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**Dynamic Transmission Economic Evaluation of Infectious Disease Interventions in Low- and Middle-Income Countries
A Systematic Literature Review**

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DYNAMIC TRANSMISSION ECONOMIC EVALUATION OF INFECTIOUS DISEASE INTERVENTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Economic evaluation using dynamic transmission models is important for capturing the indirect effects of infectious disease interventions. We examine the use of these methods in low- and middle-income countries, where infectious diseases constitute a major burden. This review is comprised of two parts: (1) a summary of dynamic transmission economic evaluations across all disease areas published between 2011 and mid-2014 and (2) an in-depth review of mosquito-borne disease studies focusing on health economic methods and reporting. Studies were identified through a systematic search of the MEDLINE database and supplemented by reference list screening. Fifty-seven studies were eligible for inclusion in the all-disease review. The most common subject disease was HIV/AIDS, followed by malaria. A diverse range of modelling methods, outcome metrics and sensitivity analyses were used, indicating little standardisation. Seventeen studies were included in the mosquito-borne disease review. With notable exceptions, most studies did not employ economic evaluation methods beyond calculating a cost-effectiveness ratio or net benefit. Many did not adhere to health care economic evaluations reporting guidelines, particularly with respect to full model reporting and uncertainty analysis. We present a summary of the state-of-the-art and offer recommendations for improved implementation and reporting of health economic methods in this crossover discipline. © 2016 The Authors. *Health Economics* published by John Wiley & Sons Ltd.

KEY WORDS: economic evaluation; dynamic transmission modelling; low income; infectious disease

1. INTRODUCTION

In recent years development health assistance has grown to exceed US\$ 30 billion annually, of which 35% is directed towards three infectious diseases: HIV/AIDS, malaria and tuberculosis (Dieleman *et al.*, 2014). Nevertheless, for these and other infectious diseases, financing is insufficient for all potential interventions. Good decision-making on how best to spend available resources can make a substantial difference to population health. Healthcare economic evaluation can identify where to direct resources so that health gains are maximised by appraising the health return on investment for technologies and services (Briggs *et al.*, 2006; Drummond *et al.*, 2005). However, economic evaluation of infectious diseases can be complex because of the additional indirect effects of infectious disease interventions. That is, a treated or prevented case is a direct outcome in itself but may also reduce disease transmission including mediation by host

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immunity and drug resistance. Commonly used tools of health economic evaluation modellers such as decision trees or ‘Markov’ models¹ seldom capture these transmission effects. Transmission effects are the focus of the usually separate field of infectious disease mathematical modelling, which aims to simulate disease transmission in a human population based on human behaviour, biology and epidemiology. By incorporating information on intervention costs and cost of illness, transmission models can be used for economic evaluation, thus capturing both the direct and indirect effects of an infectious disease intervention in the evaluation. This is particularly important for the evaluation of interventions and policies that seek to reduce the transmission of disease, such as mass vaccination, in contrast to interventions that principally seek to improve direct health outcomes without necessarily impacting disease transmission, such as case management of severe illness. While these joint models can be complex and computationally intensive, they are becoming more widely used as the computing capacity readily available to researchers continues to rise.

In 2011, Jit and Brisson published an introduction to methods for modelling infectious diseases for decision analysis (a broader discipline that encompasses economic evaluation) (Jit and Brisson, 2011), and the following year a working group report by Pitman *et al.*, offered some ‘best practices’ in dynamic transmission modelling for pharmacoeconomics (Pitman *et al.*, 2012). In this review, we use the term dynamic transmission economic evaluation (DT-EE) and define as a modelling analysis where i) the force of infection is dependent on the model state in a previous time step and ii) that makes a comparison of the costs and effects of one or more interventions or events. DT-EE methodology has thus far been developed primarily by researchers in high income country (HIC) settings. However infectious diseases are overwhelmingly a problem of low- and middle-income countries (LMICs), where evidence-based decision-making stands to make a far greater impact on health. In particular, mosquito-borne diseases such as malaria and dengue are a major burden in LMICs yet almost absent from HICs. In recent years, resources available for the control and elimination of mosquito-borne diseases, particularly malaria, have increased considerably. Political commitment to the elimination of malaria is strong, but the practical approach to achieve this remains unclear.

