect the full opportunity cost of all resources used, that is, their value in the next-best alternative use. Economic costs thus include the value of both paid-for and donated resources, making them the appropriate metric for assessing economic and allocative efficiency.

3.7. References for Chapter 3

ANSD & ICF 2018. Senegal: Enquête Démographique et de Santé Continue (EDS-Continue) 2017. Rockville, Maryland, USA: Agence Nationale de la Statistique et de la Démographie (Sénégal) and ICF.

ARROW, K. J., PANOSIAN, C. & GELBAND, H. 2004. Chapter 7. The Human and Economic Burden of Malaria. *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance.* Washington (DC): National Academies Press.

AZEMAR, C. & DESBORDES, R. 2009. Public Governance, Health and Foreign Direct Investment in Sub-Saharan Africa. *Journal of African Economies,* 18**,** 667-709.

BARAT, L. M., PALMER, N., BASU, S., WORRALL, E., HANSON, K. & MILLS, A. 2004. Do malaria control interventions reach the poor? A view through the equity lens. *American Journal of Tropical Medicine and Hygiene,* 71**,** 174-178.

BROUWER, E., LEVIN, C. & FRARE-DAVIS, J. 2015. Literature review data of cost-effectiveness ratios regarding the prevention, diagnosis, and treatment of malaria in LMICs from 2000-2015 from a provider perspective. *Disease Control Priorities.* Third ed.

CISSÉ, B., BA, E. H., SOKHNA, C., JL, N. D., GOMIS, J. F., DIAL, Y., PITT, C., M, N. D., CAIRNS, M., FAYE, E., M, N. D., LO, A., TINE, R., FAYE, S., FAYE, B., SY, O., KONATE, L., KOUEVIJDIN, E., FLACH, C., FAYE, O., TRAPE, J. F., SUTHERLAND, C., FALL, F. B., THIOR, P. M., FAYE, O. K., GREENWOOD, B., GAYE, O. & MILLIGAN, P. 2016. Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial. *PLoS Med,* 13**,** e1002175.

CISSÉ, B., SOKHNA, C., BOULANGER, D., MILET, J., BA, E. H., RICHARDSON, K., HALLETT, R., SUTHERLAND, C., SIMONDON, K., SIMONDON, F., ALEXANDER, N., GAYE, O., TARGETT, G., LINES, J., GREENWOOD, B. & TRAPE, J.-F. 2006. Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial. *The Lancet,* 367**,** 659-667.

COLE, M. A. & NEUMAYER, E. 2006. The impact of poor health on total factor productivity. *Journal of Development Studies,* 42**,** 918-938.

DE GLANVILLE, W. A., THOMAS, L. F., COOK, E. A. J., BRONSVOORT, B. M. D. C., WAMAE, N. C., KARIUKI, S. & FÈVRE, E. M. 2019. Household socio-economic position and individual infectious disease risk in rural Kenya. *Scientific Reports,* 9**,** 2972.

DEGAREGE, A., FENNIE, K., DEGAREGE, D., CHENNUPATI, S. & MADHIVANAN, P. 2019. Improving socioeconomic status may reduce the burden of malaria in sub Saharan Africa: A systematic review and meta-analysis. *PloS one,* 14**,** e0211205-e0211205.

DRAKE, T. L., DEVINE, A., YEUNG, S., DAY, N. P., WHITE, L. J. & LUBELL, Y. 2016. Dynamic Transmission Economic Evaluation of Infectious Disease Interventions in Low- and Middle-Income Countries: A Systematic Literature Review. *Health Econ,* 25 Suppl 1**,** 124-39.

DRUMMOND, M., MANCA, A. & SCULPHER, M. 2005. Increasing the generalizability of economic evaluations: Recommendations for the design, analysis, and reporting of studies. *International Journal of Technology Assessment in Health Care,* 21**,** 165-171.

EL BCHERAOUI, C., MIMCHE, H., MIANGOTAR, Y., KRISH, V. S., ZIEGEWEID, F., KROHN, K. J., EKAT, M. H., NANSSEU, J. R., DIMBUENE, Z. T., OLSEN, H. E., TINE, R. C. K., ODELL, C. M., TROEGER, C. E., KASSEBAUM, N. J., FARAG, T., HAY, S. I. & MOKDAD, A. H. 2020. Burden of disease in francophone Africa, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Global Health,* 8**,** e341-e351.

FEACHEM, R. G., PHILLIPS, A. A., HWANG, J., COTTER, C., WIELGOSZ, B., GREENWOOD, B. M., SABOT, O., RODRIGUEZ, M. H., ABEYASINGHE, R. R., GHEBREYESUS, T. A. & SNOW, R. W. 2010. Shrinking the malaria map: progress and prospects. *Lancet,* 376**,** 1566-78.

FINK, G., OLGIATI, A., HAWELA, M., MILLER, J. M. & MATAFWALI, B. 2013. Association between early childhood exposure to malaria and children's pre-school development: evidence from the Zambia early childhood development project. *Malar J,* 12**,** 12.

GALLUP, J. L. & SACHS, J. D. 2001. The economic burden of malaria. *Am J Trop Med Hyg,* 64(1-2 Suppl)**,** 85-96.

GBD COLLABORATIVE NETWORK 2018. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME).

GUNDA, R. & CHIMBARI, M. J. 2017. Cost-effectiveness analysis of malaria interventions using disability adjusted life years: a systematic review. *Cost Eff Resour Alloc,* 15**,** 10.

HANCOCK, P. A., HENDRIKS, C. J. M., TANGENA, J.-A., GIBSON, H., HEMINGWAY, J., COLEMAN, M., GETHING, P. W., CAMERON, E., BHATT, S. & MOYES, C. L. 2020. Mapping trends in insecticide resistance phenotypes in African malaria vectors. *PLOS Biology,* 18**,** e3000633.

HOLDING, P. A. & SNOW, R. W. 2001. Impact of Plasmodium falciparum malaria on performance and learning: review of the evidence. *Am J Trop Med Hyg,* 64**,** 68-75.

KLEJNSTRUP, N. R., BUHL-WIGGERS, J., JONES, S. & RAND, J. 2018. Early life malaria exposure and academic performance. *PLoS One,* 13**,** e0199542.

KYROU, K., HAMMOND, A. M., GALIZI, R., KRANJC, N., BURT, A., BEAGHTON, A. K., NOLAN, T. & CRISANTI, A. 2018. A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. *Nature Biotechnology,* 36**,** 1062-1066.

LEVIN, C. & BROUWER, E. 2015. Literature review data of the costs of preventing, diagnosing, and treating malaria. *Disease Control Priorities.* Third ed.

OECD 2019. Creditor Reporting System. Paris, France: Organisation for Economic Co-operation and Development.

OECD 2020. Creditor Reporting System. Paris, France: Organisation for Economic Co-operation and Development.

PITT, C., GOODMAN, C. & HANSON, K. 2016a. Economic Evaluation in Global Perspective: A Bibliometric Analysis of the Recent Literature. *Health Econ,* 25 Suppl 1**,** 9-28.

PNLP 2014. Cadre Strategique National de Lutte Contre le Paludisme au Senegal, 2014-2018. Dakar, Senegal: Programme National de Lutte contre le Paludisme.

PNLP. 2018. Bulletin Epidemiologique Annuel 2017 du Paludisme au Senegal. Dakar: Programme National de Lutte contre le Paludisme, Ministere de la Sante et de l'Action Sociale.

PROTOPOPOFF, N., MOSHA, J. F., LUKOLE, E., CHARLWOOD, J. D., WRIGHT, A., MWALIMU, C. D., MANJURANO, A., MOSHA, F. W., KISINZA, W., KLEINSCHMIDT, I. & ROWLAND, M. 2018. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. *The Lancet,* 391**,** 1577-1588.

ROGIER, E., HAMRE, K. E. S., JOSEPH, V., PLUCINSKI, M. M., PRESUME, J., ROMILUS, I., MONDELUS, G., ELISME, T., VAN DEN HOOGEN, L., LEMOINE, J. F., DRAKELEY, C., ASHTON, R. A., CHANG, M. A., EXISTE, A., BONCY, J., STRESMAN, G., DRUETZ, T. & EISELE, T. P. 2019. Conventional and High-Sensitivity Malaria Rapid Diagnostic Test Performance in 2 Transmission Settings: Haiti 2017. *The Journal of Infectious Diseases,* 221**,** 786-795.

SCULPHER, M. J., PANG, F. S., MANCA, A., DRUMMOND, M. F., GOLDER, S., URDAHL, H., DAVIES, L. M. & EASTWOOD, A. 2004. Generalisability in economic evaluation studies in healthcare: A review and case studies. *Health Technology Assessment,* 8**,** iii-117.

TEDIOSI, F., LENGELER, C., CASTRO, M., SHRETTA, R., LEVIN, C., WELLS, T. & TANNER, M. 2017. Malaria Control. *In:* HOLMES, K. K., BERTOZZI, S., BLOOM, B. R. & JHA, P. (eds.) *Disease Control Priorities (third edition): Volume 6, Major Infectious Diseases.* Washington (DC).

TRAPE, J. F., SAUVAGE, C., NDIAYE, O., DOUILLOT, L., MARRA, A., DIALLO, A., CISSE, B., GREENWOOD, B., MILLIGAN, P., SOKHNA, C. & MOLEZ, J. F. 2012. New malaria-control policies and child mortality in senegal: reaching millennium development goal 4. *J Infect Dis,* 205**,** 672-9.

TUSTING, L. S., BOTTOMLEY, C., GIBSON, H., KLEINSCHMIDT, I., TATEM, A. J., LINDSAY, S. W. & GETHING, P. W. 2017. Housing Improvements and Malaria Risk in Sub-Saharan Africa: A Multi-Country Analysis of Survey Data. *PLoS medicine,* 14**,** e1002234-e1002234.

UWIMANA, A., LEGRAND, E., STOKES, B. H., NDIKUMANA, J.-L. M., WARSAME, M., UMULISA, N., NGAMIJE, D., MUNYANEZA, T., MAZARATI, J.-B., MUNGUTI, K., CAMPAGNE, P., CRISCUOLO, A., ARIEY, F., MURINDAHABI, M., RINGWALD, P., FIDOCK, D. A., MBITUYUMUREMYI, A. & MENARD, D. 2020. Emergence and clonal expansion of in vitro artemisinin-resistant Plasmodium falciparum kelch13 R561H mutant parasites in Rwanda. *Nature Medicine*.

VASSALL, A., SWEENEY, S., KAHN, J. G., GOMEZ, G. B., BOLLINGER, L., MARSEILLE, E., HERZEL, B., PLOSKY, W. D., CUNNAMA, L., SINANOVIC, E., BAUTISTA-ARREDONDO, S., GHCC TECHNICAL ADVISORY GROUP, GHCC STAKEHOLDER GROUP, HARRIS, K. & LEVIN, C. 2017. *Reference Case for Estimating the Costs of Global Health Services and Interventions* [Online]. Available: https://ghcosting.org/pages/standards/reference_case.

WHITE, M. T., CONTEH, L., CIBULSKIS, R. & GHANI, A. C. 2011. Costs and cost-effectiveness of malaria control interventions - a systematic review. *Malar J,* 10**,** 337.

WHO 2011b. World malaria report 2011. Geneva, Switzerland: World Health Organization.

WHO 2012. WHO Policy Recommendation: Seasonal Malaria Chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. March 2012. (in English and French). Geneva: World Health Organization.

WHO 2018a. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva: World Health Organization.

WHO 2018b. Global Health Estimates 2016: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva: World Health Organization.

WHO 2019d. World malaria report 2019. Geneva, Switzerland: World Health Organization.

WHO. 2020a. *Evidence review groups (ERGs)* [Online]. Geneva: World Health Organization. Available: https://www.who.int/malaria/mpac/evidencereviewgroups/en/ [Accessed 23 February 2020].

WHO. 2020b. *Malaria Policy Advisory Committee* [Online]. Geneva: World Health Organization. Available: https://www.who.int/malaria/mpac/en/ [Accessed 15 January 2020].

WHO. 2020c. *Malaria Policy Advisory Committee* [Online]. Geneva: World Health Organization. Available: https://www.who.int/malaria/mpac/background/en/ [Accessed 23 February 2020].

WHO & MCEE 2018. WHO-MCEE estimates for child causes of death, 2000-2017. Geneva: World Health Organization and Maternal Child Epidemiology Estimation.

WHO EVIDENCE REVIEW GROUP 2015a. Mass drug administration, mass screening and treatment and focal screening and treatment for malaria. Background document for Session 1. Meeting report, 20–22 April 2015. Geneva: World Health Organization.

WILSON, A. L. 2011. A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment of malaria in children (IPTc). *PLoS ONE,* 6**,** e16976.

Chapter 4. Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis

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Student ID Number	477122	**Title**	Ms
First Name(s)	Catherine Krown		
Surname/Family Name	Pitt		
Thesis Title	Promoting transferability: Insights from economic evaluations of public health interventions to tackle malaria in central Senegal		
Primary Supervisor	Kara Hanson		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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SECTION E

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Original Article

Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis

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Abstract

Seasonal Malaria Chemoprevention (SMC) is recommended for children under 5 in the Sahel and sub-Sahel. The burden in older children may justify extending the age range, as has been done effectively in Senegal. We examine costs of door-to-door SMC delivery to children up to 10 years by community health workers (CHWs). We analysed incremental financial and economic costs at district level and below from a health service perspective. We examined project accounts and prospectively collected data from 405 CHWs, 46 health posts, and 4 district headquarters by introducing questionnaires in advance and completing them after each monthly implementation round. Affordability was explored by comparing financial costs of SMC to relevant existing health expenditure levels. Costs were disaggregated by administration month and by health service level. We used linear regression models to identify factors associated with cost variation between health posts. The financial cost to administer SMC to 180 000 children over one malaria season, reaching ~93% of children with all three intended courses of SMC was $234 549 (constant 2010 USD) or $0.50 per monthly course administered. Excluding research–participation incentives, the financial cost was $0.32 per resident (all ages) in the catchment area, which is 1.2% of Senegal's general government expenditure on health per capita. Economic costs were 18.7% higher than financial costs at $278 922 or $0.59 per course administered and varied widely between health posts, from $0.38 to $2.74 per course administered. Substantial economies of scale across health posts were found, with the smallest health posts incurring highest average costs per monthly course administered. SMC for children up to 10 is likely to be affordable, particularly where it averts substantial curative care costs. Estimates of likely costs and cost-effectiveness of SMC in other contexts must account for variation in average costs across delivery months and health posts.

Keywords: Seasonal malaria chemoprevention (SMC), intermittent preventive treatment, malaria, cost function, cost variation, primary health care, community health workers, mass drug administration, campaigns, Sub-Saharan Africa

Key Messages

- Our estimates of the costs of SMC are lower than previous studies, which may be attributed to the wider age range (0–10 vs 0–5 years), much larger overall scale of delivery, and more limited involvement of researchers in implementation in our study.
- We observed substantial economies of scale in the size of the catchment area of health posts; the average cost curve was L-shaped, consistent with the limited existing empirical literature on provider costs.
- The financial costs of providing SMC for children under ten represent 12% of combined government and international spending on malaria in Senegal and 1.2% of Senegal's general government expenditure on health per capita, making SMC potentially affordable especially if it were to avert substantial curative care costs.

Introduction

In 2012, the World Health Organization (WHO) recommended Seasonal Malaria Chemoprevention (SMC) for children under 5 living in areas of the Sahel and sub-Sahel with highly seasonal malaria transmission (World Health Organization 2012). Previously known as intermittent preventive treatment of malaria in children (IPTc), SMC consists of providing a treatment dose of an effective antimalarial on a monthly basis for three or four consecutive months of the year in order to maintain therapeutic levels of antimalarial drugs during the period of greatest malaria risk. SMC with sulfadoxine pyrimethamine (SP) plus amodiaquine (AQ) is a highly efficacious intervention, which clinical trials showed to reduce the incidence of malaria by 75% or more amongst children under five who received it in areas of highly seasonal transmission (Bojang *et al.* 2011; Dicko *et al.* 2011; Konate *et al.* 2011; Sinclair *et al.* 2011; Wilson 2011). A large-scale, stepped-wedge, cluster-randomized trial in Senegal found that delivering SMC to children under 10 reduced malaria incidence by 60% (95% CI 54–64) amongst children under 10 and by 26% (95% CI 18–33) in adults and children older than 10 who did not receive SMC, through indirect effects (Cisse *et al.* 2016). Preliminary findings regarding feasibility, safety, effectiveness and costs from this large-scale study were requested and reviewed by WHO's Technical Expert Group on Preventive Chemotherapy in 2011 (World Health Organization/Global Malaria Program Technical Expert Group on Preventive Chemotherapy 2011), which subsequently recommended SMC.

Since the WHO recommendation, 12 countries have begun delivering SMC and 7 of these countries have been supported by a $67 m grant from UNITAID to expand access to SMC (Malaria Consortium 2016). While 11 of these countries provide SMC for children up to 5 years of age in accordance with the WHO recommendation, on the basis of the large-scale study findings, Senegal's policy since 2013 has been to provide SMC to children up to age 10. Policy makers and programme managers in other Sahel countries are considering whether to extend the recommended age range for SMC to address the increasing proportion of the malaria burden falling on older children.

As SMC requires repeated contacts with the health system outside the existing schedule of vaccinations and health campaigns, the feasibility and cost of reaching children in rural areas on a large scale have been important factors in deliberations on SMC (World Health Organization/Global Malaria Program Technical Expert Group on Preventive Chemotherapy 2011). Studies which examined potential delivery strategies concluded that community health workers (CHWs) need to play an important role in implementation (Kweku *et al.* 2009; Bojang *et al.* 2011; Patouillard *et al.* 2011). Economic evaluations were conducted alongside several SMC studies to explore which drug combinations and delivery strategies were most cost-effective (Conteh *et al.* 2010; Bojang *et al.* 2011; Patouillard *et al.* 2011), but these were relatively small-scale trials, which may overestimate both the costs and feasibility of implementing SMC at scale. Nonvignon *et al.* (2016) also examined the cost-effectiveness of SMC implementation with intensified household visits. As all economic evaluations published to date have been conducted amongst younger children, however, they do not directly address questions about whether to extend the recommended age range.

We provide an economic analysis of the costs of administering three monthly courses of SMC in 2010 to a population of over 180 000 children aged 3 months to 10 years in central Senegal in the context of the step-wedge trial previously described (Cisse *et al.* 2016). >93% of children in the target age range received all three intended monthly courses of treatment (Ba *et al.* 2017); delivery was highly equitable (Ba *et al.* 2017) and safe (N'Diaye *et al.* 2016) and reduced the prevalence of molecular markers of resistance to SMC drugs (Cisse *et al.* 2016). Extending the preliminary findings reviewed by WHO, we provide a comprehensive analysis of cost drivers, the distribution of costs across the 3 months of administration and across health system levels, variation in costs between health posts, and economies of scale. We aim to inform decisions on whether to extend the recommended age range for SMC and draw conclusions of wider relevance to the implementation of other large-scale health campaigns and the organization of the health system.

Methods

Study setting and design

Details of the step-wedge study design (Cisse *et al.* 2016) and study setting (Ba *et al.* 2017) are provided elsewhere. In brief, following two seasons of piloting in a neighbouring district, 54 rural and semi-urban public health post catchment areas in 4 districts (Bambey, Mbour, Fatick and Niakhar) were randomized to start implementing SMC in 2008 (9 catchment areas), 2009 (18 catchment areas) or 2010 (18 catchment areas). Cost data were collected in 2010, when 45 catchment areas (comprising 45 public health posts and 1 mission facility) implemented SMC.

Senegal was classified as a low-income country until 2011, and was reclassified as such in 2017 (World Bank 2017). In the implementation area, 32% of the population was under 10 years old (Cisse *et al.* 2016). The area's rainy season runs from July to early October and the climate is sudano-sahelian, leading to highly seasonal transmission. While the malaria burden had been very high, it had fallen by 2010, when malaria incidence in the study's control areas (confirmed by a rapid diagnostic test, RDT) was 4.3 cases per

thousand children under 5 and 10.0 cases per thousand children aged 5–10 (Cisse *et al.* 2016). In 2014, malaria continued to account for 5.0% of deaths in children under 5 and 3.4% of all deaths in Senegal (PNLP 2015).

SMC delivery strategy

The existing CHW network, which already delivered a variety of interventions including twice yearly Vitamin A and anthelminthic tablets for children under 5 through door-to-door strategies, was identified as most appropriate for SMC distribution. Under the supervision of the head nurse at each health post, CHWs travelled door-to-door on designated days in September, October, and November to administer the first dose of loose, crushable AQ and SP tablets each month to children aged 3–119 months and to provide AQ tablets for the child's caregiver to administer using the household's usual water supply on the subsequent 2 days. In 2010, implementation was organized primarily by the district health management teams (DHMTs).

The head nurse at each health post trained CHWs over the course of several hours on the day before administration in September, but did not repeat this full training in October and November. For CHWs who missed this initial training, informal, on-the-job training was provided, as is standard practice for campaigns. Each head nurse was responsible for organizing the hiring of CHWs and deciding the number of days they were hired for and their payment. Health posts received a lump sum to cover CHW incentive payments, based on the estimated number of CHWs needed and the estimated number of days work it would take the CHWs to cover the target population of the health post. Some nurses chose to divide the lump sum by the number of CHWs associated with their health post and pay CHWs a fixed amount, while others paid a daily rate (Ba *et al.* 2017).

Perspective and hierarchical boundaries

Detailed data on resource use associated with delivery of SMC were collected to estimate the incremental costs of implementing SMC at scale in 2010. All 45 government health posts that delivered SMC in 2010 were included, as was one mission health post which managed SMC delivery within a defined portion of the official catchment area of one of the 45 government health posts.

The study takes a health service perspective. The opportunity cost for households to participate in SMC is expected to be low as SMC is delivered door-to-door (Conteh *et al.* 2010).

Both financial and economic costs are included. Incremental financial costs reflect the additional funding needed to pay for the intervention. Incremental economic costs reflect the full value of the additional resources used to implement SMC, including those which did not incur an incremental financial cost to the health service, such as the time required of the district health team and health post staff, and items paid for by CHWs or other organizations. The economic value of individuals' time was calculated as a fraction of their salaries (including benefits) or, for CHWs, estimated earnings, assuming 220 working days per year and an average 7.5-h working day.

We focus on costs of implementation at the district level and below. Costs incurred only at national level, such as those associated with meetings amongst national-level representatives, are not included because they only concerned research; implementation questions were devolved to district managers. Nearly all the costs of implementation from the district level and below were considered recurrent, meaning that they would have to be repeated for each year of implementation. The only capital costs (resources that last over a year) associated with SMC implementation were those of the research team vehicles, which were used in a few instances to support the distribution of SMC drugs and supervision. Straight line depreciation of the purchase price of vehicles was used with a 5-year expected life of the vehicle (based on local usage) and an assumption of 220 working days per year to estimate the daily economic value of these vehicles, in addition to the financial costs of fuel.

Costs of research activities were generally excluded from the analysis. In two cases, however, costs associated with research activities were very likely to have contributed directly to the success of the administration and so they have been included and described in detail. First, all costs of the demographic surveillance system (DSS) set up to support the trial were excluded, however, some of the DSS fieldworkers and supervisors provided supervisory support on the administration days in September and October and transported some of the drugs; the costs of their time and of drivers and vehicles for these implementation activities have, therefore, been included under supervision and supply chain, respectively. As it is standard practice for districts and health posts to request the support of local organizations such as NGOs or research institutes for health campaigns, these costs are considered incremental economic costs, but not incremental financial costs to the Ministry of Health. Second, health staff at post, district, and regional levels received incentives for participation in the research. These incentives were paid over 12 months and were intended to support participation in research activities such as morbidity surveillance. While it is not anticipated that such incentives would be paid if SMC were implemented outside a research context, these incentives may have contributed to more assiduous implementation of SMC, and so they are also presented as a separate cost category.

Data collection

Tools were developed to collect data on costs and resource use at four levels: the project, the district, the health post, and the CHW. At the district, health post, and CHW levels, questionnaires were developed, introduced to all district medical officers, head nurses, and CHWs at the SMC planning meetings before administration began in 2010, and refined to incorporate their feedback. Trained fieldworkers collected data from all 4 districts and all 46 health posts following each round of administration in September, October, and November. They also administered questionnaires to a systematic sample of CHWs each month. In total, 405 CHW interviews were conducted, reflecting 48% of the average of 822 CHWs who administered SMC each month, or 13% of the CHW-months of administration. District and health post questionnaires and health post and CHW questionnaires covered similar questions regarding resource use, activities, and payments so that data could be triangulated. In addition, several key informant interviews were conducted with local field coordinators and CHWs to compare the per diems paid to CHWs with what they could otherwise have earned on the SMC administration days.

In November, three health posts in Bambey District combined administration of SMC with administration of Vitamin A and mebendazole. For these three posts, and in some cases for Bambey's district-level costs, the cost of delivering SMC alone in November was estimated based on the costs incurred in these health posts in October.

Data management and analysis

Questionnaire data were entered into an MS Access database. Consistency checks were performed to ensure data validity and data were exported to MS Excel for analysis. Data were carefully triangulated between sources to maximize accuracy and avoid double-counting. Costs are presented in United States Dollars (USD) based on the average 2010 exchange rate with the West African Franc (1 USD = 495 XOF(OANDA)).

Costs were summarized according to the categories presented in Table 1. These categories were identified to ensure comparability with previous studies of SMC (Conteh *et al.* 2010; Bojang *et al.* 2011) and to reflect the key cost centres. We present key cost drivers and examine several aspects of the cost structure and cost variation. To facilitate projections of how costs may vary if fewer or more monthly rounds of SMC were implemented, we disaggregated costs by the month in which they were incurred. To facilitate projections of how costs may vary with different scales of delivery and in different areas, we disaggregated costs by the health system level (district, health post, CHW, child) with which they would be expected to vary approximately linearly.

Costs are analysed with respect to several measures of output described in detail elsewhere (Ba *et al.* 2017) (Table 2). Estimates of the number of monthly courses administered were based on administrative data, which was triangulated from routine data in health post reports and administration registers. Estimates of the number of children in the target age range and all residents in the catchment area were based on the DSS. The number of children receiving SMC at least once and in all 3 months was estimated by applying survey

Table 1. Description of cost categories

Cost category	Description
SMC drugs	Reflects the cost of SP and AQ tablets supplied by National Pharmacy of Senegal and Kinapharma (Accra, Ghana), respectively and actually used or wasted during SMC administration, including the costs of importation to the Port of Dakar
Drug transport/supply chain	Reflects the cost of transporting drugs from Dakar to the districts (via a local storage site) by the research team, and from the districts to the health posts by district and health post staff. Additional economic costs include the value of time and of vehicles used by the research team, districts, and health posts
Drug administration (CHWs)	Includes the cost of payments of per diems to and transport for CHWs to come to the health post, retrieve drugs and registers, administer drugs to children, and return to the health post to return their reports and remaining drugs on each day of the administration. Additional economic costs include transport costs paid by the CHW and not reimbursed by the health facility
Supervision	Reflects the cost of incentive payments to a head nurse, assistant, and in some cases trainee at each health post; to each district health management team, region, and prefecture to supervise the implementation of SMC and to manage any side effects or refusals; and the costs of any transport used for this supervision. Additional economic costs include the value of time and transport for these health staff as well as the DSS supervisors and fieldworkers for the days on which they helped districts to supervise the administration
Training of CHWs	CHWs attended a single training day at their health post before administration in September. The payment of per diems, as well as the costs of any food or supplies provided or used during the training and any transport paid for by the health post or district are included as financial costs. Additional economic costs include the value of health staff time
Training of head nurses	Head nurses travelled to their district headquarters for a one-day training before administration in September. Costs were incurred for the per diems paid to the head nurses, their transport, and the food and supplies provided. Additional economic costs include the value of participants' time and of vehicles used
Meetings (evaluation & planning)	Prior to the training, head nurses attended one or more evaluation and planning meetings at their district during which they evaluated results of the SMC implementation in 2009 and outlined plans and budgets for implementation of SMC in 2010. Costs include per diems, transport, and any food or materials provided specifically for the meetings. Meetings were held for head nurses at district level and for district managers in Dakar and at one of the districts
Sensitization	Both districts and health posts arranged activities such as travelling caravans, radio announcements, and community meetings to promote awareness of SMC with regional or local authorities and within the community. Additional economic costs include the value of participants' time and vehicle use
Drugs for side effects	The costs of the small stock of drugs and medical supplies with which to manage potential adverse events provided to health posts were included regardless of the amount used, as these supplies would need to be provided in future as a precaution. In addition, head posts were reimbursed the cost of treating children whose parents reported side effects, in cases where the head nurse used medications other than those provided
Supplies	Supplies used in the administration included hats, t-shirts, and polo shirts with SMC sensitization messages and the MoH logo; registers of children and other monitoring tools; phone cards, etc. In addition, health posts also purchased some supplies themselves, such as pencils and erasers, to complement those provided by the district. Supplies purchased by CHWs are included as economic, rather than financial costs to the health service
Research participation incentives	Regional medical officers, district medical officers and their deputies, district supervisors, and head nurses all received quarterly incentive payments throughout the year to support research activities such as morbidity surveillance. The entire value of these payments over 12 months to the 3 regions, 4 districts, and 45 health posts that implemented SMC in 2010 are included, as they are likely to have contributed to more assiduous implementation of SMC in September, October, and November. It is not expected that this level of incentive payment would be repeated outside a research context

This table provides a detailed description of the cost categories used in the analysis. Where economic costs are greater than financial costs, the source of additional economic costs are mentioned explicitly.

estimates of the proportion of children receiving 0, 1, 2, or 3 courses of SMC to the administrative estimate of the number of monthly courses administered. The latter was a conservative approach yielding lower estimates of the number of children receiving SMC (and thus higher costs per course and per child) than applying survey estimates to the target population estimated in the DSS.

Affordability was explored by assessing the annual financial cost of SMC per person (all ages) resident in the catchment area as a proportion of three relevant, existing expenditure levels. These were: (1) average annual expenditure for malaria control and elimination per person at risk in Senegal (which includes both domestic expenditure on malaria prevention and treatment and donor funding earmarked for malaria control) in 2013–2015 (WHO Global Malaria Programme, 2016); (2) Senegal's general government expenditure on health per capita in 2014 (World Health Organization 2017) and (3) Senegal's total health expenditure per capita in 2014 (World Health Organization 2017). The most recent expenditure levels available are used to explore affordability relative to current funding, but are presented in constant 2010 USD to allow comparison with our cost estimates.

We sought to identify factors associated with variation between health posts in the average cost of SMC administration per course administered. We analysed average economic costs including research participation incentives with the district-level costs divided equally among the health posts within each district. We hypothesized that the following observed variables could be associated with cost variation across health posts: the number of courses administered (i.e. output or scale), coverage, geography of the catchment area (minimum, average, and maximum distances from health post to catchment villages; catchment area; number of catchment villages), and the number of years of experience (of the head nurse and, separately, at the health post) of delivering SMC (0, 1, or 2). Coverage estimates (the number of courses administered as a proportion of the target) were based on administrative, rather than survey data, because survey-based coverage estimates were not available for each health post (Ba *et al.* 2017). As our observations (health posts) were nested within a small number of clusters (districts), we fit a linear model with fixed effects at the district level (Möhring 2012) to account for this clustering. We used STATA 14. All independent variables were centred. Scatter plots of all pairwise variable combinations were used to assess the linearity of relationships; logarithmic transformations were performed on skewed data and a quadratic term was added for any independent variables exhibiting a curvilinear relationship with costs. Possible interactions between the number of courses administered, coverage, and catchment area were explored. We began with a full model containing all independent variables and interaction terms and sequentially removed the variable from the model with the highest *P*-value. Variables were retained in the model if they contributed to the fit of the model with $P < 0.05$, if removal substantially altered coefficients of other variables in the model, or if they were component variables of retained interaction or quadratic terms. Once a parsimonious model was reached, excluded variables were individually retested. Standard regression diagnostics were performed (Chen *et al.* 2003). Likelihood ratio tests were used to determine whether individual variables and groups of variables improved model fit. We also developed a more parsimonious model based on a more stringent criterion of $P < 0.0032$, which corresponds with a Bayes factor of 20 (Altman and Krzywinski 2017) (Supplementary Materials are available at *HEAPOL* online).

Results

Costs and affordability

The financial cost to administer SMC to a population of over 180 000 children aged 3 months to 10 years in four districts of Senegal over one malaria season, reaching an estimated 93% (95% CI 91–96) of children with all three monthly courses of SMC (Ba *et al.* 2017) was $234 549 (Table 3) or $0.50 per monthly course administered (Table 2). The economic costs were 19% higher at $278 922 or $0.59 per course administered. When the value of incentives intended for research is removed, the financial and economic costs fall by $43 424 to $0.41 and $0.50 per course administered, respectively. This financial cost of $0.41 per course administered excluding research participation incentives corresponds to $1.22 per child receiving all three scheduled courses, $1.06 per child of target age in the catchment area, and $0.32 per resident (all ages) in the catchment area (Table 2).

This cost per resident represented 1.2% of Senegal's general government expenditure on health per capita, 0.6% of total health expenditure per capita and 12% of combined government and international spending on malaria in Senegal (Supplementary Table S1 is available at *HEAPOL* online).

Table 2. Financial and economic cost of SMC per output

Denominator	Number	Cost of SMC per output (US$)			
		Financial		**Economic**	
		Excluding research incentives	Including research incentives	Excluding research incentives	Including research incentives
Monthly courses administered[a]	471,283	$0.41	$0.50	$0.50	$0.59
Children receiving SMC at least once[b]	157,654	$1.21	$1.49	$1.49	$1.77
Children receiving SMC in all three months[b] (i.e. "fully adherent")	156,311	$1.22	$1.50	$1.51	$1.78
Children of target age in the catchment area[c]	181,060	$1.06	$1.30	$1.30	$1.54
Residents (all ages) of the catchment area[c]	589,332	$0.32	$0.40	$0.40	$0.47

[a]Based on administrative data, which was triangulated from routine data in health post reports and administration registers (Ba *et al.* 2017).

[b]Generated by applying survey estimates of the proportion of children receiving 0, 1, 2, or 3 courses of SMC to the estimate of the number of monthly courses administered based on administrative data (Ba *et al.* 2017).

[c]Based on the DSS (Ba *et al.* 2017).

Table 3. Total financial and economic costs of SMC

	Financial costs			Economic costs		
	Total costs US$ (2010)	Cost profile		Total Costs US$(2010)	Cost profile	
		Including research incentives (%)	Excluding research incentives (%)		Including research incentives (%)	Excluding research incentives (%)
TOTAL *including research incentives*	**$234 549**	**100.0**	NA	**$278 922**	**100.0**	NA
TOTAL *excluding research incentives*	**$191 125**	NA	**100.0**	**$235 498**	NA	**100.0**
SMC drugs (SP+AQ)	$53 010	22.6	27.7	$53 010	19.0	22.5
Drug transport/supply chain	$425	0.2	0.2	$3266	1.2	1.4
Drug administration (CHWs)	$80 651	34.4	42.2	$80 651	28.9	34.2
Supervision	$25 156	10.7	13.2	$57 563	20.6	24.4
Training of CHWs	$6946	3.0	3.6	$8956	3.2	3.8
Training of head nurses	$2283	1.0	1.2	$3813	1.4	1.6
Meetings (evaluation & planning)	$2365	1.0	1.2	$3851	1.4	1.6
Sensitization	$2519	1.1	1.3	$2962	1.1	1.3
Drugs for side effects	$2491	1.1	1.3	$2491	0.9	1.1
Supplies	$15 279	6.5	8.0	$18 935	6.8	8.0
Research participation incentives	$43 424	18.5	NA	$43 424	15.6	NA

Table 4. Cost of activities by health system level and month of administration

Level	Financial costs					Economic costs				
	Sept (and earlier)	Oct	Nov	Total costs	Cost profile (%)	Sept (and earlier)	Oct	Nov	Total costs	Cost profile (%)
District	$7019	$4234	$5549	$16 801	8.8	$12 235	$7028	$7010	$26 274	11.2
Post	$22 456	$7311	$8809	$38 576	20.2	$37 521	$14 987	$15 416	$67 924	29.1
CHW	$6920	$16	$9	$6946	3.6	$6920	$16	$9	$6946	3.0
Child	$43 939	$42 506	$42 356	$128 802	67.4	$45 351	$43 632	$43 475	$132 457	56.7
Total	$80 334	$54 067	$56 723	$191 125	100.0	$102 027	$65 664	$65 910	$233 601	100.0
Cost profile (%)	42.0	28.3	29.7	100.0		43.7	28.1	28.2	100.0	

Costs are attributed to the lowest level with which they would be expected to increase linearly. For example, if the number of CHW were doubled, but all else held constant, the CHW-level costs would be expected to double while other levels would remain approximately constant. Similarly, adding an additional month to the campaign would add 28–30% to total costs, assuming that this additional month's campaign was conducted similarly to the October and November campaigns, rather than the September campaign, which incurred additional start-up costs, especially for meetings and trainings. Research participation incentives are excluded.

Cost drivers

The main cost drivers were door-to-door drug administration (42% of non-research financial costs) and SMC drugs (28% of non-research financial costs, Table 3). Per diems paid to CHWs accounted for most of the drug administration costs and 41% of total non-research financial costs (Supplementary Table S2 is available at *HEAPOL* online). AQ tablets alone accounted for 21% of non-research financial costs, while SP tablets accounted for 7%. Incentives paid to nurses and district staff for participation in the research study increased the financial costs of the intervention by 23% (from $191 049 to $234 462). While research incentives were intended to support data collection rather than implementation and are not normally provided for comparable distribution campaigns, they may have contributed to the high coverage levels achieved, as on average they represented a 7% increase in head nurses' annual salaries—or ∼15 days' pay assuming 220 days worked per year—and a > 10% increase in the salaries of district and regional staff (Supplementary Table S1 is available at *HEAPOL* online). Publicity campaigns and other sensitization activities played an important role in achieving high coverage (Ba *et al.* 2017), although they accounted for only 1% of financial and economic costs.

Economic costs were $43 945 greater than financial costs because they also included the value of the time MoH staff and others spent in meetings, trainings, travel and supervision (74% of the additional costs), as well as the economic value of vehicles used and the cost of supplies paid for by CHWs while implementing the intervention. Key informant interviews revealed that the payments made to CHWs (median: $7.49 per day, range $5.05–16.16) were comparable to or greater than the daily rate of pay for agricultural labour, similar to rates paid by non-governmental organizations (NGOs) for health activities, and somewhat higher than health districts pay for other mass campaigns. While the qualifications and opportunities amongst CHWs varied, many were illiterate and unskilled and others were secondary school students (Ba *et al.* 2017). In addition, distribution tended to begin on weekends to ensure both that families were at home and that CHWs would be available without taking them away from other activities (Ba *et al.* 2017). The economic value of CHW time spent implementing the intervention was therefore considered to be fully reflected in the financial costs of the payments made to them, and so no additional economic costs of CHW time were calculated.

Time allocation

Most CHWs worked in pairs, delivering SMC to a mean of 46 children per CHW per day at each health post (range 25–78) (Supplementary Table S3 is available at *HEAPOL* online). Some

CHWs assisted with administrative duties in the health post for some or all of the administration days and so administered few or no courses directly; hence, for individual CHWs who administered at least one course, the average number of courses administered per day varied more widely, from 2 to 169. Health posts employed from 4 to 68 CHWs and delivery each month took from 2 to 6 days per post. CHWs worked a mean of 7 h per day, but this varied from 1 to 12 h across CHWs and the average number of hours per day per CHW also varied substantially between health posts, from an average of just 4 h per day in one health post to an average of 10 h per day in another (Supplementary Table S3 is available at *HEAPOL* online). CHW time spent on SMC was only moderately (22%) higher in September (mean 665 cumulative CHW-hours per health post) than in each subsequent month (543 h) (Supplementary Table S4 is available at HEAPOL online). Head nurses spent a median of 75 cumulative hours on SMC over the 3 months (range 7–156), more than two-thirds of which was spent on the September round (Supplementary Table S4 is available at HEAPOL online).

Across the four districts, district medical officers spent a median 78 h (range 12–116) on SMC, while their deputies spent substantially less time (Supplementary Table S4 is available at HEAPOL online). District supervisors spent a median 209 h per district (range 42–376) on SMC. Supervisors and fieldworkers from the DSS supported supervision in September and October, spending the largest amount of time in the district whose supervisors and senior officers spent the least time on SMC. The additional time district and health post staff spent in September relative to the two subsequent months was largely spent in meetings and trainings at both the district and health post level. Several separate meetings/trainings on SMC were held at the districts involving head nurses in August and September; discussions of SMC did not appear to be combined in other district meetings.

Cost structure

The first of the three monthly SMC rounds accounted for 42% of financial costs (Table 4). Adding a fourth monthly SMC round would be expected to increase total costs by ~28–30%, assuming that the additional month's campaign were conducted similarly to the October and November campaigns.

Two-thirds of financial costs (67%) were expected to vary with the number of children, while 20% were expected to vary with the number of health posts (Table 5). Only 9% of financial costs were expected to vary with the number of districts, while <4% of costs were expected to vary with the number of CHWs. Thus, for example, if a new health post were created to serve half the catchment population of the largest health post in our study, we could assume

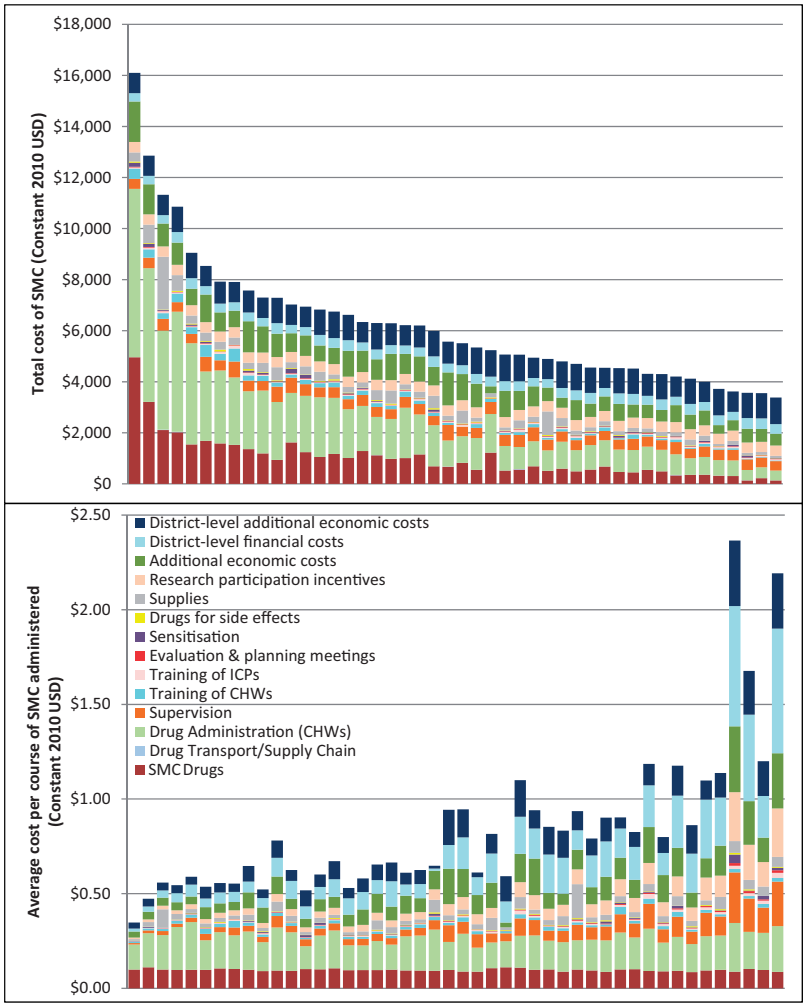

Figure 1. Total and average costs by health post with cost drivers. Health posts are ordered (left to right) in both graphs from largest to smallest total economic costs, including research participation incentives. District-level costs have been divided evenly across the health posts within each district. As total costs decrease, the average cost per course administered tends to increase, although there is some variation in this trend.

that the number of districts, CHWs and children in our analysis would remain constant, but the number of health posts (and thus the costs expected to vary with the number of health posts) would increase by 2% (1/46). Holding all else constant, the addition of this new health post could then be projected to increase the total financial costs of SMC implementation by 0.4%.

Cost variation and economies of scale across health posts

The total economic cost varied substantially across the 46 health posts, from $3223 to $15 946 when district-level costs were apportioned equally across health posts within each district and research participation incentives were included (Figures 1 and 2). Costs incurred only at the health post level and below varied from $1558 to $14 573. The average economic cost varied from $0.32 to $2.10 per course administered and from $0.30 to $1.38 when considering only costs incurred at the health post level and below (Supplementary Table S5 is available at *HEAPOL* online). The cost of SMC tablets and the cost of per diems for CHWs were relatively constant with respect to the number of courses administered (Figure 1). In contrast, the remaining significant cost centres, notably supervision, the additional economic value of health worker time, and the research participation incentives, were relatively fixed with respect to the number of health posts and thus account for most of the variation in average cost per course between health posts.

Average costs displayed a strong L-shape when plotted against the number of courses administered (Figure 3). In this sample, there was no evidence of a point at which health posts had such high levels of output that they displayed diseconomies of scale. Average costs increased steeply for health posts administering fewer than ~8000 courses of SMC (~10 000 residents), while above 10 000 courses (~12 500 residents), average costs declined, but more gradually (Figure 3). In exploring factors associated with this variation, we found that using the more stringent, Bayesian criterion of $P < 0.0032$ led to a parsimonious log–log model of average economic costs as a quadratic function of the number of courses administered (including fixed effects at the district level); this model described nearly all the

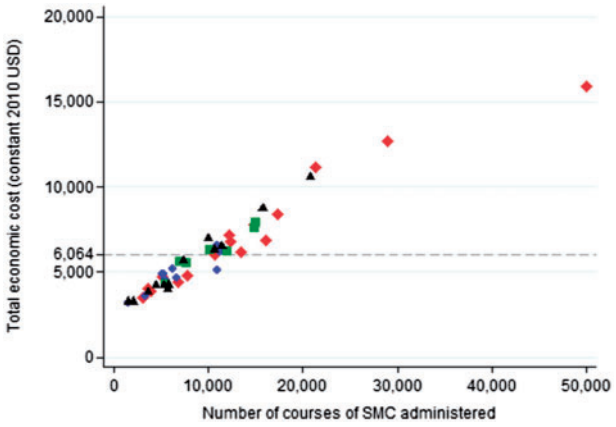

Figure 2. Total economic cost vs the number of courses administered at each health post. The figure illustrates the variation in the total costs incurred for SMC administration between health posts. Costs incurred at the district level are allocated equally across health posts in that district. Research participation incentives paid directly to head nurses and district health staff for trial participation are included as they are likely to have led to more assiduous implementation. The 46 health posts are presented with a different marker for each of the 4 districts. Dashed line: mean total economic cost per health post

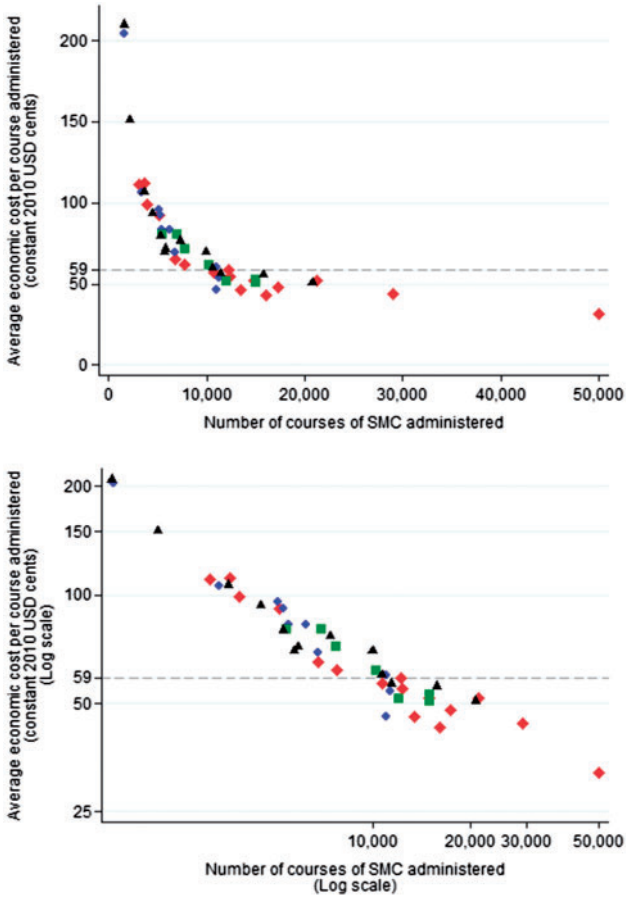

Figure 3. Economies of scale: average economic cost per course administered vs the number of courses administered at each health post. The figure illustrates the variation in the average economic cost per course of SMC administered between health posts. The upper figure presents data on a standard arithmetic scale and the lower figure illustrates the same data with both the x-axis and y-axis presented on a logarithmic scale. Costs incurred at the district level are allocated equally across health posts in that district. Research participation incentives paid directly to head nurses and district health staff for trial participation are included as they are likely to have led to more assiduous implementation. The 46 health posts are presented with a different marker for each of the 4 districts. Dashed line: mean economic cost per course administered across the entire implementation area.

variation in the data (adjusted $R^2 = 0.94$). The more traditional, frequentist threshold of $P < 0.05$ led to a more complex model (adjusted $R^2 = 0.95$), which also included variables for the interaction between coverage and size of catchment area and between size of catchment area and the logarithm of the number of courses, as well as the coverage and size of catchment area levels. While the likelihood ratio test indicated that this set of additional variables improved model fit ($P = 0.020$), the large number of variables relative to data points suggests that the more complex model may be overspecified. (Supplementary Table S6 are available at *HEAPOL* online)

Discussion

From an economic perspective, delivering SMC to children up to 10 years of age appears both affordable and sustainable, even within the highly constrained budgets of West African health systems and before accounting for savings from reductions in malaria cases. A cost-effectiveness analysis would provide further information on the

value-for-money of extending the recommended age range for SMC from children under 5 to children under 10 and on decisions regarding where to implement SMC. Two analyses of the cost-effectiveness of SMC in children under 5 have been based on findings from small-scale trials: one trial-based analysis used "cost per case averted" as its outcome metric (Conteh *et al.* 2010), making its findings difficult to compare across health conditions, while a later analysis employing a dynamic transmission model concluded that SMC in children under 5 is likely to be cost-effective or highly cost-effective relative to the arbitrary, but fairly conservative thresholds of $150 and $25 (1993 USD) per disability-adjusted life-year averted (Ross *et al.* 2011). A third analysis estimated the cost per case averted of SMC for children under 5 for a strategy requiring CHWs to visit each household on five consecutive days in each of four consecutive months (Nonvignon 2016). The cost-effectiveness of SMC in children under 10 is likely to be highly dependent on the coverage achieved and the age-specific incidence of malaria, both of which can be expected to vary significantly between countries, between regions within a country, and over time. We have shown that costs also vary substantially across health posts and across distribution rounds; this variation must also be considered in estimating the likely costs and cost-effectiveness of SMC in other settings. In disaggregating SMC costs by the health system level with which they are expected to vary, we offer a preliminary step towards taking cost variation into account in future estimates.