To the knowledge of the authors, there are no previous literature reviews on the state-of-the-art of DT-EE, whether in HICs or LMICs. This review aims to examine the literature base of such studies in LMICs and examines the scope, methods and reporting of such studies from a health economist’s perspective.

2. METHODS

The review is comprised of two parts: first, a broad summary of DT-EE studies in all infectious disease areas published in the peer-reviewed literature and second, a more in-depth review of DT-EE studies of mosquito-borne disease interventions. The two-part review provides both an understanding of the application of these methods across varied disease-specific research ‘silos’ as well as a more detailed review of mosquito-borne disease studies.

Studies are included in the general review if (1) the paper compares costs and effects of an infectious disease intervention; (2) the model includes a dynamic force of infection (i.e. incidence, a rate at which the susceptible population acquire the infection) that depends on the prevalence of infection at a previous time point; (3) the paper was published between 1 January 2011 and 31 May 2014; and (4) the study focuses partially or entirely on a population in a LMIC according to World Bank definitions (World Bank, 2015). The time period for inclusion in the all-disease review is restricted to recent years because of the time required to screen articles against the inclusion criteria and to focus on the contemporary state-of-

¹In health economics, a Markov model typically uses a pre-defined force of infection. Dynamic transmission models may also hold Markov properties but are not usually referred to as Markov models.

the-art DT-EE. Studies are included in the review of mosquito-borne diseases if they meet previous criteria 1–3 and evaluate one or more interventions against a mosquito-borne disease. In this part of the review the publication year restriction is relaxed to include studies published at any time.

2.1. Search strategy

The literature search is outlined in Figure 1. The MEDLINE database was searched for and was applied to the MEDLINE database. There are four main components to this initial search:

1. Cost OR economic* (wildcard is used to include word extensions), AND;
2. Infectious OR communicable, AND;
3. Dynamic OR transmission, AND;
4. Date: January 2011–May 2014

The terms ‘cost’ and ‘economic*’ were restricted to title or abstract, while other terms were applied to any field. This search strategy aims to be as sensitive as possible while returning a feasible number of abstracts to be screened. Secondly, the initial search results were supplemented by a series of additional disease-specific searches:

1. (Transmission OR dynamic) AND ((compartmental model OR stochastic*) OR individual-based model) AND
2. Cost [title/abstract] AND effect*
3. Date: January 2011–May 2014
4. Specific disease, for example, HIV OR AIDS OR HIV/AIDS

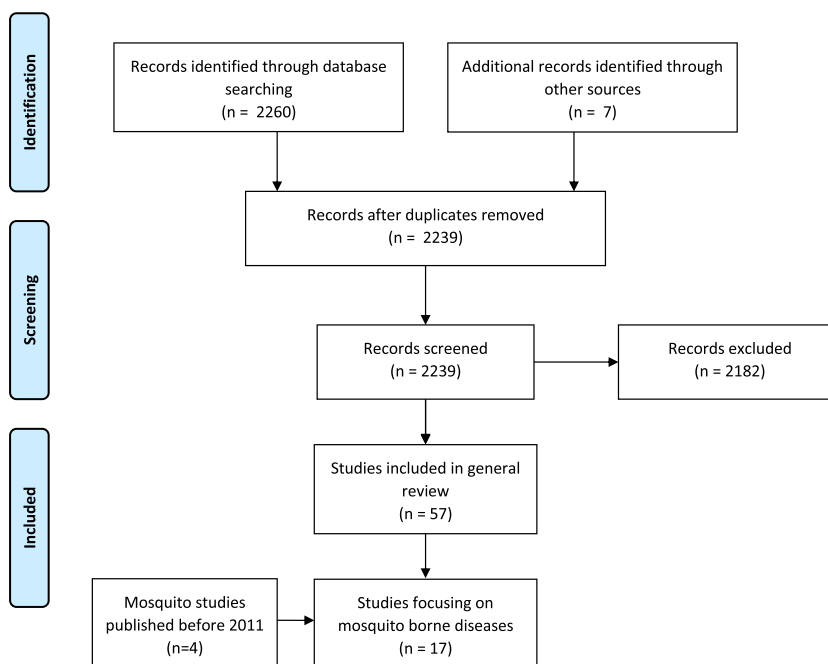


Figure 1. Database search and screening of identified records

Disease-specific search terms included HIV/AIDS, malaria, tuberculosis, influenza, schistosomiasis, polio, respiratory syncytial virus, hepatitis, human papillomavirus, measles, rabies, cholera, pneumococcal disease, meningococcal disease, dengue, rabies, yellow fever and ebola.

Further studies were identified by screening the reference lists of eligible studies or in other relevant reviews (Gomez *et al.*, 2013; Pérez Velasco *et al.*, 2012; Reiner *et al.*, 2013). Because of the nature of the inclusion criteria, abstracts were often insufficient to judge eligibility and full-text screening was frequently necessary to determine eligibility for inclusion. A cross check of the search was performed on a comprehensive database of health economic evaluations, produced for another paper in this supplement (Pitt *et al.*, 2016). No additional articles meeting the inclusion criteria were identified.

The review of mosquito-borne disease DT-EEs includes all those in the all-disease review as well as additional studies published prior to 2011. Additional studies were identified through disease-specific searches outlined in Figure 1 and screening of reference lists of identified studies and a recent review of mosquito-borne disease transmission models (Reiner *et al.*, 2013).

2.2. Data extraction

Both the general and mosquito-borne disease reviews include data extraction on six fields: disease, intervention, model, outcome measure, sensitivity analysis and journal (Table I). Some studies included more than one disease, outcome measure or sensitivity analysis therefore totals may exceed 100%. Data extraction for both the general and mosquito-borne disease reviews was undertaken independently by two reviewers. Differing results were resolved by discussion until consensus was reached.

Reporting standards have been developed within the field of health care economic evaluation so that readers might appraise the methodological integrity of a study. The most recent and widely accepted are the Consolidated Healthcare Economic Evaluation Reporting Standards (CHEERS) guidelines (Husereau *et al.*, 2013). In the mosquito-borne disease review, all studies, including supplementary materials, were reviewed against the CHEERS guidelines. Data extraction focused on reporting of the basic economic evaluation framing indicators such as perspective, cost details, model description and sensitivity or

Table I. Data extracted for all-disease review

Field	Definition
1. Disease	The infectious disease(s) subject to analysis
2. Intervention	The health care technology or programme subject to analysis
3. Model	The type of model used. Options include the following: <ul style="list-style-type: none"> - Deterministic compartmental - Stochastic compartmental - Individual-based model - Multi-model (two or more of the previously mentioned)
4. Outcome measure	The metric used to quantify human health. Options include the following: <ul style="list-style-type: none"> - Disability-adjusted life years (DALYs) - Quality-adjusted life years (QALYs) - Life years (LYs) - Infections averted - Number of deaths or mortality rate - Net health or monetary benefit (NHB or NMB) - Fixed endpoint (e.g. elimination)
5. Sensitivity or uncertainty analysis	The approach taken to quantify potential variation in model results. Options include the following: <ul style="list-style-type: none"> - Univariate deterministic - Multivariate or scenario - Probabilistic - Structural
6. Journal	The name of the publication featuring the study

uncertainty analyses (points 6, 8, 9, 13b, 15, 16, 17 and 20b). In addition, the use of advanced techniques was recorded including probabilistic decision analysis (such as cost-effectiveness acceptability curves), value of information analysis, resource allocation modelling or programme budgeting and marginal analysis and spatial analysis.