Our estimates are lower than those reported in previous analyses of SMC, which may be attributed to our study's extended age range, far larger target population, delivery strategy involving only one household visit per month, and more limited involvement of researchers in implementation. Previous studies of SMC examined the costs of delivery only to children up to 5 (or in one case 6) years of age (Conteh *et al.* 2010). In our study, increasing the age range for SMC from under-5s to under-10s virtually doubled the target population, however, it only increased the target number of households to visit by 13%, from 80 to 90% of all households in the area, and high coverage was maintained in both groups (Ba *et al.* 2017). However, the degree to which the lower costs we observed can be attributed to the extended age range rather than the far larger overall target population or other factors remains uncertain. Since our study, co-blister packs of dispersible SP+AQ have become available, which may increase tablet costs while potentially reducing CHW time on administration; these and any other changes to the distribution strategy would need to be accounted for in estimates of the likely costs of SMC in other settings.

While we have focussed on the cost per monthly course of SMC administered as our key outcome measure, other studies of the costs of SMC have reported the cost per "fully adherent child," defined as a child receiving all three (or more) intended courses of treatment. At $1.50 excluding research incentives (Table 2), the economic cost per fully adherent child in our study was lower than reported estimates from all other studies, and even somewhat lower than projections made of the likely costs of delivering SMC at scale. Inflating costs to 2010 USD to allow some comparison (Bureau of Labor Statistics 2013), the lowest previously reported cost per fully adherent child of a three-course SMC regimen was $1.66 using CHWs to deliver SP and AQ in Basse, Gambia (Bojang *et al.* 2011; Pitt *et al.* 2011). A study in trial conditions in Hohoe, Volta Region, Ghana reported the cost per fully adherent child of delivering three bimonthly courses of SP alone through CHWs at $8.30, but projected a cost of $1.74 if distribution were scaled up to the district level (Conteh *et al.* 2010; Pitt *et al.* 2011). In a wide-ranging overview of malaria control strategies, Goodman *et al.* (2000) estimated the cost of seasonal fortnightly chemoprevention with dapsone and pyrimethamine at $1.79 (90% range $1.40–2.20) using an existing CHW network, but requiring parents to take their children to the health centre. Estimates were substantially higher for the four-course strategies studied in Jasikan, Volta Region, Ghana (Patouillard *et al.* 2011; Pitt *et al.* 2011) and in Ghana's Upper West Region (Nonvignon 2016), and for the three- and six-course strategies employing artesunate (AS) with AQ in Hohoe (Conteh *et al.* 2010; Pitt *et al.* 2011). The "fully adherent child" metric includes the full cost of all the doses of SMC which were administered, but not the benefits derived by children who were protected from malaria with fewer than the intended number of courses of SMC. Given the highly mobile nature of populations both in the study area and in other areas where SMC is likely to be of benefit, children may have missed doses because they were away from the area and therefore either not exposed to malaria or potentially able to receive SMC elsewhere if it were more widely available (Ba *et al.* 2017).

Although the transferability of costs across contexts depends on many factors (Vassall *et al.* 2016), our financial cost estimate of $1.22 per fully adherent child ($1.50 including research participation incentives) is within the range of costs associated with delivering other malaria prevention interventions. A systematic review reported a median financial cost per year of protection with ITNs at $2.20 (range $0.88–9.54, constant 2009 USD), with IRS at $6.70 (range $2.22–12.85), with IPT in infants at $0.60 (range $0.48–1.08), and with IPT in pregnant women at $2.06 (range $0.47–3.36) (White *et al.* 2011). The financial cost of school-based IPT has been reported at $1.20 (constant 2006 USD) per child per year (Temperley *et al.* 2008) and school-based intermittent screening and treatment has been reported to cost $6.61 per child per year (constant 2010 USD) (Drake *et al.* 2011).

Our findings of substantial economies of scale represent an important contribution to a very limited evidence base on cost variation in health service delivery in low- and middle-income countries, particularly at the primary health care and community level and outside the HIV field (Brooker *et al.* 2008; Fiedler *et al.* 2014; Siapka *et al.* 2014). Consistent with previous studies of HIV prevention in India (Guinness *et al.* 2007; Lépine *et al.* 2015; Lépine *et al.* 2016) and of school-based albendazole distribution in Uganda (Brooker *et al.* 2008), we found that average costs exhibited an L-shape, and found no evidence in our sample of a point at which average costs would begin to increase, generating the U-shape predicted in economic theory. While our statistical analysis remains descriptive and was limited by the small number of data points and possibly by the trial context and other factors, the 46 health facilities we analysed constitute a relatively large dataset in the context of health facility costings. Our findings may be particularly relevant for other CHW mass distribution campaigns, such as deworming tablets and vitamin A, and for integrated community case management programmes, for example. They also have wider implications for the organization of the health system; many factors, such as accessibility, must be considered in deciding on the location and catchment size of health facilities, however, our findings demonstrate the substantially higher costs per person reached incurred by health posts with very small catchment areas.

Although appropriate to our study, the incremental nature of our analysis means that the existence of a functioning health system, including a network of CHWs, is assumed. In contexts where, for example, head nurses cannot easily call upon a group of CHWs for distribution campaigns, where the head nurses themselves are absent, or where districts lack the capacity to coordinate training and distribution of incentives, medicines, and materials, additional

resources would need to be invested to address or circumvent these gaps. In this way, SMC could provide an opportunity to strengthen health systems and especially CHW networks, but doing so would involve greater costs than reported here.

Furthermore, we have not included the costs of pharmacovigilance, ongoing programme evaluation, and national-level coordination, which are important aspects of SMC implementation and will need to be included in programme budgets. As in all such analyses, our data may also include errors or omissions, however, our extensive triangulation and comparisons across health facilities allowed us to correct discrepancies which might not have otherwise been detected. Nonetheless, collecting data on health worker time use, which accounted for most of the additional economic costs, is particularly challenging, and may have been subject to bias or misreporting.

Finally, while we adhered to standard practice in calculating the economic costs of health worker time based on their salaries, it is very unlikely that any health worker's salary represents their value to society, especially where they are so exceedingly scarce. Valuable health worker time should be used as efficiently as possible, taking into account the negative effects of nurses frequently absenting themselves from health posts to attend meetings at district level and to supervise CHWs in door-to-door campaigns. Strong national and district-level leadership is therefore required to bring together national child health and disease control teams to limit the total number of off-site training and campaign days each year. Similarly, the availability and supply of CHWs is not infinite. In our context, the value of incentive payments to CHWs were higher than what many CHWs could otherwise have earned, but that does not mean that they would necessarily continue to be willing to implement many more additional campaigns each year. Opportunities may exist to achieve economies of scope by combining SMC with delivery of other interventions, such as mass distribution of ITNs, health communication, or neglected tropical disease programmes; however, careful consideration and discussion with all levels of health workers will be required to ensure that additional interventions are genuinely compatible and do not cause diseconomies of scope by unduly increasing complexity.

Conclusion

Even in the context of a highly constrained health system, door-to-door delivery of SMC by CHWs to children under ten is likely to be affordable, especially if it averts substantial costs of curative care. We identified substantial variation in the cost of delivering SMC to children in Senegal, which contributes to a very limited evidence base on variation in provider costs. Both cost variation and the comparability of local health system characteristics must be accounted for in assessing the transferability of our findings to other settings.

Ethics statement

The trial protocol was approved by the Conseil National pour la Recherche en Santé, Senegal and the ethics committee of the London School of Hygiene & Tropical Medicine, UK. The trial is registered at www.clinicaltrials.gov: NCT 00712374.

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Conflict of interest statement. None declared.

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References

Altman N, Krzywinski M. 2017. Points of significance: interpreting P values. *Nature Methods* **14**: 213–4.

Ba EH, Pitt C, Dial Y *et al*. 2017. Implementation, coverage and equity of large-scale door-to-door delivery of seasonal malaria chemoprevention to children under 10 years of age in Senegal. [Working Paper].

Bojang KA, Akor F, Conteh L *et al*. 2011. Two strategies for the delivery of IPTc in an area of seasonal malaria transmission in the Gambia: a randomised controlled trial. *PLoS Medicine* **8**: e1000409.

Brooker S, Kabatereine NB, Fleming F, Devlin N. 2008. Cost and cost-effectiveness of nationwide school-based helminth control in Uganda: intra-country variation and effects of scaling-up. *Health Policy and Planning* **23**: 24–35.

Bureau of Labor Statistics. 2013. *Consumer Price Index Inflation Calculator*. http://www.bls.gov/data/inflation_calculator.htm. 4 April 2011

Chen X, Ender P, Mitchell M, Wells C. 2003. Regression diagnostics. *Regression with Stata*. http://stats.idre.ucla.edu/stata/webbooks/reg/chapter2/stata-webbooksregressionwith-statachapter-2-regression-diagnostics/.

Cisse B, Ba EH, Sokhna C *et al*. 2016. Effectiveness of seasonal malaria chemoprevention in children under ten years of age in Senegal: a Stepped-Wedge cluster-randomised trial. *PLoS Medicine* **13**: e1002175.

Conteh L, Patouillard E, Kweku M *et al*. 2010. Cost effectiveness of seasonal intermittent preventive treatment using amodiaquine & artesunate or sulphadoxine-pyrimethamine in Ghanaian children. *PLoS ONE* **5**: e12223.

Dicko A, Diallo AI, Tembine I *et al*. 2011. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Mali: a randomised, double-blind, placebo-controlled trial. *PLoS Medicine* **8**: e1000407.

Drake TL, Okello G, Njagi K *et al*. 2011. Cost analysis of school-based intermittent screening and treatment of malaria in Kenya. *Malaria Journal* **10**: 273.

Fiedler JL, Mubanga F, Siamusantu W *et al*. 2014. Child Health Week in Zambia: costs, efficiency, coverage and a reassessment of need. *Health Policy and Planning* **29**: 12–29.

Goodman C, Coleman PG, Mills AJ. 2000. *Economic Analysis of Malaria Control in Sub-Saharan Africa*. Geneva: Global Forum for Health Research, World Health Organization.

Guinness L, Kumaranayake L, Hanson K. 2007. A cost function for HIV prevention services: is there a 'u'—shape? *Cost Effectiveness and Resource Allocation* **5**: 13.

Konate AT, Yaro JB, Ouedraogo AZ *et al*. 2011. Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Burkina Faso: a randomised, double-blind, placebo-controlled trial. *PLoS Medicine* **8**: e1000408.

Kweku M, Webster J, Adjuik M *et al*. 2009. Options for the delivery of intermittent preventive treatment for malaria to children: a community randomised trial. *PLoS ONE* **4**: e7256.

Lépine A, Chandrashekar S, Shetty G *et al*. 2016. What determines HIV prevention costs at scale? Evidence from the Avahan programme in India. *Health Economics* **25**: 67–82.

Lépine A, Vassall A, Chandrashekar S, Blanc E, Le Nestour A. 2015. Estimating unbiased economies of scale of HIV prevention projects: a case study of Avahan. *Social Science and Medicine* **131**: 164–72.

Malaria Consortium. 2016. *Projects: ACCESS-SMC*. http://www.malariaconsortium.org/what-we-do/projects/41/access-smc, accessed 11 July 2016.

Möhring K. 2012. *The Fixed Effect as an Alternative to Multilevel Analysis for Cross-National Analyses*. Cologne: University of Cologne (GK Soclife working paper 16).

N'Diaye JL, Cisse B, Ba EH *et al*. 2016. Safety of seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine when delivered to children under 10 years of age by district health services in Senegal: results from a Stepped-Wedge cluster randomized trial. *PLoS ONE* **11**: e0162563.

Nonvignon J, Aryeetey GC, Issah S *et al*. 2016. Cost-effectiveness of seasonal malaria chemoprevention in upper west region of Ghana. *Malaria Journal* **15**: 367. DOI: 10.1186/s12936-016-1418-z

OANDA. *Historic Currency Converter*. http://www.oanda.com/convert/fxhistory, accessed 1 September 2012.

Patouillard E, Conteh L, Webster J *et al*. 2011. Coverage, adherence and costs of intermittent preventive treatment of malaria in children employing different delivery strategies in Jasikan, Ghana. *PLoS ONE* **6**: e24871.

Pitt C, N'Diaye M, Patouillard EPM, Conteh L. 2011. Economic Report for the WHO Technical Expert Group Meeting on Intermittent Preventive Treatment of Malaria in Children.

PNLP. 2015. *Bulletin epidemiologique annuel 2014 du plaudisme au Senegal*. Programme Nationale de Lutte Contre le Paludisme. http://www.pnlp.sn/telechargements/Rapports/BULLETIN-EPIDEMIOLOGIQUE-ANNUEL-2014-DU-PALUDISME-AU-SENEGAL.pdf, accessed 5 August 2016.

Ross A, Maire N, Sicuri E, Smith T, Conteh L. 2011. Determinants of the cost-effectiveness of intermittent preventive treatment for malaria in infants and children. *PLoS ONE* **6**: e18391.

Siapka M, Remme M, Obure CD *et al*. 2014. Is there scope for cost savings and efficiency gains in HIV services? A systematic review of the evidence from low- and middle-income countries. *Bulletin of the World Health Organization* **92**: 499–511AD.

Sinclair D, Meremikwu M, and Garner P. 2011. Seasonal Malaria Chemoprevention fo preventing malaria morbidity in children aged less than 5 years living in areas of marked seasonal transmission: GRADE tables to assist guideline development and recommendations. Background document for inaugural MPAC meeting.

Temperley M, Mueller DH, Njagi JK *et al*. 2008. Costs and cost-effectiveness of delivering intermittent preventive treatment through schools in western Kenya. *Malaria Journal* **7**: 196.

Vassall A, Mangham-Jefferies L, Gomez GB, Pitt C, Foster N. 2016. Incorporating demand and supply constraints into economic evaluations in low-income and middle-income countries. *Health Economics* **25**: 95–115.

White MT, Conteh L, Cibulskis R, Ghani AC. 2011. Costs and cost-effectiveness of malaria control interventions—a systematic review. *Malar Journal* **10**: 337.

WHO Global Malaria Programme. 2016. *World Malaria Report 2016*. Geneva, Switzerland: World Health Organization.

Wilson AL. 2011. A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment of malaria in children (IPTc). *PLoS ONE* **6**: e16976.

World Bank 2017. *Country and Lending Groups*. Washington, DC: World Bank Group.

World Health Organization 2012. WHO policy recommendation: seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. March 2012. (in English and French).

World Health Organization 2017. *Global Health Expenditure Database*. Geneva: WHO.

World Health Organization/Global Malaria Program Technical Expert Group on Preventive Chemotherapy. 2011. *Report of the technical consultation on Seasonal Malaria Chemoprevention (SMC), 4–6 May 2011*. http://www.who.int/malaria/publications/atoz/smc_report_teg_meetingmay2011.pdf. 30 June 2017

Chapter 5. Local geographic targeting of malaria hotspot strategies

5.1. Local geographic targeting of multi-component strategies in malaria hotspots in Senegal: a cost and cost-effectiveness analysis

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

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Student ID Number	477122	**Title**	Ms
First Name(s)	Catherine Krown		
Surname/Family Name	Pitt		
Thesis Title	Promoting transferability: Insights from economic evaluations of public health interventions to tackle malaria in central Senegal		
Primary Supervisor	Kara Hanson		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the cost and cost-effectiveness study and data collection instruments; supervised cost data collection; analysed the data; wrote the first draft of the manuscript, and revised the manuscript.

SECTION E

Student Signature	Catherine Pitt
Date	21 February 2020

Supervisor Signature	Kara Hanson
Date	24 February 2020

5.1.1. Abstract

Introduction: In areas of generally very low malaria transmission, incidence tends to be patchy, with highly localised “hotspots”. We compared the costs and effects of geographically targeted strategies using dihydroartemisinin-piperaquine in hotspot villages for two rounds of either mass screening and treatment (MSAT) or mass drug administration (MDA), both with and without the addition of indoor residual spraying (IRS) with Actellic 300CS.

Methods: We conducted an economic evaluation alongside a three-arm cluster-randomized controlled trial conducted over two years in a population of ~577,000 persons in rural, central Senegal, where malaria is highly seasonal. Prospective micro-costing was used to inform a model, which estimated costs of implementation across the entire study area (base case) and with different degrees and levels of targeting and number of implementation rounds (cost scenarios). Using a decision tree, we modelled the cost-effectiveness of seven alternative intervention strategies from a societal perspective over a lifetime horizon with a 3% discount rate, accounting for impacts in both hotspot and non-hotspot villages. We used probabilistic and deterministic sensitivity analysis and identified the cost-effectiveness frontier and expansion path.

Results: Average economic costs per recipient per round were $1.99 for targeted IRS, $0.82 for targeted MSAT, and $1.57 for targeted MDA (constant 2018 United States Dollars). Per 10,000 population (across hotspot and non-hotspot villages), total annual costs of targeted IRS ($7,135) were highest, followed by MSAT ($5,368), MDA ($10,048), and hotspot identification ($75). Compared to the reference strategy, which closely resembled standard practice, targeted MSAT alone cost an additional $9,839 (95% CI: $4,939 to $34,054) per disability-adjusted life-year (DALY) averted; compared to targeted MSAT, targeted IRS+MSAT cost a further $10,221 ($5,597 to $32,423) per DALY averted; and compared to targeted IRS+MSAT, targeted IRS+MDA cost a further $36,203 ($13,084 to $121,785) per DALY averted. The remaining three strategies evaluated were dominated. Plausible changes in drug, test, and insecticide prices would alter the expansion path, as would inclusion of side effects of MSAT and MDA in analysis.

Conclusions: In comparable contexts, the specific combinations of hotspot interventions evaluated in this trial are unlikely to lead to elimination in the near term and are not cost-effective as disease control measures. Our cost model demonstrates economies of scale and diseconomies of targeting and can inform decisions regarding the deployment of IRS, MDA, and MSAT in different contexts.

5.1.2. Introduction

In areas where malaria transmission is generally low, transmission also tends to be patchy, with highly localised “hotspots” and other areas with minimal or virtually no transmission. In such transmission contexts, malaria elimination is considered possible if standard malaria control activities are supplemented with additional, intensive interventions (WHO, 2017a). If no more than a few cases per week are reported at each health facility, the World Health Organization (WHO) recommends investigation of each malaria case and reactive interventions, such as indoor residual spraying (IRS), focal screening and treatment, or focal drug administration, in the immediate vicinity of the incident case (WHO, 2017a). In other areas, where malaria incidence is low but not low enough for reactive interventions to be feasible, WHO recommends ensuring universal coverage of core interventions (e.g. bed nets) and considering additional, intensive, population-wide control measures, such as mass drug administration (MDA), mass screening and treatment (MSAT), and/or intensified vector control to accelerate reductions in transmission (WHO, 2017a). Spatial and temporal clustering of cases means, however, that timely case investigations may not be feasible even in areas broadly classified as “very low transmission”, while population-wide intensive interventions in such settings may be inefficient and expose many people to unnecessary risks and discomfort. In these patchy, low transmission settings, geographical targeting at a local level (in localised “hotspots”) of MDA or MSAT, potentially in combination with IRS, may be an effective and efficient approach to reduce transmission.

A WHO Evidence Review Group identified only one randomized trial of a strategy in which MDA or MSAT were focused on malaria hotspots (WHO Evidence Review Group, 2015a, Newby et al., 2015, Bousema et al., 2016). Conducted in a low-transmission setting in highland Kenya, the trial found that combining targeted MSAT, IRS, bed nets, and larviciding in hotspots reduced parasite prevalence within but not outside hotspots and did not interrupt transmission (Bousema et al., 2016). More recently, evidence has emerged from a three-arm, cluster-randomized trial in a highly seasonal, low transmission setting in central Senegal. In that trial, two different hotspot strategies reduced malaria incidence substantially both in the hotspot villages in which they were implemented and in non-hotspot villages in which they were not implemented (Diallo et al., 2020). Nonetheless, the incidence reductions – which averaged 43% (95% CI: 35%, 50%) for MSAT with IRS and 48% (95% CI: 40%, 54%) for MDA with IRS across the hotspot and non-hotspot villages – did not achieve the original aim of “virtual elimination”. The trial team concluded that hotspot strategies may have the potential to

contribute to elimination if implemented more intensively than in the trial, with more rounds of MDA, possibly in combination with MSAT and IRS.

Maximizing the impact of resources to tackle malaria requires understanding the efficiency of alternative policy choices; however, no empirical evidence on the efficiency or costs of a hotspot strategy involving MDA or MSAT has previously been published. Even empirical evidence on the costs of MDA and MSAT delivered as blanket strategies is scarce. When WHO reviewed the costs of (targeted and blanket) MDA for malaria, cost data were identified in only one published study (regarding 720 people in Vanuatu) and two unpublished studies (regarding Sierra Leone during the Ebola emergency and the Comoros islands) (WHO Evidence Review Group, 2015b). Cost estimates for related interventions, including seasonal malaria chemoprevention (effectively MDA restricted to children under 10) in central Senegal (Pitt et al., 2017) and MDA for various neglected tropical diseases in India (Krishnamoorthy et al., 2002), Sudan (Kolaczinski et al., 2011), and Kenya (Pullan et al., 2019), vary widely. For MSAT for malaria, three dry-season rounds in a moderate transmission area in Zambia were estimated to cost $804 (2012 USD) per disability-adjusted life-year (DALY) averted, which the authors judged "highly cost-effective" (Silumbe et al., 2015). Evidence on the costs and cost-effectiveness of IRS is more extensive (Conteh et al., 2004, Goodman et al., 2001, Guyatt et al., 2002, Faraj et al., 2016, Yukich et al., 2008), but does not address IRS's added value when combined with MDA or MSAT and older studies do not address the higher costs of next generation insecticides.

While empirical evidence is scarce, a modelling study predicted how the efficiency of different combinations of malaria interventions, including MDA, MSAT and IRS, may vary across Africa, and the savings that could be achieved by targeting intervention packages to provinces or $5km^2$ land areas (Walker et al., 2016). Other researchers have proposed a geographic resource allocation framework based on cost-effectiveness (Drake et al., 2017). And IRS (Protopopoff et al., 2007), like larviciding (Worrall and Fillinger, 2011) and many other malaria interventions (Carter et al., 2000), is usually targeted to areas considered at higher risk, so economic evaluations of such vector control strategies nearly always assess geographically targeted interventions. None of these malaria studies, however, nor others we are aware of, have described or accounted for how the average cost per person reached may vary with the type and extent of targeting. Studies of the efficiency of targeting social interventions (Dutrey, 2007), vitamin A supplementation (Loevinsohn et al., 1997), and HIV prevention (Wilson et al., 2005) emphasize the costs of the targeting process itself, as well as the imperfect sensitivity

and specificity of targeting. The reductions in scale of targeted relative to blanket interventions also mean that intervention costs incurred at regional, district, and health facility level may be divided across fewer recipients than a blanket intervention. This combination of additional costs of identifying the target and diseconomies of reduced scale mean that there are likely to be diseconomies of targeting malaria interventions, that is, higher average costs per person reached than blanket strategies. These diseconomies of targeting may have important implications for understanding the efficiency of targeted and blanket strategies, especially when considering targeting interventions at increasingly fine spatial scales (Stresman et al., 2019, Kabaghe et al., 2018).

To address some of these research gaps and inform malaria policy, we conducted an economic evaluation alongside the hotspot trial in Senegal. For our economic evaluation, we first sought to inform the design and planning for other geographically targeted intervention packages by developing a flexible cost model, populated with data from the trial and secondary sources, to estimate how the costs of geographically targeted MSAT, MDA, and IRS could be expected to vary with implementation choices and context. Secondly, given the substantial relative incidence reductions achieved, we sought to determine whether the intervention packages implemented in the trial could be considered cost-effective as disease-burden reduction interventions, since virtual elimination was not achieved.

5.1.3. Methods

Setting

The trial population comprised the ~587,000 people (in 2014) living in the catchment areas of the 46 rural health posts in Mbour, Fatick, Bambey and Niakhar districts. When baseline data were collected in 2012, parasitaemia prevalence (1.9% by microscopy) and annual malaria incidence (11 cases per thousand person-years at risk) were low, having fallen dramatically in the preceding decade, and malaria was also highly seasonal, with 86% of cases occurring from September to December each year (Diallo et al., 2020). From 2008 to 2012, 80% of all malaria cases were concentrated in <40% of villages each year, indicating substantial geographical heterogeneity in local malaria transmission (Diallo et al., 2020).

Health posts are the key primary health care facilities throughout Senegal; they are led by a head nurse, who also supervises a network of community health workers (CHWs), and reports to a district health management team. Both testing and treatment with artemisinin

combination therapy are meant to be free of charge in public facilities; however, the initial consultation costs ~$0.17 (100 XOF) for children or $0.34 (200 XOF) for adults, with fee waivers intended for the poorest. Standard malaria control measures in central Senegal at the time of the trial included requiring parasitological confirmation in health facilities before treatment with artemisinin combination therapy (artemether-lumefantrine as first-line treatment), intermittent preventive treatment of malaria in pregnancy, mass LLIN distribution campaigns (in Fatick, Bambey, and Niakhar in 2011 and in Mbour in 2013), free LLIN top-ups for pregnant women at antenatal clinics, and subsidised LLINs available for purchase at health facilities (JHBSPH, 2015). In the 2012 baseline survey, 61% of the study population surveyed had slept under a bed net the previous night (Diallo et al., 2020). Senegal's life expectancy at birth was estimated at 67 years for 2016 (WHO, 2019b). With a gross domestic product of $1,522 per capita in 2018, Senegal is a lower-middle-income country (World Bank, 2019) whose malaria budget is financed primarily by the United States' President's Malaria Initiative and the Global Fund (WHO, 2018d).

Study design and comparators

The trial was designed to compare two multi-component, village-based targeting strategies (n=15 clusters each) and a reference strategy (n=10 clusters), over two malaria seasons (2013-14) (Figure 3) (Diallo et al., 2020). Clusters had a mean population (in 2014) of 14,682 people. Most clusters comprised a single health post catchment area, but 6 health posts with smaller catchment populations were merged with an adjacent catchment area to form clusters. As villages varied widely in population size, clusters comprised between 6 and 69 villages.

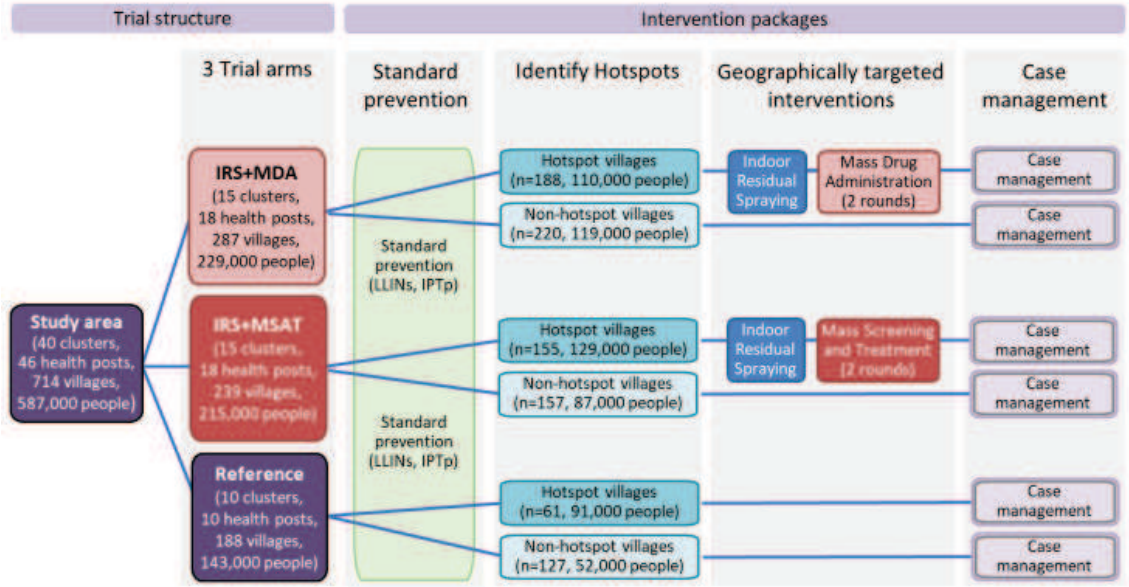
In the reference strategy, which closely resembled standard practice, in addition to standard malaria control measures described above, radio messages encouraged care-seeking for fever and the small number of people confirmed to have malaria in public health facilities was provided with a long-lasting insecticide-treated bed net (LLIN) to top up coverage. Intervention strategies comprised all elements of the reference strategy plus additional activities.

Hotspot villages were identified by tallying by village the number of RDT-confirmed malaria cases passively detected in health facilities in the previous malaria season. To ensure balance between hotspot and non-hotspot villages within each cluster for research purposes, clusters were stratified by incidence. Geospatial analysis was used to develop an algorithm by which hotspots were defined as villages with 3 or more cases in the previous June-September (for villages associated with health posts in the slightly higher incidence stratum), or 4 or more cases in the previous June-December (for villages associated with health posts in the lower

incidence stratum). Researchers reviewed the health facility records to identify hotspots in the trial; however, the algorithm was designed to be straightforward to implement by head nurses in collaboration with district staff based on data in existing clinical registers. In 2013 and 2014, 55% and 56% of study area residents, respectively, lived in villages declared “hotspots”.

Figure 3 Trial structure

Population figures and numbers of villages are estimates for 2014, the second year of the trial. The classification of hotspot and non-hotspot villages was redone each year, so the number of hotspot and non-hotspot villages within each arm (and their associated populations) were different in 2013. Case management in the trial encompassed both standard diagnosis with parasitological confirmation, and also additional radio messages to encourage care seeking and provision of a LLIN if needed for anyone diagnosed with malaria. LLIN: Long-lasting insecticide-treated bed net; IPTp: Intermittent preventive treatment of malaria in pregnancy; MDA: Mass drug administration; MSAT: Mass screening and treatment; IRS: Indoor residual spraying.

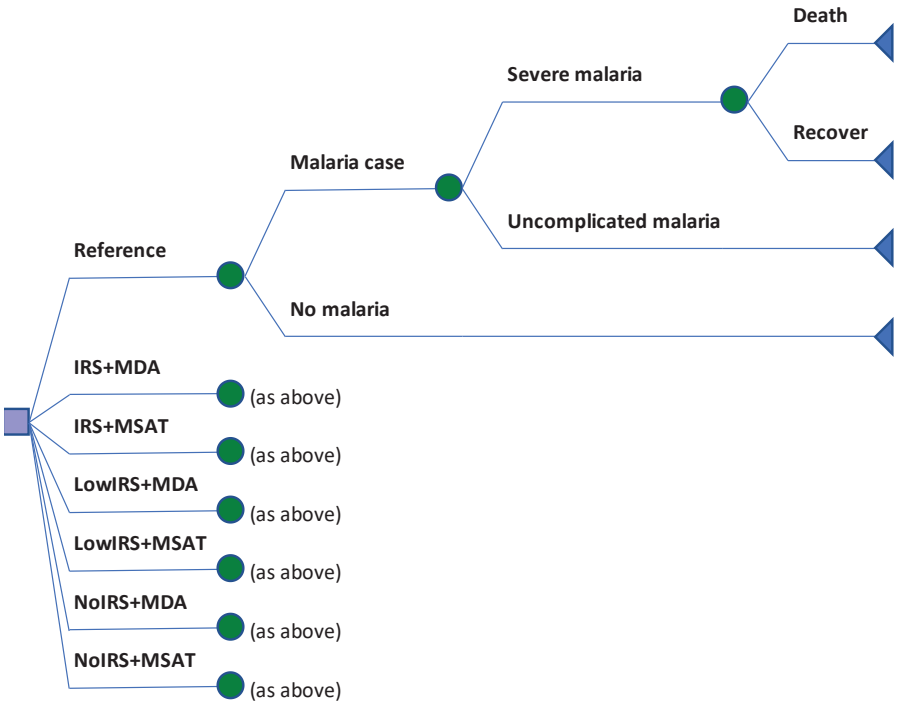


In July and August each year, residents of hotspot villages were meant to receive IRS with Actellic 300CS, a non-pyrethroid “next generation” insecticide. In September and October, CHWs conducted two rounds of door-to-door visits in hotspot villages to offer either MSAT or MDA depending upon the trial arm. In MSAT clusters, the CHWs offered RDTs to all persons aged over three months and treated anyone with a positive test result with DP, except for pregnant women and those with a known allergy, who were referred to a health facility. In MDA clusters, the CHWs offered DP to all persons aged over three months except pregnant women and those who were ill, taking other medications, or known to be allergic to antimalarials. The trial was thus designed to compare the effects in both hotspot and non-hotspot villages of implementing IRS+MDA in hotspots, IRS+MSAT in hotspots, and the reference strategy, without determining the added value of IRS as part of the intervention strategies. In 2013, however, logistical problems in obtaining the insecticide meant that only

23% of households in the hotspot villages received IRS (i.e. 12% of all households in the intervention clusters), and the quality of spraying was low, with a 24-hour mosquito mortality rate of just 37% after four months (Diallo et al., 2020); we refer to this as "LowIRS". In 2014, IRS reached 66% of households in hotspot villages in the two intervention arms, and additional training improved the quality of spraying, resulting in mosquito mortality rates of 82% after four months.

For our cost-effectiveness analysis, we assumed that policy makers would want to consider implementing either MSAT in hotspots or MDA in hotspots, either with IRS at the 66% coverage that was achieved in our study ("IRS") or without any IRS ("NoIRS"). While we assume policy makers would not choose to implement LowIRS, we include it in our analysis because the trial produced robust estimates of the effectiveness of this combination of interventions, whereas "NoIRS" strategies had to be modelled from trial data on implementation of LowIRS and IRS. Inclusion of LowIRS strategies also provides valuable information on the consequences of failure to achieve good IRS coverage and of the relative contribution of IRS to the effectiveness achieved by IRS+MSAT and IRS+MDA. We therefore compared seven alternative hotspot intervention strategies: the reference strategy (i.e. none of the intensive hotspot interventions, close to standard practice), IRS+MSAT, IRS+MDA, LowIRS+MSAT, LowIRS+MDA, NoIRS+MSAT, and NoIRS+MDA (Figure 4**Error! Reference source not found.**).

Figure 4 Decision tree
For simplicity, the full decision tree is only shown for the reference strategy. The pathway is identical for each of the other strategies. Created using Simple Decision Tree toolbar 1.4 Add-In for Excel.



Costs

We first estimated costs to the provider of each intervention (hotspot identification, IRS, MSAT, and MDA) and the societal costs (i.e. costs to the provider and to households) of passively detected cases. We assumed that receipt of interventions (at home or nearby) would not incur meaningful household costs. We then combined the intervention costs to estimate the societal costs of each of the seven strategies (Figure 4**Error! Reference source not found.**). We focus on economic costs, which reflect the full value (opportunity cost) of resources used, even if they did not require direct payment, such as donated drugs or the time of existing health workers; however, we also estimate financial costs to the provider, which represent expenditure and are useful for budgeting and assessing affordability.

The costs of identifying hotspots and of implementing targeted IRS, MSAT, and MDA were estimated through prospective micro-costing of the activities in 2014. We gathered data on resource use, costs, and outputs from project accounts, project administrative records, Ministry of Health records, international reference price lists, and a series of questionnaires. These questionnaires were administered after the single IRS round and each round of MSAT and MDA to districts, health posts, and IRS coordinators; data were entered in MS Access and analysed in Excel. For internationally traded goods (Hutton and Baltussen, 2005), notably insecticide, RDTs, antimalarials, and LLINs, international market prices were used, even where goods were donated for research purposes or subsidized.

Research costs were excluded. We included the costs of health worker time needed to identify hotspots but excluded the development and validation of the algorithm as a research cost. While data on the previous year's malaria cases were gathered and analysed in the entire study area to identify hotspots, the costs of hotspot identification in the reference arm were excluded as a research cost. Where research staff contributed directly to the implementation of interventions, such as supervision or participation in planning meetings, the value of their time has been included; similar external support would be expected outside a trial context. Separately, we also report on the incentive payments made to health service staff, which were intended to support research but likely contributed to more assiduous implementation of the interventions.

We developed a simple, flexible, and transparent mechanistic cost model to predict how provider costs for the four interventions could be expected to vary with changes to intervention characteristics and context, as well as input prices. This model reflected the cost

data collected and our understanding of how the interventions were implemented in the trial and could be implemented in future. We disaggregated costs by round and by the level of the health system (country, district, health post, CHW) or output (persons reached per round) with which those costs would be expected to vary approximately linearly (*see* Section 5.2). As a base case, we modelled the costs of implementing each intervention in the entire study area (which comprises all rural catchment areas of the 4 districts). This modelling remained close to what was observed in the trial, but reduced differences in costs between strategies that were driven by differences in contextual factors and removed the inherent inefficiencies of implementation in a trial context. For the base case, we also estimated the costs of "LowIRS".

In further scenarios, we used a somewhat stylised version of our population to model how costs of implementing the interventions could be expected to vary with the *degree* of targeting (proportion of the study area population targeted: 100%, 50%, 20%), with the *level* of the targeting unit (village-based targeting as implemented in the trial or district-based targeting), and with the number of consecutive implementation rounds (2, 4). Such modifications to the intervention could be considered to respond to different epidemiological contexts, to reduce costs, and/or to increase effectiveness relative to the strategies implemented in our trial.

In the cost-effectiveness analysis, the societal cost of illness and case management was estimated by combining primary and secondary data on the cost per case (based on local protocols and practice) with the number of uncomplicated and severe cases estimated in the cost-effectiveness model (Table 2). We assumed that the cost per case treated, whether uncomplicated (requiring only outpatient treatment) or severe (requiring hospitalisation), would be the same across study arms.

Costs were inflated to 2018 values using the consumer price index for the relevant currency (Kumaranayake, 2000) and converted to United States dollars (USD) using the average 2018 exchange rate (World Bank, 2019, Hutton and Baltussen, 2005). Economic costs to the provider in the base case scenario are presented for each intervention by activity and by cost driver, and for each strategy by intervention. Total economic and financial costs of each intervention in the base case, actual implementation in the trial, and ten further scenarios are presented per 10,000 population – including both residents of hotspot and non-hotspot villages and those who did and did not receive the interventions – to provide a more useful basis of comparison than the total study population. For each intervention, average economic costs per recipient of that intervention per round are also presented in the base case, actual implementation, and ten further scenarios to explore diseconomies of targeting. To indicate

potential budget impact, we compared total financial costs per capita with average per capita public expenditure on malaria (WHO, 2018d) and on health in Senegal (WHO, 2019a).

Cost-effectiveness analysis

We developed a decision analytic model to combine trial and secondary data to estimate economic costs and effects of each of the seven strategies for the entire study area from a societal perspective. We modelled implementation over a 1-year period and included the consequences of any malaria episodes in that year over a lifetime horizon. This short-term approach was considered appropriate because the pre-elimination strategies evaluated are not intended as a policy to be implemented indefinitely (and are not expected to be considered socially or politically acceptable if continued long-term), but rather as interim measures to reduce incidence sufficiently for case investigation and reactive interventions to become feasible. Further, they were not found to involve any "start-up" costs; all activities would need to be repeated each year. Our analysis was conducted and reported in accordance with the CHEERS checklist (Husereau et al., 2013) and reference cases for economic evaluation (Wilkinson et al., 2016) and for costing (Vassall et al., 2017).

We plotted the costs and effects of each of the seven strategies on the cost-effectiveness plane, identified the cost-effectiveness frontier and expansion path, and calculated incremental cost-effectiveness ratios (ICERs) between adjacent points on this path. The cost-effectiveness frontier is defined by the set of economically efficient strategies; it excludes inefficient strategies, which are said to be "dominated" because they are less effective and more costly than a single alternative strategy ("strict dominance") or a combination of alternative strategies ("extended dominance"). The expansion path connects strategies on the cost-effectiveness frontier from least to most effective and costly. The expansion path therefore indicates the order in which strategies should be considered for adoption given increasing availability of resources. To facilitate interpretation, we present all findings per 10,000 population.

To explore the robustness of our finding to uncertainty and heterogeneity, including plausible variation in other relevant contexts, we conducted both deterministic and probabilistic analyses. One-way deterministic sensitivity analyses are presented on separate cost-effectiveness planes for each parameter explored. Unlike tornado diagrams, which can only compare two strategies, use of cost-effectiveness planes allow illustration of the sensitivity or robustness of the expansion path – i.e. the order in which strategies should be considered for adoption – to plausible variation in each parameter (Table 1, Table 2).

Table 1 Key parameters: Model assumptions and effects

CI: Confidence Interval; CHW: Community health worker; PYAR: person-years at risk; DSA: Deterministic sensitivity analysis; LMICs: Low- and middle-income countries.

MODEL ASSUMPTIONS	Base case	Probabilistic Distribution	Probabilistic s.d.	Deterministic Low	Deterministic High	Source / Justification
Discount rate	0.03	NA	NA	0.01	0.07	iDSI Reference Case for Economic Evaluation in LMICs
EFFECTS	**Base case**	**Probabilistic Distribution**	**Probabilistic s.d.**	**Deterministic Low**	**Deterministic High**	**Source / Justification**
Incidence rate - reference arm in malaria season (cases/1000 PYAR)	14.290	Normal	0.316		29.43	Trial estimates based on passive surveillance; Base case: 2014 values; DSA: 2013 value
Rate ratio clinical malaria in malaria season - IRS+MSAT:Reference	0.569	Normal	0.037	0.501	0.646	Trial estimates based on passive surveillance; DSA: 95% CI
Rate ratio clinical malaria in malaria season - IRS+MDA:Reference	0.523	Normal	0.037	0.456	0.600	Trial estimates based on passive surveillance; DSA: 95% CI
Rate ratio clinical malaria in malaria season - LowIRS+MSAT:Referenc	0.735	Normal	0.037	0.666	0.811	Trial estimates based on passive surveillance; DSA: 95% CI
Rate ratio clinical malaria in malaria season - LowIRS+MDA:Reference	0.626	Normal	0.034	0.563	0.696	Trial estimates based on passive surveillance; DSA: 95% CI
Rate ratio clinical malaria in malaria season - NoIRS+MSAT:Reference	0.810	Normal	0.037	0.737	0.882	Modelled from trial data - see Appendix; DSA: 95% CI
Rate ratio clinical malaria in malaria season - NoIRS+MDA:Reference	0.672	Normal	0.034	0.606	0.739	Modelled from trial data - see Appendix; DSA: 95% CI
Proportion of passively detected cases that become severe	0.063	Beta	0.013	0.032	0.127	Passive surveillance; DSA: -50% to +100% of base case
Proportion of severe cases that result in death	0.039	Beta	0.013			Passive surveillance;
Duration of uncomplicated malaria (days)	3.000	Gamma	0.001			Assumption
Duration of severe malaria (days)	7.034	Gamma	0.002			Facility data on length of stay for malaria plus 2 days (assumption)
DALY weight - uncomplicated malaria (infectious disease moderate)	0.051	Beta	0.011			Salomon et al. (2015)
DALY weight - severe malaria (infectious disease severe)	0.133	Beta	0.026			Salomon et al. (2015)
Years of life lost per death (discounted)	23.151	Normal	8.114		25.687	Trial data on sex and age at death; Global Health Observatory life tables for Senegal (base) and Japan (DSA)

Table 2 Key parameters: Economic cost

CI: Confidence Interval; CHW: Community health worker; DSA: Deterministic sensitivity analysis.

ECONOMIC COST	Base case	Probabilistic Distribution	Probabilistic s.d.	Deterministic Low	Deterministic High	Source / Justification
Costs of interventions						
Hotspot identification per 10,000 population	$75	Gamma	$10			Modelled from primary cost analysis; s.d. is 25% of base case / 1.96
Hotspot IRS per 10,000 population	$7,135	Gamma	$910			Modelled from primary cost analysis; s.d. is 25% of base case / 1.96
LowIRS per 10,000 population	$2,972	Gamma	$379			Modelled from primary cost analysis; s.d. is 25% of base case / 1.96
Hotspot MSAT per 10,000 population	$5,368	Gamma	$685			Modelled from primary cost analysis; s.d. is 25% of base case / 1.96
Hotspot MDA per 10,000 population	$10,048	Gamma	$1,282			Modelled from primary cost analysis; s.d. is 25% of base case / 1.96
Economic cost per uncomplicated case (societal)	$21	Gamma	$3			Sum of relevant cost components; s.d. is 25% of base case / 1.96
Economic cost per severe case (societal)	$85	Gamma	$11			Sum of relevant cost components; s.d. is 25% of base case / 1.96
Economic cost per adverse event (societal)	$7	Gamma	$1			Sum of relevant cost components; s.d. is 25% of base case / 1.96
Probability of adverse event (MDA) resulting in care seeking	0.007	Beta	0.001			Sum of relevant cost components; s.d. is 25% of base case / 1.96
Key intervention cost components						
RDT - Antigen Pf – POCT	$0.32			$0.16	$0.48	Global Fund (2019b); DSA: +/- 50%
DP 20/160, 3 tablets (child)	$0.82			$0.41	$1.23	Global Fund (2019a); DSA: +/- 50%
DP 40/320, 9 tablets (adult)	$1.98			$0.99	$2.97	Global Fund (2019a); DSA: +/- 50%
Actellic 300 cs (per bottle)	$23.50			$11.75	$35.25	Cico and Johns (2018); DSA: +/- 50%
Daily rate for CHWs delivering MDA and IRS	$5.55				$11.10	Trial administrative records; DSA reflects +100%
Ratio of MSAT:MDA CHW daily rate	1.167			1.000		Trial administrative records
Households reached per CHW per day (IRS)	3.609					Trial administrative records;
Mean persons reached per CHW per day (MSAT)	24.118					Trial administrative records;
Mean persons reached per CHW per day (MDA)	66.217					Trial administrative records;
Duration of single delivery round (IRS days)	28.000					Trial administrative records;
Duration of single delivery round (MSAT days)	14.000					Trial administrative records;
Duration of single delivery round (MDA days)	7.000					Trial administrative records;
MSAT positivity rate	0.011				0.022	Trial administrative records; DSA: doubles with doubling incidence
Proportion of joint MDA-MSAT supervision costs attributed to MSAT	0.667					Assumption based on duration of activities
International freight for Actellic (% of product value)	2.5%					Trial administrative records
International freight for RDTs and DP (% of product value)	10.0%					Assumption based on trial administrative records

ECONOMIC COST	Base case	Probabilistic Distribution	s.d.	Deterministic Low	High	Source / Justification
Costs of case management						
Long-lasting insecticide-treated bed net (standard pyrethroid)	$2.22					Global Fund (2018), Median price
Artesunate 120mg powder for solution for injection (vial)	$2.60					Global Fund (2019a); Assumed 3 vials/ treatment (severe only)
Artemether/Lumefantrine 20/120mg, 6x4, non-dispersible tablets	$0.62					Global Fund (2019a); 1 blister pack/treatment
Cost per consultation	$1.15					WHO (2011a)
Cost of hospitalisation per day	$6.62					WHO (2011a)
Duration of hospitalisation - severe (days)	5.034					Trial estimates based on passive surveillance
Shadow price of time spent ill (per day)	$5.55					Assumed equal to standard CHW per diem rate

We used Monte Carlo simulation to reflect the combined impact of uncertainty in stochastic parameters on our ICER estimates. Distributions were selected to be consistent with our understanding of the logical bounds and shape of each parameter: beta distributions for proportions; gamma distributions for durations and costs, which are non-negative and right-skewed; and normal distributions for rates, rate ratios, and discounted YLLs. While the latter parameters cannot take on negative values, which a normal distribution may allow, the very low standard deviations made negative draws very unlikely in practice and normal distributions have the benefit of reflecting the symmetrical shape of the distributions and the potential to take on values >1. We calculated mean costs and effects for each of the seven strategies across 10,000 iterations and used percentiles to generate 95% confidence intervals for each ICER estimate. To centre our plot on the cost-effectiveness plane at the origin and reflect uncertainty relative to the reference strategy, we calculated the incremental costs and effects of each intervention strategy relative to the reference strategy for each of the 10,000 iterations and generated scatter plots. We present cost-effectiveness acceptability curves (Fenwick et al., 2001) to indicate the probability of each strategy being cost-effective at plausible and widely used cost-effectiveness thresholds (Ochalek et al., 2018, Marseille et al., 2015) (also see Section 6.1.7. Annex 2). Analyses were conducted in Microsoft Excel with Visual Basic for Applications.