The synthesis of the review examines whether relevant health economic methods are commonly employed and well reported and makes recommendations for future studies.

3. RESULTS

3.1. Search results

The database searches identified 2260 published studies for screening (Figure 1). A total of 57 DT-EEs were identified for the all-disease review (Agusto and Adekunle, 2014; Alistar *et al.*, 2014a, 2014b; Babigumira *et al.*, 2011; Bärnighausen *et al.*, 2012; Bishai *et al.*, 2011; Briët *et al.*, 2013; Briet and Chitnis, 2013; Briët and Penny, 2013; Carrasco *et al.*, 2011; Ciaranello *et al.*, 2011; Cremin *et al.*, 2013; Crowell *et al.*, 2013; Durham *et al.*, 2013; Dye, 2013; Eaton *et al.*, 2014; Enns *et al.*, 2011; Fitzpatrick *et al.*, 2014; Freiesleben de Blasio *et al.*, 2014; Giglio *et al.*, 2012; Gomez *et al.*, 2012; Granich *et al.*, 2012; Hontelez *et al.*, 2011, 2013; Hutton and Brandeau, 2013; Kato *et al.*, 2013; Kawai *et al.*, 2012; Keebler *et al.*, 2014; Levin *et al.*, 2011; Li *et al.*, 2012; Long and Stavert, 2013; Luz *et al.*, 2011; Maire *et al.*, 2011; Mbah *et al.*, 2013a, 2013b; Mbonigaba, 2013; Menzies *et al.*, 2012; Nichols *et al.*, 2013; Okell *et al.*, 2014; Okosun *et al.*, 2011, 2013; Okosun and Makinde, 2012; Palombi *et al.*, 2012; Prinja *et al.*, 2011; Ross *et al.*, 2011; Sardar *et al.*, 2013; Sartori *et al.*, 2012; Scott Braithwaite *et al.*, 2014; Stuckey *et al.*, 2014; Terris-Prestholt *et al.*, 2014; Vanni *et al.*, 2012; Verguet *et al.*, 2013; von Wyl *et al.*, 2012; Wagner and Blower, 2012; Walensky *et al.*, 2012, 2013; Winetsky *et al.*, 2012).

From this set, 13 studies of mosquito-borne diseases, plus a further 4 studies of mosquito-borne diseases published prior to 2011, were included in a more detailed review (Briët *et al.*, 2013; Briet and Chitnis, 2013; Briët and Penny, 2013; Crowell *et al.*, 2013; Durham *et al.*, 2013; Tediosi *et al.*, 2009; Laxminarayan, 2004; Laxminarayan *et al.*, 2006; Luz *et al.*, 2011; Maire *et al.*, 2011; Okell *et al.*, 2014; Okosun *et al.*, 2011, 2013; Okosun and Makinde, 2012; Ross *et al.*, 2011; Stuckey *et al.*, 2014; Tediosi *et al.*, 2006).

3.2. Summary of recent dynamic transmission economic evaluations in LMICs

By far the most common disease studied in DT-EEs was HIV/AIDS ($n=30$, 53%), followed by malaria ($n=11$, 19%). A range of interventions were studied including vaccination ($n=14$, 25%) and pharmaceutical therapy as either treatment ($n=7$, 12%), prophylaxis ($n=5$, 9%) or mass administration (including mass screening and treatment) ($n=4$, 8%). Eighteen studies used a model to consider multiple interventions simultaneously (32%). As with economic evaluation in other disease areas, pharmaceuticals and other health technologies are better represented than non-technological interventions (Drake *et al.*, 2012). This review finds only one study that focuses on a non-technological intervention (Enns *et al.*, 2011).