Effects

Our primary cost-effectiveness analysis is of the incremental cost per DALY averted, which allows our findings to be compared with alternative uses of these resources to address any health condition. We also estimate the incremental cost per malaria case averted to permit comparison with existing malaria literature and with epidemiological data, in which incidence is a common endpoint and subject to less uncertainty than DALY estimates.

The number of malaria cases expected under each strategy is estimated as the product of the simulated population size, the incidence in the reference arm of the trial, and the incidence rate ratio of the relevant intervention arm relative to the reference arm. Because incidence data were not available for 2015, incidence measures were restricted to the 4-month malaria seasons (September – December) in 2013 and 2014. This restriction assumed that the interventions did not affect incidence in the following 8 months, which may slightly underestimate the number of cases averted. The approach also assumes that the incidence rate ratios of each intervention strategy relative to the reference strategy were independent of the incidence in the reference arm, within the range seen in our study of 14.3 (in 2014, used as base case) to 29.4 (in 2013, used in sensitivity analysis) cases per thousand person-years at risk within the malaria season. In reality, lower relative impact would be expected at higher transmission intensity. To estimate the

incidence rate ratios for NoIRS+MSAT and NoIRS+MDA relative to the reference strategy, which were not measured in the trial, we took a simple but conservative approach, which assumed that they would be less effective than LowIRS+MSAT and LowIRS+MDA, respectively. We assumed that this loss of effectiveness would be a linear function of the product of efficacy and coverage based on data for 2013 and 2014, as detailed in Annex 1 (Section 5.1.6.).

Every one hundred malaria cases were assumed to generate the same number of DALYs, on average, regardless of study arm (Table 1, Section 5.1.6.). Total years of life lost (YLLs) and years of life with disability (YLDs) were summed to generate the DALY estimate for each strategy. The number of confirmed malaria cases, severe cases, and malaria-related deaths were obtained from passive surveillance data from all health facilities and CHWs providing malaria treatment across the study area. The proportion of all confirmed cases that became severe and the proportion of all severe cases that result in death were estimated across the entire study area because of the small numbers involved. For each of the 15 people who died from malaria in our study area across both years, we used life tables and age at death to estimate the individual's remaining life expectancy, which we discounted at 3% (in the base case) with no age weighting to generate the discounted YLLs for each death. We then used the mean and s.d. of discounted YLLs per death to generate a distribution for the number of YLLs associated with each death in our model. Remaining life expectancy at death was taken from life tables for Senegal, which represent the real opportunity cost in this context, and sensitivity analysis presented results based on Japanese life expectancy, which represents a theoretical maximum (WHO, 2019b). As is standard for malaria interventions, YLDs comprised only 1.3% of DALYs in our model. They were calculated separately for uncomplicated and severe cases as the product of the number of cases of malaria in each arm, the probability of becoming severe, the average duration of a case, and the disability weight (Salomon et al., 2015) for infectious disease (moderate or severe). Long-term sequelae were not included but were not expected to substantially alter overall DALY estimates.

In deterministic sensitivity analysis, we considered how including in DALY estimates the adverse events associated with receipt of MSAT and MDA by persons who were not ill affected relative effectiveness and cost-effectiveness. Adverse events included widespread minor complaints, such as dizziness (MDA) and finger pain (MSAT), and a child's death following MDA in 2013 (Section 6.1.7. Annex 2).

Ethics

The study protocol was approved by the Observational and Interventional Ethics Committee of the London School of Hygiene & Tropical Medicine (ref 6387) and Senegal's Comité National d'Ethique pour la Recherche en Santé (ref 171).

5.1.4. Results

Effects

Our probabilistic base case cost-effectiveness model indicated that the reference strategy would result in the most malaria cases, 48 per 10,000 residents in the malaria season (95% CI, 46 to 50), followed in descending order by NoIRS+MSAT (39, 35 to 42), LowIRS+MSAT (35, 31 to 39), NoIRS+MDA (32, 29 to 35), LowIRS+MDA (30, 26 to 33), IRS+MSAT (27, 23 to 31), and IRS+MDA (25, 21 to 29), the most effective strategy (Table 3**Error! Reference source not found.**). As disease progression parameters were assumed constant across intervention strategies, the numbers of cases and DALYs averted displayed the same relationships across the seven strategies (Table 3**Error! Reference source not found.**).

Table 3 Deterministic and probabilistic estimates of total effects and total costs of the 7 strategies
DA: Deterministic analysis. Mean probabilistic estimates and deterministic estimates are virtually identical

	Cases per 10,000			DALYs per 10,000			Economic costs per 10,000		
	DA	Probabilistic		DA	Probabilistic		DA	Probabilistic	
Strategy		Mean	95% CI		Mean	95% CI		Mean	95% CI
Reference	48	48	(46, 50)	2.79	2.78	(0.9, 4.7)	1,185	1,186	(958, 1,448)
NoIRS+MSAT	39	39	(35, 42)	2.26	2.25	(0.74, 3.84)	6,404	6,401	(5,122, 7,833)
LowIRS+MSAT	35	35	(31, 39)	2.05	2.05	(0.67, 3.49)	9,287	9,286	(7,826, 10,886)
IRS+MSAT	27	27	(23, 31)	1.59	1.58	(0.52, 2.72)	13,253	13,254	(11,093, 15,566)
NoIRS+MDA	32	32	(29, 35)	1.88	1.87	(0.61, 3.19)	10,920	10,928	(8,588, 13,593)
LowIRS+MDA	30	30	(26, 33)	1.75	1.74	(0.57, 2.98)	13,837	13,846	(11,392, 16,563)
IRS+MDA	25	25	(21, 29)	1.46	1.46	(0.47, 2.5)	17,878	17,889	(14,965, 21,060)

Costs

Costs of implementing geographically targeted interventions

Our base case mechanistic modelling of intervention costs throughout the study area indicated that the total economic costs of MDA were the highest of the geographically targeted interventions at $10,048 (constant 2018 USD) per 10,000 residents, followed by IRS at $7,135, MSAT at $5,368, LowIRS at $2,972, and the identification of hotspots at just $75 per 10,000 residents (Figure 5, Table 4). The average costs of MDA and MSAT were $1.57 and $0.82 per

recipient per round, respectively, while IRS and LowIRS cost $1.99 and $2.39, respectively, per person living in a household that was sprayed (Table 4).

Figure 5 Total intervention costs by activity and driver
Total economic costs per 10,000 population are presented for the base case scenario. Costs of case management reflect incidence in the reference arm. IRS: Indoor residual spraying; MDA: Mass drug administration; MSAT: Mass screening and treatment.

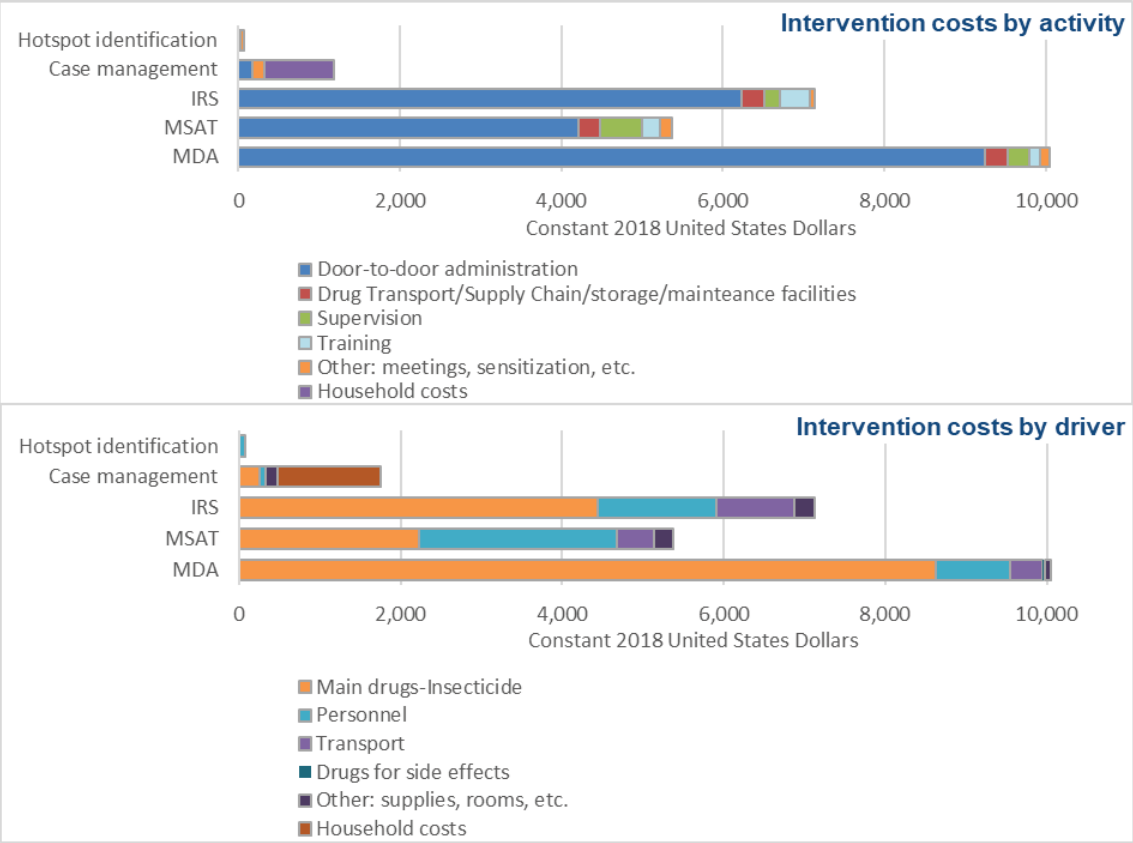


Table 4 Total economic costs of Hotspot ID, IRS, MSAT, and MDA: as implemented in trial and base case analysis
In the trial, 36% of intervention arm residents received IRS, 33% of MSAT arm residents received MSAT, and 32% received MDA, which is reflected in the "Implementation in trial" and base case. The 10 cost scenarios indicate the proportion of people targeted, and the proportion of people targeted who are reached matches the trial: 66% IRS, 55% MSAT, and 66% MDA. HP: Health post.

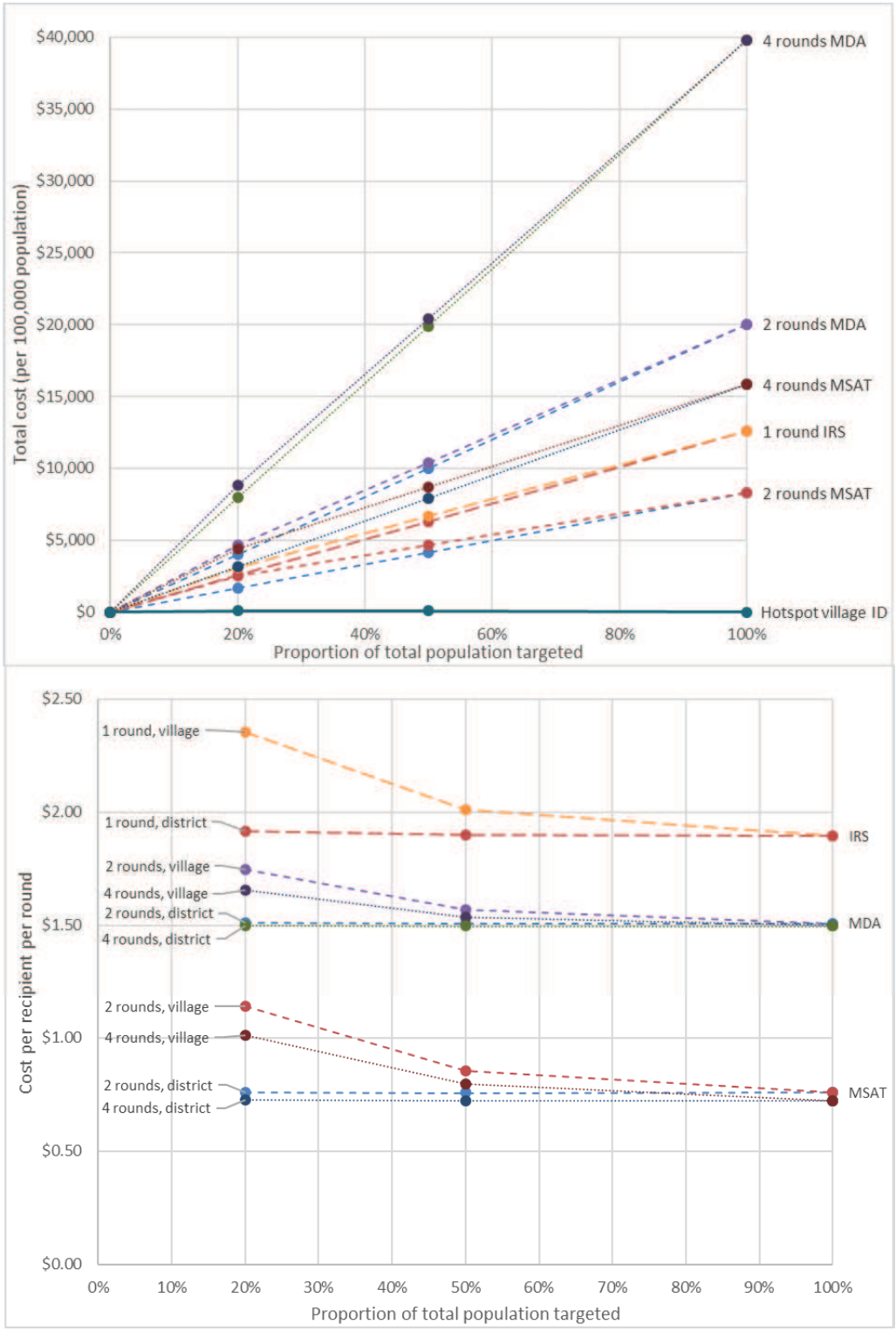
	HOTSPOT INTERVENTIONS			
Total economic costs per 10,000 population	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	$73	$7,326	$5,935	$11,183
CEA BASE CASE: 2 rounds targeted MSAT/MDA across all health posts	$75	$7,135	$5,368	$10,048
CEA BASE CASE (LowIRS): As above except lower IRS coverage	$75	$2,972	$5,368	$10,048
Average economic cost per recipient per round	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	NA	$2.05	$0.91	$1.75
CEA BASE CASE: 2 rounds targeted MSAT/MDA across all health posts	NA	$1.99	$0.82	$1.57
CEA BASE CASE (LowIRS): As above except lower IRS coverage	NA	$2.39	$0.82	$1.57
Mean number of intervention recipients (per 10,000 populatio) per round	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	NA	159,135	70,231	73,236
CEA BASE CASE: 2 rounds targeted MSAT/MDA across all health posts	NA	210,247	191,692	187,532
CEA BASE CASE (LowIRS): As above except lower IRS coverage	NA	72,930	191,692	187,532

Differences in MDA and MSAT costs were driven primarily by differences in the costs of RDTs, DP, and CHWs (Figure 5). The DP tablets ($8,619) accounted for 86% of MDA costs, while RDTs ($2,118) and DP ($112) together accounted for 42% of MSAT costs. Total payments to CHWs were 3.3 times greater for MSAT ($1,800) than for MDA ($551) primarily because far more CHW-days were required; pairs of CHWs provided MDA to a mean of 132 people per day, compared with 48 people per day for MSAT. CHWs providing MSAT were also paid 17% more per day than CHWs providing MDA to account for their more complex tasks. MSAT took substantially longer to deliver because of the additional time necessary to administer and wait for the results of each person's test and then treat positive cases, and because people had greater concerns about MSAT and therefore required more time for discussion. Coverage of MSAT (55% of people targeted) was also lower than of MDA (66%), which reduced the total costs of consumables. The insecticide, Actellic 300CS ($4,441), accounted for 62% of IRS costs, while other resources used in door-to-door delivery, including spray teams and local transport, accounted for 25% ($1,793).

Scenario analyses with our cost model (Figure 6) indicated that reducing the proportion of the population targeted would decrease total costs of IRS, MSAT, and MDA, but increase the average cost per person reached. Under the district-based targeting, the increase in average costs per person reached when moving from 50% to 20% of the population targeted was almost imperceptible; however, for the finer scale, village-based targeting strategy, the increase in average costs per person reached was substantial. For a given intervention and number of rounds, village-based targeting always costs more than district-based targeting in total and on average; however, the differences become wider as the proportion of the population targeted decreases. Furthermore, in devising an intervention strategy, the costs of identifying hotspot villages – though very low in our context – would need to be added to any village-based targeting strategy, whereas no additional resources would be needed in our context to identify higher incidence districts for a district-based targeting strategy, because these data are already routinely collected and analysed. Increasing the number of implementation rounds would increase total costs, but slightly reduce the cost per person reached because subsequent implementation rounds cost less than the first, which requires additional meetings and trainings. The difference in costs between village-based and district-based targeting was smaller for MDA than for either MSAT or IRS because a greater proportion of the costs of MDA varied with the number of people reached, meaning that MDA showed lesser economies of scale, and thus lesser diseconomies of targeting.

Figure 6 Total and average economic costs of Hotspot ID, IRS, MSAT, and MDA: modelled scenarios

The figures illustrate that village-based targeting is always more expensive than district-based targeting and the differences widen as the proportion of the population targeted narrows. The proportion of people targeted in the 10 cost scenarios are shown on the x-axis in both figures. The proportion of people targeted who are reached matches the trial: 66% IRS, 55% MSAT, and 66% MDA. Costs of identifying hotspot villages would need to be added to any village-based targeting strategy (except where 100% of the population is targeted). District-based targeting would not occur any incremental costs in this context because the necessary information is already collected and analysed sufficiently. In the lower figure, "village" and "district" indicate whether village-based or district-based targeting are assumed. Colour-coding on both figures are identical. Hotspot village identification is not shown on the lower figure because there are no direct "recipients" of this information-gathering activity.



The financial costs to Senegal's health service of implementing these four interventions are estimated to be $63 per 10,000 population for hotspot identification (if head nurses and district staff complete the task without additional per diems), $6,418 for IRS, $4,842 for MSAT, and $9,745 for MDA (Table 5). These financial costs would represent 0%, 24%, 18%, and 37%, respectively, of average combined domestic government and external expenditure on malaria per 10,000 population across Senegal, and 0%, 3%, 2%, and 5%, respectively, of Senegal's average general government expenditure on health per 10,000 population. While these targeted intensive strategies would not be expected to be implemented in the entire country, these ratios give a broad indication of the magnitude of costs relative to existing expenditures.

Table 5 Total financial costs and budget impact of Hotspot ID, IRS, MSAT, and MDA: as implemented in trial and base case analysis

"public malaria expenditure": domestic government expenditure and external donor expenditure combined; GGHE: General government expenditure on health (from all financing sources).

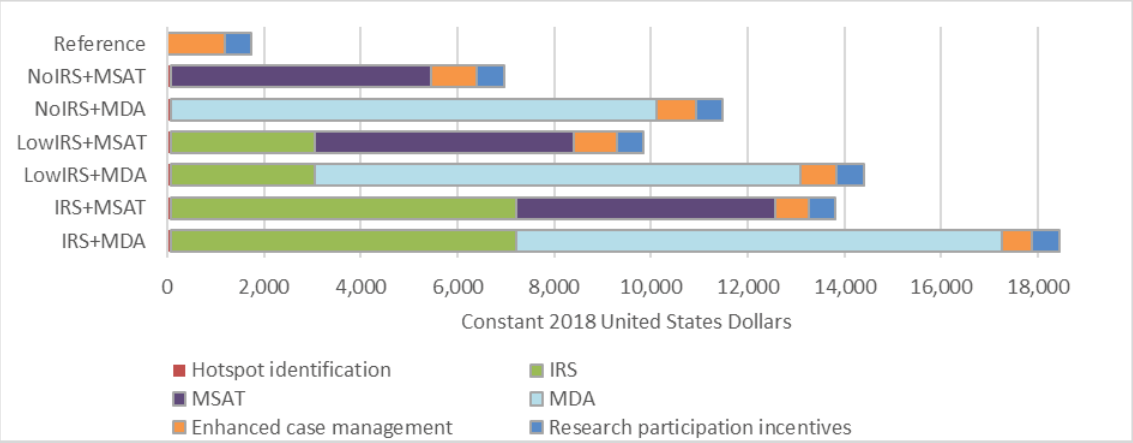
	INTERVENTIONS			
Total financial costs per 10,000 population	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	$63	$6,538	$5,310	$10,825
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	$63	$6,418	$4,842	$9,745
CEA BASE CASE (LowIRS): As above except lower IRS coverage	$63	$2,495	$4,842	$9,745
Financial costs as % public malaria expenditure	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	0%	25%	20%	41%
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	0%	24%	18%	37%
CEA BASE CASE (LowIRS): As above except lower IRS coverage	0%	9%	18%	37%
Financial costs as % GGHE	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	0%	3%	3%	5%
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	0%	3%	2%	5%
CEA BASE CASE (LowIRS): As above except lower IRS coverage	0%	1%	2%	5%

Treatment costs

The economic cost to providers of each uncomplicated or severe malaria case was estimated to be $4 or $46, respectively, on average. Including the opportunity cost to households of illness increased estimated costs to $21 and $85, respectively, per case. When combined with the proportion of all malaria cases detected by the health service that resulted in hospitalisation, we found that severe cases accounted for 22% of the economic costs to the provider of case management and 43% of the societal cost of malaria cases. In the deterministic analysis (which, unlike the probabilistic analysis, allowed breakdown of each strategy's costs by intervention), treatment of malaria cases cost $1,185 per 10,000 population with the reference strategy, and $620 with IRS+MDA (), the most effective strategy, resulting in a maximum savings of $565 in treatment costs averted per 10,000 population (Figure 7).

Figure 7 Total economic cost of strategies by intervention component

Total economic costs per 10,000 population are presented for the base case scenario. Research participation incentives are included in this graph (and not in any other graphs or tables) to indicate their magnitude, as they may have contributed to more assiduous implementation; however, they cannot be attributed to individual interventions, and as they were paid in all strategies, they do not represent incremental costs in any of the intensive strategies relative to the control. IRS: Indoor residual spraying; MDA: Mass drug administration; MSAT: Mass screening and treatment.



Combined costs of each multi-component strategy

When the base case estimates of individual intervention costs were combined in the probabilistic sensitivity analysis with estimates of the number of cases occurring with each strategy, the reference strategy was the least expensive at $1,186 ($958 to $1,448) per 10,000 population, followed by NoIRS+MSAT ($6,401, $5,122 to $7,833), LowIRS+MSAT ($9,286, $7,826 to $10,886), NoIRS+MDA ($10,928, $8,588 to $13,593), IRS+MSAT ($13,254, $11,093 to $15,566), LowIRS+MDA ($13,846, $11,392 to $16,563), and IRS+MDA ($17,889, $14,965 to $21,060), the most expensive strategy (Table 3**Error! Reference source not found.**).

In addition, research participation incentives of $562 per 10,000 population were provided to health post, district, and regional staff under all strategies (**Error! Reference source not found.**). While intended to support research, these payments likely encouraged more assiduous implementation; however, they were not specific to any of the four interventions and did not generate incremental costs for any of the intervention strategies relative to the reference strategy. They are therefore shown in **Error! Reference source not found.**, but not in other results.

Cost-effectiveness

In the base case analysis, LowIRS+MSAT, LowIRS+MDA, and NoIRS+MDA were dominated, meaning that they were both less effective and more costly than alternatives (Figure 8). Relative to the control, the first strategy on the expansion path, NoIRS+MSAT, cost an additional $9,839 (95% CI: $4,939 to $34,054) per DALY averted and was both the least costly and least effective of the targeted strategies. Relative to NoIRS+MSAT, the next strategy on the expansion path,

IRS+MSAT, cost an additional $10,221 ($5,597 to $32,423) per DALY averted. Relative to IRS+MSAT, IRS+MDA cost an additional $36,203 ($13,084 to $121,785) per DALY averted and was both the most effective and most costly strategy. At all plausible cost-effectiveness thresholds, the reference strategy was most likely to be the most cost-effective (but least effective) strategy based on the short-term disease burden reductions achieved (Figure 9).

Figure 8 Probabilistic sensitivity analysis on the cost-effectiveness plane

Points on the expansion path are labelled in black with black borders. Dominated strategies are labelled in grey. DALY: Disability-adjusted life-year; IRS: Indoor residual spraying; MDA: Mass drug administration; MSAT: Mass screening and treatment; USD: United States dollars.

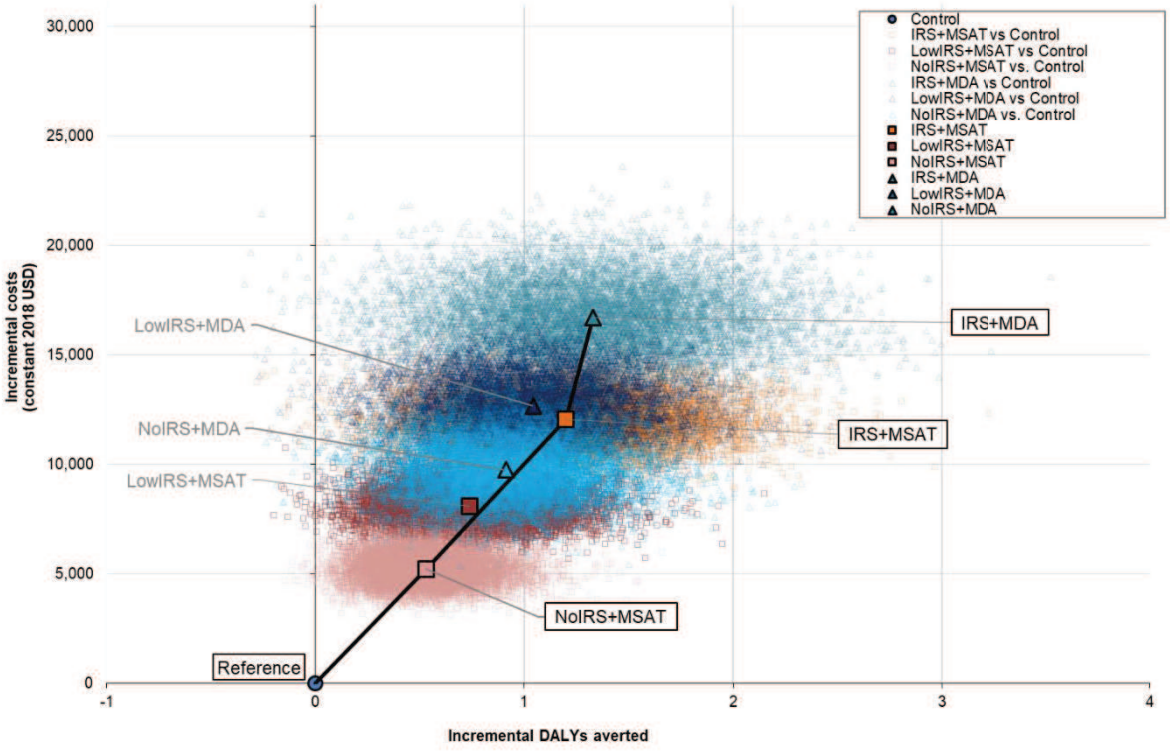
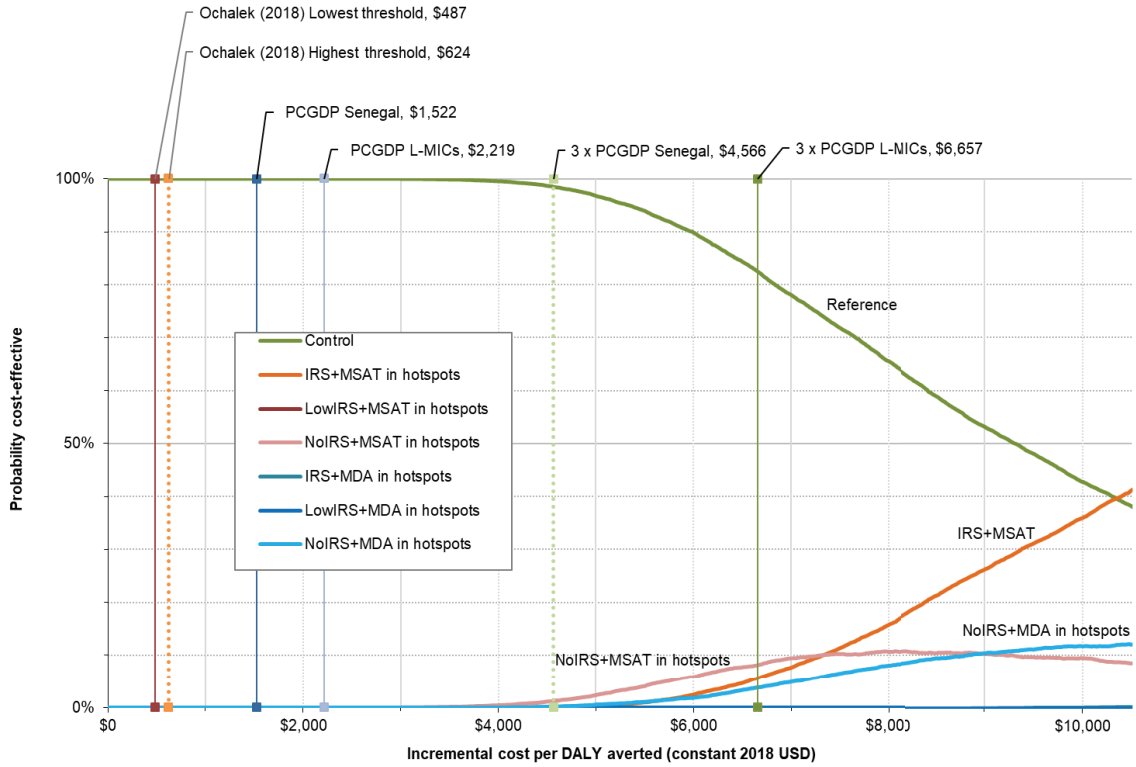


Figure 9 Cost-effectiveness acceptability curves

Thresholds are described further in Section 6.1.7. DALY: Disability-adjusted life-year; IRS: Indoor residual spraying; LICs: Low-income countries; MDA: Mass drug administration; MICs: Middle-income countries; MSAT: Mass screening and treatment; PCGDP: Per capita gross domestic product; USD: United States dollars.



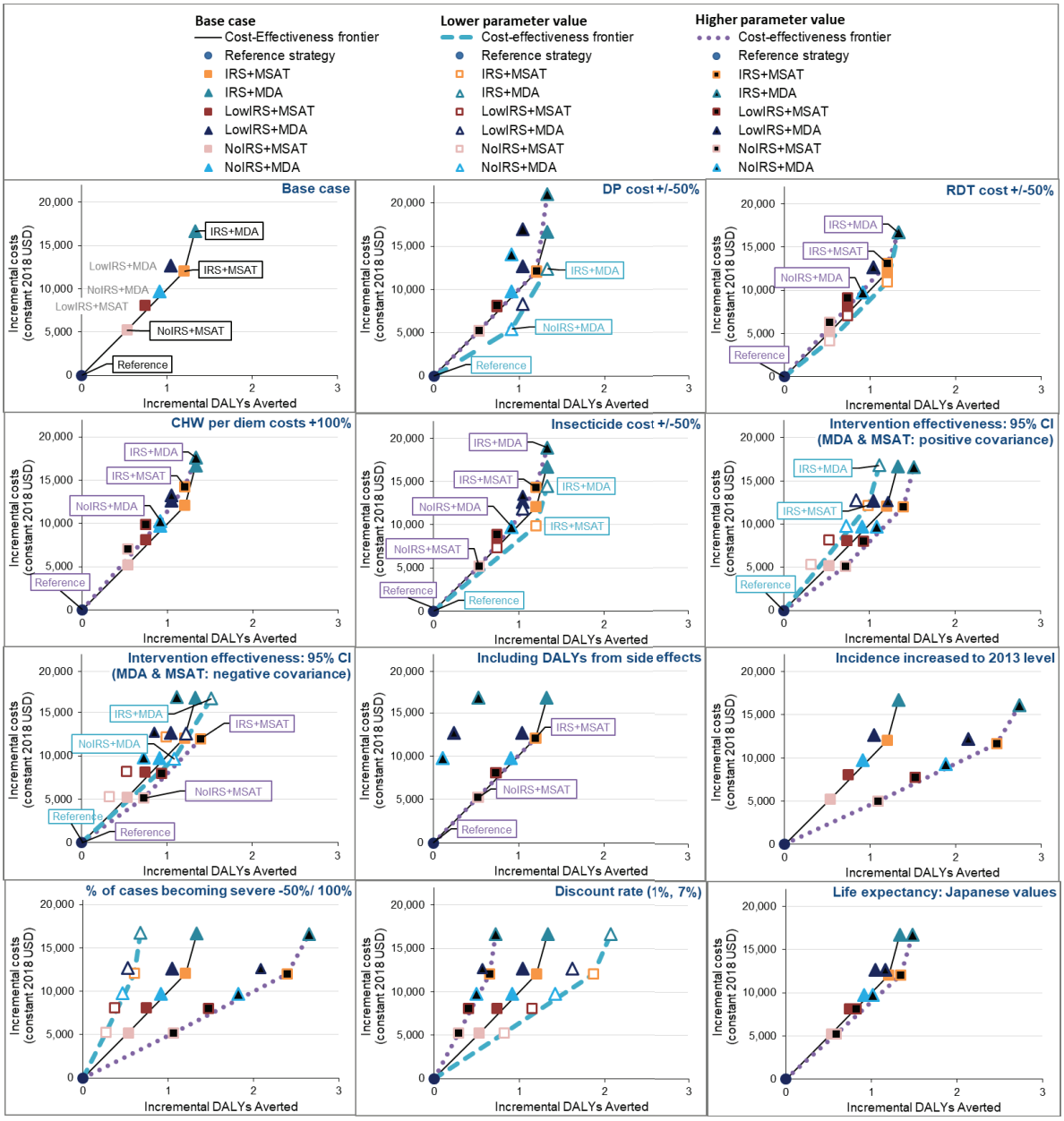
In a series of one-way sensitivity analyses, the expansion path changed to include NoIRS+MDA when DP costs decreased; if DP costs were 50% lower than in our base case, all MSAT strategies and LowIRS+MDA would be dominated and the expansion path would include only the reference strategy, NoIRS+MDA and IRS+MDA (Figure 10). When RDT costs or CHW per diem costs increased, NoIRS+MDA became the first point on the expansion path, followed by IRS+MSAT and IRS+MDA. When insecticide costs decreased by half and when the effectiveness of each of the strategies were at the upper bound of their confidence intervals, all MDA strategies and NoIRS+MSAT were dominated, and the expansion path extended directly from the reference strategy to IRS+MSAT and then IRS+MDA (Figure 10). If the effectiveness of MDA strategies were at the upper bounds of their 95% confidence intervals and the effectiveness of MSAT strategies at their lower bounds, the expansion path would extend from the reference strategy to NoIRS+MDA and IRS+MDA. In the reverse situation, with MDA strategies at their lower bounds of plausible effectiveness and MSAT strategies at their upper bounds, the expansion path would extend from the reference strategy to NoIRS+MSAT and IRS+MSAT.

The expansion path would also exclude the MDA strategies if DALY estimates were adjusted for adverse events associated with MDA and MSAT. The brief finger pain reported by 42% of MSAT recipients only added 0.004 DALYs per 10,000 population to the MSAT strategies. Accounting for the smaller proportion (19%) of MDA recipients who experienced non-serious side effects, such as headache and dizziness, added 0.3 DALYs to MDA strategies, while accounting for the child who died following MDA administration added 0.5 DALYs per 10,000 population. The non-serious adverse events alone would have caused IRS+MDA to be dominated, while inclusion of the single death (out of nearly 300,000 courses of MDA in the 2-year trial) more than halved the DALYs averted by IRS+MDA relative to control and nearly eliminated the DALYs averted by NoIRS+MDA relative to control.

Plausible variation in incidence (within our very low incidence context), the proportion of cases becoming severe, and the discount rate all led to substantial changes in ICERs, but did not alter the expansion path from the base case. The incremental cost per DALY averted of NoIRS+MSAT relative to the reference strategy fell substantially in these three analyses to $4,559 (higher incidence), $4,902 (higher proportion progressing to severe), and $6,320 (lower discount rate); however, these values remain far above all plausible cost-effectiveness thresholds. While they are near three times Senegal's per capita GDP ($4,566), this threshold is now recognized to be unaffordably high (Ochalek et al., 2018, Marseille et al., 2015). Using Japanese instead of Senegalese life expectancy values only slightly decreased ICERs and did not change the expansion path.

Figure 10 Deterministic sensitivity analysis on the cost-effectiveness plane

The deterministic base case is shown with 11 deterministic sensitivity analyses, ordered (approximately) from largest to smallest impact on the expansion path and ICERs. Solid colour points and black lines show the base case and associated cost-effectiveness frontier, respectively, and are identical on all 12 panels. The slope of each line is the incremental cost-effectiveness ratio. Points not on a line are dominated by more cost-effective alternatives. Hollow points and light blue dashed lines show strategies at the lower parameter value. Points with black centres and purple dotted lines show strategies at the higher parameter value. Where the expansion path differs from the base case, strategies on the expansion path are labelled in light blue boxes (for lower parameter value) or purple boxes (for higher parameter values). Square points show MSAT-based strategies and triangular points show MDA-based strategies. DALY: Disability-adjusted life-year; DP: Dihydroartemisinin-piperaquine; IRS: Indoor residual spraying; MDA: Mass drug administration; MSAT: Mass screening and treatment; USD: United States Dollars.



5.1.5. Discussion

In the trial setting, the hotspot strategies evaluated successfully reduced both incidence and transmission, but did not achieve "virtual elimination" as intended. Our cost analysis is valuable in showing how the costs of geographically targeted MDA, MSAT, and IRS could be expected to vary with changes in context or input prices, or with strategy modifications which decision-makers may want to consider. We demonstrate the diseconomies of village-based targeting relative to district-based targeting or blanket intervention. That is, the average costs per recipient increases as the proportion of the population targeted in a village-based targeting strategy falls. The costs of identifying hotspot villages were very low in our study relative to the costs of the interventions themselves; however, such information costs may be much higher in contexts with weaker health systems. In our study, the diseconomies of targeting were primarily driven by diseconomies of reduced scale as costs incurred at health post, district, and higher levels were divided across a decreasing proportion of the population. Targeting interventions to a fraction of the population can substantially decrease total costs, but these cost reductions are not linear. For a given degree of targeting (e.g. 20% of the population), employing district-based targeting rather than the village-based targeting evaluated in our trial would reduce total costs, especially if <50% of the population are targeted. Increasing the number of consecutive monthly rounds would substantially increase total costs, while slightly decreasing the cost per recipient per round of MSAT and, to a lesser extent, MDA. If implemented in a large proportion of the country, these interventions would require substantial relative increases in donor and/or domestic government expenditure, which would likely displace other activities, whether for malaria or other health priorities in Senegal or elsewhere. Nonetheless, targeting interventions at villages rather than higher-level units, such as districts, may prove more economically efficient in contexts where high sensitivity and specificity of targeting at fine spatial scale can be achieved.

In contexts with comparably low incidence and case fatality rates and similar costs, neither two rounds of targeted MDA nor two rounds of targeted MSAT, with or without the addition of targeted IRS, can be considered cost-effective for short-term reductions in disease burden because the same value of resources could avert substantially more DALYs if used for alternative interventions in Senegal or other low- or lower-middle-income countries. These strategies would become more cost-effective in contexts with higher incidence or rates of progression to severe disease (e.g. where immunity and/or access to care were lower) than observed in our trial setting, or if the costs of tests, drugs, and insecticides were substantially lower. The relative efficiency of MDA and MSAT strategies was sensitive to the costs of DP, RDTs, and CHWs, and to uncertainty in

effectiveness estimates. While these targeted strategies are inherently equitable in that they preferentially benefit people at greatest malaria risk within the implementation area (even if they do not personally receive the interventions), they could also be viewed as an inequitable prioritisation of malaria control amongst people at low overall risk when the same resources could generate more substantial health benefits if used towards other health areas or populations at greater risk.

Our development of a flexible and transparent cost model based on detailed primary data collection is a particular strength of our research. It allowed us to generate findings of wider use beyond the study setting to inform future intervention design and analysis. In particular, it showed how to account for economies of scale and diseconomies of targeting, and how these differed between IRS, MDA, and MSAT. Whereas Larson and colleagues' approach recommended calculating the average unit cost for each activity (e.g. cost per training) comprising an intervention (Larson et al., 2016) and PMI's approach involved identifying fixed costs of IRS at a national level and considering all other costs variable (with the number of structures sprayed) (Cico and Johns, 2018), our analysis recognized that some costs vary with the output level, but other costs vary with the number of CHWs, health posts, or districts involved in the intervention. Understanding this cost structure is particularly important in analysing geographically targeted strategies, and also explains some of the variation in average costs across different health system contexts.

The trial's design allowed it to capture both the direct and indirect effects of intervention strategies within and outside the targeted hotspot villages, and thus measure the impact on transmission directly. It was not, however, designed to assess the incremental costs and effects of adding targeted IRS to targeted MDA or MSAT, nor the effectiveness of targeted IRS alone. We exploited the unintended variation in strength of IRS implementation between the first and second implementation years to explore the value of adding targeted IRS to either targeted MSAT or MDA. This exploration indicated that targeted IRS produced only small incremental gains when added to targeted MDA, but that targeted IRS+MSAT produced more than twice the health benefits of targeted NoIRS+MSAT, possibly because the imperfect sensitivity of RDTs and higher rates of MSAT refusal meant that MSAT alone missed cases that could have been averted by either IRS or MDA. The many assumptions underpinning this modelling, however, mean that these findings warrant further evaluation in field trials robustly designed for this purpose.

We did not model potential changes in effectiveness that could be expected from other possible modifications to the strategies (i.e. changes in the degree and/or level of targeting or number of

implementation rounds) because doing so would require highly complex and uncertain transmission modelling, beyond the scope of existing models (Stresman et al., 2019). We considered a range of discount rates; however, because PMI funds most of Senegal's (and many other countries') NMCP activities, with additional support from other donors, a discount rate representing donors' opportunity costs (3%), rather than Senegal's, seemed most appropriate for the base case. The DALY weights used to calculate the years of life lived with disability for malaria have many limitations; however, more accurate weights and accounting for long-term sequelae are unlikely to substantially alter overall DALY estimates, which are driven almost entirely by the years of life lost from deaths. The reference strategy comprised standard practice plus some additional malaria control measures and research participation incentives paid to health workers, which were also paid in the intervention strategies. The fact that the reference strategy did not perfectly match usual practice may have either underestimated the effectiveness of the hotspot strategies (by reducing scope for impact) or overestimated their effectiveness (if the extra nets provided in the reference strategy had a synergistic effect with the hotspot strategies, as predicted in transmission models, or if the incentives encouraged more assiduous implementation of the interventions). Any such impact is, however, unlikely to have affected our overall conclusions. By comparing financial costs per capita for each intervention scenario with relevant national per capita budgets, we provided a useful indication of the scale of expenditure required for implementation; however, we did not conduct a full budget impact analysis, which would require identification of all districts in Senegal for which intensive strategies were recommended and adaptation of the cost model to these districts. While we populated our decision analytic model with best available evidence, including carefully collected primary cost and outcome data, and selected plausible parameter distributions, our estimates may have been biased by missing data, misclassification, and incorrect parameter distributions, and there is structural uncertainty in our models.

This paper contributes to scant literature on the economics of MDA, MSAT, next generation IRS, and geographical targeting of public health interventions. Our estimates of the financial costs of delivering MDA ($0.21 per person-round excluding DP costs) were lower than the three experiences of (blanket) MDA for malaria for which WHO collected retrospective financial data in 2015 ($0.36 per person-round in Sierra Leone, $11.05 in Comoros, and $0.53 in Vanuatu excluding drug costs, constant 2015 USD) (WHO Evidence Review Group, 2015b). Two of these studies were implemented on a relatively small scale on remote islands, which may partially explain their higher costs. The enormous scale of delivery of malaria MDA to 2.5m people in Sierra Leone during the Ebola emergency likely led to some economies of scale; however, the extremely

challenging health system context may explain why we estimated lower costs in the stable, relatively well-functioning health system context of central Senegal, where formal health workers, CHWs, and families were already familiar with MDA for children under 10 (i.e. SMC). In virtually the same context as our study, the economic costs of blanket (i.e. not geographically targeted) SMC was estimated around $0.50 (constant 2010 USD) per child per round (Pitt et al., 2017), which, given the low cost of the sulphadoxine-pyrimethamine and amodiaquine used (~$0.11) reflects somewhat higher delivery costs than in our study. This is unsurprising, as while geographical targeting and only having two administration rounds slightly increases the cost per person per round, including all people in the household in drug distribution would be expected to decrease average costs per recipient.

We only identified one previous empirical MSAT cost estimate; three dry-season rounds in Zambia cost $4.39 (range: $1.62-13.96, constant 2012 USD) per person-round (Silumbe et al., 2015), substantially more than our estimate of $0.91 per person-round. This difference may reflect the far higher test positivity rate (13% vs. 1% in our study), higher coverage rates achieved, higher transport costs, and inclusion of substantial overhead costs in the Zambian setting, as well as other factors (Silumbe et al., 2015). While Silumbe and colleagues described MSAT as "highly cost-effective" relative to WHO thresholds in their study's moderate transmission setting, their estimate of an incremental cost of $804 per DALY averted would not be considered cost-effective relative to thresholds more recently proposed (Ochalek et al., 2018). An earlier modelling exercise projected substantially higher MSAT costs than in our study, of $5 to $11 (constant 2007 USD) per person-round plus the costs of treatment (Crowell et al., 2013), largely because it assumed that CHWs could administer MSAT to far fewer people per day and that the costs of CHW per diems and RDTs were more than twice as high as we observed in practice.

More recent modelling (Walker et al., 2016) used many of the same parameter estimates as Crowell and colleagues and, like them, only considered outcomes as cases, and not deaths or DALYs. For IRS, Walker et al used a median cost of $8.80 per person protected in 2012 across countries receiving PMI IRS funding. This median was substantially higher than PMI's estimate for Senegal in 2017 of $6.57 (Cico and Johns, 2018), and more than four times our own estimate of $1.99 per person protected in 2015. Our IRS cost estimates may have been lower than PMI's because we did not include the fixed national-level costs associated with the existence of an IRS programme, and because our study was conducted in an easier-to-reach area than the four southern Senegalese districts in PMI's IRS programme. Further, Walker and colleagues' model did not account for the effects of interventions on neighbouring areas or account for economies of

scale or the level at which interventions are targeted. Despite these differences, our findings concur with modelling indicating that MSAT is unlikely to be cost-effective in low transmission settings (Crowell et al., 2013) and questioning the added value of IRS in central Senegal if MSAT or MDA are implemented (Walker et al., 2016). That our estimates may underestimate the costs of these interventions further underscores our overall conclusion that these interventions, as implemented in our study, cannot be considered cost-effective in comparable contexts.

Future research should explore the effects of strategies involving different combinations of interventions, degrees and levels of targeting, and numbers of rounds of intensive interventions in different contexts, and their associated costs. While additional field research is important, the choice of which strategies to test in which contexts should be guided by analysis using both transmission models and the cost model developed here. Further economic research should be conducted to improve understanding of how cost data on new interventions from trials such as this one can be used to develop models that accurately inform wider decision-making across contexts.

Our findings are particularly relevant for policy making in low transmission settings and other contexts where MDA, MSAT, and IRS are considered. While the NMCPs of Senegal and other countries, as well as WHO, the Gates Foundation, and many other institutions and individuals vociferously champion malaria elimination, the question of whether malaria elimination can be achieved and is an equitable goal in the medium term remains highly contested (Lines et al., 2008, Shah, 2010, McNeil Jr., 2008). The challenges in malaria elimination are not only technical and economic, but social (Hausmann-Muela and Eckl, 2015), political, and ecological (Little, 2013). One concern is that the push towards elimination, like the Global Malaria Eradication Plan of the 1950s to 1960s, may prove unsuccessful, in which case any resources used will carry a high opportunity cost in terms of lives that could have been saved if the resources had been focused on those areas with the greatest disease burdens. Others argue that malaria programme efforts should focus on disease control (rather than elimination), with greater efforts focused on social and economic development, including housing improvements, which could lead to sustainable elimination and wider social benefits (Tusting et al., 2013). Elimination advocates counter that elimination cannot wait, and must be achieved before drug and insecticide resistance and waning global commitment lead to a deadly global resurgence, and that continuous, effective control is not possible. Our findings provide important empirical evidence on the affordability, efficiency, and trade-offs involved in several interventions expected to play a role in elimination efforts, and thus make an important contribution to the elimination debate.

5.1.6. Annex 1: Additional information on the effectiveness analysis

Projecting potential effectiveness of MSAT or MDA in hotspots without IRS

To estimate the incidence rate ratios for NoIRS+MSAT and NoIRS+MDA relative to control, we used the data collected in the trial to model the rate ratio for an intervention strategy relative to the control as a linear function of the effective coverage of IRS, as follows:

$$RR_{Strategy} = m * \ EffectiveCoverage_{IRS} + b$$

Where $RR_{Strategy}$ denotes the incidence rate ratio for either the MDA or MSAT strategy relative to control, *m* and *b* are constants, and $EffectiveCoverage_{IRS}$ is the product of the proportion of targeted households that received IRS (IRS coverage) and the efficacy of that spraying (IRS efficacy), expressed as the % of mosquitoes that die in a 24-hour knockdown test, performed 4 months after the spraying.

As the effectiveness of the MDA strategy was only slightly lower when combined with LowIRS (RR=0.68) rather than IRS (RR=0.62), the model predicted only a slight further diminution in effectiveness if MDA were to be combined with NoIRS (RR=0.71) (Table 6). For MSAT, however, the effectiveness when combined with IRS (RR=0.65) was substantially higher than when combined with LowIRS (RR=0.78), and so the model predicted a larger diminution in effectiveness if MSAT were combined with NoIRS (RR=0.84). This analysis suggests that in the IRS+MSAT strategy, roughly 54% of the malaria cases, deaths, and DALYs averted were attributable to the use of IRS, whereas 46% were attributable to MSAT.

Table 6 Modelled estimates of the effectiveness of MDA and MSAT strategies with No IRS

		IRS coverage scenario		
	Variable	**IRS (based on 2014 data)**	**LowIRS (based on 2013 data)**	**NoIRS (modelled)**
	IRS coverage	0.74	0.23	0
	IRS efficacy	0.82	0.37	0
	***EffectiveCoverage*$_{IRS}$**	0.74	0.23	0.00
Effectiveness (rate ratio relative to control)	**MDA strategy (RR_{MDA})**	0.52	0.63	0.67
	MSAT strategy (RR_{MSAT})	0.57	0.74	0.81
Standard error (SE) for effectiveness estimate	**MDA strategy (SE_{MDA})**	0.037	0.034	0.034
	MSAT strategy (SE_{MSAT})	0.037	0.037	0.037

All four standard errors for the rate ratios that were empirically estimated based on IRS and LowIRS combined with MDA or MSAT were very similar with one another. We therefore assumed that the standard error for NoIRS combined with either MSAT or MDA would match the standard error for either strategy combined with LowIRS.

DALY calculations

We estimated DALYs as follows:

$$DALYs = YLDs + YLLs$$

To estimate YLDs for each strategy, the number of severe and uncomplicated cases of malaria were estimated and multiplied by the average duration of each case and a disability weight reflecting the severity of the case, as follows:

$$YLD = (Cases_{severe} * Duration_{severe} * \ DisabilityWeight_{severe}) \ + (Cases_{uncomplicated} * Duration_{uncomplicated} * \ DisabilityWeight_{uncomplicated})$$

The number of malaria cases for each strategy in our model was estimated as the product of the hypothetical population, the incidence in the reference arm, and the rate ratio of malaria incidence in the relevant arm with respect to the reference arm:

$$Cases = Population * Incidence_{Control} * RateRatio$$

To estimate YLLs for each strategy, we multiplied the number of deaths expected in each strategy and an estimate of the number of years of life lost with each death. The number of deaths expected was estimated as the product of the number of severe cases and the probability that a severe case would result in death based on analysis of the passive surveillance data.

We estimated the number of YLLs associated with each of the 15 malaria-related deaths observed in the entire study area in the 2-year period.

$$YLL = Cases_{severe} * Prob_{death} * YLLs$$

We also used additional analyses of passive surveillance data from all health facilities and CHWs providing malaria treatment across the study area to determine the proportion of severe malaria cases that resulted in death and the age and sex of people who died of malaria. Across the entire study area and two-year intervention period, only 15 malaria-related deaths were recorded. As the number of YLLs associated with each death depends upon the person's remaining life expectancy, which in turn depends on their age at death and sex, we estimated the YLLs associated with each death separately, using discounting but no age weighting. The discounting

used reflected the overall discount rate for costs and effects used in our model, which was 3% in the base case and varied in our sensitivity analyses. Based on the discounted YLLs estimated for each of our 15 observations, we estimated the mean and standard deviation (s.d.) for the number of YLLs per death in our setting, which were then used in probabilistic sensitivity analysis.

DALYs associated with side effects

In the deterministic sensitivity analysis, we examined the impact on effectiveness and cost-effectiveness estimates of including DALYs associated with side effects, which are not usually accounted for in malaria (or other) models (Table 7).

Table 7 Additional parameters: DALYs associated with side effects of MDA and MSAT

ADDITIONAL EFFECTS PARAMETERS	Base case	Source
Side effects of MSAT (only included in deterministic sensitivity analysis)		
Probability of finger pain	0.419	Trial estimates from Day 4 survey
Duration of symptoms (days)	0.083	Assumption
DALY weight pain (open wound, short term)	0.006	Salomon et al, 2015
Side effects of MDA (only included in deterministic sensitivity analysis)		
Risk of death per year from MDA across the population (hotspot and non-hotspot)	2.2E-06	Trial estimate from 1 death in MDA arm across 2 administration years
Probability of non-fatal side effects from MDA	0.187	Trial estimates from Day 4 survey
Duration of symptoms (days)	2.000	Assumption
Probability headache	0.225	Trial estimates from Day 4 survey
Probability dizziness	0.250	Trial estimates from Day 4 survey
Probability diarrhea	0.168	Trial estimates from Day 4 survey
Probability fever	0.170	Trial estimates from Day 4 survey
Probability abdominal pain	0.115	Trial estimates from Day 4 survey
Probability nausea	0.107	Trial estimates from Day 4 survey
Probability vomiting	0.137	Trial estimates from Day 4 survey
DALY weight headache (tension-type)	0.037	Salomon et al, 2015
DALY weight dizziness (infectious disease moderate)	0.051	Salomon et al, 2015
DALY weight diarrhea (mild)	0.074	Salomon et al, 2015
DALY weight fever (infectious disease mild)	0.006	Salomon et al, 2015
DALY weight abdominal pain (mild)	0.011	Salomon et al, 2015
DALY weight nausea (mild)	0.011	Salomon et al, 2015
DALY weight vomiting (infectious disease moderate)	0.051	Salomon et al, 2015

5.1.7. Annex 2: Additional information on thresholds used

As neither Senegal nor other countries that might want to consider these strategies have explicit cost-effectiveness thresholds, two sets of thresholds were used because they were either widely used or considered plausible.

The first set of thresholds, based on multiples of per capita gross domestic product (GDP) per DALY averted, have long been referred to as "the WHO thresholds", although they are no longer supported by WHO and accepted to be too high (Marseille et al., 2015, Bertram et al., 2016). Based on these thresholds, interventions costing less than per capita GDP per DALY averted were considered "highly cost-effective", while those costing less than three times per capita GDP per DALY averted were considered "cost-effective." This approach was applied using estimates of per capita GDP in 2018 for Senegal, low-income countries, and lower-middle-income countries.

The second set of thresholds were based on work by Ochalek and colleagues (2018) to define empirically supply-side cost-per-DALY thresholds for countries globally. They generated four alternative estimates for each country based on different sets of assumptions. To update the estimates for Senegal to 2018 values, we used the published estimates of the threshold as a proportion of GDP in 2015, and then applied these same proportions to Senegal's GDP in 2018. While the proportions should be expected to vary with the per capita GDP level, this approach appeared a sufficient approximation, especially as the ICERs generated were very distant from these estimated thresholds. While these thresholds are relevant for provider costs and our ICERs reflect societal costs, the societal perspective produces lower ICERs than a provider perspective for our interventions, making it more likely that they would fall below the threshold. However, even with this advantage, the societal ICERs we produced remained far above the supply-side thresholds.

5.1.8. Annex 3: Additional results: Costs of hotspot identification, IRS, MSAT, and MDA

Table 8 Economic costs of Hotspot ID, IRS, MSAT, and MDA: as implemented in trial and for modelled scenarios

In the trial, 36% of intervention arm residents received IRS, 33% of MSAT arm residents received MSAT, and 32% received MDA, which is reflected in the "Implementation in trial" and base case. The 10 cost scenarios indicate the proportion of people targeted, and the proportion of people targeted who are reached matches the trial: 66% IRS, 55% MSAT, and 66% MDA. HP: Health post; S: Scenario. *Identifying hotspot health posts is assumed not to incur incremental costs because incidence by health post is already reported to Dakar.

	INTERVENTIONS			
Total economic costs per 10,000 population	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	$73	$7,326	$5,935	$11,183
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	$75	$7,135	$5,368	$10,048
CEA BASE CASE (LowIRS): As above except lower IRS coverage	$75	$2,972	$5,368	$10,048
S1: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted	$0	$12,566	$8,286	$20,035
S2: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	$75	$6,664	$4,664	$10,411
S3: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	$75	$3,122	$2,491	$4,637
S4: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted (by village)	$0	$12,566	$15,828	$39,767
S5: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	$75	$6,664	$8,696	$20,416
S6: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	$75	$3,122	$4,416	$8,805
S7: 2 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	$0*	$6,294	$4,143	$10,018
S8: 2 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	$0*	$2,544	$1,662	$4,013
S9: 4 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	$0*	$6,294	$7,914	$19,884
S10: 4 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	$0*	$2,544	$3,168	$7,958
Cost per recipient per round	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	NA	$2.05	$0.91	$1.75
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	NA	$1.99	$0.82	$1.57
CEA BASE CASE (LowIRS): As above except lower IRS coverage	NA	$2.39	$0.82	$1.57
S1: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted	NA	$1.90	$0.76	$1.51
S2: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	NA	$2.01	$0.85	$1.57
S3: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	NA	$2.35	$1.14	$1.75
S4: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted (by village)	NA	$1.90	$0.72	$1.50
S5: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	NA	$2.01	$0.80	$1.54
S6: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	NA	$2.35	$1.01	$1.66
S7: 2 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	NA	$1.90	$0.76	$1.51
S8: 2 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	NA	$1.92	$0.76	$1.51
S9: 4 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	NA	$1.90	$0.72	$1.50
S10: 4 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	NA	$1.92	$0.72	$1.50
Mean number of intervention recipients per round	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	NA	159,135	70,231	73,236
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	NA	210,247	191,692	187,532
CEA BASE CASE (LowIRS): As above except lower IRS coverage	NA	72,930	191,692	187,532
S1: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted	NA	389,403	320,953	389,797
S2: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	NA	194,702	160,477	194,899
S3: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	NA	77,881	64,191	77,959
S4: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted (by village)	NA	389,403	320,953	389,797
S5: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	NA	194,702	160,477	194,899
S6: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	NA	77,881	64,191	77,959
S7: 2 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	NA	194,702	160,477	194,899
S8: 2 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	NA	77,881	64,191	77,959
S9: 4 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	NA	194,702	160,477	194,899
S10: 4 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	NA	77,881	64,191	77,959

Table 9 Financial costs and budget impact of Hotspot ID, IRS, MSAT, and MDA: as implemented in trial and for modelled scenarios

"public malaria expenditure": domestic government expenditure and external donor expenditure combined; GGHE: General government expenditure on health (from all financing sources).

	INTERVENTIONS			
Total financial costs per 10,000 population	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	$63	$6,538	$5,310	$10,825
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	$63	$6,418	$4,842	$9,745
CEA BASE CASE (LowIRS): As above except lower IRS coverage	$63	$2,495	$4,842	$9,745
S1: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted	$0	$11,536	$7,759	$19,733
S2: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	$63	$5,974	$4,137	$10,109
S3: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	$63	$2,637	$1,964	$4,334
S4: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted (by village)	$0	$11,536	$14,881	$39,250
S5: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	$63	$5,974	$7,749	$19,898
S6: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	$63	$2,637	$3,469	$8,287
S7: 2 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	$0	$5,774	$3,880	$9,866
S8: 2 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	$0	$2,322	$1,556	$3,952
S9: 4 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	$0	$5,774	$7,441	$19,625
S10: 4 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	$0	$2,322	$2,980	$7,855
Financial costs as % public malaria expenditure	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	0%	25%	20%	41%
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	0%	24%	18%	37%
CEA BASE CASE (LowIRS): As above except lower IRS coverage	0%	9%	18%	37%
S1: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted	0%	43%	29%	74%
S2: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	0%	22%	16%	38%
S3: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	0%	10%	7%	16%
S4: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted (by village)	0%	43%	56%	148%
S5: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	0%	22%	29%	75%
S6: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	0%	10%	13%	31%
S7: 2 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	0%	22%	15%	37%
S8: 2 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	0%	9%	6%	15%
S9: 4 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	0%	22%	28%	74%
S10: 4 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	0%	9%	11%	30%
Financial costs as % GGHE	Hotspot ID	IRS	MSAT	MDA
Implementation in trial	0%	3%	3%	5%
CEA BASE CASE: 2 rounds MSAT/MDA across all health posts	0%	3%	2%	5%
CEA BASE CASE (LowIRS): As above except lower IRS coverage	0%	1%	2%	5%
S1: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted	0%	5%	4%	9%
S2: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	0%	3%	2%	5%
S3: 2 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	0%	1%	1%	2%
S4: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 100% targeted (by village)	0%	5%	7%	19%
S5: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 50% targeted (by village)	0%	3%	4%	9%
S6: 4 rounds MSAT/MDA across all 4 districts, 46 HPs; 20% targeted (by village)	0%	1%	2%	4%
S7: 2 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	0%	3%	2%	5%
S8: 2 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	0%	1%	1%	2%
S9: 4 rounds MSAT/MDA across 2 districts, 23 HPs; 50% targeted (by district and HP)	0%	3%	4%	9%
S10: 4 rounds MSAT/MDA across 1 district, 9 HPs; 20% targeted (by district and HP)	0%	1%	1%	4%

5.2. Mechanistic cost modelling of intensive malaria strategies

5.2.1. Mechanistic cost model: Approach

The mechanistic cost model we developed generated estimates of how the costs of implementing each intervention (IRS, MSAT, MDA, hotspot identification) would vary with specific aspects of the implementation context and modifications to the interventions, as well as changes in input prices, resource use, and epidemiology.

The model disaggregates the total costs of each intervention in the trial context in 2014 by implementation round and by what we refer to as "**variation unit**". We define "variation units" as the level of the health system or output with which the costs would be expected to vary linearly. This approach facilitates modelling of costs in another context based on relatively easily obtainable data, while accounting for potential economies and diseconomies of scale and targeting strategy. Costs were disaggregated by whether they were expected to vary with the number of countries, districts, health posts, or CHWs involved in the intervention, or with the output quantity. Output metrics differed between the interventions; for IRS, costs were identified that were expected to vary with the number of households sprayed, while for MDA and MSAT, costs were identified that were expected to vary with the number of people receiving the interventions. In addition, for MSAT, costs were also identified which were expected to vary with the number of people who tested positive, which is a function of the number of people screened and the screening positivity rate (a function of local epidemiology and the test's sensitivity and specificity).

For each implementation round for each intervention in our trial setting, we generated the average cost per variation unit for each of the variation units we identified (i.e. countries, districts, health posts, CHWs, households or persons receiving the intervention). For example, we divided the costs of implementing the first round of MSAT that were expected to vary with the number of health posts ($14,237) by the number of health posts in our trial context (n=18), to generate an average cost per health post of implementation costs associated with the number of health posts ($791). Rather than model this average cost as a constant, we structured our model so that these average costs *AC* per health system or output level *i* and implementation round *j*, were a function of input prices *p*, resource use *q*, and local epidemiology *e*, to permit further modelling:

$$AC_{ij} = f_{ij}(p, q, e)$$

We assumed that these average costs for each variation unit could be used to estimate the total costs of implementing the given intervention in a different context, with a somewhat different targeting strategy, and/or with a different number of implementation rounds. That is, we assumed that for each intervention, the total costs could be modelled as:

$$TC = \sum_{j=1}^{y} \sum_{i=1}^{x} AC_{ij} * n_{ij}$$

Where *TC* is total costs of implementation, *i* is a factor variable denoting *x* different variation units involved in implementation, *j* is a factor variable denoting the *y* implementation rounds, *AC* is the average cost of implementation per round per variation unit, and *n* is the number of variation units *i* for round *j* in which the intervention is implemented. Drawing in part on the analysis of the costs of three monthly rounds of SMC (Pitt et al., 2017), we assume that estimates of the costs of subsequent implementation rounds can be modelled based on the costs of implementing the second implementation round in the trial context.

This approach of disaggregating costs by variation unit is different from disaggregating costs by the level at which they are incurred. For example, in our model, the costs of training health post nurses at their district headquarters were broken down into those costs that could be expected to vary with the number of districts, such as the costs of facilitators and room rental, and those costs that could be expected to vary with the number of health posts, namely the costs of per diems, food, travel, and time associated with attending the training for each health post's head nurse. This approach assumed that, for example, there would be one district-level training in each district if and only if the intervention were implemented in at least one area in that district, but that a nurse would only participate in the training if his or her health post were implementing the intervention.

To model expansion of the interventions from one or two trial arms to the entire study area, which we used for the base case, we changed the value n_{ij} for each variation unit *i* and implementation round *j*, as necessary. While the number of countries (n=1) and districts (n=4) remained the same as in implementation in the trial context, the number of health posts increased to 46 and the population increased to 587,285. For the base case, we assumed that the proportion of the total population (hotspot and non-hotspot villages) who received each of the interventions remained the same as in the trial: 36% of intervention arm residents received IRS, 33% of MSAT arm residents received MSAT, and 32% of MDA arm residents received MDA. To

estimate the required number of CHWs for each intervention, we assumed that the number of households reached per CHW would remain the same as in the trial implementation. Populating this model thus required only additional estimates of the number of districts, health posts, and population across the area of interest.

In further analyses, we modelled the costs of potential changes to the interventions across our study area. We modelled the costs of implementing the interventions with a more narrowly targeted approach and compared the costs of targeted strategies with the costs of a blanket approach (i.e. without geographical targeting) across our study area. We also predicted the costs of extending to 3 or 4 rounds of MDA or MSAT and of targeting by district and health post instead of by village. For these analyses, we defined a proportion of the population that was targeted (100%, 50%, 20%), and then applied the coverage rates achieved in the trial (IRS: 66%, MSAT: 55%, and MDA: 66%) to estimate the number of people who would receive each intervention under the given scenario.

While we explored the sensitivity of our cost-effectiveness model to plausible variation in key parameters, we did not model explicitly how costs might vary outside our study area. Our model is designed to facilitate such estimates with limited additional data in future, notably on the numbers of each variation unit across which the interventions would be implemented, and any changes in prices (e.g. salary levels), epidemiology (broadly, as the screening positivity rate is not a major cost driver at low incidence levels), or aspects of intervention delivery that would be expected to differ substantially in the new context.

In our scenario analyses, we assumed that coverage i.e. the proportion of people targeted to receive the intervention who actually received it, remained constant and the same as observed in the trial. The model is set up to allow the coverage rate to be varied; however, it only accounts for the additional costs associated with greater outputs. For example, if the interventions were implemented in a context in which the same approach to intervention delivery resulted in 95% coverage, our model would account for the additional costs associated with the additional people reached. Any additional efforts necessary to achieve higher coverage – such as additional communication activities or extra visits to reach missed households or individuals – would need to be costed separately.

5.2.2. Mechanistic cost model: Implementation in Excel

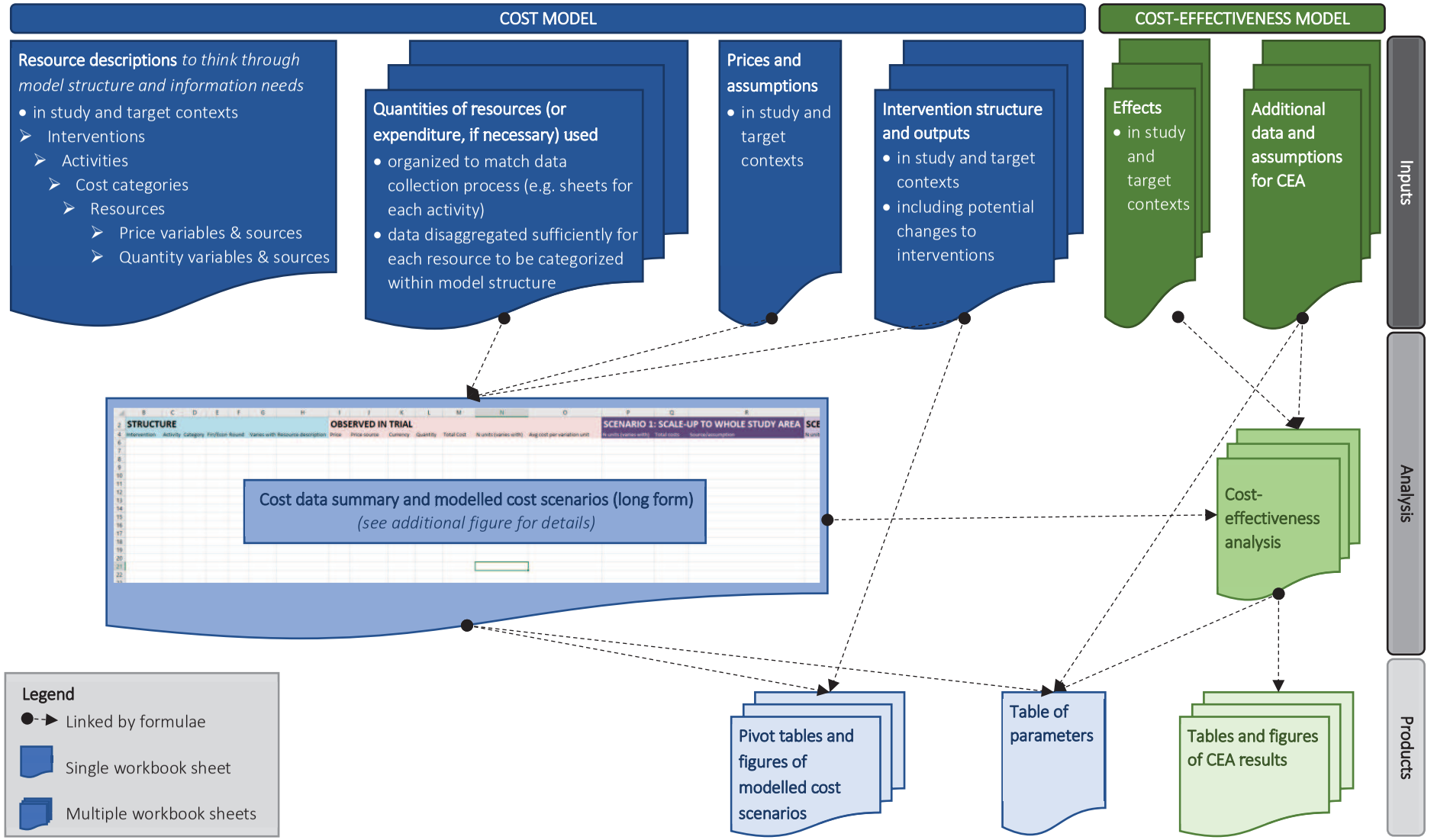
In Figure 12, we illustrate the structure of the Excel workbook we developed to implement this approach. In the left-hand two-thirds of the diagram, we illustrate (in blue) the cost model, and on the right (in green), we show the additional elements necessary to implement the cost-effectiveness model. Most of the worksheets are used to organize inputs and are illustrated in the top third of the diagram. Cost model inputs are linked to a single cost model analysis worksheet at the centre of the diagram. On the righthand side of the diagram, the numerous worksheets required for the cost-effectiveness analysis (including probabilistic sensitivity analysis) are illustrated. Products of the analysis (illustrated at the bottom of the diagram) are a set of tables and figures with cost estimates, a table of parameters, and a set of tables and figures to communicate the cost-effectiveness findings.

Four types of inputs are required for the cost model. Firstly, as a starting point, we generated a set of **resource descriptions** to think through the model structure and information needs in the trial and scenarios we modelled. We began by listing each intervention, for each intervention listing the activities, and then breaking down each activity into cost categories. For each cost category, we then identified the specific resources involved and formulated precise price and quantity variable descriptions and identified sources for this information. This process was iterative, beginning with an initial brainstorm, and refined over the course of the research.

Quantities of resources used were recorded in sheets organized to match the data collection process. For example, we separated sheets by activity and in some cases by data source to match our data collection tools, which, in turn, matched the source, timing, and topic for our data collection, largely from the respondent's perspective. For example, we administered questionnaires at the district, health post, and CHW levels and did so separately for IRS and for each round of MDA and MSAT. Within these sheets, we ensured that data were disaggregated sufficiently to be categorized according to the model structure. In some cases, only expenditure data were available and so expenditure data were used instead.

Prices and assumptions were collated in a single sheet with multiple tables, generated from primary and secondary sources. Within these tables, prices were converted into United States dollars, and to a variety of appropriate units, such as the cost per hour and cost per minute of health worker time, to match the quantities used in data collection.

Figure 11 Schematic of cost model workbook



The intervention structure and outputs in both the trial context and scenarios of interest were described in a set of sheets with quantitative data on each level of the (hierarchical) structure involved in intervention delivery. These sheets included simple data, such as the number of districts and health posts involved in each intervention in the trial, as well as more complex data on the numbers of villages, households, and individuals who actually received each intervention. For additional modelling to other contexts, further information could be added. These data served as an important starting point for identifying the **variation units** used to structure the model.

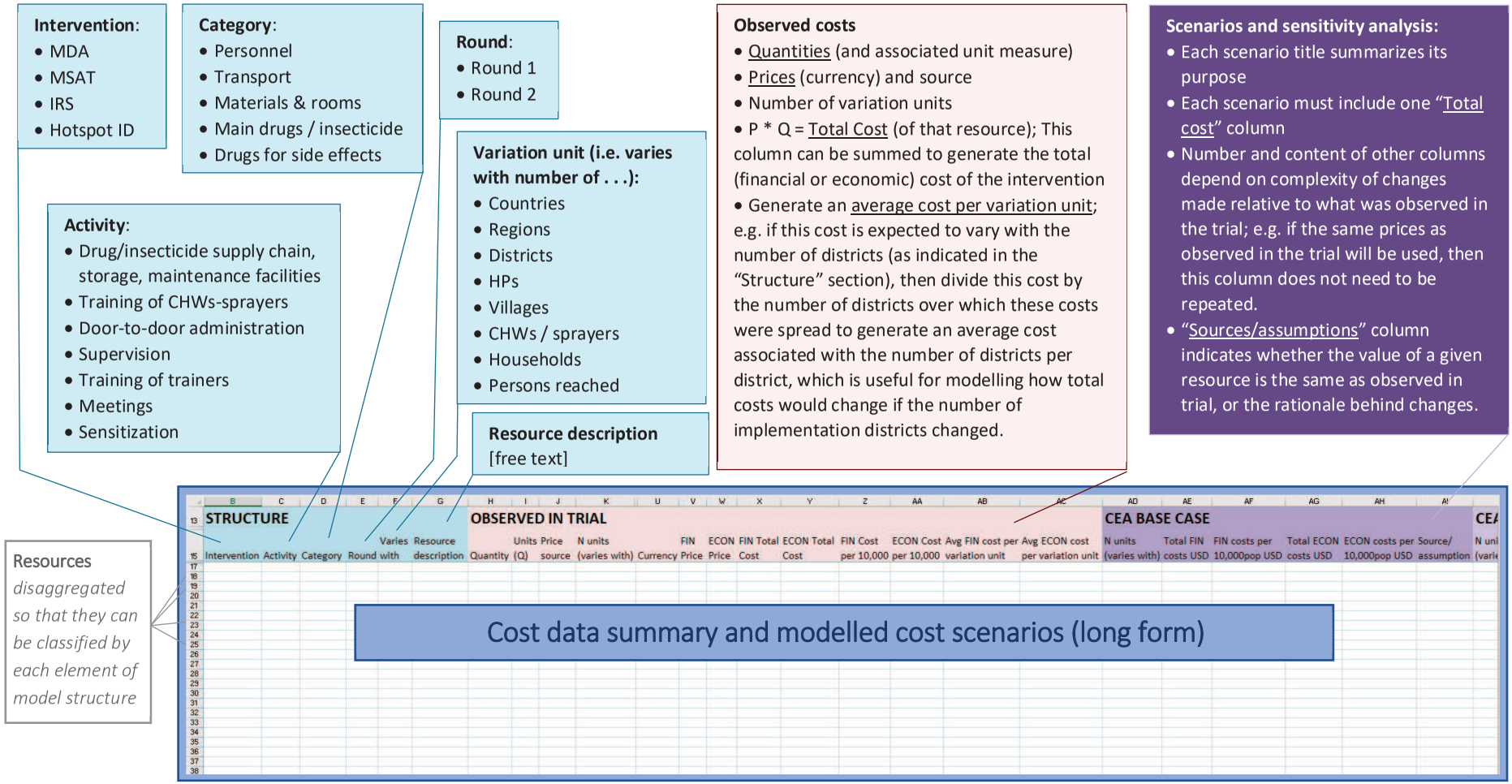
In Figure 13, we explain the **cost data summary and modelled cost scenarios** sheet in greater depth. Six of the seven variables used to define the model structure were categorical, while the resource description required free text. Each row of the worksheet reflected a resource, sufficiently disaggregated that it could be categorized according to all the dimensions of the model structure. While resources may be disaggregated in greater depth than required by the model structure, this approach highlights how far disaggregation is actually necessary for the intended analyses, which may avoid time spent in collecting data in unnecessary detail.

In the "**observed in trial**" section, two columns contain formulae linked to input worksheets with data on the **quantity** and **price** of each resource. In a third column, price and quantity are multiplied to generate a **cost** of that resource. This "long form" structuring of the data facilitates flexible analysis along multiple dimensions through the use of pivot tables. The total cost of a given intervention – the key product of the cost model – was generated by using pivot tables to sum the "cost" column and to filter, stratify, and cross-tabulate the analysis by the given intervention, activity, or other variables.

For each resource, the **variation unit** with which it was associated was indicated in the "structure" section and the number of units at this variation level over which costs were spread in the trial was indicated in the "observed in trial" section. For example, the cumulative quantity of time of all head nurses to receive training was expected to vary with the number of health posts (as indicated in the "structure" section). In the "observed costs in trial" section, the total costs of this resource in the trial were therefore divided by the 18 health posts in which MDA was implemented to generate an average cost per health post of head nurse time receiving training. This variable, in turn, was an input in subsequent scenario analyses.

Additional sets of columns were used to generate **scenario analyses** in the cost analysis and **deterministic sensitivity analyses** for the cost-effectiveness analysis. The number and content

Figure 12 Structure of the cost model: Cost data summary and modelled scenarios (long form)



of additional columns required for each scenario analysis depended on the complexity of the changes made. At a minimum, each scenario analysis included three columns: one in which a change is made to prices, quantities, or the number of variation units across which the intervention is implemented; one indicating the sources and assumptions behind any such changes; and one recalculating the total cost of that resource in the new scenario. All values in the scenario and sensitivity analyses use formulae to link to other columns in the same worksheet or in the input worksheets; values are not input directly into the "cost data summary and modelled cost scenarios" sheet.

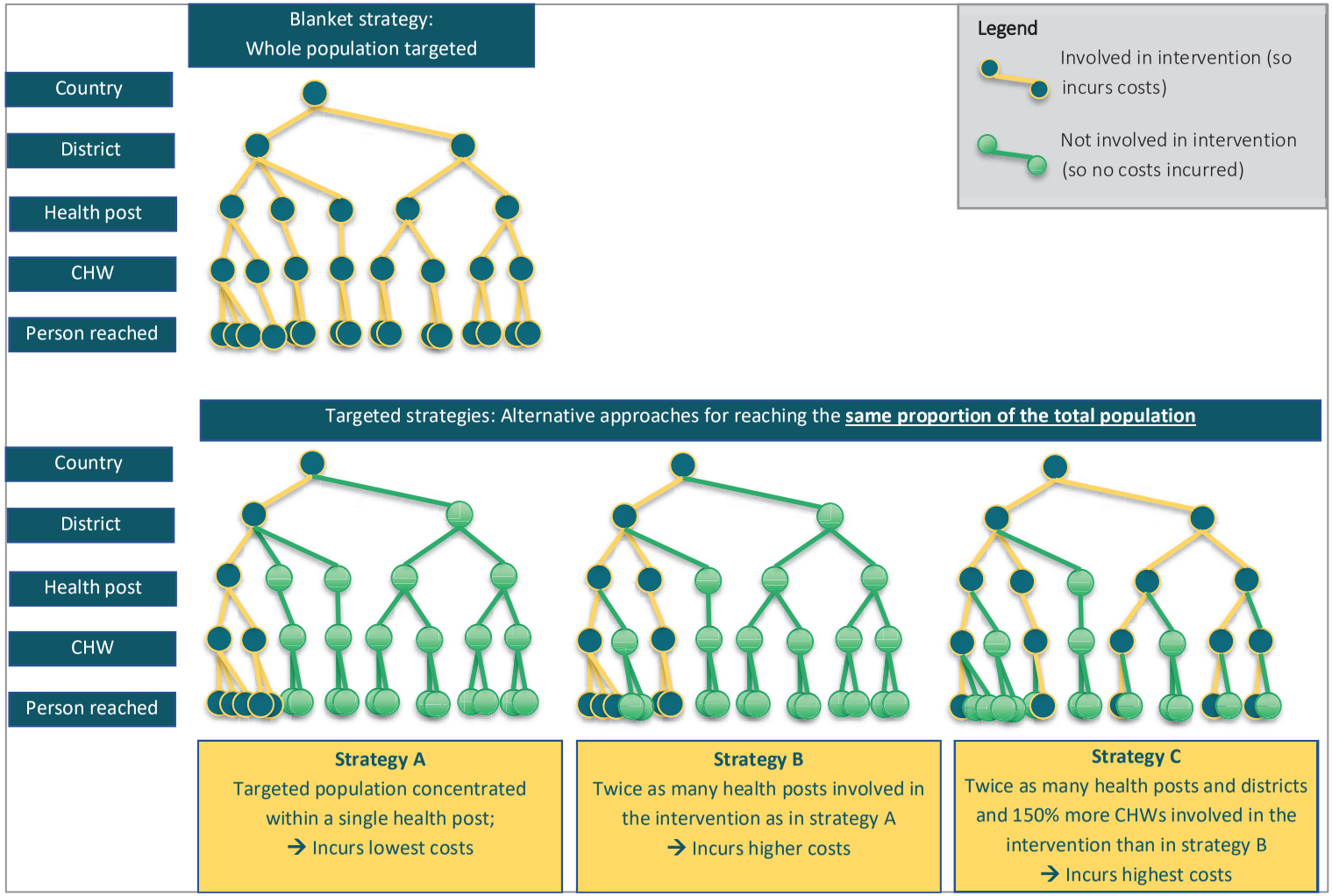
In our cost analysis, we evaluated all costs deterministically; probabilistic analysis was only implemented in our cost-effectiveness analysis. It would, however, be possible to conduct a probabilistic sensitivity analysis within the structure of this workbook by defining price, quantity, or cost variables as distributions rather than fixed values.

5.2.3. Mechanistic cost model: Insights for understanding the costs of scale-up and alternative approaches to targeting

This approach to cost modelling offers several insights for understanding the costs of "scale up" and the costs of alternative targeting strategies. The term "scale-up" can mean many things (Mangham and Hanson, 2010). Our model gives some insights into what economies may be reasonable to expect, and how this may differ based on the cost structure of the particular interventions. The degree to which economies of scale are likely depends on the proportion of total intervention costs that are associated with variation levels higher than the output level, which in turn depends on the degree and level of targeting and the number of implementation rounds.

Our analysis shows that the total and average costs per person targeted or reached depend on both the proportion of a total population targeted, i.e. the *degree* of targeting, and also the structure of that targeting, i.e. the *level* at which the targeting takes place. In Figure 14, we show how alternative approaches for reaching the same proportion of the population would result in different costs. They involve different numbers of CHWs, health posts, and districts to reach the same number of people.

Figure 13 The cost implications of alternative targeting approaches



5.3. References for Chapter 5

BERTRAM, M. Y., LAUER, J. A., DE JONCHEERE, K., EDEJER, T., HUTUBESSY, R., KIENY, M. P. & HILL, S. R. 2016. Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ,* 94**,** 925-930.

BOUSEMA, T., STRESMAN, G., BAIDJOE, A. Y., BRADLEY, J., KNIGHT, P., STONE, W., OSOTI, V., MAKORI, E., OWAGA, C., ODONGO, W., CHINA, P., SHAGARI, S., DOUMBO, O. K., SAUERWEIN, R. W., KARIUKI, S., DRAKELEY, C., STEVENSON, J. & COX, J. 2016. The Impact of Hotspot-Targeted Interventions on Malaria Transmission in Rachuonyo South District in the Western Kenyan Highlands: A Cluster-Randomized Controlled Trial. *PLoS Medicine,* 13.

CICO, A. & JOHNS, B. 2018. PMI IRS Country Programs: 2017 Comparative Cost Analysis. Rockville, MD: PMI Africa Indoor Residual Spraying Project, Abt Associates Inc.

CONTEH, L., SHARP, B. L., STREAT, E., BARRETO, A. & KONAR, S. 2004. 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,* 9**,** 125-32.

CROWELL, V., BRIËT, O. J., HARDY, D., CHITNIS, N., MAIRE, N., PASQUALE, A. D. & SMITH, T. A. 2013. Modelling the cost-effectiveness of mass screening and treatment for reducing Plasmodium falciparum malaria burden. *Malaria Journal,* 12.

DIALLO, A., CISSE, B., BA EL, H., TAIROU, F., FLACH, C., PITT, C., SY, O., FAYE, O., GAUDART, J., GOMIS, J. F., WANG, D., NDOYE, T., BA, M., BA-FALL, F., NDIOP, M., NDIAYE, J. L., TINE, R., FAYE, B., SOKHNA, C., GAYE, O. & MILLIGAN, P. 2020. Accelerating malaria transmission reduction in Senegal: a cluster-randomized trial of the effectiveness of targeted control in hotspots using Indoor Residual Spraying (IRS) combined with either Mass Screening and Treatment (MSAT) or Mass Drug Administration (MDA). *[Working Paper]*.

DRAKE, T. L. & LUBELL, Y. 2017. Malaria and Economic Evaluation Methods: Challenges and Opportunities. *Appl Health Econ Health Policy,* 15**,** 291-297.

EISELE, T. P., BENNETT, A., SILUMBE, K., FINN, T. P., CHALWE, V., KAMULIWO, M., HAMAINZA, B., MOONGA, H., KOOMA, E., KAWESHA, E. C., YUKICH, J., KEATING, J., PORTER, T., CONNER, R. O., EARLE, D., STEKETEE, R. W. & MILLER, J. M. 2016. Short-term impact of mass drug administration with dihydroartemisinin plus piperaquine on malaria in southern province Zambia: A cluster-randomized controlled trial. *Journal of Infectious Diseases,* 214**,** 1831-1839.

FARAJ, C., YUKICH, J., ADLAOUI EL, B., WAHABI, R., MNZAVA, A. P., KADDAF, M., EL IDRISSI, A. L., AMEUR, B. & KLEINSCHMIDT, I. 2016. Effectiveness and Cost of Insecticide-Treated Bed Nets and Indoor Residual Spraying for the Control of Cutaneous Leishmaniasis: A Cluster-Randomized Control Trial in Morocco. *Am J Trop Med Hyg,* 94**,** 679-85.

FENWICK, E., CLAXTON, K. & SCULPHER, M. 2001. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ,* 10**,** 779-87.

GLOBAL FUND. 2018. *Pooled Procurement Mechanism Reference Pricing: LLINs* [Online]. Geneva: Global Fund. Available: https://www.theglobalfund.org/media/5861/psm_llinreferenceprices_table_en.pdf?u=637066531800000000 [Accessed 7 November 2019].

GLOBAL FUND. 2019a. *Pooled Procurement Mechanism Reference Pricing: Antimalarial medicines* [Online]. Geneva: Global Fund. Available: https://www.theglobalfund.org/media/5812/ppm_actreferencepricing_table_en.pdf?u=636706531880000000 [Accessed 7 November 2019].

GLOBAL FUND. 2019b. *Pooled Procurement Mechanism Reference Pricing: Malaria Rapid Diagnostic Tests (MRDT)* [Online]. Geneva: Global Fund. Available: https://www.theglobalfund.org/media/7565/psm_malariardtreferencepricing_table_en.pdf?u=637066531810000000 [Accessed 7 November 2019].

GOODMAN, C. A., MNZAVA, A. E., DLAMINI, S. S., SHARP, B. L., MTHEMBU, D. J. & GUMEDE, J. K. 2001. Comparison of the cost and cost-effectiveness of insecticide-treated bednets and residual house-spraying in KwaZulu-Natal, South Africa. *Trop Med Int Health,* 6**,** 280-95.

GUNDA, R. & CHIMBARI, M. J. 2017. Cost-effectiveness analysis of malaria interventions using disability adjusted life years: a systematic review. *Cost Eff Resour Alloc,* 15**,** 10.

GUYATT, H. L., KINNEAR, J., BURINI, M. & SNOW, R. W. 2002. A comparative cost analysis of insecticide-treated nets and indoor residual spraying in highland Kenya. *Health Policy Plan,* 17**,** 144-53.

HAUSMANN-MUELA, S. & ECKL, J. 2015. Re-imagining malaria - A platform for reflections to widen horizons in malaria control. *Malaria Journal,* 14.

HUSEREAU, D., DRUMMOND, M., PETROU, S., CARSWELL, C., MOHER, D., GREENBERG, D., AUGUSTOVSKI, F., BRIGGS, A. H., MAUSKOPF, J. & LODER, E. 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value Health,* 16**,** e1-5.

HUTTON, G. & BALTUSSEN, R. 2005. Cost valuation in resource-poor settings. *Health Policy Plan,* 20**,** 252-9.

KOLACZINSKI, J. H., ROBINSON, E. & FINN, T. P. 2011. The cost of antibiotic mass drug administration for trachoma control in a remote area of South Sudan. *PLoS Negl Trop Dis,* 5**,** e1362.

KRISHNAMOORTHY, K., RAJENDRAN, R., SUNISH, I. P. & REUBEN, R. 2002. Cost-effectiveness of the use of vector control and mass drug administration, separately or in combination, against lymphatic filariasis. *Ann Trop Med Parasitol,* 96 Suppl 2**,** S77-90.

KUMARANAYAKE, L. 2000. The real and the nominal? Making inflationary adjustments to cost and other economic data. *Health Policy Plan,* 15**,** 230-4.

LARSON, B. A., NGOMA, T., SILUMBE, K., RUTAGWERA, M. R. I., HAMAINZA, B., WINTERS, A. M., MILLER, J. M. & SCOTT, C. A. 2016. A framework for evaluating the costs of malaria elimination interventions: An application to reactive case detection in Southern Province of Zambia, 2014. *Malaria Journal,* 15.

LINES, J., SCHAPIRA, A. & SMITH, T. 2008. Tackling malaria today. *BMJ,* 337.

LITTLE, R. M. 2013. The challenges of malaria elimination. *The Lancet,* 382**,** 1700.

MANGHAM, L. J. & HANSON, K. 2010. Scaling up in international health: what are the key issues? *Health Policy Plan,* 25**,** 85-96.

MARSEILLE, E., LARSON, B., KAZI, D. S., KAHN, J. G. & ROSEN, S. 2015. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bull World Health Organ,* 93**,** 118-24.

MCNEIL JR., D. G. 2008. Eradicate Malaria? Doubters Fuel Debate. *New York Times*.

NEWBY, G., HWANG, J., KOITA, K., CHEN, I., GREENWOOD, B., VON SEIDLEIN, L., SHANKS, G. D., SLUTSKER, L., KACHUR, S. P., WEGBREIT, J., IPPOLITO, M. M., POIROT, E. & GOSLING, R. 2015. Review of mass drug administration for malaria and its operational challenges. *Am J Trop Med Hyg,* 93**,** 125-34.

OCHALEK, J., LOMAS, J. & CLAXTON, K. 2018. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health,* 3**,** e000964.

PITT, C., NDIAYE, M., CONTEH, L., SY, O., HADJ BA, E., CISSE, B., GOMIS, J. F., GAYE, O., NDIAYE, J. L. & MILLIGAN, P. J. 2017. Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis. *Health Policy Plan,* 32**,** 1256-1266.

PULLAN, R. L., HALLIDAY, K. E., OSWALD, W. E., MCHARO, C., BEAUMONT, E., KEPHA, S., WITEK-MCMANUS, S., GICHUKI, P. M., ALLEN, E., DRAKE, T., PITT, C., MATENDECHERO, S. H., GWAYI-CHORE, M. C., ANDERSON, R. M., NJENGA, S. M., BROOKER, S. J. & MWANDAWIRO, C. S. 2019. Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. *Lancet*.

SALOMON, J. A., HAAGSMA, J. A., DAVIS, A., DE NOORDHOUT, C. M., POLINDER, S., HAVELAAR, A. H., CASSINI, A., DEVLEESSCHAUWER, B., KRETZSCHMAR, M., SPEYBROECK, N., MURRAY, C. J. & VOS, T. 2015. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health,* 3**,** e712-23.

SHAH, N. K. 2010. Assessing Strategy and Equity in the Elimination of Malaria. *PLoS Medicine,* 7**,** e1000312.

SICURI, E., EVANS, D. B. & TEDIOSI, F. 2015. Can Economic Analysis Contribute to Disease Elimination and Eradication? A Systematic Review. *PLoS ONE,* 10**,** e0130603.

SILUMBE, K., YUKICH, J. O., HAMAINZA, B., BENNETT, A., EARLE, D., KAMULIWO, M., STEKETEE, R. W., EISELE, T. P. & MILLER, J. M. 2015. Costs and cost-effectiveness of a large-scale mass testing and treatment intervention for malaria in Southern Province, Zambia. *Malar J,* 14**,** 211.

TUSTING, L. S., WILLEY, B., LUCAS, H., THOMPSON, J., KAFY, H. T., SMITH, R. & LINDSAY, S. W. 2013. Socioeconomic development as an intervention against malaria: A systematic review and meta-analysis. *The Lancet,* 382**,** 963-972.

VASSALL, A., SWEENEY, S., KAHN, J. G., GOMEZ, G. B., BOLLINGER, L., MARSEILLE, E., HERZEL, B., PLOSKY, W. D., CUNNAMA, L., SINANOVIC, E., BAUTISTA-ARREDONDO, S., GHCC TECHNICAL ADVISORY GROUP, GHCC STAKEHOLDER GROUP, HARRIS, K. & LEVIN, C. 2017b. *Reference Case for Estimating the Costs of Global Health Services and Interventions* [Online]. Available: https://ghcosting.org/pages/standards/reference_case.

WALKER, P. G., GRIFFIN, J. T., FERGUSON, N. M. & GHANI, A. C. 2016. Estimating the most efficient allocation of interventions to achieve reductions in Plasmodium falciparum malaria burden and transmission in Africa: a modelling study. *Lancet Glob Health,* 4**,** e474-84.

WHITE, M. T., CONTEH, L., CIBULSKIS, R. & GHANI, A. C. 2011. Costs and cost-effectiveness of malaria control interventions - a systematic review. *Malar J,* 10**,** 337.

WHO 2011a. WHO-CHOICE unit cost estimates for service delivery. Geneva: World Health Organization.

WHO 2015. The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria. Recommendations. Geneva: World Health Organization.

WHO 2017a. A framework or malaria elimination. Geneva: WHO.

WHO 2018d. World malaria report 2018. Geneva, Switzerland: World Health Organization.

WHO 2019a. Global Health Expenditure Database. Geneva: World Health Organization.

WHO. 2019b. *Global Health Observatory data repository: Life tables by country* [Online]. Geneva: World Health Organization. Available: http://apps.who.int/gho/data/view.main.61450?lang=en [Accessed 26 October 2019].

WHO EVIDENCE REVIEW GROUP 2015a. Mass drug administration, mass screening and treatment and focal screening and treatment for malaria. Background document for Session 1. Meeting report, 20–22 April 2015. Geneva: World Health Organization.

WHO EVIDENCE REVIEW GROUP 2015b. Review of delivery cost data on mass drug administration for malaria. Background document for Session 1. Meeting report, 20–22 April 2015. Geneva: World Health Organization.

WILKINSON, T., SCULPHER, M. J., CLAXTON, K., REVILL, P., BRIGGS, A., CAIRNS, J. A., TEERAWATTANANON, Y., ASFAW, E., LOPERT, R., CULYER, A. J. & WALKER, D. G. 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value Health,* 19**,** 921-928.

WORLD BANK 2019. World Development Indicators 2019. 24 April 2018 ed. Washington, D.C.

YUKICH, J. O., LENGELER, C., TEDIOSI, F., BROWN, N., MULLIGAN, J. A., CHAVASSE, D., STEVENS, W., JUSTINO, J., CONTEH, L., MAHARAJ, R., ERSKINE, M., MUELLER, D. H., WISEMAN, V., GHEBREMESKEL, T., ZEROM, M., GOODMAN, C., MCGUIRE, D., URRUTIA, J. M., SAKHO, F., HANSON, K. & SHARP, B. 2008. Costs and consequences of large-scale vector control for malaria. *Malar J,* 7**,** 258.

Chapter 6. Designing economic evaluations for transferability: A critical review and practical guide

6.1. Preface to Chapter 6

Many important methodological questions emerge from the two economic evaluations, which are worth exploring in greater depth. In this sixth chapter, I focus on how to improve the transferability of economic evaluation evidence from trials and pilots beyond the particular context of the trial or pilot itself. I focus on transferability – that is, the degree to which evidence from one context may be appropriately used to inform decision-making in another context - because of its broad relevance and importance to all economic evaluations and especially to those conducted in LLMICs. Transferability emerged as a key challenge from the bibliometric analysis presented in Chapter 2, which demonstrated the acute scarcity of economic evaluation evidence, especially in LLMICs. The first economic evaluation in this thesis, presented in Chapter 4, was conducted in accordance with standard guidance on improving the generalizability or transferability of economic evaluations; however, shortcomings were identified in the recommended statistical approach to improving transferability. In both economic evaluations presented in Chapters 4 and 5, some progress was made in addressing the shortcomings in methodological guidance by demonstrating how mechanistic cost modelling can usefully inform understanding of how costs may be expected to vary outside the trial context or with specific changes to the interventions.