The majority of studies ($n=33$, 58%) used a deterministic compartmental model, while 18 studies (32%) used an individual-based model. Three studies (5%) used a stochastic implementation of a compartmental model, and a further three studies (5%) deployed multiple model structures. A variety of outcome metrics were reported, the most common of which were infections averted ($n=40$, 69%) and DALYs ($n=22$, 38%). The majority of studies ($n=41$, 72%) reported two or more outcome measures. Elimination was used as an outcome metric by two studies (4%). While not all studies performed explicit sensitivity analysis, all went some way towards exploring variation in results. The majority of studies conducted univariate sensitivity analysis ($n=32$, 78%), multivariate or scenario analysis ($n=27$, 66%) and/or

probabilistic analysis ($n = 19$, 46%). Probabilistic analysis was in some cases incorporated into the transmission model from the outset rather than conducted as a post hoc sensitivity or uncertainty analysis. Results for the all-disease review are summarised in Table II. Studies were published in a wide range of journals. The most common journal was PLoS One ($n = 8$, 14%). PLoS Medicine, Vaccine, AIDS and Malaria Journal had all published four studies each (7%).

Table II. Summary of dynamic transmission economic evaluations in low- and middle-income contexts (all diseases, 2011 to May 2014)

Field	Frequency	%
Disease		
Cholera	1	2%
Dengue	2	4%
HIV	26	46%
Human papilloma virus	2	4%
Malaria	11	19%
Measles	3	5%
Pandemic influenza	1	2%
Rabies	1	2%
Seasonal influenza	1	2%
Tuberculosis	2	4%
Hepatitis A	1	2%
Hepatitis B	1	2%
Herpes simplex virus	1	2%
HIV and tuberculosis	2	4%
HIV and schistosomiasis	2	4%
	57	100%
Intervention type		
Contact reduction	1	2%
Diagnostic	3	5%
Mass treatment	2	4%
Mass screening and treatment	2	4%
Multiple	18	32%
Prophylaxis	5	9%
Screening	1	2%
Treatment	7	12%
Vaccine	14	25%
Vector control	4	7%
	57	100%
Primary outcome		
Disability-adjusted life year	22	38%
Elimination	2	3%
Infections averted	40	69%
Life year	12	21%
Mortality	16	28%
Net health benefit	4	7%
Net monetary benefit	4	7%
Quality-adjusted life year	14	24%
	114	197%
Model type		
Deterministic compartmental	33	58%
Stochastic compartmental	3	5%
Individual	18	32%
Multi-model	3	5%
	57	100%
Sensitivity analysis		
Univariate	32	78%
Multivariate or scenario	27	66%
Probabilistic	19	46%
Structural	5	12%
	83	202%

3.3. Review of mosquito-borne disease studies

Of the 17 studies of mosquito-borne diseases, 15 consider malaria interventions and two dengue interventions (Table III). A range of interventions were evaluated including vaccination ($n=4$, 24%), treatment ($n=3$, 18%), vector control ($n=4$, 24%), mass screening ($n=1$, 6%) and intermittent preventive treatment ($n=1$, 6%). Some studies evaluated multiple integrated approaches ($n=4$, 24%). The evaluation perspective and time horizon were generally identifiable but often not explicitly stated. The same number of studies purported to take a societal perspective ($n=7$, 41%) as a provider perspective ($n=7$, 41%), but it was not always clear that all relevant societal costs, such as patient financial costs and the opportunity costs of patient and caregivers' time were included in studies reporting a societal perspective. Time horizons varied considerably, and most studies did not include time horizon in the sensitivity analysis. The most common outcome metrics reported were DALYs ($n=9$) and infections averted ($n=9$). No studies explicitly cited elimination as an outcome metric; four studies (24%) use the relatively uncommon net health benefit metric. Clear and detailed costing information is only reported in full in a minority of studies. Cost information is in some cases fragmented in different sections of the paper or supporting documents and is usually not tabulated with the other model parameters.