This chapter aims to begin to respond more holistically to some of the shortcomings in current methodological guidance on how to improve the transferability of economic evaluation evidence, focusing especially on LLMICs. First, I conduct a critical review to identify insights from wide-ranging literature, including research not framed as pertinent to transferability or to economic evaluation. I then draw on both this literature review and my own experience conducting economic evaluations to propose some initial methodological guidance regarding how to make economic evaluations more transferable in future.

The critical review was conducted alongside and after the economic evaluations presented in this thesis; it therefore informed some of the analyses previously presented, but could not inform their study designs, which instead reflected standard guidance at the time when they were done. The designing for transferability guide was developed after both the economic evaluations and critical review were conducted, and so represents a proposal for how future

economic evaluations should be conducted. As this guidance has not yet been tested, post-doctoral research could seek to apply, evaluate, and refine it.

6.2. Abstract

The costs, effects, and cost-effectiveness of interventions vary across contexts. Understanding when and how to transfer evidence appropriately across geographies or jurisdictions and from small-scale trial or pilots to much larger, real-world decision contexts is therefore challenging. Nonetheless, such transfers are crucial for optimizing the efficiency of policy choices and the value of evidence. This article aims to promote more efficient priority setting by increasing the transferability of economic evaluation evidence generated from trials and pilots. A wide-ranging critical review identified ten literature streams which contribute to understanding how to make economic evaluations more transferable. Drawing on this review and experience conducting economic evaluations, I propose guidance on how to design economic evaluations alongside trials or pilots in ways that promote transferability. I argue that transferability is a complex question requiring a complexity perspective, even for seemingly simple interventions. Making economic evaluation evidence more transferable requires understanding and communicating what an intervention is and the mechanisms of action through which it interacts with context to produce changes in costs and effects. Model-based economic evaluations alongside trials or pilots can facilitate the transfer of findings generated within trials and pilots to relevant decision context(s). Questions are presented to guide researchers through four iterative stages: I) Framing the economic evaluation, II) Model identification and/or development, III) Data needs identification, and IV) Analysis and reporting. Identifying and closing – where possible – the transferability gap between planned implementation in the study context and anticipated implementation in one or more decision contexts are important first steps. Future research should pilot and further refine this guidance.

6.3. Introduction

Policy makers at every level face constant decisions about whether to maintain the status quo or to adopt a new course of action. Only rarely, however, can they draw on robust evidence from an empirical economic evaluation conducted to inform the exact decision problem they face in their own decision context (Drummond et al., 2015, Kalo et al., 2016, Pichon-Riviere et al., 2012). While they may sometimes commission empirical research, such investment is not feasible for every decision in every context and takes time. Instead, especially for new interventions, any potentially relevant evidence is often drawn from small-scale pilots or trials of interventions that may not precisely reflect the ones under consideration and may have been carried out in in contexts that do not precisely match the decision context.

Judgments about the relevance of evidence to a particular decision context are challenging because the effectiveness, costs, and cost-effectiveness of interventions vary across contexts. Both overly wide and overly narrow definitions of "relevant evidence" risk sub-optimal policy choices (Drummond et al., 2009). While maximizing the usefulness of empirical evidence is important in any setting, the particularly acute scarcity of data in low- and lower-middle-income countries (LLMICs) intensifies the need to ensure that opportunities for data collection afforded by trials and pilots are fully exploited.

This article aims to promote more efficient priority setting by increasing the transferability – and thus usefulness – of economic evaluation evidence generated from trials and pilots, especially in LLMICs. In the following sections, I first define transferability and the associated challenges. Second, I critically review wide-ranging literature pertinent to improving the transferability of economic evaluation evidence. Third, I present initial guidance on how to make economic evaluations conducted alongside trials and pilots more transferable, before concluding with some final reflections.

6.4. Defining transferability and its challenges

I use the term "transferability" to refer to the degree to which evidence regarding interventions in one context may be appropriately used to inform decisions regarding another context, with or without modifications to the analysis or interpretation. Transferability is

related to the term “generalizability” and sometimes (erroneously) used interchangeably. Barbieri and colleagues usefully distinguish between the terms:

> *Studies may be considered generalizable if they can be applied . . . without any adjustment needed for interpretation. In addition, some studies may be transferable if they can be adapted to apply to other settings. Finally, some may be so specific to a given jurisdiction that they are simply not transferable to any other jurisdiction. . . It is probably best to think of the transferability of data as being represented by a spectrum, with ‘generalizable’ being at one end and ‘not transferable’ at the other.* (Barbieri et al., 2010)

In this sense, which I adopt, the concept of generalisability is nested within a wider concept of transferability.

I apply the term “transferability” both to the transfer of findings across geographies or jurisdictions, as referenced above, as well as to the transfer of findings from small-scale trials or pilots to much larger, real-world contexts. These two dimensions of evidence transfer often occur simultaneously, as findings from a trial or pilot in one country may be used to inform national policies in another country. While the transfer to real-world contexts is often discussed in terms of “external validity” (Mantopoulos et al., 2015, Ramsey et al., 2015, Van Staa et al., 2009) and “scale up” (Colbourn et al., 2015, Johns et al., 2005, Kumaranayake, 2008), I argue that using the term “transferability” usefully highlights the common challenges faced in both dimensions of evidence transfer.

When transferring evidence across contexts, other “contexts” may include other geographical areas, either within the same country or in another country, or they may include different population groups, types of contact points, degrees of researcher involvement, or policy, political, economic, or social contexts. For example, policy makers may seek to use an evaluation of an intervention implemented nationally in hospitals to inform decisions about whether to roll out a similar intervention in primary care or amongst a different patient group. Secular trends, exogenous shocks, and policy changes may also change a local context, so that an evaluation of past implementation may not reflect the future context even in the same geographical location.

Both effects and costs may vary across contexts and thus change the incremental cost-effectiveness ratio and the optimal adoption decision. Transferring evidence across geographies even within the same jurisdiction raises numerous challenges, such as accounting for differences in health service structures, epidemiology, population characteristics, or price

levels. Transferring evidence across jurisdictions may raise additional challenges, such as adapting to different decision-making processes, currencies, or laws.

The effects or benefits of an intervention as measured in trials, pilots, and small-scale studies are often substantially greater than the benefits achieved in subsequent expansion, such as in national roll-out (Blonde et al., 2018, Carls et al., 2017, Glasgow et al., 1999). This dilution of effectiveness at scale occurs even when the initial evaluations are framed as "effectiveness" rather than "efficacy" studies and may reflect a reduction in implementation effort, resource inputs, fit of the intervention to the new context, and other factors.

Average costs in trial or pilot settings may also differ from the "real world" (Batura et al., 2014, Johns et al., 2005, Kumaranayake, 2008, Ramsey et al., 2015). They may be higher than in the "real world" because of diseconomies of small-scale production (e.g. of medicines) for a trial, the involvement of more highly paid consultants and researchers, the smaller number of recipients over which fixed costs may be spread, inefficiencies in implementation caused by the research context, and the fact that evaluations are often conducted in the early stages of implementation, before implementation has been optimized. Conversely, average costs from trials and small-scale pilots may appear lower than at scale if national-level costs have not been included or if the standard of care to which a new intervention is compared is substantially different from standard practice.

Despite all these challenges in appropriately transferring cost, effectiveness, and cost-effectiveness evidence across contexts, transfers happen whenever research evidence is used to inform prospective decision-making. To help ensure that such transfers are appropriate and to maximize the value generated from individual studies, primary studies must be designed with the need to inform new contexts in mind.

6.5. A Critical review of transferability literatures

6.5.1. Critical review methods

To examine contributions to improving the transferability of economic evaluation evidence from a far wider scope of literature than a systematic review would allow, a critical review was conducted. In their typology of reviews, Grant and Booth write:

> *"An effective critical review presents, analyses and synthesizes material from diverse sources . . . . A critical review provides an opportunity to 'take stock' and evaluate what is of value from the previous body of work. . . . [There] is no formal requirement to present methods of the search, synthesis and analysis explicitly. The emphasis is on the conceptual contribution of each item of included literature, not on formal quality assessment. While such a review does serve to aggregate the literature on a topic, the interpretative elements are necessarily subjective and the resulting product is the starting point for further evaluation, not an endpoint in itself."*

I identified relevant literature through an iterative process of searches in databases, including Web of Science, Scopus, Pubmed, and Google; review and selection of relevant publications; review of publications cited by and citing each of these relevant publications; and suggestions from reviewers. Initial searches combined the following terms: ("transferability" OR "generalizability") AND ("health economic evaluation" OR "cost-effectiveness analysis"). Subsequent searches combined ("transferability" OR "generalizability") with alternative terms ("health intervention" OR "health system"), and then employed new terms (e.g. "scale-up cost", "external validity", "health system constraints") to identify literature on themes relevant to the research question, which were known to me or emerged as potentially relevant and had not yet been captured. I therefore include work which omits the words "transferability" or "generalizability" if I believe it contributes to answering the research question. The advantage of this approach is that allows for a more holistic, multidisciplinary review of conceptual contributions to the research question without restriction on the study design, type of publication, or focus of the publication.

I include research from countries of all income levels about all types of health interventions, but focus particularly on the degree to which findings are relevant to LLMICs and facilitate comparison of a broad range of clinical and non-clinical interventions designed to improve or maintain health. I focus on the transferability of findings, rather than on methodological requirements or preferences of decision-makers, which vary between contexts. For example, while some decision-makers specify a societal perspective and others a provider perspective, I do not focus here on the need to adapt an analysis to meet such differences in decision-makers' expectations, which have been explored elsewhere (Welte et al., 2004, Knies et al., 2010).

6.5.2. Critical review findings

Many literature streams have made relevant contributions to understanding how to make economic evaluations alongside trials and pilots more transferable, but these literature streams have tended to run in parallel, with different vocabularies and framings and little communication between them. I identified ten such literature streams emerging from four wider (and somewhat overlapping) research areas (10, Figure 14). In the following sections, I critically review the main contributions and limitations of each of these literature streams in turn, with a focus on relevance for LLMICs, before summarizing findings and key research gaps.

1) Increasing the generalisability of economic evaluations alongside trials

The first literature stream is framed around making economic evaluations conducted alongside trials more "generalisable", especially to real-world settings. This literature underscores the value of conducting economic evaluations alongside naturalistic, rather than highly artificial trials (Ramsey et al, 2015); statistically analysing within-trial heterogeneity to allow adjustment of findings for contexts outside the trial (Grieve et al., 2005, Sculpher et al., 2004, Manca et al., 2005); separate reporting of resource use and unit costs (Ramsey et al, 2015); description of the study setting (Drummond, 2005); and, using data from trials within decision analytic models, which appropriately reflect the decision context, rather than conducting entirely trial-based economic evaluations, which are restricted to the costs and outcomes measured in the trial (Sculpher et al., 2006, Sculpher, 2015).

As this literature focused on clinical interventions in high-income countries, authors assume that cost and outcome data are collected from individual patients through case report forms, which may not be possible for public health interventions delivered at a community, rather than individual level. Recommendations to improve generalisability through more representative study sites (Gheorghe et al., 2013) may not be feasible, especially for public health interventions, which may need to be conducted in a single geographic area to identify and measure community (herd) effects and to evaluate the feasibility of delivery before deciding to implement in multiple locations or on a very large scale. The analysis of the costs of SMC presented in Chapter 4 used statistical methods to examine within-study heterogeneity, as recommended; however, while this analysis yielded some useful findings regarding economies of scale, it also revealed limitations to such an approach, which did not exploit understanding of how the intervention worked and incurred costs.

Figure 14 Literature streams contributing to understanding of how to improve transferability of economic evaluation evidence

Green pentagons denote major research areas. Blue rectangles denote specific literature streams. Green arrows denote an intellectual relationship between areas and streams (evidenced by e.g. citations).

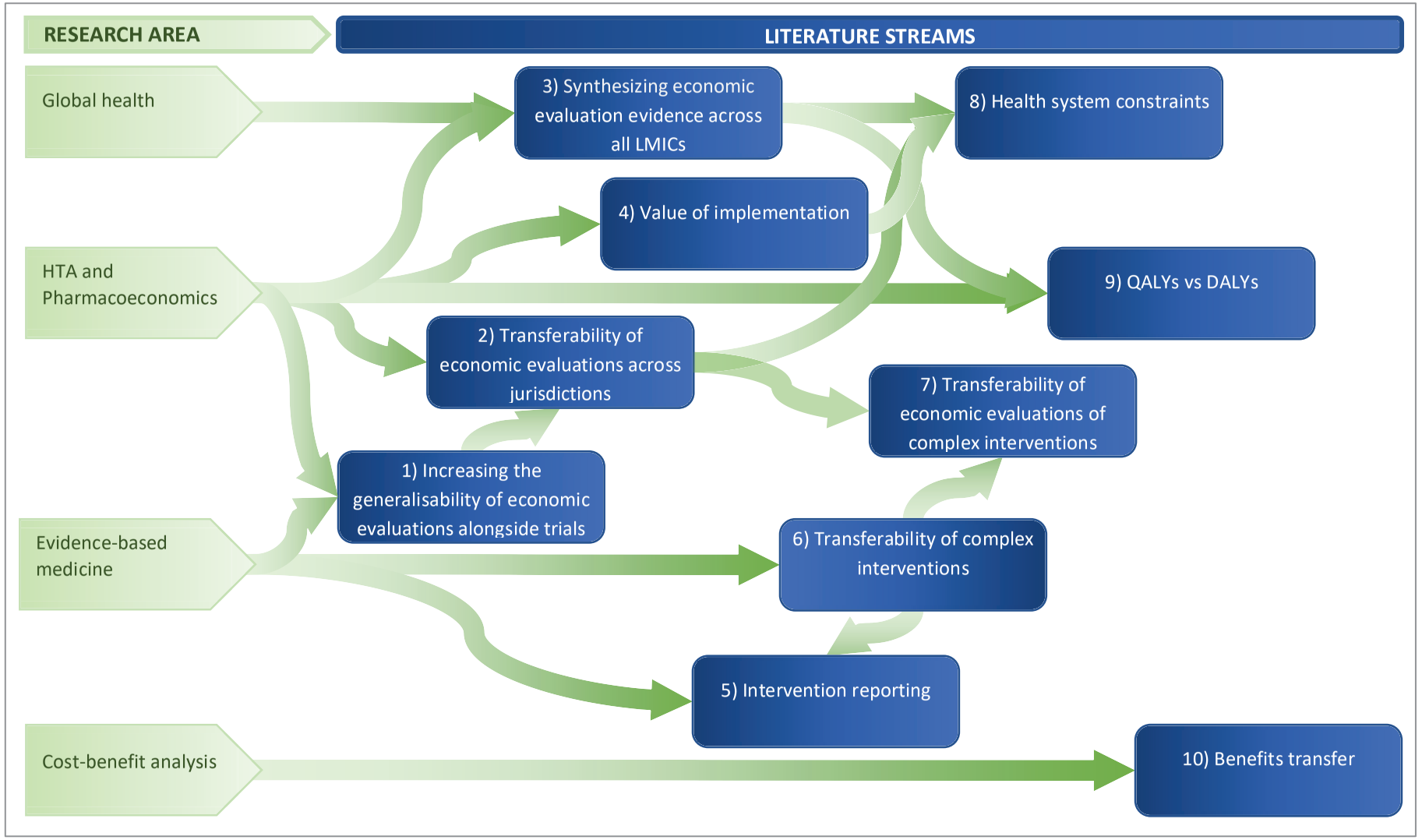


Table 10 Ten literature streams: Overview

Literature stream	Origin/tradition	Standpoint	Component(s)	Where published (illustrative)	Main country income groups / regions of focus
1) Increasing the generalizability of economic evaluations alongside trials	HTA, Pharmacoeconomics	Prospective	Costs and effects	*Health Economics, Health Technology Assessment, Value in Health, PlosONE*	Western Europe and HICs
2) Transferability of economic evaluations across jurisdictions	HTA, Pharmacoeconomics	Retrospective	Costs and effects	*European Journal of Health Economics, ClinicoEconomics and Outcomes Research, Value in Health, PharmacoEconomics, Health Technology Assessment, Health Economics*	Western Europe and HICs
3) Synthesis of economic evaluation evidence across all LMICs	Global health	modelling, prospective, retrospective	Costs and effects	Reports, websites, books, *Health Economics, Lancet, American Journal of Public Health, Cost Effectiveness and Resource Allocation, Value in Health*	LMICs
4) Value of implementation	HTA, Pharmacoeconomics	Prospective	Costs and effects	*Medical Decision Making*	Western Europe and HICs
5) Intervention reporting	Evidence-based medicine & systematic review methodology	Prospective	Effects only	*BMJ, BMC Medical Research Methodology, Trials*	Primarily HICs
6) Transferability of complex interventions	Complex behavioural and public health interventions	Prospective & retrospective	Effects only	*Trials, BMJ, BMC Health Services Research,* book, *Implementation Science, Health Research Policy System, European Journal of Public Health*	Primarily HICs
7) Economic evaluation of complex interventions	Complex behavioural and public health interventions & HTA	Primarily retrospective	Costs and effects	*National Institute Economic Review,* book, *Evaluation*	Primarily HICs
8) Health system constraints	Global Health & HTA	Modelling	Costs and effects	*PLoS Medicine, Health Economics, Health Systems & Reform*	LMICs
9) QALYs and DALYs	Global Health & HTA	Prospective	Effects only	*Health Policy & Planning, Value in Health*	Global
10) Benefits transfer	CBA	Retrospective	Effects only	*Journal of Benefit-Cost Analysis, Value in Health, Journal of Health Economics*	HICs

2) Transferability of economic evaluations across jurisdictions

A second literature stream focuses retrospectively on the transfer of existing economic evaluation evidence. I identify three stages: assessment, comparison, and transfer. First, economic evaluations may be assessed for their "potential transferability" (Nixon et al., 2009, Boulenger et al., 2005) to determine whether they have employed adequate methods and reported enough information for transferability to another context to be assessed. Many economic evaluations fall at this first hurdle (Mandrik et al., 2015, Augustovski et al., 2009). Second, relevance to another specific decision context may be assessed. Welte and colleagues (Welte et al., 2004) provide the seminal guidance on these first two stages, describing three "general knock-out criteria" (lack of comparability of intervention or comparator or insufficient methodological quality) and 14 transferability factors on which the study and target decision contexts should be compared (Goeree et al., 2011). Third, adjustments may be made to permit evidence transfer. The ISPOR report on transferability across jurisdictions (Drummond et al., 2009) recommended (in their order of preference): no adjustments; simple adjustments, such as use of purchasing power parities to adjust prices, where appropriate; re-analysis of patient-level data where multi-country studies have included the jurisdiction of interest; or adjustment through decision analytic modelling.

This literature stream makes the important point that researchers should not to be too restrictive in what evidence is considered transferable, nor too demanding in how much data and effort is considered necessary to adjust existing evaluations to a sufficient degree to use their evidence to inform decision-making (Essers et al., 2010). Limitations of this literature stream include its narrow focus on clinical interventions – often "pricing and/or reimbursement of health technologies" (Drummond et al., 2009) – and on Western Europe and North America. There is little consideration of how the organization of the health system or wider population characteristics may affect transferability, except as described by "practice patterns" or "case mix" – large and complex concepts, which are not unpacked. While several recommendations advocate the use of "expert opinion" in determining whether evidence is transferable or which data or estimates to use, they do not specify what particular expertise is necessary or how experts should assess the evidence. This gap is particularly problematic for LLMICs, where economic evaluation expertise is scarce and economic evaluation experts may lack knowledge of the specific aspects of the local health system most critical for the particular decision. While considerable attention is paid to whether the "decision problem" is transferable, little attention is given to understanding the intervention itself and how it may interact with context to produce changes in health outcomes. Some (especially large) UMICs

are discussed (Alshreef et al., 2018, Mandrik et al., 2015, Augustovski et al., 2009, Barbieri et al., 2010, Drummond et al., 2009), but virtually no mention is made of LLMICs.

3) Synthesis of economic evaluation evidence across all LMICs

A third literature stream consists of initiatives addressing the transferability challenge in LMICs by synthesizing – or facilitating synthesis of – economic evaluation evidence across all LMICs. This literature underscores the scarcity of economic evaluation evidence in LMICs; the trade-offs between precise contextualization and time, resources, and broad applicability; and the importance of methodological quality, standardization, and aggregation of evidence in promoting transferability.

Arguing that "one major factor limiting the transferability of [standard, incremental] . . . CEA results from one population to another . . . [is the] different current mixes of interventions" (Tan-Torres Edejer et al., 2003), WHO developed generalised cost-effectiveness analysis (GCEA) (Murray et al., 2000), in which intervention packages are compared to a null set representing the natural course of illness without preventive or curative interventions. By decontextualizing analyses and requiring comparison of all options for a given disease or sub-sector, however, GCEA is ill-suited for analysing evidence on new interventions and may lack face validity for decision-makers seeking context-specific advice.

A second set of initiatives compiled and – to varying degrees – synthesized evidence. For example, the Gates Foundation funded development of cost-per-DALY (CEVR, 2019) and intervention cost databases (GHCC, 2019). The Disease Control Priorities project synthesized evidence, including cost-effectiveness analyses; generated league tables; and combined league tables with other evidence and expert opinion to recommend benefits packages (Jamison and Mosley, 1991, Jamison et al., 2018, Horton, 2017). WHO-CHOICE used econometric analyses to estimate outpatient consultation and inpatient bed-day costs for all LMICs (Stenberg et al., 2018). Numerous United Nations agencies collaborated to develop the OneHealth Tool, which models the costs and health impacts of various combinations of interventions in any LMIC (WHO, 2019c). While recognizing the importance of context, this second set of approaches is retrospective, relying on limited existing data, which constrain the accuracy and context-specificity of their findings. Data underpinning WHO-CHOICE estimates, for example, are drawn from only 30 countries, are of questionable quality and comparability, and are at least a decade old (Stenberg et al., 2018).

A third set of initiatives developed general reference cases for conducting economic evaluations in LMICs (Wilkinson et al., 2016, Vassall et al., 2017), and guidance in specific areas (Walker et al., 2010a) in order to improve comparability, quality, and reporting, but do not address other aspects of how to make interventions more transferable.

4) Value of implementation

A small literature on "value of implementation" (Fenwick et al., 2008) does not use the term "transferability", but focuses on how to replicate the effectiveness achieved in clinical trials in real-world implementation, or how to transfer findings from clinical trials to real-world settings in ways that take into account the reduced uptake of a new technology outside a trial setting (Kim and Basu, 2017). In doing so, it speaks to the scope of the alternative courses of action that should be evaluated and potentially transferred. Specifically, it demonstrates the importance of an integral (rather than sequential) assessment of the cost-effectiveness of a new technology and "implementation activities" aiming to instigate and maintain its use (Hoomans et al., 2009, Kim and Basu, 2017). In the sequential evaluation, which reflects standard practice in HTA, interventions that appear less cost-effective under idealised conditions of "perfect" implementation (Andronis and Barton, 2016b, Andronis and Barton, 2016a) may be eliminated from consideration at an initial stage, even where they are more readily implementable and therefore potentially more cost-effective in practice than those interventions that remain under consideration at a later stage (Hoomans et al., 2009).

Yet, the value of implementation literature (Fenwick et al., 2008, Willan and Eckermann, 2010, Whyte et al., 2016, Faria et al., 2017, Kim and Basu, 2017, Hoomans et al., 2009) remains narrowly focused on clinical interventions in Western Europe and North America and does not engage meaningfully with implementation as a potentially complex process of behaviour change whose effectiveness and costs require research. This gap is important because incorporating implementation activities into integral cost-effectiveness estimates may raise substantial challenges for transferability, as variations in human behaviour between contexts are especially difficult to predict.

5) Intervention reporting

A fifth literature stream grappled with identifying the essential features defining an intervention, the interconnections between interventions and their context, and the potential for interventions to require "tailoring" to work in similar ways in new contexts. Despite evident relevance, few publications in this stream refer to "transferability" explicitly and none engage meaningfully with questions of costs or cost-effectiveness. Hoffman and colleagues' (2014) "template for intervention description and replication (TIDieR) checklist and guide" extended reporting guidelines for randomized trials (Schulz et al., 2010) and protocols (Chan et al., 2013), but was "intended to apply across all evaluative study designs", "with the objective of improving the completeness of reporting, and ultimately the replicability, of interventions". It clarified that an intervention cannot be defined solely by "a label or the ingredients list" – as is common in HTA – and must include the "why, what (materials), what (procedure), who provided, how, where, when and how much", as well as information on planned tailoring and unplanned modifications to the intervention, which "can all influence efficacy and replicability but are often missing or poorly described" (Hoffmann et al., 2014). While their 11 checklist items are designed to apply both to an intervention and comparator and both to "apparently simple drug interventions" and to all components of more complex interventions, they focus on clinical decision-making.

While narrowly framed, two extensions to TIDieR appear useful for all interventions. One extension makes an important contribution in arguing that "providing the underlying rationale of the intervention enables readers to understand its essential components" (Campbell et al., 2018). Another usefully promotes reflexivity by asking who filled out the checklist (Cotterill et al., 2018).

Alternatives to TIDieR (Kagesten et al., 2017, Mohler et al., 2015, WHO, 2017b) emphasize the usefulness of clear reporting at the early stages of intervention development as a means of improving intervention design and implementation. One of these checklists features the only reporting item focused on transferability, seeking somewhat simplistic "[reflections] on the context-dependence of the programme and on the degree of effort that would be needed to implement it in/adapt it to other settings" (Kagesten et al., 2017).

6) Transferability of complex interventions

A sixth literature stream is framed around complex interventions. The key insight from this literature is that understanding transferability requires understanding the mechanisms of action through which an intervention interacts with context to produce changes in outcomes (Grant et al., 2013, Moore et al., 2015, Bunce et al., 2014, Oakley et al., 2006). Theories of change are important tools for understanding mechanisms of action; they can inform and, in turn, be refined by process evaluations and "[provide] a comprehensive set of indicators to evaluate all stages of the causal pathway through which an intervention achieves impact." (De Silva et al., 2014) Many authors justify including process evaluations in wider evaluations on the basis that they achieve "deep understanding of the 'how' and the 'why' behind intervention outcomes" (Bunce et al., 2014) or "greater explanatory power" (Oakley et al., 2006), which are "crucial to understanding . . . how these effects might be replicated by similar future interventions" (Moore et al., 2015); that is, process evaluations "[improve] the credibility and transferability of study findings" (Bunce et al., 2014). Pawson and Tilley (2004), leading proponents of one type of theory-based evaluation, explain that "[realist] evaluations asks not, 'What works?' or, 'Does this program work?' but asks instead, 'What works for whom in what circumstances and in what respects, and how?'"

Whereas other literature streams tend to mention context vaguely, the complex intervention literature specifies that the most important contextual features depend on the mechanisms of action of the particular intervention. Context is "those features of the conditions in which programmes are introduced that are relevant to the operation of the programme mechanisms" (Pawson and Tilley, 2004) or "anything external to the intervention that may act as a barrier or facilitator to its implementation, or its effects" (Moore et al., 2015).

The literature stream also emphasizes that complex interventions may require "tailoring" or "adaptation" to work in similar ways in new contexts. Villeval and colleagues (2019) argue that the key functions (or mechanisms) of a complex intervention may be transferable, but their "specific form (i.e. concrete activities implemented)" must be adapted to local contexts by "local actors [who] will decide on the form of the replicated intervention according to the specificities of and the knowledge they have about the features of their context". This insight is important; however, the implications of changes in the "form" of an intervention for costs are not mentioned (Villeval et al., 2019).

In fact, most of the complex intervention literature stream ignored costs (Villeval et al., 2019, Burchett et al., 2018) or treated economic questions superficially, referring to costs, for

example, as a characteristic of an intervention (Schloemer and Schroder-Back, 2018) or of the context, rather than a dynamic product of the interaction between the intervention components (which themselves require resource inputs) and the context. Authors therefore failed to consider that an intervention that may be effective in or adaptable to another context should not necessarily be implemented if it is not also an efficient use of resources in that context.

The complex intervention literature largely frames its contributions as not relevant to "simple" interventions, such as "drugs or surgical procedures" (Lewin et al., 2017, Rogers, 2008, Oakley et al., 2006), although some authors recognized that "[few] interventions are truly simple" (MRC, 2008) and that even simple interventions may have complex interactions with context (Moore et al., 2015). Petticrew (2011) argued that interventions are not inherently complex or simple, but rather, that researchers may choose to view an intervention as simple or complex, depending on the research questions and purpose of the analysis. This insight has important implications for understanding the manifestly complex question of transferability.

7) Economic evaluation of complex interventions

A seventh, very small literature stream argues that articulating theories of change with specific reference to resources can improve the transferability of economic evaluation evidence. In particular, Anderson and Hardwick extended their prior work – including Walker et al. (2010b) – and drew on Pawson and Tilley (2004), Byford and Sefton (2003), and others to propose "explanatory economic evaluation" drawing on realist principles (Anderson and Hardwick, 2016). They argued that "most economic evaluations . . . are archetypal 'black box' evaluations, with minimal interest in how and why a particular configuration of resources (an intervention) changes outcomes" and that this approach "has important [negative] consequences for the generalisability and use of their findings". They proposed that the main evaluation team "could more explicitly theorise and capture the resource requirements and consequences of hypothesised programme mechanisms, outcomes and contexts". In addition to better incorporating resources within the main programme theory, Anderson and Hardwick also promoted development of "programme theories which explicitly seek to explain cost-effectiveness or altered costs". They illustrated their proposal for a "cost-effectiveness-specific programme theory" with a realist review of economic evaluations of "shared care" for chronic conditions in HICs.

While these authors repeatedly argued that "context matters", however, they did not elaborate on which aspects of context mattered (Walker et al., 2010b) and did not include context in their example of a "cost-effectiveness-specific programme theory" (Anderson and Hardwick, 2016). As with the previous literature stream, authors also tended to frame their recommendations as relevant for complex but not "simple" interventions. Most crucially, they did not discuss how "explanatory economic evaluation" principles might be enacted in primary economic evaluations (rather than reviews) (Anderson and Hardwick, 2016). They also focussed exclusively on the transferability of the economic evaluation evidence relating to an intervention's function, without considering how evidence on the costs of a particular "form" of an intervention could be transferred.

8) Health system constraints

An eighth literature stream framed around health system constraints offers an explicitly economic framing of context within economic evaluations, which is wider and more relevant for guiding policy choices in LMICs than Welte's framework (2004). Mikkelsen and colleagues (2017) used WHO's health system building blocks as a framework to describe supply constraints and identified demand constraints such as "stigma, limited knowledge about HIV, fatalism, out-of-pocket payments, and waiting times". Vassall and colleagues (of which I was one) (2016a) presented a conceptual model of distal and proximal demand and supply constraints which may affect the "care pathway", and some of the relationships between interventions, the supply and demand context, and population health outcomes.

The constraints literature deals with both the transfer of trial and small-scale evidence to real-world implementation and the extension of findings across geographies in ways that recognize heterogeneity between contexts. While most do not focus on "transferability" as such, authors in this stream articulate a tension between generating evidence to support "generic advice to a wide range of countries" (Hauck et al., 2016) and "[taking] into account the local health system" (Mikkelsen et al., 2017).

Throughout this literature stream, however, conceptualization of what interventions are and how they interact with context to produce changes in outcomes – i.e. the mechanisms of action – remain poorly defined. Descriptions of the cost-effectiveness of a technology and of "enabling interventions" (2016a) – and indeed, the very notion of a "constraint" to optimizing

utility – mirror the dichotomized conceptualization within the value of implementation literature of a technology divorced from actors or actions to instigate its use.

9) DALYs, QALYs, and 10) Benefits

The final two literature streams emerge from different research traditions, but both deal with the appropriate measure of effect to use in economic evaluations. Both QALYs (Sassi, 2006) and the benefits in CBAs (Robinson et al., 2019) are designed to reflect a specific society's preferences, and are thus considered appropriate measures of utility or societal welfare . Most LLMICs have not conducted valuation surveys for QALYs (Kularatna et al., 2013, Welie et al., 2020) or willingness-to-pay for a change mortality or morbidity risk, however, which inhibits adjustment of QALYs or benefits to most contexts in LLMICs. Further, the contingent valuation methods used in CBA to value changes in health outcomes or health risks do not reference the available health budget, so risk displacing more health benefits than they gain (Culyer and Chalkidou, 2019, Ochalek et al., 2018). A literature stream framed around "benefits transfer" deals with the transfer of the valuation of non-market goods – originally, environmental goods, and more recently, preference-based health outcomes – across contexts for use in CBAs. This literature emphasizes the tension between a preference-based approach, which is necessarily about local, context-specific preferences, and efforts to promote transferability. Brower and colleagues showed that simple transfers are more appropriate for "similar" contexts, while more complex transfers are required for "dissimilar" contexts, but do not provide any generalizable insights into how "similar" and "dissimilar" contexts should be defined for any given intervention (Brouwer and Bateman, 2005). Finally, the validity of contingent valuation methods and asking people in LLMICs to value health risks is unproven.

While criticized for many shortcomings, including their focus on health rather than welfare and their exclusion of context-specific factors affecting a person's lived experience of a condition (e.g. educational opportunities or public transport) (Nord, 2015, Chen et al., 2015), DALYs are explicitly designed to be universal (Sassi, 2006), which facilitates their transfer across contexts. As most full health economic evaluations to date in LLMICs have used DALYs, cost-per-DALY estimates can also be compared with existing literature.

6.5.3. Summary: Transferability literatures

Insights into how to make economic evaluations more transferable have emerged from many different literature streams. I have sought to delineate these literature streams in meaningful ways; however, each stream includes publications that overlap with one or more other streams, and some of these literature streams, which vary tremendously in size, could have been grouped differently.

From this review, I conclude that transferability is a complex question requiring a complexity perspective, even for seemingly simple interventions. As well as adherence to standard economic evaluation guidelines, making economic evaluation evidence more transferable requires understanding and communicating what an intervention is and the mechanisms of action through which an intervention interacts with context to produce changes in costs and effects. The key contextual features are those implicated in the mechanisms of action through which the intervention produces costs and effects. Interventions may require adaptation to work in similar ways in new contexts, and such changes are likely to affect the costs of the interventions. By contrast, similar forms of interventions may be deployed to serve very different functions, creating additional opportunities to maximize the use of scarce primary cost data. Articulation of theories of change with respect to both costs and effects in primary economic evaluations seems to offer a promising avenue for further research. Despite their widely-discussed limitations, DALYs facilitate evidence transfer and should therefore be used whenever possible, potentially alongside additional effect measures.

6.6. Designing for transferability guide

Drawing on my critical review and experience conducting economic evaluations, I propose some initial guidance on the design of economic evaluations alongside trials or pilots in ways that promote transferability. This guidance is intended to apply to all types of interventions and strategies in all settings when implemented in the context of trials or pilots, but responds particularly to the context of LLMICs, where so few economic evaluations are conducted that each economic evaluation must seek to inform a wide range of decisions, for which the

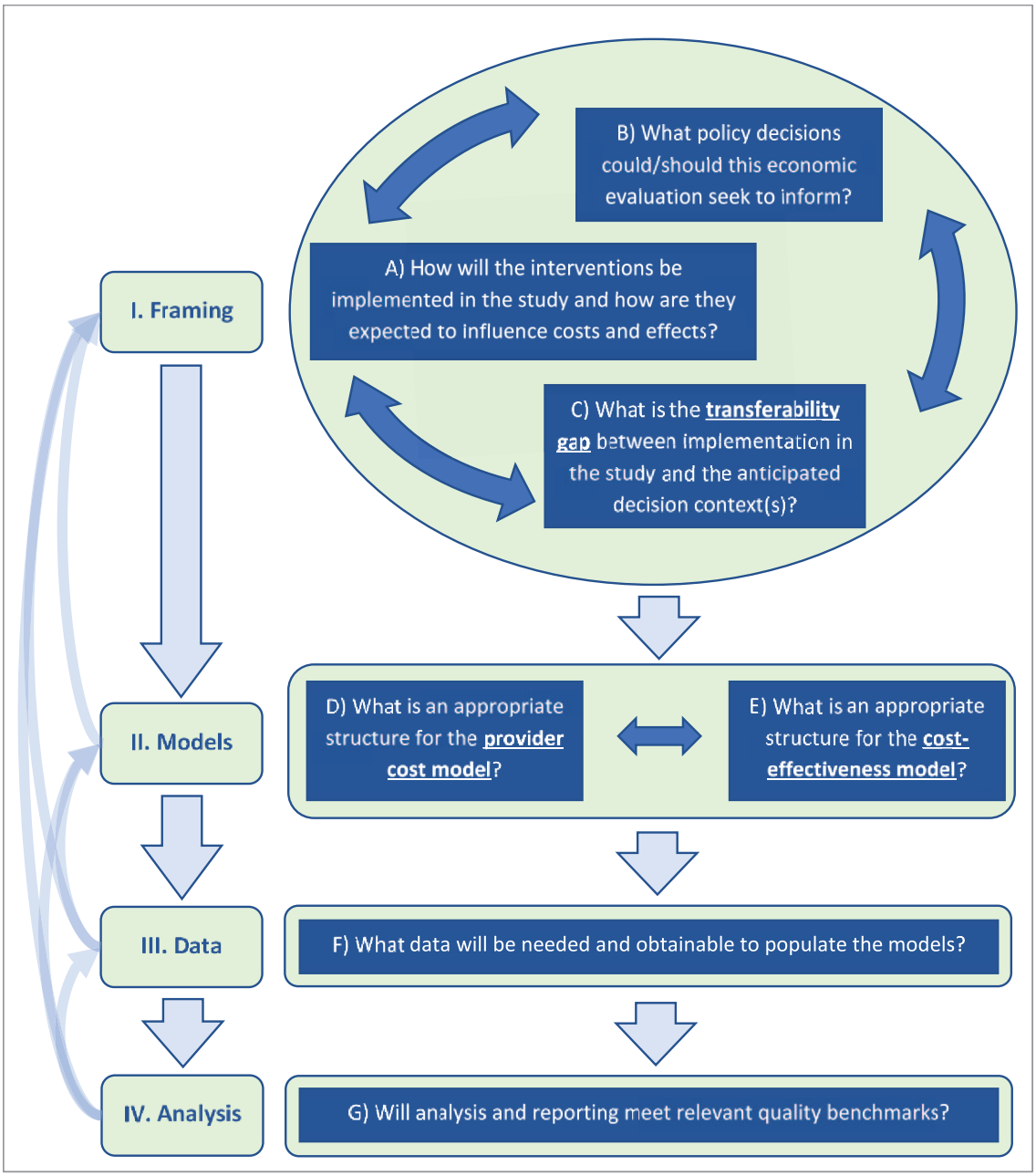
decision-makers are many and not necessarily known. The proposed approach encourages development of an in-depth understanding of how an intervention or strategy works in a particular context as a means of exploring how its costs and effects may be expected to vary in another context. An assumption underlying this approach is that understanding if and how cost-effectiveness evidence can be transferred across contexts is a complex research question, requiring a complexity lens (Petticrew, 2011).

The purpose of this approach is to help economic evaluations do more than report retrospectively on the cost-effectiveness of precisely what was done in a trial or pilot, and instead to inform prospective decision-making – in a plausible and transparent way – both for the local context and, to the extent possible and appropriate, for different contexts and modified versions of the interventions studied. To achieve this aim, the invaluable opportunity to collect data alongside a trial or pilot should be conceived of as a means of developing and populating flexible and transparent mechanistic cost models and a decision analytic model alongside the trial or pilot. While decision analytic models are often used in economic evaluations alongside trials in LLMICs, this practice is not reflected in standard guidelines (Husereau et al., 2013), and mechanistic cost models are uncommon. This approach responds to Sculpher's criticisms of "trial-based economic evaluations" (Sculpher et al., 2006, Sculpher, 2015), which only analyse data within a trial, and uses the opportunity afforded by the trial or pilot to gain in-depth understanding of the alternative strategies, how they work, and how they incur costs and produce effects in a given context. It also responds to Anderson and Hardwick's (2016) exhortations for explanatory economic evaluation, while focusing on the design and conduct of primary economic evaluations.

The guidance that follows proposes a reversal in the order in which activities are commonly undertaken. Instead of treating transferability as an afterthought, transferability becomes the guiding principle of the economic evaluation; the focus remains throughout on generating evidence to inform prospective decision-making outside of the trial or pilot. The four main stages of this model-based economic evaluation alongside a trial or pilot are: I) **Framing** the economic evaluation, II) **Model** identification and/or development, III) **Data** needs identification, and IV) **Analysis** and reporting (Figure 15, **Box 1**). These stages share many commonalities with existing guidelines, but also differ in several important ways, notably: i) the order in which activities are conducted, ii) the use of theory of change and process evaluation for all intervention types, iii) the development of mechanistic provider cost models (as well as a decision analytic model), iv) a more targeted, model-driven approach to data

collection, and v) an explicitly iterative approach. The following guidance therefore necessarily covers some of the same ground as existing guidance, referring to such guidance as appropriate, but focuses on where this approach diverges from standard guidance.

Figure 15 Designing for transferability: A flowchart of questions to consider in designing and conducting an economic evaluation alongside a trial or pilot



Box 1 Designing for transferability: Questions to guide the design of economic evaluations alongside a trial or pilot

These questions are intended to guide initial design of an economic evaluation and to be revisited throughout the study, incorporating emerging findings and reflecting changing policy contexts, to maximize the transferability – and thus usefulness – of the economic evaluation produced. The four stages (I-IV) and seven steps (A-G) are explained below and illustrated in Figure 15. All references to "interventions" should be understood to refer both to a new intervention and to a comparator. Implementation of interventions in the study (i.e. trial or pilot) context is distinguished from intervention implementation in the decision context.

I. Framing

Framing is an iterative process – broken into three steps here – of A) understanding what is planned for intervention implementation in the study, B) considering what decisions an economic evaluation based on study implementation plans could or should inform, and C) assessing the transferability gap, that is, how planned implementation in the study and the associated costs and effects may differ from implementation in the decision contexts that the evaluators seek to inform. Understanding of the transferability gap should inform revisions to plans for the study in (A) and to the decision problems to address in (B), as well as model development in stage II. While (A) is shown as the starting point – as is often the case, from the perspective of economic evaluators, when they join a study for which initial plans have already been developed – (B) would be the ideal starting point. To answer the questions posed at this stage, evaluators will need to consult documents (academic literature and policy documents) and various people (e.g. policy experts, decision-makers, practitioners, and academics) at local, national, and potentially international levels. Detailed guidance available elsewhere on intervention reporting (Hoffmann et al., 2014, Mohler et al., 2015, Kagesten et al., 2017, WHO, 2017b, Campbell et al., 2018, Cotterill et al., 2018) *may be used to structure descriptions and discussions regarding planned intervention implementation in the study context and anticipated implementation in the decision context, as well as eventual reporting of what was done.*

A) INTERVENTION IMPLEMENTATION AND MECHANISMS OF ACTION: How will the interventions be implemented in the study? How are they expected to influence costs and effects?

1. How are the proposed intervention activities expected to interact with the existing context to produce changes in health outcomes (i.e. what is the **theory of change** and what are the key aspects of the local context that the intervention will modify)?
2. What are expected to be the **resources used** for: i) the activities to instigate change, including the intervention itself (e.g. policy change, training, radio campaigns, materials, drugs) and ii) downstream consequences of the interventions (e.g. changes in case management following introduction of a preventive intervention, reductions in complications or onward transmission following introduction of an improved case management intervention)?

RELEVANT DECISIONS: What policy decisions could/should this economic evaluation seek to inform?

3. In which **contexts outside of the specific research context** might the same or similar interventions be relevant for consideration?
4. How likely is it that **additional economic evaluations** of the same or similar interventions will be undertaken in the same, similar, or different contexts and on what time scale? For example, if few or none are expected in the near future, then this economic evaluation should consider seeking to inform a wider range of decisions than if many other related economic evaluations are expected imminently.
5. Is the form of the intervention – e.g. door-to-door visits by CHWs – potentially relevant for informing decisions regarding **similar interventions for other health areas**?
6. Are there **other interventions relevant to the decision context**, which are not planned for implementation in the study context?

B) TRANSFERABILITY GAP: What is the transferability gap between planned implementation in the study and decision contexts?

7. How may aspects of the **research context** affect the costs and effects measured relative to implementation outside a research context? For example, will research staff be involved in implementation or will their research activities influence the effects measured? Will the people implementing or receiving the interventions receive more (or fewer) resources than they would if the intervention were implemented outside a study context? Is it possible to avoid or mitigate the influence of the research activities on the costs and health outcomes measured so as to approximate a real-world context more closely?
8. What **changes to implementation** (and associated resource use) in the research context, if any, may need to be made (and by whom) to . . .
   a. . . . ensure feasibility and/or affordability in the decision context (e.g. lower the cadre/qualifications of implementing staff)?
   b. . . .maintain or increase effectiveness in the decision context (e.g. additional community meetings in more sceptical communities, or doubling the frequency of patient contacts)?
9. What **changes to effects and associated downstream costs** would be expected in any new context considered and for each of the changes above? e.g. might lesser access to care outside the research context decrease incremental treatment costs and increase incremental health benefits for a preventive intervention? Might lowering the cadre of staff implementing the intervention also lead to reduced health benefits?
10. **Who has participated in discussions** regarding the preceding questions? Should others also be consulted, e.g. people who may play substantial roles in intervention implementation in the study, in the policy decision process, or in eventual implementation in the anticipated decision contexts?

II. Models

Based on an understanding of the decision problem and the transferability gap, the evaluator can develop an appropriate model structure or identify an existing model structure to use. Detailed guidance on how to conceptualize a cost-effectiveness model (Roberts et al., 2012) and specific issues pertaining to different model types are provided elsewhere (Karnon et al., 2012, Pitman et al., 2012, Siebert et al., 2012, Squires et al., 2016) and therefore not repeated here.

C) PROVIDER COST MODEL: What is an appropriate model structure?

11. Are there any **existing cost models** for similar interventions?
12. What **activities and resources** are involved in each intervention?
13. Which **administrative or implementation levels** (i.e. countries, provinces, districts, health facilities), and **outputs** (e.g. persons reached, cases treated) are involved in the process of intervention delivery and downstream costs? Do these variation units provide an appropriate **structure for the cost model**, or are there additional factors which may need to be incorporated, such as the number of delivery rounds or the proportion of cases that are severe, to generate a plausible cost model using readily available data?
14. Are **prices expected to vary with the scale** of implementation of this particular intervention? If so, has this relationship been incorporated into the cost model?
15. For each resource, with which **implementation level or output can the quantity used be expected to vary**? For example, the quantity of a specific drug used may vary with the number of patients reached or the number of illness episodes, and the quantity of nursing hours spent in receiving training may vary with the number of facilities involved in the intervention (if a fixed number of nurses per facility are trained).

D) COST-EFFECTIVENESS MODEL: What is an appropriate model structure?

16. To what extent and how can **changes in effectiveness** be modelled across the decision contexts? e.g. would dynamic transmission modelling be required or might a decision tree assuming equal efficacy and different coverage be sufficient? Could coverage data for similar types of interventions in the decision context be used?
17. How do the **cost model and cost-effectiveness model interact**? Are there feedback loops, or can cost model outputs be used as inputs in the cost-effectiveness model?

III. Data

After framing the evaluation and identifying appropriate model structures, the evaluator should consider what data may be needed to populate the model, and the extent to which relevant data may be obtained from the study, or from additional sources such as routine health information systems, secondary data, or existing models such as WHO-CHOICE (2011). Initial sensitivity analysis should be used to prioritise parameters for which obtaining accurate and precise estimates will have the greatest impact on improving the overall model's precision and accuracy.

E) DATA: What data are needed and obtainable to populate the models?

18. What **resource use data** are needed to populate the model? What level of detail will be needed to ensure that resource use data can be disaggregated according to the model structure? For example, will the total time nurses spend on the intervention need to be separated into time spent with patients (which may vary with the number of patients) and time spent in training (which may be fixed per nurse)? For each resource and scenario, will quantities reflect the research context or estimates for or observations from another context?
19. Will the **prices** of resources used in the study implementation differ from likely prices in the decision-making context(s)? Do any price differences reflect differences in the quality of the resource (e.g. substitution with lower cadre of staff)? Which prices are consistent with the effect measures used? Which are relevant for decision-making? Are these prices expected to vary with location and/or with other factors (e.g. technological improvements over time lowering prices of tests, economic improvements increasing wages)?
20. What data on **effects** are needed and obtainable? How are they expected to differ between the study context and the decision context?
21. What data – qualitative or quantitative – are necessary to check **the assumptions** in the model structure and parameters? Have they been incorporated into data collection?
22. Are resources available within this study to collect data in any or all of the **decision contexts** to which the findings may be transferred? For example, would it be possible to collect data on the numbers of units at each administrative level for the entire country?

IV. Analysis

The evaluator should ensure that the analysis is conducted and reported in accordance with relevant guidelines for high-quality economic evaluation research. During this stage, evaluators should revisit the previous stages of the evaluation to consider whether the framing of the analysis should change (perhaps in response to policy changes over the course of the study), if any aspects of model structure warrant revisiting, and if any further data would be useful and obtainable within the current study to maximize the usefulness of the results presented.

F) ANALYSIS: Will analysis and reporting meet relevant quality benchmarks?

23. Will the economic evaluation meet the iDSI reference case (Wilkinson et al., 2016), CHEERS checklist (Husereau et al., 2013), and other relevant **quality** benchmarks for study conduct and reporting? These may include guidelines for the country/countries of the study and any other countries in which the intervention(s) may be considered, as well as the World Health Organization, potential funders, and any other relevant decision-makers.
24. Will the costs incurred in implementing the intervention(s) in the research context and any modelled costs be presented separately and **transparently**?
25. Has the structure of the **model(s)** been presented?

6.7. Conclusion

Drawing on a wide-ranging critical review of 10 different literature streams and my own experience conducting economic evaluations, this article proposes preliminary guidance on how to make economic evaluations conducted alongside trials and pilots more transferable. Rather than remaining an afterthought, promoting transferability of economic evaluation evidence should become the guiding principle of intervention research. Promoting transferability requires efforts from the earliest phases of intervention design to identify and close – where possible – the transferability gap between planned implementation in the study context and anticipated implementation in one or more decision contexts. I argue that transferability is a complex question requiring a complexity perspective, even for seemingly simple interventions. Making economic evaluation evidence more transferable requires understanding and communicating what an intervention is and the mechanisms of action through which it interacts with context to produce changes in costs and effects. The key contextual features are those implicated in the mechanisms of action. I identify four stages for a model-based economic evaluation alongside a trial or pilot: I) Framing the economic evaluation, II) Model identification and/or development, III) Data needs identification, and IV) Analysis and reporting. For each stage, I articulate key questions to guide analysts to close the transferability gap. Future research should pilot and further refine the "Designing for transferability" guide as part of wider efforts to improve the transferability of economic evaluation evidence and maximize the value for money of empirical research.

6.8. References for Chapter 6

ALSHREEF, A., MACQUILKAN, K., DAWKINS, B., RIDDIN, J., WARD, S., MEADS, D., TAYLOR, M., DIXON, S., CULYER, T., HOFMAN, K., RUIZ, F., CHALKIDOU, K., LORD, J. & EDOKA, I. 2018. Assessing the Appropriateness of Existing Model Adaptation Methods for Low and Middle-Income Countries. *Value in Health,* 21**,** S8-S8.

ANDERSON, R. & HARDWICK, R. 2016. Realism and resources: Towards more explanatory economic evaluation. *Evaluation (London),* 22**,** 323-341.

ANDRONIS, L. & BARTON, P. M. 2016a. Adjusting Estimates of the Expected Value of Information for Implementation: Theoretical Framework and Practical Application. *Med Decis Making,* 36**,** 296-307.

ANDRONIS, L. & BARTON, P. M. 2016b. Adjusting Expected Value of Sample Information Using Realistic Expectations around Implementation. *Med Decis Making,* 36**,** 284.

AUGUSTOVSKI, F., IGLESIAS, C., MANCA, A., DRUMMOND, M., RUBINSTEIN, A. & MARTI, S. G. 2009. Barriers to generalizability of health economic evaluations in Latin America and the Caribbean region. *Pharmacoeconomics,* 27**,** 919-29.

BARBIERI, M., DRUMMOND, M., RUTTEN, F., COOK, J., GLICK, H. A., LIS, J., REED, S. D., SCULPHER, M., SEVERENS, J. L. & ISPOR GOOD RESEARCH PRACTICES ECONOMIC DATA TRANSFERABILITY TASK FORCE 2010. What do international pharmacoeconomic guidelines say about economic data transferability? *Value Health,* 13**,** 1028-37.

BOULENGER, S., NIXON, J., DRUMMOND, M., ULMANN, P., RICE, S. & DE POUVOURVILLE, G. 2005. Can economic evaluations be made more transferable? *Eur J Health Econ,* 6**,** 334-46.

BUNCE, A. E., GOLD, R., DAVIS, J. V., MCMULLEN, C. K., JAWORSKI, V., MERCER, M. & NELSON, C. 2014. Ethnographic process evaluation in primary care: explaining the complexity of implementation. *BMC Health Services Research,* 14**,** 607.

BURCHETT, H. E. D., BLANCHARD, L., KNEALE, D. & THOMAS, J. 2018. Assessing the applicability of public health intervention evaluations from one setting to another: a methodological study of the usability and usefulness of assessment tools and frameworks. *Health Res Policy Syst,* 16**,** 88.

BYFORD, S. & SEFTON, T. 2003. Economic Evaluation of Complex Health and Social Care Interventions. *National Institute Economic Review,* 186**,** 98-108.

CAMPBELL, M., FITZPATRICK, R., HAINES, A., KINMONTH, A. L., SANDERCOCK, P., SPIEGELHALTER, D. & TYRER, P. 2000. Framework for design and evaluation of complex interventions to improve health. *BMJ,* 321**,** 694-6.

CAMPBELL, M., KATIKIREDDI, S. V., HOFFMANN, T., ARMSTRONG, R., WATERS, E. & CRAIG, P. 2018. TIDieR-PHP: a reporting guideline for population health and policy interventions. *BMJ,* 361**,** k1079.

CEVR 2019. Global Health Cost Effectiveness Analysis Registry. Boston, MA, USA: Center for Evaluation of Value and Risk in Health (CEVR), Tufts Medical Center.

CHAN, A. W., TETZLAFF, J. M., ALTMAN, D. G., LAUPACIS, A., GOTZSCHE, P. C., KRLEZA-JERIC, K., HROBJARTSSON, A., MANN, H., DICKERSIN, K., BERLIN, J. A., DORE, C. J., PARULEKAR, W. R., SUMMERSKILL, W. S., GROVES, T., SCHULZ, K. F., SOX, H. C., ROCKHOLD, F. W., RENNIE, D. & MOHER, D. 2013. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med,* 158**,** 200-7.

COTTERILL, S., KNOWLES, S., MARTINDALE, A. M., ELVEY, R., HOWARD, S., COUPE, N., WILSON, P. & SPENCE, M. 2018. Getting messier with TIDieR: embracing context and complexity in intervention reporting. *BMC Med Res Methodol,* 18**,** 12.

DE SILVA, M. J., BREUER, E., LEE, L., ASHER, L., CHOWDHARY, N., LUND, C. & PATEL, V. 2014. Theory of Change: a theory-driven approach to enhance the Medical Research Council's framework for complex interventions. *Trials,* 15**,** 267.

DRUMMOND, M., BARBIERI, M., COOK, J., GLICK, H. A., LIS, J., MALIK, F., REED, S. D., RUTTEN, F., SCULPHER, M. & SEVERENS, J. 2009. Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report. *Value in Health,* 12**,** 409-418.

ESSERS, B. A., SEFERINA, S. C., TJAN-HEIJNEN, V. C., SEVERENS, J. L., NOVAK, A., POMPEN, M., ORON, U. H. & JOORE, M. A. 2010. Transferability of model-based economic evaluations: the case of trastuzumab for the adjuvant treatment of HER2-positive early breast cancer in the Netherlands. *Value Health,* 13**,** 375-80.

FARIA, R., WALKER, S., WHYTE, S., DIXON, S., PALMER, S. & SCULPHER, M. 2017. How to Invest in Getting Cost-effective Technologies into Practice? A Framework for Value of Implementation Analysis Applied to Novel Oral Anticoagulants. *Med Decis Making,* 37**,** 148-161.

FENWICK, E., CLAXTON, K. & SCULPHER, M. 2008. The value of implementation and the value of information: combined and uneven development. *Med Decis Making,* 28**,** 21-32.

GHCC 2019. Unit Cost Study Repository. Global Health Cost Consortium.

GOEREE, R., HE, J., REILLY, D., TARRIDE, J. E., XIE, F., LIM, M. & BURKE, N. 2011. Transferability of health technology assessments and economic evaluations: A systematic review of approaches for assessment and application. *ClinicoEconomics and Outcomes Research,* 3**,** 89-104.

GRANT, A., TREWEEK, S., DREISCHULTE, T., FOY, R. & GUTHRIE, B. 2013. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. *Trials,* 14**,** 15.

GRIEVE, R., NIXON, R., THOMPSON, S. G. & NORMAND, C. 2005. Using multilevel models for assessing the variability of multinational resource use and cost data. *Health Econ,* 14**,** 185-96.

HAUCK, K., THOMAS, R. & SMITH, P. C. 2016. Departures from Cost-Effectiveness Recommendations: The Impact of Health System Constraints on Priority Setting. *Health Systems & Reform,* 2**,** 61-70.

HOFFMANN, T. C., GLASZIOU, P. P., BOUTRON, I., MILNE, R., PERERA, R., MOHER, D., ALTMAN, D. G., BARBOUR, V., MACDONALD, H., JOHNSTON, M., LAMB, S. E., DIXON-WOODS, M., MCCULLOCH, P., WYATT, J. C., CHAN, A. W. & MICHIE, S. 2014. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ,* 348**,** g1687.

HOOMANS, T., SEVERENS, J. L., EVERS, S. M. & AMENT, A. J. 2009. Value for money in changing clinical practice: should decisions about guidelines and implementation strategies be made sequentially or simultaneously? *Med Decis Making,* 29**,** 207-16.

HORTON, S. 2017. Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition. *In:* RD, JAMISON, D. T., GELBAND, H., HORTON, S., JHA, P., LAXMINARAYAN, R., MOCK, C. N. & NUGENT, R. (eds.) *Disease Control Priorities: Improving Health and Reducing Poverty.* Washington (DC).

JAMISON, D. T., ALWAN, A., MOCK, C. N., NUGENT, R., WATKINS, D., ADEYI, O., ANAND, S., ATUN, R., BERTOZZI, S., BHUTTA, Z., BINAGWAHO, A., BLACK, R., BLECHER, M., BLOOM, B. R., BROUWER, E., BUNDY, D. A. P., CHISHOLM, D., CIEZA, A., CULLEN, M., DANFORTH, K., DE SILVA, N., DEBAS, H. T., DONKOR, P., DUA, T., FLEMING, K. A., GALLIVAN, M., GARCIA, P. J., GAWANDE, A., GAZIANO, T., GELBAND, H., GLASS, R., GLASSMAN, A., GRAY, G., HABTE, D., HOLMES, K. K., HORTON, S., HUTTON, G., JHA, P., KNAUL, F. M., KOBUSINGYE, O., KRAKAUER, E. L., KRUK, M. E., LACHMANN, P., LAXMINARAYAN, R., LEVIN, C., LOOI, L. M., MADHAV, N., MAHMOUD, A., MBANYA, J. C., MEASHAM, A., MEDINA-MORA, M. E., MEDLIN, C., MILLS, A., MILLS, J. A., MONTOYA, J., NORHEIM, O., OLSON, Z., OMOKHODION, F., OPPENHEIM, B., ORD, T., PATEL, V., PATTON, G. C., PEABODY, J., PRABHAKARAN, D., QI, J., REYNOLDS, T., RUACAN, S., SANKARANARAYANAN, R., SEPULVEDA, J., SKOLNIK, R., SMITH, K. R., TEMMERMAN, M., TOLLMAN, S., VERGUET, S., WALKER, D. G., WALKER, N., WU, Y. & ZHAO, K. 2018. Universal health coverage and intersectoral action for health: key messages from Disease Control Priorities, 3rd edition. *Lancet,* 391**,** 1108-1120.

JAMISON, D. T. & MOSLEY, W. H. 1991. Disease control priorities in developing countries: health policy responses to epidemiological change. *Am J Public Health,* 81**,** 15-22.

KAGESTEN, A. E., TUNCALP, O., PORTELA, A., ALI, M., TRAN, N. & GULMEZOGLU, A. M. 2017. Programme Reporting Standards (PRS) for improving the reporting of sexual, reproductive, maternal, newborn, child and adolescent health programmes. *BMC Med Res Methodol,* 17**,** 117.

KIM, D. D. & BASU, A. 2017. New Metrics for Economic Evaluation in the Presence of Heterogeneity: Focusing on Evaluating Policy Alternatives Rather than Treatment Alternatives. *Medical Decision Making,* 37**,** 930-941.

LEWIN, S., HENDRY, M., CHANDLER, J., OXMAN, A. D., MICHIE, S., SHEPPERD, S., REEVES, B. C., TUGWELL, P., HANNES, K., REHFUESS, E. A., WELCH, V., MCKENZIE, J. E., BURFORD, B., PETKOVIC, J., ANDERSON, L. M., HARRIS, J. & NOYES, J. 2017. Assessing the complexity of interventions within systematic reviews: development, content and use of a new tool (iCAT_SR). *BMC Medical Research Methodology,* 17**,** 76.

MANDRIK, O., KNIES, S., KALO, Z. & SEVERENS, J. L. 2015. Reviewing Transferability in Economic Evaluations Originating from Eastern Europe. *Int J Technol Assess Health Care,* 31**,** 434-41.

MIKKELSEN, E., HONTELEZ, J. A., JANSEN, M. P., BARNIGHAUSEN, T., HAUCK, K., JOHANSSON, K. A., MEYER-RATH, G., OVER, M., DE VLAS, S. J., VAN DER WILT, G. J., TROMP, N., BIJLMAKERS, L. & BALTUSSEN, R. M. 2017. Evidence for scaling up HIV treatment in sub-Saharan Africa: A call for incorporating health system constraints. *PLoS Med,* 14**,** e1002240.

MOHLER, R., KOPKE, S. & MEYER, G. 2015. Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2). *Trials,* 16**,** 204.

MOORE, G. F., AUDREY, S., BARKER, M., BOND, L., BONELL, C., HARDEMAN, W., MOORE, L., O'CATHAIN, A., TINATI, T., WIGHT, D. & BAIRD, J. 2015. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ,* 350**,** h1258.

MRC. 2008. Developing and evaluating complex interventions: new guidance. Available: https://mrc.ukri.org/documents/pdf/complex-interventions-guidance/

MURRAY, C. J., EVANS, D. B., ACHARYA, A. & BALTUSSEN, R. M. 2000. Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ,* 9**,** 235-51.

NIXON, J., RICE, S., DRUMMOND, M., BOULENGER, S., ULMANN, P. & DE POUVOURVILLE, G. 2009. Guidelines for completing the EURONHEED transferability information checklists. *European Journal of Health Economics,* 10**,** 157-165.

OAKLEY, A., STRANGE, V., BONELL, C., ALLEN, E. & STEPHENSON, J. 2006. Process evaluation in randomised controlled trials of complex interventions. *British Medical Journal,* 332**,** 413-416.

PAWSON, R. & TILLEY, N. 2004. Realist Evaluation. London, UK: British Cabinet Office.

PETTICREW, M. 2011. When are complex interventions 'complex'? When are simple interventions 'simple'? *Eur J Public Health,* 21**,** 397-8.

PETTICREW, M., KNAI, C., THOMAS, J., REHFUESS, E. A., NOYES, J., GERHARDUS, A., GRIMSHAW, J. M., RUTTER, H. & MCGILL, E. 2019. Implications of a complexity perspective for systematic reviews and guideline development in health decision making. *BMJ Glob Health,* 4**,** e000899.

PFADENHAUER, L. M., GERHARDUS, A., MOZYGEMBA, K., LYSDAHL, K. B., BOOTH, A., HOFMANN, B., WAHLSTER, P., POLUS, S., BURNS, J., BRERETON, L. & REHFUESS, E. 2017. Making sense of complexity in context and implementation: the Context and Implementation of Complex Interventions (CICI) framework. *Implement Sci,* 12**,** 21.

ROGERS, P. J. 2008. Using Programme Theory to Evaluate Complicated and Complex Aspects of Interventions. *Evaluation,* 14**,** 29-48.

SCHLOEMER, T. & SCHRODER-BACK, P. 2018. Criteria for evaluating transferability of health interventions: a systematic review and thematic synthesis. *Implement Sci,* 13**,** 88.

SCHULZ, K. F., ALTMAN, D. G., MOHER, D. & GROUP, C. 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ,* 340**,** c332.

SCULPHER, M. 2015. Clinical Trials Provide Essential Evidence, but Rarely Offer a Vehicle for Cost-Effectiveness Analysis. *Value in Health,* 18**,** 141-142.

SCULPHER, M. J., CLAXTON, K., DRUMMOND, M. & MCCABE, C. 2006. Whither trial-based economic evaluation for health care decision making? *Health Economics,* 15**,** 677-687.

SCULPHER, M. J., PANG, F. S., MANCA, A., DRUMMOND, M. F., GOLDER, S., URDAHL, H., DAVIES, L. M. & EASTWOOD, A. 2004. Generalisability in economic evaluation studies in healthcare: A review and case studies. *Health Technology Assessment,* 8**,** iii-117.

SHIELL, A., HAWE, P. & GOLD, L. 2008. Complex interventions or complex systems? Implications for health economic evaluation. *BMJ,* 336**,** 1281-3.

STENBERG, K., LAUER, J. A., GKOUNTOURAS, G., FITZPATRICK, C. & STANCIOLE, A. 2018. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. *Cost Eff Resour Alloc,* 16**,** 11.

TAN-TORRES EDEJER, T., BALTUSSEN, R., ADAM, T., HUTUBESSY, R., ACHARYA, A., EVANS, D. & MURRAY, C. (eds.) 2003. *Making Choices in Health: World Health Organisation Guide to Cost-Effectiveness Analysis,* Geneva: WHO.

VASSALL, A., MANGHAM-JEFFERIES, L., GOMEZ, G. B., PITT, C. & FOSTER, N. 2016a. Incorporating demand and supply constraints in economic evaluation in low- and middle-income countries. *Health Econ,* 25.

VASSALL, A., SIAPKA, M., FOSTER, N., CUNNAMA, L., RAMMA, L., FIELDING, K., MCCARTHY, K., CHURCHYARD, G., GRANT, A. & SINANOVIC, E. 2017a. Cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation. *Lancet Glob Health,* 5**,** e710-e719.

VASSALL, A., SWEENEY, S., KAHN, J. G., GOMEZ, G. B., BOLLINGER, L., MARSEILLE, E., HERZEL, B., PLOSKY, W. D., CUNNAMA, L., SINANOVIC, E., BAUTISTA-ARREDONDO, S., GHCC TECHNICAL ADVISORY GROUP, GHCC STAKEHOLDER GROUP, HARRIS, K. & LEVIN, C. 2017b. *Reference Case for Estimating the Costs of Global Health Services and Interventions* [Online]. Available: https://ghcosting.org/pages/standards/reference_case.

VILLEVAL, M., GABORIT, E., BERAULT, F., LANG, T. & KELLY-IRVING, M. 2019. Do the key functions of an intervention designed from the same specifications vary according to context? Investigating the transferability of a public health intervention in France. *Implement Sci,* 14**,** 35.

WALKER, D. G., HUTUBESSY, R. & BEUTELS, P. 2010a. WHO Guide for standardisation of economic evaluations of immunization programmes. *Vaccine,* 28**,** 2356-2359.

WALKER, D. G., TEERAWATTANANON, Y., ANDERSON, R. & RICHARDSON, G. 2010b. Generalisability, Transferability, Complexity and Relevance. *In:* SHEMILT, I., MUGFORD, M., VALE, L., MARSH, K. & DONALDSON, C. (eds.) *Evidence-Based Decisions and Economics: Health Care, Social Welfare, Education and Criminal Justice, Second Edition.* Oxford: Wiley-Blackwell.

WELTE, R., FEENSTRA, T., JAGER, H. & LEIDL, R. 2004. A decision chart for assessing and improving the transferability of economic evaluation results between countries. *PharmacoEconomics,* 22**,** 857-876.

WHO 2017b. Programme reporting standards for sexual, reproductive, maternal, newborn, child and adolescent health. Geneva: World Health Organization.

WHO. 2019c. *OneHealth Tool* [Online]. Geneva: WHO. Available: https://www.who.int/choice/onehealthtool/en/ [Accessed 22 May 2019].

WHYTE, S., DIXON, S., FARIA, R., WALKER, S., PALMER, S., SCULPHER, M. & RADFORD, S. 2016. Estimating the Cost-Effectiveness of Implementation: Is Sufficient Evidence Available? *Value in Health,* 19**,** 138-144.

WILKINSON, T., SCULPHER, M. J., CLAXTON, K., REVILL, P., BRIGGS, A., CAIRNS, J. A., TEERAWATTANANON, Y., ASFAW, E., LOPERT, R., CULYER, A. J. & WALKER, D. G. 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value Health,* 19**,** 921-928.

WILLAN, A. R. & ECKERMANN, S. 2010. Optimal clinical trial design using value of information methods with imperfect implementation. *Health Econ,* 19**,** 549-61.

Chapter 7. Discussion

In this final chapter, I summarize my empirical and methodological findings and relate them to the first four objectives of the thesis. I then discuss key strengths and limitations of the thesis and conclude.

7.1. Empirical findings (Objectives 1, 2, and 3)

Objective 1

In Chapter 2, I met the first objective of the thesis, which was to examine the size, scope, and distribution of the recent, applied, economic evaluation literature. This uniquely comprehensive analysis provided an important snapshot of the economic evaluation literature, and in so doing, has provided a valuable, quantitative basis for debates around research prioritization, research capacity, and research methods. The analysis showed that more than 1200 economic evaluations were published annually in the 28-month period we studied in 2012-14. Of these, just 4% addressed LICs, 4% addressed lower-middle-income countries, and 14% addressed UMICs, while francophone Africa and West Africa emerged as regions in which economic evaluations were particularly scarce. Moreover, 33 (18%) of the 184 economic evaluations identified as having studied at least one LLMIC examined more than 10 countries, further underscoring the importance of addressing the transferability challenge in LLMICs and in francophone and West Africa especially.

The careful way in which I searched, screened, and communicated my search strategy and findings also provided valuable information for anyone reviewing the economic evaluation literature, which is especially useful now that NHS EED has ceased to be updated and the Wiley Health Economics Database is no longer available. While the Tufts Cost-Effectiveness Registry now offers a valuable database of cost-per-DALY studies (CEVR, 2019), my bibliometric analysis showed that less than half of full economic evaluations in LLMICs used DALYs, and thus quantified the limitations of relying exclusively on this registry in reviewing the economic evaluation literature. While the iDSI reference case now specifies that economic evaluations should report costs per DALY averted, my analysis demonstrates the scale of the changes in research practices necessary to meet this new requirement.

The experience of conducting this review also afforded me the opportunity to engage with systematic review and bibliometric methods, and, in the process of individually screening 15,057 publications, to gain insights into the field of economic evaluation as a whole. These observations informed my critical review of transferability literatures and designing for transferability guide, which I presented in Chapter 6.

Objective 2

The second and third objectives of the thesis were met in Chapters 4 and 5, respectively, where I presented two economic evaluations of malaria interventions in central Senegal. The second objective was to explore the costs of delivering SMC to children under 10 on a large scale in central Senegal. As recommended (Sculpher et al., 2004), this evaluation explored heterogeneity in costs within the trial as a means of better understanding transferability beyond the trial. The Global Health Cost Consortium has also highlighted the importance of exploring cost heterogeneity (Vassall et al., 2017). My analysis demonstrated substantial economies of scale in the size of the health post catchment areas used to deliver the interventions. This finding indicated that the average cost of delivery across the intervention area should not be generalised to any setting, and that instead, costs should be understood as a function of the size of the catchment populations. The identification of an L-shaped average cost curve was consistent with the very limited literature on economies of scale in health care provision, but inconsistent with economic theory, which predicts a U-shape. This finding has important implications for efforts to improve the efficiency of health service provision, and suggests that the scale at which average costs begin to increase is greater than that observed in any of the facilities in our study area. Some other analyses of the costs of public health interventions have not explored uncertainty or heterogeneity in costs because they only collected costs of the overall programme without disaggregation; however, my analysis of SMC demonstrated that in-depth cost data collection and analysis of public health interventions is feasible and informative.

The analysis of SMC also demonstrated the limits of an econometric approach to understanding cost variation. While many potential explanatory variables, such as geographical features, the number of years of experience with the intervention, and coverage rates, were hypothesized to be associated with the cost per course administered, the analysis was unable to identify robust statistical relationships with these variables. This absence of evidence may reflect a genuine absence of relationship; more likely, however, it reflects a degree of homogeneity within our study area, which may partly reflect the area itself and also perhaps the influence of the trial in standardizing procedures. It may also reflect the sample

size (n=46 facilities), which, while large for facility-based costings, remains small in statistical terms when exploring associations between multiple variables.

The economic evaluation of SMC has already informed major changes in global malaria policy at WHO, which has led to the adoption of SMC as national policy in 12 countries and delivery of SMC to 19 million children under five in 2018 (WHO, 2019d). In addition, in the south of Senegal, SMC has been delivered to children under ten since shortly after the conclusion of our trial. While the economic evaluation of SMC responded directly to policy makers' stated questions at the time, it was a partial rather than full economic evaluation as it did not incorporate a cost-effectiveness analysis. The economic evaluation of SMC presented in this thesis remains the only cost analysis in children up to age 10 and so may play an important role in informing deliberations about the potential expansion of current WHO guidance to recommend SMC for a wider age range. Direct comparisons of the costs and effects of delivering SMC to different age ranges would be ideal; however, in the absence of such head-to-head field trials, mechanistic cost modelling, as used in the hotspot trial, could be extended to examine potential economies of scale in expanding the age range for SMC. In-depth comparison of the costs of delivering SMC to children under 10 in central Senegal as reported in this thesis with the costs of delivery of SMC to children under 5 across other countries of West Africa would be a valuable opportunity to better understand cost variation and transferability.

Objective 3

The third objective of the thesis was to assess the costs and cost-effectiveness of various combinations of MSAT, MDA, and IRS, which were geographically targeted at "hotspot" villages. This evaluation was conducted alongside a cluster-randomized trial, which was implemented in approximately the same geographical area of central Senegal as the first trial, but restricted to the rural areas (and thus excluding the semi-urban areas). The analysis provided important insights into how the efficiency of these interventions can be expected to vary with intervention choices, including the degree and level of targeting and number of rounds of implementation, as well as with contextual factors, including local epidemiology, prices, and health system structure. It showed that, despite the substantial relative reductions in malaria incidence achieved, the targeted interventions could not be considered cost-effective in reducing the short-term disease burden in this context.

The WHO's latest approach, "High burden to high impact", launched in 2018 (WHO, 2018c), reflects a desire to rebalance global efforts towards both improved control in high burden

areas and elimination in others. This renewed focus on tackling malaria in the highest burden areas may be a response to criticism that the focus of both attention and financial investment on malaria elimination was both inequitable and inefficient and resonates with the empirical findings presented in my economic evaluation of targeted MSAT, MDA, and IRS.

Future research could combine the cost models I developed with transmission dynamic models to consider how the cost-effectiveness of alternative combinations of interventions, with varying degrees of geographical targeting, may vary across contexts. As current transmission dynamic models in the malaria field tend to integrate costs only as a fixed cost per person reached, with no consideration of how costs may vary with context, scale, or targeting (Drake et al., 2016), such integration of cost functions would be valuable. Future research could also further explore the concept of "diseconomies of targeting" and seek to understand the broader implications for malaria and other health areas.

Together, these two economic evaluations of malaria interventions make important contributions to a very limited evidence base on malaria interventions delivered door-to-door by CHWs. This scarcity of evidence is particularly remarkable in light of the large global and national investments in malaria control and elimination. Both these analyses also offer important insights for the analysis of public health interventions beyond the field of malaria. Many large-scale programmes for the control and elimination of neglected tropical diseases (NTDs), for example, are based around similar, mass drug administration campaigns and face questions of if and how to target these efforts by age and geography (Pullan et al., 2019). A major multi-country study in Africa is now exploring community-based distribution of self-testing kits for HIV (Neuman et al., 2018), which shares many features with MSAT for malaria, which we explored in the cost-effectiveness analysis alongside the hotspot trial. My analyses offer useful empirical findings to inform decision-making in these other areas, as well as methodological insights into how to collect and analyse data on these types of public health interventions, which are discussed further in the next section.

7.2. Methodological findings (Objective 4)

The fourth objective of the thesis was to develop and apply methods for the analysis of cost data in ways that promote transferability and to develop more general guidance on how to

design economic evaluations for transferability. In this section, I summarize how I met the first part of this objective in Chapter 5 and how I met the second part of this objective in Chapter 6.

Analysing cost data in ways that promote transferability

Estimates of intervention costs are critical for budgeting and priority setting. They must, however, reflect how costs vary within countries, between countries, and with scale. Where large-scale costing studies have been possible and large numbers of data points are available which reflect sufficient variation across relevant characteristics (including scale), econometric analyses have the potential to offer insights into cost variation (Lépine et al., 2016, Lépine et al., 2015, Meyer-Rath and Over, 2012). Econometric analyses can then be used to inform decision-making about continuation, modification, and/or expansion of the intervention of interest. These analyses are only possible, however, when the intervention has already been implemented at a very large scale, across sufficiently diverse contexts, and where good quality cost data relevant to the intervention is available, making them essentially "ex post" evaluations, meaning that they occur after very substantial scale-up has already occurred.

While ex-post evaluations are undoubtedly important and underutilized, earlier stage economic evaluations are needed to inform decisions about whether such large-scale implementation should be undertaken at all. When new interventions are implemented initially, whether in small-scale pilots or trials, economic evaluations can generate initial cost estimates. To use findings from such small-scale studies to inform decision-making for real-world implementation, however, analytical adjustments may be needed. These adjustments may need to reflect the cost implications of changes in the scale of delivery and extension or transfer to other geographical areas. Further, all possible variants of an intervention cannot be piloted in all settings, so those data that do exist need to be used to explore how modifications to an intervention may affect costs.

In the cost analysis of SMC, I disaggregated the costs of delivering SMC across the three monthly implementation rounds and the levels of the health system with which each cost component would be expected to vary. I explained and provided examples of how this simple disaggregation of costs could be used to estimate the costs of implementation of SMC in the entire study area, including the control areas, and thus adjust for the inherent inefficiencies in trial-based implementation, in which meetings and trainings, for example, must be held at regional and district level, but not all health post catchment areas within the given districts and regions implement the intervention. I also discussed how costs could be expected to vary if the

intervention strategy were extended to include four or more monthly implementation rounds, which have been implemented and considered for implementation elsewhere.

In the subsequent evaluation of the hotspot strategies, I substantially developed and extended the approach initiated in the cost analysis of SMC. I began by disaggregating the costs of each of the interventions – hotspot identification, IRS, MDA, and MSAT – in the same way as in the SMC analysis, that is, by implementation round and by the health system or output level with which each cost component would be expected to vary, as well as by activity and cost driver. I then developed a simple mechanistic model to estimate how costs could be expected to vary if the number of rounds of implementation or the number of units at any level of the health system or output were changed. This approach allowed me to estimate the costs of implementation if each of the interventions were implemented throughout the study area, thereby adjusting for the inherent diseconomies of trial-based implementation. In addition, this adjustment also accounted for variation in population, epidemiology, and catchment sizes between arms. Failure to account for such imbalances may lead to differences in cost estimates which reflect differences in economies of scale between the different populations in which the alternative strategies were implemented, rather than meaningful differences in the costs of implementing the interventions in the same areas. Further, the cost models allowed me to explore how costs may be expected to vary with changes to how the interventions are implemented, including different levels and degrees of targeting, in order to increase the usefulness of the analysis across a wide range of contexts and interventions.

The hotspot evaluation thus illustrated how in-depth prospective data collection alongside a trial can be used to develop a simple, transparent, and flexible mechanistic cost model, which can predict how costs may vary with specific changes to context, scale, and scope of the interventions. This model could be adapted to estimate the costs of delivering similar interventions for other diseases, and provides a useful framework for costing public health interventions implemented through a cascade of activities.

Designing economic evaluations for transferability

In Chapter 6, I completed the fourth objective of the thesis by developing more general guidance on how to design economic evaluations for transferability. The need for such guidance emerged from my experience conducting the bibliometric analysis in Chapter 2 and the two economic evaluations in Chapters 4 and 5. The bibliometric analysis demonstrated the stark need to transfer economic evaluation evidence, especially across LLMICs. My experience conducting the SMC cost analysis in Chapter 4 then demonstrated some of the shortcomings of

standard guidance on how to improve the transferability of economic evaluations. Drawing on initial work in Chapter 4, I developed in Chapter 5 a mechanistic cost model, which usefully indicated how costs of several interventions could be expected to vary with contexts and some modifications to the interventions. While a very valuable contribution, the development of this cost model was a post-hoc analysis focused on better analysis of provider cost data.

In Chapter 6, I sought to generate more general guidance on how to improve the transferability of economic evaluations conducted alongside trials or pilots in ways that would be relevant to all intervention types and contexts. Nonetheless, I paid particular attention to ensuring the usefulness and relevance of the guidance to LLMICs. As the need for such guidance emerged from the experience of conducting the economic evaluations in Chapters 4 and 5, the critical review of transferability literatures presented in Chapter 6 was conducted alongside and after the economic evaluations. The critical review therefore informed some of the analyses conducted in the preceding chapters, but could not inform their study designs, which instead reflected standard guidance at the time when they were done. The designing for transferability guide in Chapter 6 was developed after both the economic evaluations and critical review were complete.

In the designing for transferability guide, I draw on both my experience conducting economic evaluations and also a wide-ranging critical review of literature streams, which offer insights for improving the transferability of economic evaluations conducted alongside trials or pilots. I argue that promoting transferability requires efforts from the earliest phases of intervention design and that transferability is a complex question requiring a complexity perspective, even for seemingly simple interventions. I identify four stages for a model-based economic evaluation alongside a trial or pilot: I) Framing the economic evaluation, II) Model identification and/or development, III) Data needs identification, and IV) Analysis and reporting. For each stage, I articulate key questions to guide analysts to close the transferability gap.

Future research could pilot the guidance and seek to: understand how it has been used; explore perceptions of its usefulness and contributions to the research process and to eventual influence of the research on decision-making; and solicit recommendations for its improvement. For such purposes, it would be valuable to pilot the guidance with research teams working on both trials and pilot studies, for different types of health conditions, and different types of delivery platforms, and in contexts where researchers have different pre-existing relationships with decision-makers. Given that the guidance emerged from the

experience of conducting the two economic evaluations presented in this thesis, it would be particularly valuable to pilot the tool in interventions for communicable diseases other than malaria, as well as non-communicable diseases, especially in a hospital setting and for curative interventions. It would also be valuable to pilot the tool in a range of LLMICs, as well as in upper-middle and high-income countries to understand the perceived relevance of the framework and questions in diverse country contexts. Reporting examples of how the guidance has been used, especially where theories of change have been developed with specific reference to costs and effects, would likely facilitate wider use of the guidance, along with critical reflections on areas for improvement.

7.3. Strengths and limitations

As the individual chapters within this thesis already include discussion of their individual strengths and limitations, I reflect here on some of the strengths and limitations of the thesis as a whole.

A key feature of this thesis is that it offers both policy-relevant findings in the field of malaria control and methodological findings relevant for the conduct of economic evaluations. This dual aim was valuable in bringing methodological considerations and rigour to the empirical work and in ensuring that the methodological innovations drew on and could feasibly inform practical experience in this applied, policy-focused field. Nonetheless, it could be argued that pursuit of this dual aim has been at the expense of greater depth, which could have been achieved if only one aspect or the other had been the sole focus.

This thesis also combines wide-ranging literature reviews and in-depth analyses. Engagement with a very wide range of literature provided valuable perspective on the "big picture". In reviewing the applied economic evaluation literature, I examined a comprehensive cross-section of the literature and conducted a range of quantitative analyses, which provided insights into the economic evaluation field as a whole. In examining the literature related to transferability, I again took a wide, multi-disciplinary approach, which allowed me to draw valuable insights. By contrast, in conducting two economic evaluations, I collected and analysed primary data in depth in a single geographical area and in doing so made substantial contributions to areas of public health importance. I believe that this combination of breadth

and depth has produced valuable insights, but it inevitably also leaves numerous gaps that could be explored further in future.

The research setting in Senegal was both a strength and a limitation of the thesis. The research benefitted from strong existing research collaborations between the London School of Hygiene & Tropical Medicine, the Department of Parasitology at Université Cheikh Anta Diop, and the Institut de Recherche pour le Développement, which greatly facilitated the inclusion of economic evaluation components alongside the trials. Conducting the second economic evaluation in the same locations and with the same institutional collaborators as the first reduced the time required to familiarize myself with the local context and research partners and to adapt data collection tools and made understanding and interpretation of the data easier. The common setting for both studies also facilitated the direct application and further development in the second evaluation of ideas generated in the first evaluation regarding the role of health system structure and monthly implementation rounds in driving costs.

That the research only took place in a single setting was also a limitation. As the need for new methods for making economic evaluations more transferable emerged from the economic evaluations presented in the thesis, these economic evaluations and the PhD as a whole were not originally designed with the aim of improving transferability. Exploration of transferability could have benefitted from a multi-country study. The context in which the trials were conducted seemed *prima facie* broadly representative of and potentially relevant to a large number of people living with ostensibly similar epidemiological and socio-economic contexts; however, the extent to which this assumption holds has not yet been examined, because this thesis research was confined to a single setting. Comparing predictions generated by the cost model for another context with the actual costs of implementation in that other context would be a useful opportunity for model validation and possible refinement. Such an opportunity may exist for SMC, which has now been implemented across much of the Sahel. A consultancy report on SMC implementation in 7 countries in 2015 has been produced (Gilmartin and Collins, 2017); however, meaningful comparison of model projections with these findings would require engagement from and with individuals involved in implementation and cost estimation in those countries and the usefulness of such an exercise would depend on the availability of more detailed data (e.g. on resource use and prices) than currently reported. The proposed guidance on designing for transferability has yet to be applied, and feedback from practical experience of implementing this guidance – especially alongside pilots or trials of very

different types of interventions, for different health areas, and in other contexts – would be likely to contribute usefully to its further development.

The two economic evaluations were not originally undertaken with a focus on transferability; rather, the importance of transferability emerged from the experience of conducting these evaluations, the bibliometric analysis, and wider experience of leading the supplementary issue in *Health Economics*. In part, the focus on transferability also reflects the explosion of literature around transferability in the last few years. The ways in which transferability was addressed were therefore constrained by the data that had already been collected.

This thesis recommends understanding the mechanisms of action through which costs are incurred and outcomes produced as a means of improving transferability. While both trials contained process evaluations, which helped to generate such understanding, these process evaluations were not theory-driven and could have been more extensive, especially for the hotspot trial. In one sense, this absence of explicit programme theory (represented in a diagram) is understandable, as the central mechanisms of action for the interventions in both trials involved medicines and diagnostic tests, and therefore could be viewed as "simple", just as many pharmaceutical interventions are described (Oakley et al., 2006). While the hotspot trial involved many components, some might argue that the strategies evaluated were "complicated", rather than "complex" (Rogers, 2008). Yet, each intervention also involved hundreds of community health workers travelling door-to-door to administer medicines, diagnostic tests, and insecticide to large numbers of people, who were not ill, but who nonetheless largely accepted these interventions. The interventions involved a cascade of training and planning across levels of the health system and effects were generated both at the individual and community levels, through indirect effects. As Petticrew (2011) observed, "on close examination most interventions, including medical interventions, reveal themselves to be complex." Petticrew argued that the choice to view an intervention as complex or simple should reflect the research questions, and not just the intervention. Producing an initial theory of change, incorporating both costs and effects, and refining this theory of change through a process evaluation is recommended for future evaluations; however, the practicalities of how to do this usefully are unclear. Anderson and Hardwick's "explanatory economic evaluation" drawing on realist principles (Anderson and Hardwick, 2016) provided one example of how resources could be included within a theory of change, but this example was drawn from a retrospective literature review, rather than a prospective evaluation.

I focused on methods for modelling transfer of costs and did not simultaneously model how costs of implementation and effectiveness may covary. Incremental effects of preventive malaria interventions are a function of underlying incidence, intervention coverage, intervention efficacy, and care pathways and outcomes for malaria cases, all of which may vary across contexts and with changes to the intervention. Understanding how costs and coverage may covary across contexts is particularly challenging; a conservative approach is to model coverage achieved through comparable delivery platforms in a given context and to model the costs of achieving that level of coverage through a simple model, like the one developed in this thesis. Achieving a higher level of coverage would require additional activities, which are themselves interventions, whose effectiveness and costs would need to be measured. For SMC and especially the hotspot strategies, the indirect effects of the interventions are a complex function of intervention coverage and underlying incidence. Further work to model the transfer of both costs and effectiveness across contexts would be valuable and would require collaboration between health economists and infectious disease modellers to ensure that both cost and effects are modelled with an appropriate balance of complexity and simplicity.

7.4. Conclusion

This thesis provides evidence generated alongside two trials in central Senegal on the efficiency of SMC and packages of intensive malaria interventions geographically targeted at a local level. The analysis of SMC showed that it was potentially affordable, even in highly constrained contexts, but that the cost per child receiving the intervention varied substantially across health post catchment areas, and, to a lesser extent, across the three monthly rounds of administration. SMC has now been administered to tens of millions of children across the Sahel. The second analysis revealed that relative to existing malaria budgets, targeted MSAT and targeted MDA each incurred substantial costs, which were considerably increased when combined with targeted IRS. As implemented in a low transmission context in central Senegal, these geographically targeted strategies were found not to be cost-effective in reducing the short-term disease burden.

This thesis also provides systematic evidence of the scarcity of economic evaluation research, especially in LMICs, and therefore the imperative to make each economic evaluation as useful as possible across a wide range of contexts. To improve the transfer of economic evaluation

evidence from trials and pilots across contexts, transferability should become the guiding principle throughout all stages of an economic evaluation. In particular, evaluators must clearly conceptualize and articulate what an intervention is, and use understanding of the mechanisms of action through which an intervention incurs costs and produces effects to gain insights into the transferability of findings. From the outset of the evaluation, evaluators should seek to identify and (where possible) narrow the "transferability gap" between planned implementation within the trial or pilot and the intended decision contexts. Data collected within the trial or pilot can and should be used to develop and populate simple, mechanistic provider cost models to estimate how costs might be expected to vary with particular changes to context or the intervention, thereby increasing the transferability of the findings. Future research should explore, refine, and extend these approaches to promoting transferability so that opportunities for data collection alongside trials or pilots can be fully exploited and used to inform priority setting decisions across a broader set of contexts.

7.5. References for Chapter 7

ANDERSON, R. & HARDWICK, R. 2016. Realism and resources: Towards more explanatory economic evaluation. *Evaluation (London),* 22**,** 323-341.

CEVR 2019. Global Health Cost Effectiveness Analysis Registry. Boston, MA, USA: Center for Evaluation of Value and Risk in Health (CEVR), Tufts Medical Center.

DRAKE, T. L., DEVINE, A., YEUNG, S., DAY, N. P., WHITE, L. J. & LUBELL, Y. 2016. Dynamic Transmission Economic Evaluation of Infectious Disease Interventions in Low- and Middle-Income Countries: A Systematic Literature Review. *Health Econ,* 25 Suppl 1**,** 124-39.

GILMARTIN, C. & COLLINS, D. 2017. The cost of seasonal malaria chemoprevention in the Sahel region of Africa. Medford, MA, USA: Prepared by Management Sciences for Health for the ACCESS-SMC project.

GRIEVE, R., NIXON, R., THOMPSON, S. G. & NORMAND, C. 2005. Using multilevel models for assessing the variability of multinational resource use and cost data. *Health Econ,* 14**,** 185-96.

HUSEREAU, D., DRUMMOND, M., PETROU, S., CARSWELL, C., MOHER, D., GREENBERG, D., AUGUSTOVSKI, F., BRIGGS, A. H., MAUSKOPF, J. & LODER, E. 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value Health,* 16**,** e1-5.

KARNON, J., STAHL, J., BRENNAN, A., CARO, J. J., MAR, J., MOLLER, J. & ISPOR-SMDM MODELING GOOD RESEARCH PRACTICES TASK FORCE 2012. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. *Value Health,* 15**,** 821-7.

LÉPINE, A., CHANDRASHEKAR, S., SHETTY, G., VICKERMAN, P., BRADLEY, J., ALARY, M., MOSES, S., CHARME INDIA GROUP & VASSALL, A. 2016. What determines HIV prevention costs at scale? Evidence from the Avahan programme in India. *Health Econ,* 25.

LÉPINE, A., VASSALL, A., CHANDRASHEKAR, S., BLANC, E. & LE NESTOUR, A. 2015. Estimating unbiased economies of scale of HIV prevention projects: A case study of Avahan. *Social Science and Medicine,* 131**,** 164-172.

MEYER-RATH, G. & OVER, M. 2012. HIV treatment as prevention: Modelling the cost of antiretroviral treatment-state of the art and future directions. *PLoS Medicine,* 9.

NEUMAN, M., INDRAVUDH, P., CHILONGOSI, R., D'ELBEE, M., DESMOND, N., FIELDING, K., HENSEN, B., JOHNSON, C., MKANDAWIRE, P., MWINGA, A., NALUBAMBA, M., NCUBE, G., NYIRENDA, L., NYRIENDA, R., KAMPE, E. O. I., TAEGTMEYER, M., TERRIS-PRESTHOLT, F., WEISS, H. A., HATZOLD, K., AYLES, H. & CORBETT, E. L. 2018. The effectiveness and cost-effectiveness of community-based lay distribution of HIV self-tests in increasing uptake of HIV testing among adults in rural Malawi and rural and peri-urban Zambia: protocol for STAR (self-testing for Africa) cluster randomized evaluations. *BMC Public Health,* 18**,** 1234.

OAKLEY, A., STRANGE, V., BONELL, C., ALLEN, E. & STEPHENSON, J. 2006. Process evaluation in randomised controlled trials of complex interventions. *British Medical Journal,* 332**,** 413-416.

PETTICREW, M. 2011. When are complex interventions 'complex'? When are simple interventions 'simple'? *Eur J Public Health,* 21**,** 397-8.

PETTICREW, M., KNAI, C., THOMAS, J., REHFUESS, E. A., NOYES, J., GERHARDUS, A., GRIMSHAW, J. M., RUTTER, H. & MCGILL, E. 2019. Implications of a complexity perspective for systematic reviews and guideline development in health decision making. *BMJ Glob Health,* 4**,** e000899.

PITMAN, R., FISMAN, D., ZARIC, G. S., POSTMA, M., KRETZSCHMAR, M., EDMUNDS, J., BRISSON, M. & ISPOR-SMDM MODELING GOOD RESEARCH PRACTICES TASK FORCE 2012. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--5. *Value Health,* 15**,** 828-34.

PULLAN, R. L., HALLIDAY, K. E., OSWALD, W. E., MCHARO, C., BEAUMONT, E., KEPHA, S., WITEK-MCMANUS, S., GICHUKI, P. M., ALLEN, E., DRAKE, T., PITT, C., MATENDECHERO, S. H., GWAYI-CHORE, M. C., ANDERSON, R. M., NJENGA, S. M., BROOKER, S. J. & MWANDAWIRO, C. S. 2019. Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. *Lancet*.

ROBERTS, M., RUSSELL, L. B., PALTIEL, A. D., CHAMBERS, M., MCEWAN, P., KRAHN, M. & ISPOR-SMDM MODELING GOOD RESEARCH PRACTICES TASK FORCE 2012. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--2. *Value Health,* 15**,** 804-11.

ROGERS, P. J. 2008. Using Programme Theory to Evaluate Complicated and Complex Aspects of Interventions. *Evaluation,* 14**,** 29-48.

SCULPHER, M. 2015. Clinical Trials Provide Essential Evidence, but Rarely Offer a Vehicle for Cost-Effectiveness Analysis. *Value in Health,* 18**,** 141-142.

SCULPHER, M. J., CLAXTON, K., DRUMMOND, M. & MCCABE, C. 2006. Whither trial-based economic evaluation for health care decision making? *Health Economics,* 15**,** 677-687.

SCULPHER, M. J., PANG, F. S., MANCA, A., DRUMMOND, M. F., GOLDER, S., URDAHL, H., DAVIES, L. M. & EASTWOOD, A. 2004. Generalisability in economic evaluation studies in healthcare: A review and case studies. *Health Technology Assessment,* 8**,** iii-117.

SIEBERT, U., ALAGOZ, O., BAYOUMI, A. M., JAHN, B., OWENS, D. K., COHEN, D. J., KUNTZ, K. M. & ISPOR-SMDM MODELING GOOD RESEARCH PRACTICES TASK FORCE 2012. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. *Value Health,* 15**,** 812-20.

SQUIRES, H., CHILCOTT, J., AKEHURST, R., BURR, J. & KELLY, M. P. 2016. A Framework for Developing the Structure of Public Health Economic Models. *Value Health,* 19**,** 588-601.

VASSALL, A., SWEENEY, S., KAHN, J. G., GOMEZ, G. B., BOLLINGER, L., MARSEILLE, E., HERZEL, B., PLOSKY, W. D., CUNNAMA, L., SINANOVIC, E., BAUTISTA-ARREDONDO, S., GHCC TECHNICAL ADVISORY GROUP, GHCC STAKEHOLDER GROUP, HARRIS, K. & LEVIN, C. 2017b. *Reference Case for Estimating the Costs of Global Health Services and Interventions* [Online]. Available: https://ghcosting.org/pages/standards/reference_case.

WHO-CHOICE. 2011. *Note on the methodology used to predict unit costs for patient services* [Online]. Geneva: World Health Organization,. Available: http://www.who.int/choice/country/Meth_predictUnitCPS2011.pdf [Accessed 26 November 2012 2012].

WHO 2018c. High burden to high impact: a targeted malaria response. Geneva: World Health Organization.

WHO 2019d. World malaria report 2019. Geneva, Switzerland: World Health Organization.

WILKINSON, T., SCULPHER, M. J., CLAXTON, K., REVILL, P., BRIGGS, A., CAIRNS, J. A., TEERAWATTANANON, Y., ASFAW, E., LOPERT, R., CULYER, A. J. & WALKER, D. G. 2016. The International Decision Support Initiative Reference Case for Economic Evaluation: An Aid to Thought. *Value Health,* 19**,** 921-928.

Appendices

Appendix 1. Ethics approval for the thesis

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
+44 (0)20 7636 8636 • www.lshtm.ac.uk

Catherine Pitt
RD Student
LSHTM

14 August 2018

Dear Catherine,

Re: Research Degree Project

Thank you for submitting further information following the audit initiated by Professor Della Freeth, former Pro-Director (Learning & Teaching) in 2017. The aim of the audit was to assure the School that all Research Degree (RD) candidates had obtained the appropriate approvals before they start their projects.