Half the malaria studies ($n=9$, 53%) used versions of the same 'open malaria' individual-based model. One other malaria study (6%) used a different individual-based model, while the remaining five malaria studies and two dengue studies (12%) used deterministic compartmental models. The majority of studies ($n=11$, 65%) referred to previously published work for a full description of the transmission model. In some cases, but not all, a brief description of the model was provided. Conversely, the three studies (18%) by Okosun and colleagues focused primarily on reporting the description and behaviour of the model, such as the identification of equilibria, model boundaries and optimal control points (Okosun *et al.*, 2011, 2013; Okosun and Makinde, 2012). In these studies, less attention was paid to the description of and justification of economic or operational factors. A majority of studies conducted a multivariate or scenario sensitivity analysis ($n=10$, 59%), and just under half conducted probabilistic analysis ($n=8$, 47%). A common theme in the quantification of parameter sensitivity or uncertainty is that studies frequently focus principally on epidemiological parameters. In the majority of studies ($n=10$, 59%), cost parameters were not included in the sensitivity or uncertainty analysis or were treated separately. The most common funder was the Bill and Melinda Gates Foundation ($n=7$, 41%). One study (6%) was funded by a commercial bed net manufacturer.

The majority of studies ($n=14$, 82%) did not use advanced health economic methods. The study by Maire *et al.* is a notable exception as it used a complex dynamic transmission model to undertake probabilistic decision analysis and also performed a value of information analysis (Maire *et al.*, 2011). The two dengue studies also employed probabilistic decision analysis and presented results in terms of a cost-effectiveness acceptability curve (Durham *et al.*, 2013; Luz *et al.*, 2011). Okell *et al.* undertook spatially explicit analysis, applying their model to country-specific data in sub-Saharan Africa (Okell *et al.*, 2014). No studies included resource allocation or programme budgeting in their analysis.

4. DISCUSSION

This review outlines the literature base for dynamic transmission economic evaluation (DT-EE) in LMICs and appraises reporting practices and health economic methods for a smaller number of studies addressing mosquito-borne disease.

The first section of the review outlines the scope of the literature across all disease areas. The majority of studies consider either HIV or malaria. Both diseases are the focus of major global efforts to reduce disease transmission and both are relatively well financed. The potential impact of efficient resource allocation is therefore greater and research funds are more readily available. There were notably fewer studies on other major infectious disease burdens in LMICs, including tuberculosis, pneumonia and diarrhoeal disease. This

Table III. Review of dynamic transmission economic evaluations in low- and middle-income countries (mosquito-borne diseases, any publication year)