The Research Governance Committee considered the initial results of this audit and recommended further action. As a result, a sub-group of the Research Governance Committee reviewed RD projects without valid LSHTM ethics approval in their name, as this has been a requirement since 2014.

As members of this sub-group of the Research Governance Committee, we have reviewed your project and supporting documents. We are satisfied that the aims and analyses are sufficiently detailed in your supervisor(s)' project, LSHTM ref 5366, 6281, 6387.

Should other data collection or analytical methods not detailed in the existing ethics approval be required for your project, please submit an application to the LSHTM ethics committee prior to any further data collection or analysis of the data/tissue.

Should you have any queries, please contact Patricia Henley in the first instance.

Yours sincerely,

[redacted]

Prof Sasha Shepperd
Pro-Director Learning

Prof Audrey Prost
Head of the Doctoral College

Ms Patricia Henley
Head of Research Governance & Integrity

Cc Kara Hanson

Improving Health Worldwide

Appendix 2. Summary of ethics approvals for thesis components

Overall Ethical Approval for PhD

Candidate: Catherine Pitt

Title: Promoting transferability: Lessons from economic evaluations of complex public health interventions to control and eliminate malaria in central Senegal

Summary of ethics approval status:

The PhD comprises three empirical components, described below. For the first component, ethics approval was not sought because only publicly available data were analysed and there were no human subjects involved. The second and third components were economic evaluations within cluster-randomized controlled trials; these economic evaluations were listed amongst the objectives and methods in the approved protocols for each of these trials and were covered in the ethical approvals obtained for each trial. The table below summarizes this information, along with the names of the relevant attachments.

PhD component	Ethics approval
1. Bibliometric Analysis	Not necessary. All data obtained from 14 literature databases: National Health Service Economic Evaluations Database (NHS EED), the Health Economic Evaluations Database (HEED), EconLit, Scopus, Science Citation Index Extended (SCI), Social Science Citation Index, Embase, Medline including in-process, Latin American Health Sciences Literature (LILACS), Global Health, PsycInfo, Scielo, Biosis, and Cinahl.
Published article:	1 - Bibliometrics Pitt_et_al-2016-Health_Economics.pdf
2. Economic evaluation of "seasonal intermittent preventive treatment (sIPT)", also known as "seasonal malaria chemoprevention (SMC)	Granted by LSHTM (#5366) and Senegal's *Comité National d'Ethique* of the *Conseil National de Recherche en Santé* (CNRS, #00034). The amendment allowed for the extension of the age range of children included in the trial to also include children aged 5 – 10 years.
LSHTM approvals:	2 - SMC LSHTM approval - Milligan 5366 01.09.08.pdf 3 - SMC LSHTM amendment - Milligan-Cisse - 5366 16.09.09.pdf
Senegal approvals:	4 - SMC CNRS ethical and scientific approval Prof Gaye.pdf 5 - SMC CNRS admin approval Prof Gaye.pdf
Protocol:	6 - SMC protocol
3. Economic evaluation of targeted control	Granted by LSHTM (#6387) and Senegal's *Comité National d'Ethique de Recherche en Santé* (CNERS, #0087).
LSHTM approvals:	7 - Targeted control baseline survey LSHTM approval - Cisse_6281_26102012.pdf 8 - Targeted control LSHTM approval - Milligan_6387_07052013.pdf
Senegal approvals:	9 - Targeted control baseline survey CNERS approval - Cisse SEN12_500001 2012 10 - Targeted control trial CNERS approval SEN13_200001 2013.pdf
Protocol:	11 - Targeted control trial approved protocol Mar 2013 V2.3_pq.pdf

Appendix 3. Supplementary materials for Chapter 2 (as published)

SUPPLEMENTARY MATERIALS

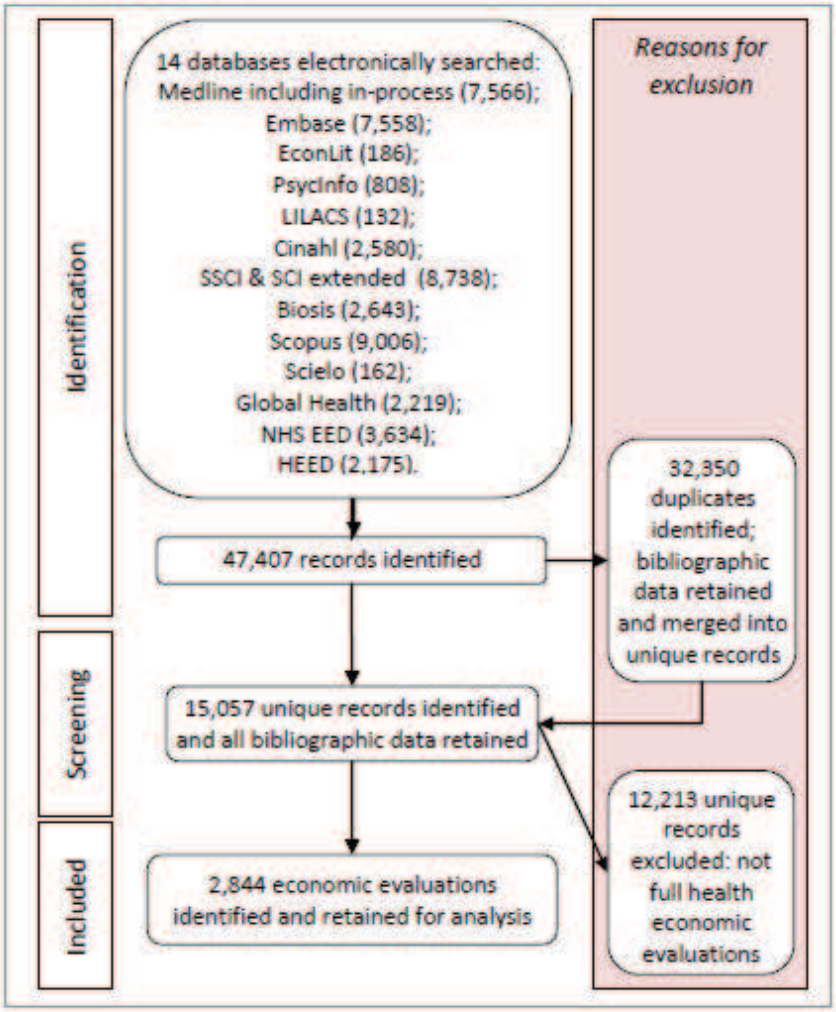
Economic evaluation in global perspective: A bibliometric analysis of the recent literature

PITT, C., GOODMAN, C. & HANSON, K. 2016. Economic evaluation in global perspective: A bibliometric analysis of the recent literature. *Health Economics*, 25 (Suppl. S1).

Contents

Figure S1 Flow diagram of the data development process

The figure is adapted from the flow diagram recommended in the PRISMA statement on systematic reviews (Liberati et al., 2009). The "eligibility" stage recommended by PRISMA is not used here as articles were not reviewed for quality; decisions to include records were based primarily on the record's source, title, and abstract; the full text was only screened where the title was unclear and the abstract was not available in any of the downloaded data.



Text S1 A note on database indexing terms

In developing our search strategy, we explored the use of controlled vocabulary indexing terms, if available, in each of the databases; unlike author-defined keywords, these terms are generally applied to publications by professional indexers from a pre-defined set. While this standardization should offer advantages, one drawback is the delays in their application; while many of the databases offer basic citation data as supplied by the journal first, indexing takes more time and so searches based exclusively on indexing terms will exclude the most recent literature, to which index terms have not yet been applied.

In Medline and Embase, indexing terms are known as medical subject headings (MeSH) and Emtree (which is not an acronym), respectively; both are organized hierarchically. While the only MeSH term relevant to our search is "cost-benefit analysis", Emtree appears much more detailed and appropriate, as it distinguishes "cost effectiveness analysis", "cost utility analysis", and "cost benefit analysis" from "cost control", "cost minimization analysis", and "cost of illness" within the broader indexing term "economic evaluation." When we compared the results of our searches in the title, abstract, and author-defined keywords for the key terms we identified above with the results of searches using MeSH terms (in Medline) and Emtree terms (in Embase), we found that the controlled vocabulary terms were both less specific and less sensitive. Our search terms identified many relevant articles missed by the MeSH and Emtree indexers. By contrast, the controlled vocabulary terms greatly increased the number of search results, but a review of the first hundred records identified by the MeSH term and, separately, by each of the three Emtree terms (i.e. 400 records in total) after excluding records identified by our search terms identified only one additional article meeting our inclusion criteria (identified by the Emtree term "cost-effectiveness analysis"). We used this article to develop an additional set of search terms (based on "cost per x") and concluded that the MeSH and Emtree BM indexing terms were not useful for our final searches, as they identified a vast number of articles, many of which contained no cost or other economic data or analysis , while omitting many relevant publications .

Another database applying its own indexing is HEED . On the "compound search" page, HEED offers "type of econ eval" as a search category, as well as a "type of article". While the associated picklist does not make this obvious, HEED in fact categorizes economic evaluations as "cost effectiveness analysis", "cost utility analysis", "cost benefit analysis", "cost analysis", "cost of illness", "cost benefit analysis", and "cost consequences analysis"; it allows a single record to be classified as multiple types of economic evaluation, allows the user to specify only "applied study" as the "type of article", and reports that its indexers are professional health economists. After examining this classification, we found that the terms for CEA, CUA, and CBA were highly specific and useful when combined with "applied study" as type of study , however, many publications in the HEED database were not classified at all, making the search relatively insensitive even within the HEED database. In HEED, we therefore implemented two separate searches: 1) using the HEED classification of the type of economic evaluation, and 2) using our search terms in the title, abstract, and author-defined keywords, and excluding records containing the specified categories, such that any records identified by this search would be additional to records identified by the use of HEED's indexing.

The EconLit database uses the Journal of Economic Literature (JEL) classification system, however, unlike the indexing systems previously described, JEL codes are applied by the authors themselves. They break down the wider health economics field into 6 specified sub-fields, none of which mention in their descriptions or examples either applied or methodological work in economic evaluation; "general" and "other" health economics categories are also provided. On reviewing a

selection of health economic evaluations in the EconLit database identified by title and abstract searches, we found that while some authors combine the codes "D61: Allocative Efficiency; Cost-benefit analysis" (within the microeconomics heading) and "I12: Health Production" (within the health economics heading), other authors did not use these codes at all, choosing instead a wide variety of other codes within the health, microeconomics, and "miscellaneous" headings in particular, as well as others. Rather than using the JEL codes, we therefore decided to take a more sensitive approach in EconLit, and instead searched for "health" in all fields, which would capture the word "health" in JEL codes, but also in journal title, keywords, article title, or abstract; we combined this with keyword searches for our definition of economic evaluation.

Text S2 Supplementary information on article classification

Health areas

We developed a classification of 25 health areas so as to allow comparability with the Global Burden of Disease (GBD) estimates (World Health Organization., 2014), to be implementable with an electronic key term search, and to permit meaningful analysis. The GBD uses four hierarchical levels to classify disease. At its highest level, it classifies diseases as "Communicable, maternal, perinatal and nutritional conditions", "Non-communicable diseases" or "Injuries", while at its lowest levels, it breaks these down into 154 more specific conditions. We did not maintain the GBD's highest level classification because in some cases, it was not implementable (e.g. key term searches could not distinguish between communicable and non-communicable causes of respiratory diseases) and in other cases, we felt the distinction did not map coherently onto preventive and curative interventions (e.g. we separated "intentional injuries: self harm" from other injury categories and placed it in a single category with mental health issues).

A set of up to 49 search terms was developed for each of our health areas through an iterative process. We began by reviewing the names of sub-categories in the GBD and the categories and descriptions provided in the ICD-10 (World Health Organization., 2011) to develop an initial set of search terms. We then reviewed the titles and keywords of unclassified records in our database, and continued adding search terms until all records in our database which could be classified were classified according to at least one health area. Throughout the process, we reviewed samples of records within each health area, and reviewed in-depth the records identified by search terms we considered potentially ambiguous, before finalizing our search terms and disease classification.

Institutional and geographic affiliations of authors

We analyzed data on the institutional affiliation of all authors to develop a comprehensive picture of the institutions and countries contributing to health economic evaluations. We began by transferring the institutional affiliation data from wide to long form and implementing the country keyword searches previously developed. As affiliation data frequently did not name a country, unclassified affiliations were then iteratively reviewed and search terms for city names and non-geographic institution names (e.g. Harvard, Yale) were identified and linked to countries, taking care to avoid misclassifying search terms such as "York", which could refer to the city (York) or county (Yorkshire) in the United Kingdom, to York University in Canada, or to the city or state of New York in the United States. In this way, nearly all articles for which affiliation data were available were classified as being produced by researchers in one or more specified countries. This data was further cross-checked against the data on countries studied and inconsistencies reviewed. The original articles were sought to resolve inconsistencies and to obtain institutional affiliation data for any articles remaining without data. Articles were then classified by the income group of the country or countries of the author affiliations and the countries producing the greatest volume of economic evaluations were ranked within each income group.

We further identified the top ten institutions within each income group by volume of economic evaluations produced. The affiliation data for top-ranked countries within each income group were carefully reviewed to develop sets of specific key terms for institutions. As in previous work (Wagstaff and Culyer, 2012, Rubin and Chang, 2003), schools, colleges and institutes were aggregated with the university to which they belonged, with the exception of the highly federal Universities of London, California, Texas, and other similar university systems, whose constituent members were analyzed separately. To the extent possible, hospitals and institutes were associated

with their parent institution, even when that institution was not explicitly named. Even though they are independently owned and managed, Harvard's 16 affiliated hospitals were aggregated with Harvard. Once an initial set of ten institutions were identified for each income group, only affiliations from countries which had produced more than the tenth-ranked institution for that income group were reviewed to identify institutions which could have produced more economic evaluations than the currently tenth-ranked institution. For example, the tenth-ranked UMIC institution, the *Instituto Mexicano del Seguro Social*, produced 7 economic evaluations, and so only affiliations from UMICs which had produced at least 7 economic evaluations were reviewed to identify individual institutions which could have produced at least this number. The searches for city names were then used to facilitate the identification of institutions.

In addition, search terms were developed for international and inter-governmental organizations, such as United Nations agencies and the World Bank, and for multi-national pharmaceutical companies, regardless of the country, if any, with which they were associated in their affiliation data. These were then aggregated into two groups, "international organizations" and "pharmaceutical industry", to permit consideration of their relative influence.

This process allowed a comprehensive assessment of the total volume of articles produced by each country and by income group, as well as a comprehensive assessment of top institutions, taking into account the many and unpredictable variations in their listing. Less thorough approaches would be likely to bias rankings towards institutions such as Yale, with its unique name which also appears in the name of all its constituent schools and hospital, and away from institutions with a wider variety of permutations, abbreviations and possibly ambiguous versions of its name, such as the University of York (Univ York, U York, but not York University), with Hull-York Hospital (Hull-York Hosp), which were not always listed with the university name in the affiliation data.

We considered a number of possible approaches for analysing articles with more than one institutional affiliation. Both Wagstaff and Culyer (2012) and Rubin and Chang (2003) were constrained by the EconLit database, which only provides data on the first three or four authors, whereas we obtained institutional affiliation data for all authors. We considered assigning a fractional value (and even weighted fractional values reflecting author order) to each institution based on the number of different authors or institutions represented on a given article (Aksnes et al., 2012, Hagen, 2013, Retzer and Jurasinski, 2009). However, we rejected such approaches for two reasons: first, we believe that the use of zero-sum metrics establishes a perverse incentive against collaboration between institutions and against the crediting of collaborators. We therefore assigned one point per institution per article, regardless of the number of institutions or authors on a given article. This has the disadvantage of weighting the analysis towards articles from multiple institutions, as these articles are counted multiple times.

Table S1 Searches in bibliographic databases

Database (Interface)	Search
National Health Service Economic Evaluation Database (Centre for Reviews and Dissemination) ***Note: this database is still available, however, updating ceased in March 2015***	NHS EED: tick box (DARE: blank, HTA: blank) Publication year: 2012 to 2014 Export: "Full record" → produces a single RIS document with consecutively numbered records
Health Economic Evaluations 'Database (Wiley) ***Note: this database ceased to be available from the end of 2014.***	**Search 1: Identifies studies already reviewed and categorized by HEED** Search type (from purple button on left): Compound Search Use pull-down menus to select: | Journal Date | >= 2012 | AND | |Type of Econ eval | 'EFFECTIVENESS' Or 'UTILITY' Or 'BENEFIT' | AND | | Type of Article | 'APPLIED' | **Search 2: Identifies additional studies not yet reviewed and categorized by HEED** Search type (from purple button on left): Expert Search 1. EE= 'EFFECTIVENESS' Or 'UTILITY' Or 'BENEFIT' AND TE= 'APPLIED' AND JD>= 2012 2. TI='Cost-effective*' OR 'Cost-Utility' OR 'Cost-benefit' OR 'Cost effective*' OR 'Cost Utility' OR 'Cost benefit' OR 'economic evaluation' AND (JD>= 2012) 3. AB='Cost-effectiveness' OR 'Cost-Utility' OR 'Cost-benefit' OR 'Cost effectiveness' OR 'Cost Utility' OR 'Cost benefit' OR 'economic evaluation' AND (JD>= 2012) 4. KW='Cost-effectiveness' OR 'Cost-Utility' OR 'Cost-benefit' OR 'Cost effectiveness' OR 'Cost Utility' OR 'Cost benefit' OR 'economic evaluation' AND (JD>= 2012) 5. AB='cost per death averted' or 'cost per death avoided' or 'cost per case averted' or 'cost per case avoided' or 'cost per infection' or 'cost per life' or 'cost per disability-adjusted' or 'cost per quality-adjusted' or 'cost per qaly' or 'cost per daly' 6. CS = LINE 1 OR LINE 2 OR LINE 3 OR LINE 5
LILACS (Bireme/WHO/ PAHO)	cost-effective or "cost effective" or cost-effectiveness or "cost effectiveness" or cost-utility or "cost utility" or cost-benefit or "cost benefit" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability adjusted" or "cost per quality adjusted" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per

	daly" [Words] and 2012 or 2013 or 2014 [Country, year publication] and not study and protocol [Title words]
ADOLEC (Bireme/WHO/PAHO)	cost-effective or "cost effective" or cost-effectiveness or "cost effectiveness" or cost-utility or "cost utility" or cost-benefit or "cost benefit" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability adjusted" or "cost per quality adjusted" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly" [Words] and 2012 or 2013 or 2014 [Country, year publication] and not study and protocol [Title words]
Medline (including in-process) (Ovid SP)	1. ("2012" or "2013" or "2014").yr. 2. (cost-effectiveness or cost-utility or cost-benefit or "economic evaluation").ti,ab,kw. 3. cost-effective.ti. 4. ("cost-per-death-av*" or "cost-per-case-av*" or "cost-per-infection" or "cost-per-life" or "cost-per-disability-adjusted-life-year" or "cost-per-quality-adjusted-life-year" or "cost-per-qaly" or "cost-per-daly").ti,ab,kw. 5. 2 or 3 or 4 6. 1 and 5 7. limit 6 to (autobiography or bibliography or biography or case reports or classical article or comment or congresses or consensus development conference or consensus development conference, nih or editorial or festschrift or guideline or historical article or in vitro or interactive tutorial or interview or lectures or letter or news or newspaper article or patient education handout or practice guideline or published erratum or technical report or twin study or video-audio media or webcasts) 8. 6 not 7 9. limit 8 to animals 10. limit 9 to human 11. 9 not 10 12. 8 not 11 13. study protocol.ti. 14. 12 not 13
Embase (Ovid SP)	1. ("2012" or "2013" or "2014").yr. 2. (cost-effectiveness or cost-utility or cost-benefit or "economic evaluation").ti,ab,kw. 3. cost-effective.ti. 4. ("cost-per-death-av*" or "cost-per-case-av*" or "cost-per-infection" or "cost-per-life" or "cost-per-disability-adjusted-life-year" or "cost-per-quality-adjusted-life-year" or "cost-per-qaly" or "cost-per-daly").ti,ab,kw. 5. 2 or 3 or 4 6. 1 and 5 7. limit 6 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or

	editorial or erratum or letter or note or report) 8. 6 not 7 9. limit 8 to (animals or animal studies) 10. limit 9 to humans 11. 9 not 10 12. 8 not 11 13. study protocol.ti. 14. 12 not 13
EconLit (Ovid SP)	1. ("2012" or "2013" or "2014").yr. 2. health.af. 3. (cost-effective* or cost-utility or cost-benefit or "economic evaluation").af. 4. ("cost-per-death-av*" or "cost-per-case-av*" or "cost-per-infection" or "cost-per-life" or "cost-per-disability-adjusted-life-year" or "cost-per-quality-adjusted-life-year" or "cost-per-qaly" or "cost-per-daly").af. 5. 3 or 4 6. 1 and 2 and 5 7. study protocol.ti. 8. limit 6 to (books or book reviews or collective volume articles or dissertations) 9. 6 not 8 10. limit 9 to working papers 11. 9 not 10
PsycInfo(Ovid SP)	1. ("2012" or "2013" or "2014").yr. 2. (cost-effectiveness or cost-utility or cost-benefit or "economic evaluation").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 3. cost-effective.ti. 4. ("cost-per-death-av*" or "cost-per-case-av*" or "cost-per-infection" or "cost-per-life" or "cost-per-disability-adjusted-life-year" or "cost-per-quality-adjusted-life-year" or "cost-per-qaly" or "cost-per-daly").ti,ab,kw. 5. 2 or 3 or 4 6. 1 and 5 7. limit 6 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract" or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or "erratum/correction" or letter or obituary) 8. 6 not 7 9. limit 8 to animal 10. limit 9 to human 11. 9 not 10 12. 8 not 11 13. study protocol.ti. 14. 12 not 13
Global Health (Ovid SP)	1. ("2012" or "2013" or "2014").yr. 2. (cost-effectiveness or cost-utility or cost-benefit or "economic evaluation").af.

	3. cost-effective.ti. 4. ("cost-per-death-av*" or "cost-per-case-av*" or "cost-per-infection" or "cost-per-life" or "cost-per-disability-adjusted-life-year" or "cost-per-quality-adjusted-life-year" or "cost-per-qaly" or "cost-per-daly").af. 5. 2 or 3 or 4 6. 1 and 5 7. limit 6 to (annual report or annual report section or book or book chapter or bulletin or conference or conference proceedings or conference paper or correspondence or editorial or patent or thesis) 8. 6 not 7 9. study protocol.ti. 10. 8 not 9
Scopus (Scopus)	**MAIN SEARCH:** ((((TITLE("cost-effective*" OR "cost-utility" OR "cost-benefit" OR "economic evaluation") AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 2011) OR (TITLE("cost per death" OR "cost per case" OR "cost per infection" OR "cost per life" OR "cost per disability-adjusted" OR "cost per quality-adjusted" OR "cost per qaly" OR "cost per daly") AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 2011) OR (ABS("cost-effectiveness" OR "cost-utility" OR "cost-benefit" OR "economic evaluation") AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 2011) OR (ABS("cost per death" OR "cost per case" OR "cost per infection" OR "cost per life" OR "cost per disability-adjusted" OR "cost per quality-adjusted" OR "cost per qaly" OR "cost per daly") AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 2011) OR (AUTHKEY("cost-effectiveness" OR "cost-utility" OR "cost-benefit" OR "economic evaluation") AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 2011)) AND (SUBJAREA(mult OR immu OR neur OR phar OR mult OR medi OR nurs OR dent OR heal OR deci OR econ OR psyc))) AND NOT (TITLE("study protocol"))) AND NOT (DOCTYPE(bk OR ch OR bz OR cp OR cr OR ed OR er OR le OR no OR pr OR rp OR sh)) **BREAKING UP THE SEARCH:** **BY YEAR: 2014 – 1,216** **BY YEAR: 2013 – 4,039** **Broke this one up further – by "cost-effectiveness" in title, abstract, and keywords (3,148) and not (891)** **BY YEAR: 2012 – 3,751**
Social Science Citation Index & Science Citation Index extended (Web of Science)	# 1 4,006,203 PY=(2012 or 2013 or 2014) # 2 5,706 TI=("cost-effective*" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") # 3 13,274 TS=("cost-effectiveness" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost

	per daly") # 4 1,091 TITLE: ("study protocol") # 5 14,237 #3 OR #2 # 6 14,237 #5 AND #1 # 7 14,054 #6 not #4 # 8 2,900 (#7) AND DOCUMENT TYPES: (Abstract of Published Item OR Art Exhibit Review OR Bibliography OR Biographical-Item OR Book OR Book Chapter OR Book Review OR Chronology OR Correction OR Correction, Addition OR Dance Performance Review OR Database Review OR Discussion OR Editorial Material OR Excerpt OR Fiction, Creative Prose OR Film Review OR Hardware Review OR Item About an Individual OR Letter OR Meeting Abstract OR Meeting Summary OR Music Performance Review OR Music Score OR Music Score Review OR News Item OR Note OR Poetry OR Proceedings Paper OR Record Review OR Reprint OR Script OR Software Review OR TV Review, Radio Review OR TV Review, Radio Review, Video OR Theater Review) # 9 11,154 #7 NOT #8 # 10 8,739 #9 AND WC=(PATHOLOGY OR BEHAVIORAL SCIENCES OR MEDICAL LABORATORY TECHNOLOGY OR BIOLOGY OR SOCIAL SCIENCES INTERDISCIPLINARY OR SOCIAL WORK OR HEALTH CARE SCIENCES SERVICES OR VIROLOGY OR MEDICINE GENERAL INTERNAL OR HEALTH POLICY SERVICES OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH SCI OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR MICROBIOLOGY OR PHARMACOLOGY PHARMACY OR RHEUMATOLOGY OR SOCIAL SCIENCES BM OR ECONOMICS OR NEUROSCIENCES OR PARASITOLOGY OR SURGERY OR ONCOLOGY OR REHABILITATION OR DENTISTRY ORAL SURGERY MEDICINE OR OPERATIONS RESEARCH MANAGEMENT SCIENCE OR FOOD SCIENCE TECHNOLOGY OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH SSCI OR CARDIAC CARDIOVASCULAR SYSTEMS OR CRITICAL CARE MEDICINE OR INFECTIOUS DISEASES OR NURSING OR IMMUNOLOGY OR OPHTHALMOLOGY OR ANESTHESIOLOGY OR CLINICAL NEUROLOGY OR EMERGENCY MEDICINE OR MULTIDISCIPLINARY SCIENCES OR NUTRITION DIETETICS OR TOXICOLOGY OR MEDICINE RESEARCH EXPERIMENTAL OR SUBSTANCE ABUSE OR PSYCHIATRY OR DERMATOLOGY OR GASTROENTEROLOGY HEPATOLOGY OR GENETICS HEREDITY OR TRANSPLANTATION OR OBSTETRICS GYNECOLOGY OR TROPICAL MEDICINE OR MEDICAL INFORMATICS OR GERIATRICS GERONTOLOGY OR OTORHINOLARYNGOLOGY OR PERIPHERAL VASCULAR DISEASE OR ORTHOPEDICS OR MANAGEMENT OR PEDIATRICS OR UROLOGY NEPHROLOGY OR PSYCHIATRY SCI OR RESPIRATORY SYSTEM OR ENDOCRINOLOGY METABOLISM OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR PRIMARY HEALTH CARE OR ENGINEERING ENVIRONMENTAL OR HEMATOLOGY) Indexes=SCI-EXPANDED, SSCI Timespan=2012-2014
Scielo (Web of Science)	# 1 79,842 PY=(2012 or 2013 or 2014) # 2 98 TI= ("cost-effective*" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") # 3 221 TS=("cost-effectiveness" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") # 4 227 #2 or #3 # 5 2 TI=("study protocol") # 6 227 #4 not #5

	# 7 175 #6 AND SU=(PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR LEGAL MEDICINE OR GENERAL INTERNAL MEDICINE OR PEDIATRICS OR CARDIOVASCULAR SYSTEM CARDIOLOGY OR DENTISTRY ORAL SURGERY MEDICINE OR ANESTHESIOLOGY OR DERMATOLOGY OR PHARMACOLOGY PHARMACY OR ENDOCRINOLOGY METABOLISM OR GASTROENTEROLOGY HEPATOLOGY OR ENVIRONMENTAL SCIENCES ECOLOGY OR HEALTH CARE SCIENCES SERVICES OR NURSING OR MEDICAL LABORATORY TECHNOLOGY OR NEUROSCIENCES NEUROLOGY OR OPERATIONS RESEARCH MANAGEMENT SCIENCE OR OTORHINOLARYNGOLOGY OR OBSTETRICS GYNECOLOGY OR OPHTHALMOLOGY OR PSYCHIATRY OR PATHOLOGY OR RESPIRATORY SYSTEM OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR TROPICAL MEDICINE OR SURGERY OR RHEUMATOLOGY OR UROLOGY NEPHROLOGY OR BIOTECHNOLOGY APPLIED MICROBIOLOGY OR INFECTIOUS DISEASES OR EConomics) # 8 13 (#7) AND DOCUMENT TYPES: (Announcement OR Article-Commentary OR Case-Report OR Editorial OR Letter OR Rapid-Communication) # 9 162 #7 not #8
Biosis (Web of Science)	# 1 1,608,659 PY=(2012 or 2013 or 2014) # 2 1,741 TI= ("cost-effective*" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") # 3 3,846 TS=("cost-effectiveness" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") # 4 4,109 #2 or #3 # 5 4,109 #1 and #4 # 6 35 TI= ("study protocol") # 7 4,104 #5 not #6 # 8 777 (#7) AND DOCUMENT TYPES: (Annual Report OR Article Thesis Dissertation OR Book OR Book Chapter OR Book Review OR Company Profile OR Index OR Letter OR Main Cite OR Meeting OR Meeting Paper OR Obituary OR Patent OR Reprint OR Software OR Technical Report OR Thesis Dissertation) # 9 3,327 #7 NOT #8 # 10 123 (#9) AND LITERATURE TYPE: (Annual Report OR Bibliography OR Biography OR Catalog OR Checklist OR Correction OR Dictionary OR Editorial OR Errata OR Identification Guide OR Manual OR Meeting Abstract OR Meeting Address OR Meeting Paper OR Meeting Poster OR Meeting Report OR Meeting Slide OR Meeting Summary OR Nomenclator OR Nomenclature OR Obituary OR Protocol OR Retraction OR Software Review OR Standard OR Taxonomic Key OR Taxonomic Review) # 11 3,204 #9 not #10 # 12 2,643 #11 AND SU=(TOXICOLOGY OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR REPRODUCTIVE BIOLOGY OR HEMATOLOGY OR ANESTHESIOLOGY OR DEVELOPMENTAL BIOLOGY OR INFECTIOUS DISEASES OR ORTHOPEDICS OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR BEHAVIORAL SCIENCES OR EVOLUTIONARY BIOLOGY OR IMMUNOLOGY OR REHABILITATION OR ONCOLOGY OR NURSING OR PHYSIOLOGY OR CARDIOVASCULAR SYSTEM CARDIOLOGY OR NUTRITION DIETETICS OR DENTISTRY ORAL SURGERY MEDICINE OR NEUROSCIENCES NEUROLOGY OR ALLERGY OR SURGERY OR OPHTHALMOLOGY OR GENETICS HEREDITY OR OBSTETRICS GYNECOLOGY OR GASTROENTEROLOGY HEPATOLOGY OR DERMATOLOGY OR GENERAL INTERNAL MEDICINE OR

	PARASITOLOGY OR HEALTH CARE SCIENCES SERVICES OR PSYCHIATRY OR PEDIATRICS OR GERIATRICS GERONTOLOGY OR ENDOCRINOLOGY METABOLISM OR RHEUMATOLOGY OR UROLOGY NEPHROLOGY OR RESPIRATORY SYSTEM OR OTORHINOLARYNGOLOGY)
Cinahl (EBSCO)	S1. TI ("cost-effective*" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") S2. AB ("cost-effectiveness" or "cost-benefit" or "cost-utility" or "economic evaluation" or "cost per death" or "cost per case" or "cost per infection" or "cost per life" or "cost per disability-adjusted" or "cost per quality-adjusted" or "cost per qaly" or "cost per daly") S3. S1 OR S2 S4. TI ("study protocol") S5. S3 NOT S4 S6. S5 and PT (Algorithm OR Anecdote OR Bibliography OR Biography OR Book OR Book Chapter OR Book Review OR Brief Item OR Care Plan OR Cartoon OR Case Study OR CEU OR Classification Term OR Code of Ethics OR Commentary OR Computer Program OR Consumer/Patient Teaching Materials OR Critical Path OR Directories OR Doctoral Dissertation OR Editorial OR Evidence-Based Care Sheet OR Exam Questions OR Forms OR Games OR Glossary OR Historical Material OR Interview OR Legal Case OR Letter OR Masters Thesis OR Nurse Practice Acts OR Obituary OR Pamphlet OR Pamphlet Chapter OR Periodical OR Poetry OR Practice Acts OR Proceedings OR Quick Lesson OR Research Instrument Validation OR Response OR Standards OR Statistics OR Teaching Materials OR Tracings OR Trade Publication OR Website) S7. S5 NOT S6

Table S2 Mapping of 25 disease areas onto the Global Burden of Disease (GBD), International Classification of Disease (ICD-10), and search terms used

Health areas developed for this analysis are listed in alphabetical order in the lefthand column. We mapped each component of the Global Burden of Disease (World Health Organization., 2014) onto one health area. The mapping of the ICD-10 codes (World Health Organization., 2011) onto GBD codes is taken from the GBD appendices. Both GBD and ICD-10 definitions were used to inform the development of search terms for each health areas, which were applied as necessary to the titles, abstracts, and/or keywords in the final database of economic evaluations. Underscores ("_") have been used here to show single spaces and question marks ("?") reflect a single wildcard character. GBD: Global Burden of Disease. ICD-10: International Classification of Disease, version 10.

Health area	GBD	ICD-10	Search terms used to identify economic evaluations in this area
Anaemia	58: Iron-deficiency anaemia	D50, D64.9	Anaemia, Anemia, Anemic, Anaemic, Iron?deficien, _iron_, iron?supplement,
Cancer and other neoplasms	61: Malignant neoplasms, 79: Other neoplasms	C00-C97, D00-D48	Adenocarcinoma, Adenoma, Cancer, carcinoma, chemoradiotherapy, Chemotherapy, Glioblastoma, glioma, Neoplasm, Radiation_therapy, Radiotherapy, Melanoma, Lymphoma, myeloma, neoplastic, Leukaemia, microcalcification, neoplasia, myelodysplas, leukemia, metastatic, sarcoma, paclitaxel, Hematopoietic_Stem_Cell, autologous_stem_cell, cervical_screen, pap_smear, lynch_syndrome, tumour, tumor, breast_reconstruction, metastasis,
Cardiovascular diseases	110: Cardiovascular diseases	I00-I99	Angina, Angioplasty, Anticoagulants, aorta, aortic, Arrhythmia, Arrhythmic, arterial, artery, Atrial_Fibrillation, blood_pressure, blood_vessel, cardiac, cardio, carotid, Chest, cholesterol, Coronary, Deep_Vein_Thrombosis, embolism, heart, hypertensi, myocarditis, endocarditis, Myocardial, pulmonary, stroke, aneurysm, circulatory, warfarin, rheumatic, varicose_vein, venous'ulcer, vascular_disease,
Communicable childhood diseases	12: Childhood-cluster diseases	A33-A37, B05	chickenpox, Pertussis, Whooping_cough, Diphtheria, Measles, Tetanus, chicken_pox, rubella, immunization,
Congenital anomalies	140: Congenital anomalies	Q00-Q99	chromosom, cleft lip, Dwarfism, cystic fibrosis, Neural tube defect, Cleft lip, Congenital, cleft palate, Down Syndrome, Down's Syndrome, Down's Syndrome, disabilities, disabled children, neural tube, congenital, Tetralogy of Fallot, spina bifida, trisomy, polydactyl, teratogenic
Diabetes	80: Diabetes mellitus	E10-E14	Diabetes, glucose, diabetic, hyperglycemi,
Diarrhoeal diseases	11: Diarrhoeal diseases	A00, A01, A03, A04, A06-A09	diarrhea, diarrhoea, rotavirus, cholera, typhoid, shigell, amoebiasis, amoeba, rotaviral, enteritis, norwalk, adenovir, escherichia_coli, campylobacter, clostridium_difficile, dysentery, giardia, cryptosporid, norovirus,
Digestive diseases	121: Digestive diseases	K20-K92	celiac, cholera, coeliac, crohn, Digestive, gallbladder, gallstones, gall?stones, gastric, gastro, helicobacter, ileostomy, colitis, constipation, Appendectomy, appendicitis, hernia_, bowel_, Intestinal_Polyps, Peptic_ulcer, diverticulitis, Cholecystolithiasis, pancreatitis, Cholecystitis, liver_, biliary, duodenal, vomit, ileus, hepatic, inguinal_hernia,

Health area	GBD	ICD-10	Search terms used to identify economic evaluations in this area
Endocrine, blood, and immune disorders (not diabetes or HIV)	81: Endocrine, blood, immune disorders	D55-D64 (minus D64.9), D65-D89, E03-E07, E15-E34, E65-E88	graves_disease, Hormones, hyperthyroidism, hypothyroidism, Goiter, Endocrin, Haemophilia, Adrenal, Allerg, Anaphylaxis, hemophilia, thyroid, hematological, neutropenia, Ischaemi, Ischemi, tonsil, thalassaemia, thalassemia, Thrombocytopenia, Fabry_disease, lysosomal, sickle_cell,
Genitourinary diseases, family planning & fertility	126: Genitourinary diseases	N00-N64, N75-N76, N80-N98	Gynecolog, Gynaecolog, contraception, contraceptive, embryo, fertility, fertilization, prostat, urologic, urinary, urethral_, genito, Kidney, Urolithiasis, nephrolog, Infertility, infertile, Nephrostomy, dialysis, pyelography, ovulation, urodynamic, ureter, hypogonadism, menstrual, nephropathy, microalbuminur, nephritis, bladder, varicocele,
HIV/AIDS	10: HIV/AIDS	B20-B24	Acquired Immune Deficiency Syndrome, CD4, HAART, retroviral, hiv?aids, hiv , Human Immunodeficiency Virus, cd4 ,
Malaria	22: Malaria	B50-B54, P37.3, P37.4	bed?net, malaria, bednet, artemesenin,
Malnutrition (including obesity and exercise)	54: Nutritional deficiencies (*except 58: Iron-deficiency anaemia*)	E00-E02, E40-E46, E50-E64, D51-D53	bariatric, Body_Mass_Index, Body_Weight, nutrition, Iodine, Vitamin_A, obesity, obese, physical_activity, exercise, pedometer, vegetable, dietary, biofortif, weight_management,
Maternal and neonatal conditions	42: Maternal conditions, 49: Neonatal conditions	O00-O99, P00-P96 excl P37.3, P37.4	low?birth?weight, Preterm, Birth, Neonat, Newborn, New-born, Amniocentesis, Birth, caesarean, cesarean, fetal, folic_acid, gestational, preeclampsia, eclampsia, pregnancy, prenatal, abortion, endometrial, obstetric, premature_infant, prematurity, vaginal_deliver,
Meningitis	17: Meningitis	A39, G00, G03	mening,
Mental health, cognition, and developmental and behavioural disorders (including self-harm and addictions)	82: Mental and behavioural disorders, 161: Self-harm	F04-F99, X41-X42, X45, X60-X84, Y870	ADHD, Agoraphobi, Antidepressant, Antidepressive, Anxiety, autism, Autistic, Schizophreni, Bipolar, _cognition, cognitive, Dementia, depression, substance_use_disorder, opiate_substitution, Eating_Disorder, _Emotions, mental_health, heroin, psychosis, psychotic, Unipolar, cocaine, addiction, Alcohol_use, Drug_use, developmental_disorder, behavioural_disorder, intellectual, behavio?r_disorder, clinically_isolated_syndrome, mentally_ill, Somatoform, depressive_disorder, Alcohol, Drug_Abuse, Drug_Addiction, Narcotic_Control, smoking, substance_abuse, Psychotherapy, mental_illness, Mental_Disorder, suicide, smoker, methadone, methadone, delirium, Nicotine, attention?deficit?hyperactivity?disorder, fear of, behavior disorder, cannabis,
Musculoskeletal diseases (including back and neck pain)	134: Musculoskeletal diseases	M00-M99	ankle, Bone, Carpal_Tunnel, Cartilage, elbow, fracture, Joint, knee, Ligament, arthritis, Lumbar, Diskectomy, discectomy, musculoskeletal, Physical_Therapy_, osteoporo, fibromyalgia, Spinal, foot, shoulder, orthopedic, hip_replacement, lupus, Gout, low?back_pain,
Neurological	94: Neurological	F01-F03, G06 -G98	cerebral, nervous_system, neurological, Epilepsy, Alzheimer, Parkinson,

Health area	GBD	ICD-10	Search terms used to identify economic evaluations in this area
conditions (including headache and sleep disorders)	conditions		Epileptic, Multiple_sclerosis, Migraine, headache, sleep, Myasthenia_gravis, thymectomy, neurosurgery, neuropath, chronic_fatigue_syndrome, neuralgia,
Other infectious diseases (including encephalitis, hep A, B, C, and other parasitic and vector-borne diseases, and nematode infections)	18: Encephalitis, 19: Acute hepatitis B, 20: Acute hepatitis C, 21: Parasitic and vector diseases (*except* 22: *Malaria*), 33: Intestinal nematode infections, 37: Other infectious diseases	A83-A86, B94.1, G04, B16-B19 (minus B17.1, B18.2), B17.1, B18.2, A30, A71, A82, A90-A91, B55-B57, B65, B73, B74.0-B74.2, B76-B77, B79, A02, A05, A20-A28, A31, A32, A38, A40-A49, A65-A70, A74-A79, A80-A81, A87-A89, A92-A99, B00-B04, B06-B15, B25-B49, B58-B60, B64, B66-B72, B74.3-B74.9, B75,B78, B80-B89, B91-B99 (minus B94.1)	Encephaliti, Dengue, lyme_, deworming, hepatitis, hep_b, hep_c, Trypanosomiasis, Chagas, Schistosom, Leishmania, Lymphatic_filariasis, Onchocerciasis, Leprosy, leprous, Trachoma, Rabies, Ascariasis, Trichuriasis, Hookworm, hep_a, rubella, herpes_zoster, clostridium, Staphylococc, Bacteremia, hospital-acquired_infection, septic_shock, sepsis, Staphylococc, scabies, systemic_Candida_infection, cytomegalovirus, infection_control, hcv, Creutzfeldt?Jakob, _invasive_Candid, Helminth, roundworm, antimicrobial,
Respiratory diseases	38: Respiratory infections, 117: Respiratory diseases	J00-J22, H65-H68,P23, U04, J30-J98	Respiratory, Pulmonary, Lung, Bronchial, Trachea, Bronchitis, Airway, Asthma, H1N1, Influenza, bird_flu, avian_flu, interstit, Pleural_effusion, sore_throat, pneumonia, Respiration, pneumococcal, Haemophilus, breathing, pharyngitis, pneumonia,
Sense organ diseases	102: Sense organ diseases	H00-H61, H69-H93	Blindness, Cataract, cochlear, deafness, eye_, Glaucoma, hearing, Macular, rhino, Nasolacrimal, Refractive_error, vision_loss, hearing_loss, canaloplasty, Trabeculectomy, retina, Ophthalmolog, keratoplasty, otitis_media,
Skin and oral conditions	133: Skin diseases, 147: Oral conditions	L00-L98, K00-K14	debridement, Dental, Dentistry, Denture, gingival, Edentulism, Periodontal, peritonsillar, Dentition, Orthodontics, Dermatitis, Dermatolog, Eczema, skin_disease, tinea, psoriasis, dermatophytic, plantar_wart, skin?graft, soft tissue, foam dressing, pressure ulcer,
Sexually Transmitted Infections (not HIV)	4: STDs excluding HIV	A50-A64, N70-N73	chlamydia, condoms, Gonorrhea, Papillomavirus, Syphilis, Gonorrhoea, Trichomoniasis, Sexually_Transmitted, hpv,
Tuberculosis	3: Tuberculosis	A15-A19, B90	antitubercular, BCG, TB, tuberculos, bacille_Calmette-Guerin,
Wounds and injuries	151: Injuries (*except 161: Self-harm*)	V01-X59, Y871-Y89,	Injury, Injuries, Accident, Burn, violence, Poisoning, Drown, child abuse, domestic abuse, Domestic Violence, trauma, fall prevention, falls prevention, venom, antidote, whiplash, _radon_, road_safety,

Health area	GBD	ICD-10	Search terms used to identify economic evaluations in this area
conditions (including headache and sleep disorders)	conditions		Epileptic, Multiple_sclerosis, Migraine, headache, sleep, Myasthenia_gravis, thymectomy, neurosurgery, neuropath, chronic_fatigue_syndrome, neuralgia,
Other infectious diseases (including encephalitis, hep A, B, C, and other parasitic and vector-borne diseases, and nematode infections)	18: Encephalitis, 19: Acute hepatitis B, 20: Acute hepatitis C, 21: Parasitic and vector diseases (*except 22: Malaria*), 33: Intestinal nematode infections, 37: Other infectious diseases	A83-A86, B94.1, G04, B16-B19 (minus B17.1, B18.2), B17.1, B18.2, A30, A71, A82, A90-A91, B55-B57, B65, B73, B74.0-B74.2, B76-B77, B79, A02, A05, A20-A28, A31, A32, A38, A40-A49, A65-A70, A74-A79, A80-A81, A87-A89, A92-A99, B00-B04, B06-B15, B25-B49, B58-B60, B64, B66-B72, B74.3-B74.9, B75,B78, B80-B89, B91-B99 (minus B94.1)	Encephaliti, Dengue, lyme_, deworming, hepatitis, hep_b, hep_c, Trypanosomiasis, Chagas, Schistosom, Leishmania, Lymphatic_filariasis, Onchocerciasis, Leprosy, leprous, Trachoma, Rabies, Ascariasis, Trichuriasis, Hookworm, hep_a, rubella, herpes_zoster, clostridium, Staphylococc, Bacteremia, hospital-acquired_infection, septic_shock, sepsis, Staphylococc, scabies, systemic_Candida_infection, cytomegalovirus, infection_control, hcv, Creutzfeldt?Jakob, _invasive_Candid, Helminth, roundworm, antimicrobial,
Respiratory diseases	38: Respiratory infections, 117: Respiratory diseases	J00-J22, H65-H68,P23, U04, J30-J98	Respiratory, Pulmonary, Lung, Bronchial, Trachea, Bronchitis, Airway, Asthma, H1N1, Influenza, bird_flu, avian_flu, interstit, Pleural_effusion, sore_throat, pneumonia, Respiration, pneumococcal, Haemophilus, breathing, pharyngitis, pneumonia,
Sense organ diseases	102: Sense organ diseases	H00-H61, H69-H93	Blindness, Cataract, cochlear, deafness, eye_, Glaucoma, hearing, Macular, rhino, Nasolacrimal, Refractive_error, vision_loss, hearing_loss, canaloplasty, Trabeculectomy, retina, Ophthalmolog, keratoplasty, otitis_media,
Skin and oral conditions	133: Skin diseases, 147: Oral conditions	L00-L98, K00-K14	debridement, Dental, Dentistry, Denture, gingival, Edentulism, Periodontal, peritonsillar, Dentition, Orthodontics, Dermatitis, Dermatolog, Eczema, skin_disease, tinea, psoriasis, dermatophytic, plantar_wart, skin?graft, soft_tissue, foam_dressing, pressure_ulcer,
Sexually Transmitted Infections (not HIV)	4: STDs excluding HIV	A50-A64, N70-N73	chlamydia, condoms, Gonorrhea, Papillomavirus, Syphilis, Gonorrhoea, Trichomoniasis, Sexually_Transmitted, hpv,
Tuberculosis	3: Tuberculosis	A15-A19, B90	antitubercular, BCG, TB, tuberculos, bacille_Calmette-Guerin,
Wounds and injuries	151: Injuries (*except 161: Self-harm*)	V01-X59, Y871-Y89,	Injury, Injuries, Accident, Burn, violence, Poisoning, Drown, child_abuse, domestic_abuse, Domestic_Violence, trauma, fall_prevention, falls_prevention, venom, antidote, whiplash, _radon_, road_safety,

Table S3 Classification of journal types

The following is a comprehensive list of how we classified journals publishing at least one economic evaluation meeting our criteria.

Health economics, policy, services, and/or social science journals	
Administration and Policy in Mental Health and Mental Health Services Research	International Journal of Technology Assessment in Health Care
AIDS and behavior	Israel Journal of Health Policy Research
Alter	Journal d Economie Medicale
American Health and Drug Benefits	Journal of Benefit-Cost Analysis
Applied Health Economics and Health Policy	Journal of health economics
Behaviour research and therapy	JOURNAL OF HEALTH SERVICES RESEARCH and POLICY
BMC HEALTH SERVICES RESEARCH	Journal of Medical Economics
BMC Medical Informatics and Decision Making	Journal of Mental Health Policy and Economics
British Journal of Health Care Management	Journal of Nursing Management
Bulletin of the World Health Organization	JOURNAL OF NUTRITION EDUCATION AND BEHAVIOR
Cancer Management and Research	Journal of Pain and Symptom Management
CHILDREN AND YOUTH SERVICES REVIEW	Journal of Pharmaceutical Health Services Research
ClinicoEconomics and Outcomes Research	Journal of Public Health Management and Practice
Cost Effectiveness and Resource Allocation	Medical Decision Making
Decision Sciences	Mediterranean Journal of Social Sciences
Epilepsy and Behavior	Ontario Health Technology Assessment Series
European Journal of Health Economics	Open Pharmacoeconomics and Health Economics Journal
European Review of Agricultural Economics	
Expert review of pharmacoeconomics and outcomes research	PharmacoEconomics
	PharmacoEconomics - Italian Research Articles
Gesundheitsokonomie und Qualitatsmanagement	Pharmacoeconomics - Spanish Research Articles
GMS health technology assessment	Population Health Management
Health Affairs	Psychological Services
Health Economics	Research in Social and Administrative Pharmacy
Health Economics Review	Revista medica del Instituto Mexicano del Seguro Social
Health Policy	
Health Policy and Planning	Social Psychiatry and Psychiatric Epidemiology
Health Policy and Technology	South African Journal of Economic and Management Sciences
Health Services Research	
Health Technology Assessment	Substance abuse treatment, prevention, and policy
Healthcare Policy	Therapeutics and Clinical Risk Management
International Journal of Behavioral Nutrition and Physical Activity	Value in Health
	Value in Health Regional Issues
International Journal of Drug Policy	Vascular Health and Risk Management
Other	
American Water Works Association Journal	Journal of Water and Health
Child Abuse and Neglect	MATHEMATICAL MODELLING OF NATURAL PHENOMENA
Disasters	
Environment International	PLoS One
European Journal of Operational Research	Traffic Injury Prevention
Journal of interpersonal violence	
Biomedical journals	
[Rinsho ketsueki] The Japanese journal of clinical hematology	Iowa Orthopaedic Journal
	Iranian journal of neurology
Academic Emergency Medicine	Iranian Journal of Pediatrics
Academic Pediatrics	Iranian Journal of Pharmaceutical Research
Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca	Iranian Journal of Radiology
	Iranian Red Crescent Medical Journal
Acta Chirurgica Belgica	Irish Journal of Medical Science

Acta clinica Belgica	ISRN Gastroenterology
Acta gastroenterologica Latinoamericana	ISRN Obstetrics and Gynecology
Acta Medica Indonesiana	Italian Journal of Public Health
Acta neurochirurgica	JACC: Heart Failure
Acta Neurologica Scandinavica	JAMA
Acta Neuropsychiatrica	JAMA Ophthalmology
Acta Obstetricia et Gynecologica Scandinavica	JAMA Pediatrics
Acta Oncologica	Japanese Journal of Ophthalmology
Acta Ophthalmologica	Japanese Pharmacology and Therapeutics
Acta Oto-Laryngologica	Joint Commission Journal on Quality and Patient Safety
Acta Psychiatrica Scandinavica	Joint, Bone, Spine
Acta Radiologica	Jornal Portugues de Gastrenterologia
Actas dermo-sifiliograficas	Journal de Mycologie Medicale
Actas Urologicas Espanolas	Journal for Healthcare Quality
Acupuncture in Medicine	Journal of Acquired Immune Deficiency Syndromes
Addiction	Journal of Adolescent Health
Advances in Clinical and Experimental Medicine	Journal of Advanced Nursing
Advances in Skin and Wound Care	Journal of affective disorders
Advances in Therapy	Journal of Aging Research
Aesthetic Surgery Journal	Journal of Allergy and Clinical Immunology
African health sciences	Journal of Alternative and Complementary Medicine
African Journal of AIDS Research	Journal of Antivirals and Antiretrovirals
African Journal of Urology	Journal of Anxiety Disorders
Age and Ageing	Journal of Arthroplasty
AIDS	Journal of Arthropod-Borne Diseases
AIDS Care	Journal of Asthma
Alcohol and Alcoholism	Journal of bone and joint surgery
Alcoholism Clinical and Experimental Research	Journal of Bone and Mineral Research
Alimentary Pharmacology and Therapeutics	Journal of Brain Science
Allergologie	Journal of Bronchology and Interventional Pulmonology
Alzheimer's and Dementia	
American heart journal	Journal of Burn Care and Research
American Journal of Cardiology	Journal of Cancer
American Journal of Cardiovascular Drugs	Journal of Cancer Epidemiology
American Journal of Clinical Dermatology	Journal of Cardiothoracic Surgery
American Journal of Clinical Oncology	Journal of Cardiovascular Computed Tomography
American Journal of Emergency Medicine	Journal of Cardiovascular Electrophysiology
American Journal of Gastroenterology	Journal of Cardiovascular Magnetic Resonance
American Journal of Geriatric Psychiatry	Journal of Cardiovascular Medicine
American Journal of Health-System Pharmacy	Journal of Cardiovascular Nursing
AMERICAN JOURNAL OF HYPERTENSION	Journal of Cataract and Refractive Surgery
American Journal of Industrial Medicine	Journal of Child and Adolescent Substance Abuse
American Journal of Infection Control	Journal of Child and Family Studies
American Journal of Kidney Diseases	Journal of Children's Orthopaedics
American Journal of Managed Care	Journal of Clinical Apheresis
American Journal of Medical Genetics Part A	Journal of Clinical Endocrinology and Metabolism
American Journal of Medicine	Journal of clinical gastroenterology
American Journal of Neuroradiology	Journal of Clinical Hypertension
American Journal of Obstetrics and Gynecology	Journal of clinical lipidology
American journal of ophthalmology	JOURNAL OF CLINICAL MICROBIOLOGY
American Journal of Perinatology	Journal of clinical nursing
American Journal of Pharmacy Benefits	Journal of Clinical Oncology
American Journal of Physical Medicine and Rehabilitation	Journal of Clinical Periodontology
	Journal of Clinical Psychiatry
American Journal of Preventive Medicine	Journal of Clinical Sleep Medicine
American Journal of Public Health	Journal of Clinical Ultrasound
American Journal of Rhinology and Allergy	Journal of Clinical Virology

American Journal of Roentgenology	Journal of Cognitive and Behavioral Psychotherapies
American Journal of Speech-Language Pathology	Journal of community health
American journal of sports medicine	Journal of Comparative Effectiveness Research
American Journal of Surgery	JOURNAL OF CROHNS and COLITIS
AMERICAN JOURNAL OF THERAPEUTICS	Journal of Crohn's and Colitis
American Journal of Transplantation	Journal of Cystic Fibrosis
American Journal of Tropical Medicine and Hygiene	Journal of Dental Research
Anesthesiology	Journal of Dermatological Treatment
Angiology	Journal of Endourology
Annali di igiene : medicina preventiva e di comunita	Journal of Endovascular Therapy
Annals of Allergy, Asthma and Immunology	JOURNAL OF EPIDEMIOLOGY AND COMMUNITY HEALTH
Annals of cardiothoracic surgery	Journal of evaluation in clinical practice
Annals of Emergency Medicine	Journal of Food and Drug Analysis
Annals of General Psychiatry	Journal of Food Protection
Annals of Hematology	JOURNAL OF FOOT AND ANKLE RESEARCH
Annals of Internal Medicine	JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY
Annals of Nuclear Medicine	Journal of Gastrointestinal Cancer
Annals of Oncology	Journal of Gastrointestinal Surgery
Annals of Pharmacotherapy	Journal of General Internal Medicine
Annals of Plastic Surgery	Journal of Global Health
Annals of rehabilitation medicine	Journal of gynecologic oncology
Annals of Surgery	Journal of hand surgery
Annals of Surgical Oncology	journal of headache and pain
Annals of the Rheumatic Diseases	Journal of Hearing Science
Annals of the Royal College of Surgeons of England	Journal of Heart and Lung Transplantation
Annals of Thoracic Surgery	JOURNAL OF HEPATOLOGY
Annals of Vascular Surgery	Journal of Hospital Infection
Antimicrobial Agents and Chemotherapy	Journal of Hospital Medicine
Antiviral therapy	Journal of Hypertension
ANZ Journal of Surgery	Journal of Infection
Archives of Disease in Childhood	Journal of Infectious Diseases
Archives of Gynecology and Obstetrics	Journal of Interventional Cardiology
Archives of Internal Medicine	Journal of Korean Academy of Nursing Administration
Archives of Iranian Medicine	Journal of Korean Medical Science
Archives of Medical Research	Journal of long-term effects of medical implants
Archives of Medical Science	Journal of Lower Genital Tract Disease
Archives of Ophthalmology	Journal of Managed Care Medicine
Archives of Pathology and Laboratory Medicine	Journal of Managed Care Pharmacy
Archives of Pediatrics and Adolescent Medicine	journal of maternal-fetal and neonatal medicine
Archives of Surgery	Journal of Medical Colleges of PLA
ARCHIVOS DE BRONCONEUMOLOGIA	Journal of Medical Internet Research
Archivos de Neurociencias	Journal of Mental Health
Arquivos brasileiros de cardiologia	Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi
Arquivos Brasileiros de Oftalmologia	Journal of Nervous and Mental Disease
Arquivos de Gastroenterologia	Journal of Neurology
Arthritis Care and Research	Journal of Neurology Neurosurgery and Psychiatry
Arthroscopy	Journal of Neuro-Ophthalmology
ARYA Atherosclerosis	Journal of neurosurgery
Asian Biomedicine	Journal of neurosurgery. Spine
Asian Pacific Journal of Cancer Prevention	Journal of Neurosurgery: Spine
Asian Pacific Journal of Tropical Disease	JOURNAL OF NEUROSURGERY-SPINE
Asia-Pacific Journal of Clinical Oncology	Journal of Nuclear Medicine
Asia-Pacific Journal of Public Health	Journal of Nursing Scholarship
Atencion Farmaceutica	Journal of Nutrition
Atencion Primaria	JOURNAL OF OBSTETRICS AND GYNAECOLOGY
Australian and New Zealand Journal of Obstetrics and Gynaecology	

Australian and New Zealand journal of public health	Journal of Obstetrics and Gynaecology Canada
Australian Health Review	Journal of Occupational and Environmental Medicine
Australian Journal of Primary Health	Journal of Occupational Rehabilitation
Autism	Journal of Oncology Pharmacy Practice
Biochemia medica	Journal of Oncology Practice
BioDrugs	Journal of Orthopaedic Research
Biologics in Therapy	Journal of orthopaedic trauma
Biology of Blood and Marrow Transplantation	Journal of Otolaryngology - Head and Neck Surgery
BioMed research international	Journal of Pain and Palliative Care Pharmacotherapy
Biomedica	Journal of pediatric ophthalmology and strabismus
BIOMEDICAL ENGINEERING-BIOMEDIZINISCHE TECHNIK	Journal of Pediatrics
	Journal of Perinatology
Biomedical Journal	Journal of Periodontology
Biosecurity and Bioterrorism	Journal of Pharmacy Practice
BIOSYSTEMS	Journal of Plastic, Reconstructive and Aesthetic Surgery
BIOTECHNOLOGY and BIOTECHNOLOGICAL EQUIPMENT	Journal of Population Therapeutics and Clinical Pharmacology
BJOG: An International Journal of Obstetrics and Gynaecology	Journal of Practical Oncology
	Journal of primary care and community health
BJU International	Journal of Psychiatric Research
Blood purification	Journal of Psychosomatic Research
BMC Anesthesiology	Journal of Public Health
BMC Cancer	JOURNAL OF PUBLIC HEALTH DENTISTRY
BMC Cardiovascular Disorders	Journal of Radiation Research
BMC Clinical Pharmacology	Journal of Rehabilitation Medicine
BMC Complementary and Alternative Medicine	Journal of research in health sciences
BMC family practice	Journal of Sexual Medicine
BMC Gastroenterology	Journal of Shoulder and Elbow Surgery
BMC infectious diseases	Journal of Spinal Disorders and Techniques
BMC Medical Research Methodology	Journal of Stroke and Cerebrovascular Diseases
BMC Medicine	Journal of Studies on Alcohol and Drugs
BMC Musculoskeletal Disorders	Journal of Substance Abuse Treatment
BMC Neurology	Journal of Surgical Oncology
BMC ophthalmology	Journal of Surgical Research
BMC Pediatrics	Journal of Telemedicine and Telecare
BMC pregnancy and childbirth	Journal of the Academy of Nutrition and Dietetics
BMC Psychiatry	Journal of the American Academy of Audiology
BMC PUBLIC HEALTH	Journal of the American Academy of Dermatology
BMC research notes	Journal of the American College of Cardiology
BMJ	Journal of the American College of Surgeons
BMJ Open	JOURNAL OF THE AMERICAN GERIATRICS SOCIETY
BMJ quality and safety	Journal of the American Medical Directors Association
BMJ supportive and palliative care	Journal of the American Medical Informatics Association
Boletin Medico del Hospital Infantil de Mexico	
Bone	Journal of the American Pharmacists Association
bone and joint journal	Journal of the American Society of Nephrology
Brachytherapy	Journal of the Balkan Union of Oncology
Brazilian Journal of Infectious Diseases	Journal of the European Academy of Dermatology and Venereology
Brazilian Journal of Pharmaceutical Sciences	
Breast Cancer Research and Treatment	JOURNAL OF THE FORMOSAN MEDICAL ASSOCIATION
Breast Cancer: Targets and Therapy	Journal of the International Association of Providers of AIDS Care
Breast Care	
Breastfeeding Medicine	Journal of the Medical Association of Thailand
British Journal of Anaesthesia	Journal of the National Cancer Institute
British Journal of Cancer	Journal of the National Comprehensive Cancer Network
British Journal of Dermatology	
British Journal of General Practice	Journal of the Neurological Sciences

British Journal of Haematology	Journal of the Pakistan Medical Association
British Journal of Ophthalmology	Journal of the Royal Society Interface
British Journal of Psychiatry	Journal of the Royal Society of Medicine
British Journal of Sports Medicine	Journal of Theoretical Biology
British Journal of Surgery	Journal of Thoracic and Cardiovascular Surgery
Bulletin du Cancer	Journal of Thoracic Oncology
Cadernos de Saude Publica	Journal of Thrombosis and Haemostasis
CADTH technology overviews	Journal of thrombosis and thrombolysis
Canadian Journal of Cardiology	Journal of Traditional Chinese Medicine
Canadian Journal of Infectious Diseases and Medical Microbiology	Journal of Trauma and Acute Care Surgery
Canadian Journal of Ophthalmology	Journal of Urban Health
Canadian Journal of Surgery	Journal of Urology
Canadian Journal of Urology	Journal of vascular and interventional neurology
Canadian Journal on Aging	Journal of Vascular and Interventional Radiology
Canadian Medical Association Journal	Journal of Vascular Nursing
Canadian Urological Association Journal	Journal of Vascular Surgery
Cancer	JOURNAL OF VIRAL HEPATITIS
Cancer Causes and Control	Journal of Women's Health
Cancer Epidemiology Biomarkers and Prevention	Journal of wound care
Cancer Epidemiology, Biomarkers and Prevention	Kardiologia Polska
Cancer Prevention Research	KARDIOLOGIYA
Cardiogenetics	Kidney and Blood Pressure Research
CardioVascular and Interventional Radiology	Klimik Dergisi
Cardiovascular Drugs and Therapy	Klinische Monatsblatter fur Augenheilkunde
Cardiovascular journal of Africa	Klinische P+ndiatrie
Cardiovascular Therapeutics	Knee Surgery, Sports Traumatology, Arthroscopy
Caries Research	Korean Journal of Thoracic and Cardiovascular Surgery
Catheterization and Cardiovascular Interventions	La Radiologia medica
Cerebrovascular Diseases	Lancet
Ceska Gynekologie	Lancet Global Health
Chest	Lancet Infectious Diseases
Child and Adolescent Psychiatry and Mental Health	Laryngoscope
Childhood Obesity	Leukemia and Lymphoma
Chinese Journal of Cancer Prevention and Treatment	Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery
Chinese Journal of Clinical Nutrition	Liver Transplantation
Chinese Journal of Clinical Oncology	Lung Cancer
Chinese Journal of Evidence-Based Medicine	Malaria Journal
Chinese Journal of Lung Cancer	Managed Care
Chinese Journal of New Drugs	Maternal and Child Health Care of China
Chinese Journal of Oncology	Mathematical Biosciences and Engineering
Chinese Journal of Schistosomiasis Control	Medical Care
Chinese Journal of Tissue Engineering Research	MEDICAL HYPOTHESES
Chinese Pharmaceutical Journal	MEDICAL JOURNAL OF AUSTRALIA
Chinese Preventive Medicine	Medical Journal of Chinese People's Liberation Army
Chongqing Medicine	Medical Journal of Malaysia
Ciencia and saude coletiva	Medicina Preventiva
Ciencia y Enfermeria	Medicine, Health Care and Philosophy
Circulation	Methodist DeBakey cardiovascular journal
Circulation: Cardiovascular Quality and Outcomes	Midwifery
Circulation: Heart Failure	Modern Preventive Medicine
CIRCULATION-CARDIOVASCULAR QUALITY AND OUTCOMES	Molecular and Clinical Oncology
Cirugia Espanola	Molecular Diagnosis and Therapy
Cirugia y Cirujanos	MOVEMENT DISORDERS
Clinica e Investigacion en Ginecologia y Obstetricia	Multiple Sclerosis
Clinical and Experimental Nephrology	Mycoses

Clinical and experimental obstetrics and gynecology	Nan fang yi ke da xue xue bao = Journal of Southern Medical University
Clinical and Experimental Rheumatology	National Medical Journal of China
Clinical and translational allergy	Nephrology Dialysis Transplantation
Clinical Breast Cancer	Netherlands Journal of Medicine
Clinical Cardiology	Neurologia
Clinical drug investigation	Neurologia medico-chirurgica
Clinical Gastroenterology and Hepatology	Neurologist
Clinical Infectious Diseases	Neurology
Clinical Journal of Pain	Neuro-oncology
Clinical Journal of the American Society of Nephrology	Neurosurgery
Clinical Laboratory	Neurourology and Urodynamics
Clinical Medicine Insights: Therapeutics	New Biotechnology
Clinical Microbiology and Infection	NEW ENGLAND JOURNAL OF MEDICINE
Clinical Nephrology	Nicotine and Tobacco Research
Clinical Neurology and Neurosurgery	North Carolina medical journal
Clinical Neurophysiology	Nutrition and Diabetes
Clinical Nutrition	OBESITY
Clinical Oncology	Obesity Research and Clinical Practice
Clinical orthopaedics and related research	Obesity surgery
Clinical Otolaryngology	Obstetrics and Gynecology
Clinical pediatrics	Occupation and Health
Clinical Pharmacology and Therapeutics	Occupational Medicine
Clinical Rehabilitation	Ochsner journal
Clinical Research in Cardiology	Oncologist
CLINICAL RHEUMATOLOGY	Oncology
Clinical Therapeutics	Open Respiratory Medicine Journal
Clinical Transplantation	Open Rheumatology Journal
Clinical Trials	Ophthalmic Epidemiology
Clinics	Ophthalmologica
CNS Drugs	Ophthalmology
Cochrane Database of Systematic Reviews	Oral Oncology
Cocuk Enfeksiyon Dergisi	Orphanet journal of rare diseases
Colorectal Disease	Orthopedics
Community Dental Health	Osteoarthritis and Cartilage
Community Dentistry and Oral Epidemiology	Osteoporosis International
Community Oncology	Otolaryngology - Head and Neck Surgery
Contact Dermatitis	Pacing and Clinical Electrophysiology
Contraception	Paediatric Anaesthesia
Crisis	Paediatrics and Child Health
Critical Care Medicine	PAEDIATRICS AND INTERNATIONAL CHILD HEALTH
Critical Pathways in Cardiology	Pain Medicine
Current Alzheimer Research	Pain physician
Current Medical Research and Opinion	Pain Practice
Current Oncology	Pan African Medical Journal
Danish Medical Journal	PARASITES and VECTORS
DARU	Payesh Health Monitor
Das Gesundheitswesen	PEDIATRIC ALLERGY AND IMMUNOLOGY
Dementia and Geriatric Cognitive Disorders	Pediatric Cardiology
Dermatology	Pediatric Drugs
Dermatology and therapy	PEDIATRIC EMERGENCY CARE
Diabetes and Vascular Disease Research	Pediatric Infectious Disease Journal
Diabetes care	Pediatric obesity
Diabetes Research and Clinical Practice	Pediatric Transplantation
Diabetes Technology and Therapeutics	Pediatrics
Diabetes Therapy	Pediatrics International
Diabetes, Obesity and Metabolism	Perioperative Medicine
Diabetic Medicine	

Digestive and Liver Disease	Peritoneal Dialysis International
Digestive diseases and sciences	Personalized Medicine
Digestive Surgery	Pharmacogenetics and Genomics
Diseases of the Colon and Rectum	Pharmacogenomics
DMW Deutsche Medizinische Wochenschrift	Pharmacotherapy
Drug and Alcohol Dependence	Pharmazie
Drug Metabolism and Pharmacokinetics	Physis: Revista de Saude Coletiva
Drugs and Aging	Plastic and reconstructive surgery
Ear and hearing	PLOS MEDICINE
ecancermedicalscience	PloS Neglected Tropical Diseases
Eksperimental'naia i klinicheskaia gastroenterologiia = Experimental and clinical gastroenterology	PM and R
EMERGENCIAS	Polski Merkuriusz Lekarski
Emergency Medicine Journal	Postepy Dermatologii I Alergologii
Emerging Infectious Diseases	Postgraduate medicine
Endoscopy	Practical Pharmacy and Clinical Remedies
Enfermedades Infecciosas y Microbiologia Clinica	Prenatal Diagnosis
Epidemiology and Infection	Presse Medicale
Epidemiology and Psychiatric Science	Preventing chronic disease
Epilepsia	PREVENTION SCIENCE
Epilepsy Research	Preventive Medicine
Europace	Primary care diabetes
European Annals of Otorhinolaryngology, Head and Neck Diseases	Primary Care Respiratory Journal
European Child and Adolescent Psychiatry	Proceedings of the National Academy of Sciences of the United States of America
European Heart Journal	Progresos de Obstetricia y Ginecologia
EUROPEAN HEART JOURNAL-CARDIOVASCULAR IMAGING	Progress in Modern Biomedicine
European Journal of Cancer	Progress in Neuro-Psychopharmacology and Biological Psychiatry
European Journal of Cardio-Thoracic Surgery	Prostate cancer and prostatic diseases
European Journal of Clinical Microbiology and Infectious Diseases	Psychiatrische Praxis
European Journal of Clinical Nutrition	Psychological Medicine
European Journal of Gastroenterology and Hepatology	Psychologische Rundschau
European Journal of Haematology	Psycho-Oncology
European Journal of Heart Failure	Psychosomatics
European Journal of Hospital Pharmacy: Science and Practice	Psychotherapy Research
European Journal of Human Genetics	Public health nutrition
European Journal of Integrative Medicine	QJM
European Journal of Neurology	QUALITY OF LIFE RESEARCH
European Journal of Nuclear Medicine and Molecular Imaging	Radiol. bras
EUROPEAN JOURNAL OF OBSTETRICS and GYNECOLOGY AND REPRODUCTIVE BIOLOGY	Radiological Physics and Technology
European Journal of Obstetrics Gynecology and Reproductive Biology	Radiology
European Journal of Orthopaedic Surgery and Traumatology	Rational Pharmacotherapy in Cardiology
European Journal of Paediatric Neurology	Rehabilitacion
EUROPEAN JOURNAL OF PAIN	Renal Failure
European Journal of Preventive Cardiology	Reproductive biomedicine online
European journal of public health	Research in Autism Spectrum Disorders
European Journal of Radiology	Research Journal of Pharmacy and Technology
European Journal of Vascular and Endovascular Surgery	Respiratory medicine
European Neurology	Reumatologia
European Neuropsychopharmacology	Reumatologia Clinica
	Revista Brasileira de Cardiologia Invasiva
	Revista Brasileira de Cirurgia Cardiovascular
	Revista Clinica de Medicina de Familia
	Revista clinica espanola
	Revista Colombiana de Cardiologia
	Revista Colombiana de Obstetricia y Ginecologia
	REVISTA DA ASSOCIACAO MEDICA BRASILEIRA

European Radiology	Revista de Associacao Medica Brasileira
European Respiratory Journal	Revista de enfermeria (Barcelona, Spain)
European Review for Medical and Pharmacological Sciences	Revista de la Sociedad Espanola del Dolor
European Spine Journal	Revista de Salud Publica
European Urology	Revista de Saude Publica
Evaluation and Program Planning	Revista espanola de anestesiologia y reanimacion
Evidence Based Medicine	Revista Espanola de Cardiologia
Experimental and Therapeutic Medicine	Revista Espanola de Cirugia Ortopedica y Traumatologia
Expert Review of Anticancer Therapy	Revista Espanola de Quimioterapia
Familial Cancer	Revista Espanola de Salud Publica
Farmacia Hospitalaria	Revista Mexicana de Neurociencia
Female pelvic medicine and reconstructive surgery	Revista Panamericana de Salud Publica
Fertility and Sterility	Revista Portuguesa de Cardiologia
Fisioterapia	Revista Salud Publica (Bogota)
Food and Nutrition Bulletin	Revue de Medecine Interne
Foot and Ankle International	Revue de Neuropsychologie, Neurosciences Cognitives et Cliniques
Foot and Ankle Surgery	
Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin	Revue des maladies respiratoires
Forum of Clinical Oncology	Revue du Rhumatisme (Edition Francaise)
Frontiers in oncology	Rheumatology
Gastroenterologia y Hepatologia	Rheumatology International
Gastroenterology	Risk Analysis
Gastrointestinal Endoscopy	RUSSIAN JOURNAL OF CARDIOLOGY
Gazzetta Medica Italiana	Salud Publica de Mexico
Genetics in Medicine	Salud[i]Ciencia
Gerodontology	Sarcoma
Ginecologia y Obstetricia de Mexico	Saudi Medical Journal
GLOBAL HEALTH ACTION	Scandinavian Cardiovascular Journal
Global Journal of Health Science	SCANDINAVIAN JOURNAL OF INFECTIOUS DISEASES
Global Public Health	SCANDINAVIAN JOURNAL OF PUBLIC HEALTH
Gut	Scandinavian Journal of Urology and Nephrology
Gut and Liver	Scandinavian Journal of Work Environment and Health
Gynecologic Endocrinology	Schizophrenia Research
Gynecologic Oncology	Semergen
Haematologica	Seminars in Spine Surgery
Haemophilia	Sex Education
Hawaii Journal of Medicine and Public Health	Sexual Health
Health	Sexually transmitted diseases
Health Outcomes Research in Medicine	Sexually Transmitted Infections
Health promotion international	Singapore Medical Journal
Health Psychology	Sleep
Heart	South African Journal of Obstetrics and Gynaecology
Heart Lung and Circulation	South African Medical Journal
Heart Rhythm	Spine
Hellenic Journal of Cardiology	Spine Deformity
Hematological Oncology	Spine Journal
Hematology/ Oncology and Stem Cell Therapy	SpringerPlus
Hepatitis Monthly	STOCHASTIC ENVIRONMENTAL RESEARCH AND RISK ASSESSMENT
Hepato-Gastroenterology	Stroke
HEPATOLOGY	Supportive Care in Cancer
Hepatology Research	Surgery
Hinyokika kiyo. Acta urologica Japonica	Surgical Endoscopy
HIP International	Surgical Endoscopy and Other Interventional Techniques
HIV Clinical Trials	
HIV MEDICINE	Surgical Laparoscopy, Endoscopy and Percutaneous

Hong Kong Medical Journal	Techniques
Hormone Research in Paediatrics	Swiss Medical Weekly
Hospital Practice	Technology in Cancer Research and Treatment
HPB	Telemedicine and e-Health
Human Reproduction	Theoretical biology and medical modelling
Human Vaccines	Therapeutic Advances in Psychopharmacology
Human Vaccines and Immunotherapeutics	Thorax
Imaging in Medicine	Thrombosis and Haemostasis
Indian Journal of Community Medicine	Thrombosis Journal
Indian Journal of Dermatology	Thrombosis Research
Indian Journal of Medical and Paediatric Oncology	Tijdschrift voor Geneeskunde
Indian Journal of Pharmacology	Tobacco Control
Indian journal of public health	Toxicon
Infant, Child and Adolescent Nutrition	Toxins
Infection	TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE
Infection Control and Hospital Epidemiology	Transfusion
Infectious Diseases in Obstetrics and Gynecology	Transfusion and Apheresis Science
Inflammatory Bowel Diseases	TRANSPLANT INTERNATIONAL
Influenza and other Respiratory Viruses	Transplantation
Injury	Transplantation Proceedings
Injury Prevention	Trials
Insights into Imaging	Tropical Medicine and International Health
Intensive care medicine	Tumor
Internal medicine journal	Turkderm Deri Hastaliklari ve Frengi Arsivi
International Brazilian Journal of Urology	TURKISH JOURNAL OF MEDICAL SCIENCES
International Forum of Allergy and Rhinology	Ultrasound in Obstetrics and Gynecology
International Health	University of Toronto Medical Journal
International Journal for Quality in Health Care	Vaccine
International journal of Alzheimer's disease	Vakcinologie
International Journal of Antimicrobial Agents	Vascular and endovascular surgery
International Journal of Cancer	Vector-Borne and Zoonotic Diseases
International Journal of Cardiology	Vestnik Dermatologii i Venerologii
International journal of chronic obstructive pulmonary disease	Vojnosanitetski pregled. Military-medical and pharmaceutical review
International journal of clinical pharmacy	Voprosy Onkologii
International journal of clinical practice	Vox sanguinis
International Journal of COPD	Wiener Klinische Wochenschrift
International Journal of Dermatology	Wiener Medizinische Wochenschrift
International Journal of Drug Development and Research	Work
International Journal of Eating Disorders	World Chinese Journal of Digestology
International Journal of Environmental Research and Public Health	World Journal of Emergency Surgery
International Journal of Geriatric Psychiatry	World Journal of Gastroenterology
International Journal of Group Psychotherapy	World journal of surgery
International Journal of Gynecological Cancer	World Journal of Surgical Oncology
International Journal of Gynecology and Obstetrics	World Neurosurgery
International Journal of Health Care Quality Assurance	Wounds
International journal of inflammation	ZDRAVSTVENO VARSTVO
International Journal of Medical Engineering and Informatics	Zeitschrift fur Evidenz Fortbildung und Qualitat im Gesundheitswesen
International Journal of Nursing Studies	Zeitschrift fur Gerontologie und Geriatrie
International Journal of Obesity	Zhongguo Shiyong Neike Zazhi / Chinese Journal of Practical Internal Medicine
International journal of pediatric otorhinolaryngology	Zhongguo Xinyao yu Linchuang Zazhi
International Journal of Pharmaceutical Sciences Review and Research	Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese journal of integrated traditional and Western medicine / Zhongguo Zhong xi yi jie he
International Journal of Pharmacology	

International Journal of Pharmacy and Pharmaceutical Sciences	xue hui, Zhongguo Zhong yi yan jiu yuan zhu ban
International Journal of Preventive Medicine	Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica
International Journal of Radiation Oncology, Biology, Physics	Zhonghua lao dong wei sheng zhi ye bing za zhi = Zhonghua laodong weisheng zhiyebing zazhi = Chinese journal of industrial hygiene and occupational diseases
International Journal of Spine Surgery	
International Journal of Stroke	
International Journal of Tuberculosis and Lung Disease	Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi
International Journal of Urology	
International Journal of Vascular Medicine	Zhonghua wei chang wai ke za zhi = Chinese journal of gastrointestinal surgery
International Orthopaedics	
INTERNATIONAL UROGYNECOLOGY JOURNAL	Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]
International Wound Journal	
IOVS	Zhonghua zhong liu za zhi [Chinese journal of oncology]

Table S4 Search terms to classify cost-utility and cost-benefit analyses

The following search terms were used to classify articles within our final database of full health economic evaluations according to study type. Searches were conducted in titles and abstracts. Search terms could classify an article as a cost-utility analysis, cost-benefit analysis, both, or neither. Articles in our database which did not contain search terms for cost-utility analyses or cost-benefit analyses were categorized as cost-effectiveness analyses. Question marks ("?") represent a single wildcard character or space.

Type of analysis	Search terms implemented in Excel database
Cost-utility analysis	Cost?utility [Additionally, all results of DALY and QALY searches also included]
CUA employing DALYs	DALY, Disability?adjusted?life?year
CUA employing QALYs	QALY, Quality?adjusted?life?year, EQ?5D, SF?36, SF?12, SF?6D
Cost-benefit analysis	Cost?benefit, benefit?cost, net?benefit, net?monetary?benefit

Table S5 Search findings by database – all articles and databases

All searches were conducted on 3 May 2014, except for the LILACS database, which was searched on 12 May 2014. The first database listed identified the largest number of economic evaluations. Remaining databases are listed in order of those which identified the most additional economic evaluations beyond those already identified by other databases higher on the list.

Database	Number of records identified by search	Number of economic evaluations meeting inclusion criteria	Sensitivity (% of total economic evaluations)	Specificity (% of search results classified as economic evaluations)	Additional economic evaluations *(Beyond those found in databases higher on this list)*	Cumulative %
Scopus	9006	2409	85%	27%	2409	85%
NHS EED	3634	2280	80%	63%	314	96%
Medline	7566	2254	79%	30%	65	98%
Global Health	2219	691	24%	31%	19	99%
Wiley HEED	2175	1707	60%	78%	13	99%
Web of Science	8738	1852	65%	21%	6	99%
Biosis	2643	834	29%	32%	5	100%
Embase	7558	2217	78%	29%	4	100%
Cinahl	2580	1097	39%	43%	4	100%
Scielo	162	53	2%	33%	3	100%
PsycInfo	808	183	6%	23%	1	100%
EconLit	186	42	1%	23%	1	100%
Lilacs	132	42	1%	32%	0	100%
TOTAL	22807	2844				

Table S6 Search findings by database – excluding NHS EED and Wiley HEED

All searches were conducted on 3 May 2014, except for the LILACS database, which was searched on 12 May 2014. The first database listed identified the largest number of economic evaluations. Remaining databases are listed in order of those which identified the most additional economic evaluations beyond those already identified by other databases higher on the list. As NHS EED ceased to update records from March 2015 and Wiley HEED ceased to be available from the end of 2014, they have been placed at the bottom of the list to permit examination of available databases.

Database	Number of records identified by search	Number of economic evaluations meeting inclusion criteria	Sensitivity (% of total economic evaluations)	Specificity (% of search results classified as economic evaluations)	Additional economic evaluations *(Beyond those found in databases higher on this list)*	Cumulative %
Scopus	9006	2409	85%	27%	2409	85%
Medline	7566	2254	79%	30%	156	90%
Global Health	2219	691	24%	31%	35	91%
Web of Science	8738	1852	65%	21%	22	92%
Embase	7558	2217	78%	29%	14	93%
Biosis	2643	834	29%	32%	7	92%
Cinahl	2580	1097	39%	43%	5	93%
Scielo	162	53	2%	33%	3	93%
EconLit	186	42	1%	23%	1	93%
PsycInfo	808	183	6%	23%	1	93%
Lilacs	132	42	1%	32%	0	93%
(NHS EED)	*(3634)*	*(2280)*	*(80%)*	*(63%)*	*(183)*	*(100%)*
(Wiley HEED)	*(2175)*	*(1707)*	*(60%)*	*(78%)*	*(8)*	*(100%)*
TOTAL	22807	2844				

Table S7 Search findings by database – only articles studying low- and middle-income countries, excluding NHS EED and Wiley HEED

All searches were conducted on 3 May 2014, except for the LILACS database, which was searched on 12 May 2014. The first database listed identified the largest number of economic evaluations. Remaining databases are listed in order of those which identified the most additional economic evaluations beyond those already identified by other databases higher on the list. L&MIC: Low- and middle-income country. As NHS EED ceased to update records from March 2015 and Wiley HEED ceased to be available from the end of 2014, they have been placed at the bottom of the list to permit examination of available databases.

Database	Number of records identified by search	Number of L&MIC economic evaluations meeting inclusion criteria	Sensitivity (% of total L&MIC economic evaluations)	Specificity (% of search results classified as L&MIC economic evaluations)	Additional L&MIC economic evaluations *(Beyond those found in databases higher on this list)*	Cumulative %
Scopus	9006	428	81%	5%	428	81%
Medline	7566	380	72%	5%	40	89%
Global Health	2219	287	54%	13%	23	93%
Biosis	2643	181	34%	7%	4	94%
Embase	7558	403	76%	5%	4	95%
Web of Science	8738	316	60%	4%	3	95%
Cinahl	2680	119	23%	5%	1	95%
Scielo	162	43	8%	27%	1	96%
Lilacs	132	39	7%	30%	0	96%
PsycInfo	808	21	4%	3%	0	96%
EconLit	186	6	1%	3%	0	96%
(NHS EED)	*(3634)*	*(378)*	*(72%)*	*(10%)*	*(21)*	*(100%)*
(Wiley HEED)	*(2175)*	*(294)*	*(56%)*	*(14%)*	*(2)*	*(100%)*
TOTAL	47407	527				

Table S8 Journal concentration by income group of countries studied

	LICs	Lower-MICs	Upper-MICs	HICs	All
Total articles	104	121	391	2350	2844
Avg articles per journal	2.4	2.0	1.7	2.9	2.9
Total journals	44	61	226	802	967
% articles in top 10 journals	62%	52%	27%	22%	21%
Total articles in top 10 journals	64	63	105	509	600
% articles in top 20 journals	77%	66%	38%	29%	29%
Total articles in top 20 journals	80	80	147	684	813

Table S9 Number and proportion of economic evaluations by type and income group

In this table, "cost-effectiveness analyses" refers to articles meeting our definition of a full economic evaluation but not containing any keywords to define it more specifically as a cost-utility or cost-benefit analysis. Articles can be classified as both cost-utility and cost-benefit analyses if they contain keywords for both. DALY: disability-adjusted life year, QALY: quality-adjusted life-year.

	Income group studied											
	LICs		Lower-MICs		Upper-MICs		HICs		Multiple income groups		Total	
Type of analysis	N	%	N	%	N	%	N	%	N	%	N	%
Cost-utility analysis (only)	51	49%	63	52%	172	44%	1391	59%	39	61.9%	**1605**	56%
DALY	44	42%	40	33%	49	13%	34	1%	28	44.4%	**112**	4%
QALY	7	7%	22	18%	120	31%	1332	57%	10	15.9%	**1465**	52%
Cost-benefit analysis (only)	5	5%	3	2%	13	3%	60	3%	1	1.6%	**79**	3%
Cost-benefit & cost-utility analysis	1	1.0%	3	2.5%	10	2.6%	57	2.4%	1	1.6%	**68**	2%
Cost-effectiveness analysis	47	45%	52	43%	196	50%	842	36%	22	34.9%	**1092**	38%
Total	**104**	100%	**121**	100%	**391**	100%	**2350**	100%	**63**	100.0%	**2844**	100%
%	3.7%		4.3%		13.7%		82.6%		2.2%		100.0%	

References

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GOTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol,* 62, e1-34.

WORLD HEALTH ORGANIZATION. 2011. *International statistical classification of diseases and related health problems, 10th revision, edition 2010,* Geneva, World Health Organization.

WORLD HEALTH ORGANIZATION. 2014. Global Health Estimates 2014 Summary Tables: DALY by cause, age and sex, by World Bank income group category, 2000-2012. Geneva: World Health Organization.

SUPPLEMENTARY MATERIALS

Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis

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Supplementary Table S1. SMC costs in context

This table compares the overall costs of SMC and individual incentive payments to relevant expenditure levels or local costs.

SMC cost category	SMC cost		Comparator		Ratio of SMC cost: Comparator
Financial cost of SMC (excluding research participation incentives) per capita	Financial cost of SMC (excluding research participation incentives) per capita	$0.32	General government expenditure on health per capita in Senegal in 2014 (World Health Organization, 2017)	$26	1.2%
	Financial cost of SMC (excluding research participation incentives) per capita	$0.32	Total health expenditure per capita in Senegal in 2014 (World Health Organization, 2017)	$50	0.6%
	Financial cost of SMC (excluding research participation incentives) per capita	$0.32	Average annual expenditure for malaria control and elimination per capita in Senegal in 2013-15 (includes both domestic expenditure on malaria prevention and treatment and donor funding earmarked for malaria control) (WHO Global Malaria Programme., 2016)	$2.59	12.4%
Incentive payments for SMC administration	CHW daily per diem (mean)	$7.73	Daily wage for unskilled labour	$4.04	193.6%
	Head nurse incentive payments for SMC administration	$242	Head nurse mean annual net salary	$5,894.69	4.1%
	Assistant nurse incentive payments for SMC administration	$121	Assistant nurse mean annual net salary	Not available	NA
Research participation incentives	Head nurse (Total per year per person)	$404	Head nurse mean annual net salary	$5,894.69	6.9%
	District Medical Officer (Total per year per person)[2]	$1,818	District medical officer mean annual net salary	$12,000.00	15.2%
	Deputy District Medical Officer (Total per year per person)[2]	$1,212	Deputy District Medical Officer mean annual net salary	$11,176.77	10.8%
	District Supervisor (Total per year per person)[2]	$889	District Supervisor mean annual net salary	$6,048.68	14.7%
	Regional Medical Officer (Total per year per person)	$1,818	Regional Medical Officer mean annual net salary	$12,000.00	15.2%

Supplementary Table S2. Input costs of key cost drivers

This table provides detailed data on the articles (items and payments) that make up the largest proportions of the overall costs of the intervention. For each article, the following is presented: the cost of one unit of the article, the total quantity of the article used in the intervention, the unit measure (e.g. tablets, nurses), and the percentage of total costs of the intervention attributable to that article.

Category	Article	Unit costs (USD)	Total quantity		% Total financial cost (excluding research incentives)	% Total financial cost (including research incentives)
SMC Drugs	Sulphadoxine-pyrimethamine (SP)	$0.02	584,210	Tablets	6.8%	5.5%
	Amodiaquine (AQ)	$0.02	1,837,606	Tablets	21.0%	17.1%
Incentive payments for SMC administration	CHW per diem (mean)	$7.82	10,345	CHW-days	41.4%	33.7%
	CHW per diems received for one month of SMC administration (mean)	$32.41	2497	CHW-months[1]	41.4%	33.7%
	Head nurse SMC incentive payments (total per year per nurse)	$242	46	Nurses	5.8%	4.8%
	Assistant nurse SMC incentive payments (total per year per nurse)	$121	46	Assistant nurses	2.9%	2.4%
Funds provided for fuel costs for supervision	District payments (total per year per district)	$585	4	Districts	1.2%	1.0%
	Prefecture payments (total per year per prefecture)	$390	4	Prefectures	0.8%	0.7%
Research participation incentives	Health Post / Head nurse (Total per year per nurse)	$404	45	Nurses	NA	9.5%
	District (Total per year per district)[2]	$5,697	4	Districts	NA	10.4%
	District Medical Officer (Total per year)[3]	$1,818	4	DMOs	NA	3.7%
	Deputy District Medical Officer (Total per year per district)[4]	$1,212	3	DDMOs	NA	1.9%
	District Supervisor (Total per year per district)[5]	$889	9	Supervisors	NA	4.7%
	Region / Regional Medical Officer (Total per year per RMO)	$1,818	3	RMOs	NA	2.9%

Notes: 1) "CHW-months" of administration refers to the period of 1-6 days within a month spent delivering SMC. 2) Unit cost refers to three of four districts. One district received a smaller incentive payment of $2,697 (or 1,335,000 XOF). 3) Unit cost refers to three of four districts. One DMO received 11 rather than 12 months' payments. 4) One DDMO did not receive payments. 5) One district's supervisors did not receive payments.

Supplementary Table S3. Resources used in SMC delivery

		Number or mean	Health post range		
			s.d.	Low	High
Health structures	Regions	3	NA	NA	NA
	Districts	4	NA	NA	NA
	Health posts[1]	46	NA	NA	NA
Health workers	Head nurses	46	NA	NA	NA
	Assistant nurses[2]	46	NA	NA	NA
	CHWs administering SMC each month (mean)	831.0	NA	NA	NA
	CHWs administering SMC each month per health post	18.3	14.1	4.0	70.0
	Number of days worked on SMC administration per month per CHW	4.2	0.6	1.0	6.0
	Average number of hours worked on SMC per day per CHW (health post mean)	7.4	1.1	4.2	10.0
	Number of hours worked on SMC per day per CHW (individual CHW)	7.2	1.8	1.0	12.0
Outputs per structure or worker	SMC courses administered each month per health post (mean)	3415.1	2,749.7	502.0	16,720.0
	Average number of SMC courses administered per CHW per day (health post mean)	46.0	10.4	25.1	77.5
	Average number of SMC courses administered per CHW per month (health post mean)	190.0	36.5	104.5	272.7
	SMC courses administered each month per CHW (individual CHW)	195.8	147.1	7.0	677.5
	SMC courses administered per CHW per day (individual CHW)	49.4	74.6	1.8	169.4

Supplementary Table S4. Variation in health worker time spent on SMC by month and catchment area

The table shows the cumulative number of hours worked at each health post and at each district and how these varied across health posts and districts.

*While the demographic surveillance system staff are primarily employed to carry out research activities, the time presented here represents their contribution to the implementation of SMC, rather than research activities.

Level	Role	Cumulative hours at each health post or district over the season				Distribution of cumulative mean hours spent on SMC across months		
		min	median	Mean	max	Sept	Oct	Nov
Health Post	Head nurse	7	75	80	156	46	17	16
	Assistant head nurse	0	48	48	120	23	14	11
	CHWs (Relais)	331	1555	1751	5740	665	543	543
	CHWs (ASC)	0	1	10	109	6	3	1
Districts	District medical officer	12	75	60	80	35	10	15
	Deputy district medical officer	0	13	39	132	14	6	19
	District Supervisor	42	206	208	376	113	53	42
	Demographic surveillance system supervisor*	44	73	82	137	44	38	0
	Demographic surveillance system fieldworker*	35	123	148	309	71	77	0

Supplementary Table S5. Descriptive statistics: Cost variation across health posts

HP: Health post. S.D.: standard deviation.

Variable		Obs	Mean	SD	Min	Max
Costs by health post (District costs allocated equally across health posts within each district and research participation incentives included)	AVERAGE Economic Costs, US Cents	46	76.75	36.09	31.93	210.42
	TOTAL Economic Costs, USD	46	6,064	2,540	3,223	15,946
	Log(AVERAGE Economic Costs, US Cents)	46	1.85	0.17	1.50	2.32
Output quantity (i.e. scale)	Courses of SMC administered	46	10,245	8,205	1,562	49,941
	Log(Courses)	46	3.90	0.31	3.19	4.70
Coverage	Coverage (number of courses administered as % of target)	46	0.82	0.14	0.52	1.16
Prior experience	Years of experience with SMC at health post	46	1.80	0.74	1.00	3.00
	Years of experience with SMC of head nurse	46	1.70	0.78	1.00	3.00
Health post geography	Number of villages in health post catchment	46	25.22	19.53	1.00	78.00
	Catchment area, square kilometers	46	25.65	32.33	0.00	126.97
	Minimum from HP to nearest catchment village, kilometers	46	0.17	0.20	0.01	1.08
	Mean from HP to catchment villages, kilometers	46	2.51	1.48	0.16	5.83
	Maximum from HP to furthest catchment village, kilometers	46	5.34	3.16	0.19	14.26

Supplementary Table S6. Factors associated with average costs

The factors associated with variation in average cost per course administered between health posts were explored using linear regression with fixed effects at the district level, as follows: $\boldsymbol{Log(AC_{ij}) = \alpha_i + x'_{ij}\beta + e_{ij}}$, where: AC: average economic cost of SMC; *i*: health posts; *j*: districts; α: district dummy variable; *x':* covariate vector; β: coefficient on each covariate; e_{ij}: error, independent and normally distributed. Standard regression diagnostics were performed to check for unusual and influential data, normality of residuals, heteroscedasticity, multicollinearity, non-linearity, and model specification error. (Chen et al., 2003) All independent variables were centred. ***p<0.0032, **p<0.01, *p<0.05

	Estimates of coefficients (95% confidence intervals) for log_{10} (average economic costs)	
Parameters	**Model 1: Complex model with interaction terms**	**Model 2: Parsimonious model**
Log_{10} (Number of courses)	-0.498 (-0.543, -0.452)***	-1.65 (-2.53,-0.76)***
(Log_{10} (Number of courses))^2	0.339 (0.201, 0.478)***	0.171 (0.058,0.285)***
Size of catchment area (km^2)	0.0005 (-0.0001, 0.0010)	-
Coverage (%)	0.092 (-0.012, 0.196)	-
Log_{10} (Number of courses) x Size of catchment area (km^2)	-0.002 (-0.003, -0.00009)*	-
Size of catchment area (km^2) x Coverage (%)	0.005 (0.001, 0.008)**	-
District:		-
District 1	Reference	Reference
District 2	-0.002 (-0.038, 0.033)	-0.018 (-0.063,0.027)
District 3	-0.016 (-0.058, 0.027)	0.009 (-0.032,0.050)
District 4	-0.032 (-0.067, 0.002)	0.000 (-0.049,0.049)
Constant	1.841 (1.815, 1.867)***	1.837 (1.812, 1.861)***
No. of observations	46	46
R^2	0.962	0.950
Adjusted R^2	0.952	0.944

CHEN, X., ENDER, P., MITCHELL, M. & WELLS, C. 2003. Regression diagnostics. *Regression with Stata.* http://stats.idre.ucla.edu/stata/webbooks/reg/chapter2/stata-webbooksregressionwith-statachapter-2-regression-diagnostics/.

REFERENCES

CHEN, X., ENDER, P., MITCHELL, M. & WELLS, C. 2003. Regression diagnostics. *Regression with Stata*. http://stats.idre.ucla.edu/stata/webbooks/reg/chapter2/stata-webbooksregressionwith-statachapter-2-regression-diagnostics/.

WHO GLOBAL MALARIA PROGRAMME. 2016. World malaria report 2016. Geneva, Switzerland: World Health Organization.

WORLD HEALTH ORGANIZATION 2017. Global Health Expenditure Database. Geneva: WHO.