CHEERS review							
First author	Year	Country or region	Perspective (6.)	Intervention (7.)	Time horizon (8.)	Health outcome measure (10.)	Describes costs including sources and approximations using opportunity cost (13b.)
Okell	2014	Africa	Provider	Treatment	5 years	Infections averted	Clear description of costs and sources
Stuckey	2014	Kenya	Societal	Multiple	5 years	DALY and infections averted and mortality	Clear description of costs and sources
Briët (a)	2013	Not specified	Provider ('health system')	Vector control	Lifetime of the intervention	DALY and NHB	Refers to previous paper
Briët (b)	2013	Not specified	Provider (health system)	Vector control	Lifetime of the intervention	DALY and infections averted and NHB	Some information but not comprehensive
Briët (c)	2013	Not specified	Provider (health system)	Vector control	60 years	DALY and NHB	Some information but not comprehensive
Crowell	2013	Sub-Saharan Africa	Provider	MSAT	1 year	Infections averted	Clear description of costs and sources
Okosun (a)	2013	Not specified	Not found	Multiple	140 days	Infections averted	Little information
Durham ¹	2013	Brazil	Societal (but only cost of vaccine and cost of illness)	Vaccine	73 years	DALY and NHB	Some information. Cites a study on the cost of dengue treatment in the Americas, little information on processing or generalisability
Okosun (b)	2012	Not specified	Not found	Multiple	1 year	Infections averted	Little information
Maire	2011	Sub-Saharan Africa	Societal	Vaccine	10 years	DALY	Clear description of costs and sources
Ross	2011	Sub-Saharan Africa	Provider (implied)	Intermittent presumptive treatment	10 years	DALY	Some information. Describes intervention costs but does not report case management unit costs in the methods
Okosun (c)	2011	Not specified	Not found	Multiple	100 days	Infections averted	Little information
Luz ¹	2011	Brazil	Societal	Vector control	5 years	DALY	Clear description of costs and sources (in web appendix)
Tediosi (a)	2009	Tanzania	Societal	Vaccine	10 years	DALY and infections averted	Clear description of costs and sources, although referencing is relied on
Tediosi (b)	2006	Tanzania	Societal	Vaccine	20 years	DALY and life years and infections averted and mortality	Clear description of costs and sources, although referencing is relied on (reference paper is part of the same journal supplement)
Laxminarayan (a)	2006	Sub-Saharan Africa	Societal (implied)	Treatment	10 years	Mortality	Clear description of costs and sources, although cost parameters are not tabulated
Laxminarayan (b)	2004	Sub-Saharan Africa	Provider (implied)	Treatment	5, 10 and 20 years	Infections treated	Clear description of costs and sources, although cost parameters are not tabulated

Table III (Continued)

First author	Describe and justify model (15.)		Parameter uncertainty for all parameters and structural uncertainty (20b.)		Advanced Analyses			
	Model type	Pre-published model (Y/N)	Sensitivity analysis methods used	Includes cost parameters?	Probabilistic decision analysis (Y/N)	Value of information analysis (Y/N)	Resource allocation or programme budgeting (Y/N)	Spatial modelling (Y/N)
O'kell	Individual	Y	Univariate and probabilistic	N	N	N	N	Y
Stuckey	Individual	Y	Univariate and probabilistic and structural	Only univariate	N	N	N	N
Briët (a)	Individual	Y	Probabilistic	N	N	N	N	N
Briët (b)	Individual	Y	Probabilistic	N	N	N	N	N
Briët (c)	Individual	Y	Scenario and probabilistic and structural	N	N	N	N	N
Crowell	Individual	Y	Multivariate	N	N	N	N	N
Okosun (a)	Deterministic	N	Scenario	N	N	N	N	N
Durham ^a	Deterministic	N	Scenario and probabilistic	Y	Y	N	N	N
Okosun (b)	Deterministic	N	Scenario	N	N	N	N	N
Maire	Individual	Y	Probabilistic	Y	Y	Y	N	N
Ross	Individual	Y	Multivariate	Y	N	N	N	N
Okosun (c)	Deterministic	N	Scenario	N	N	N	N	N
Luz ¹	Deterministic	Y	Probabilistic	Y	Y	N	N	N
Tediosi (a)	Individual	Y	Multivariate	Mentioned but not quantified in main paper	N	N	N	N
Tediosi (b)	Individual	Y	Scenario	Y	N	N	N	N
Laxminarayan (a)	Deterministic	Y	Scenario	Y	N	N	N	N
Laxminarayan (b)	Deterministic	N	Univariate	Y	N	N	N	N

^a Dengue studies, all others are on malaria.

may be to be because of challenges in modelling disease transmission, particularly for pneumonia and diarrhoeal disease where multiple aetiologies exist. Tuberculosis, like HIV and malaria, has a dedicated modelling consortium to support a range of modelling studies including DT-EEs (Dowdy *et al.*, 2014).

The role of DT-EE is particularly important in the evaluation of vaccinations and in the comparison of multiple interventions. For single intervention evaluations, vaccination was the most common intervention. This is not surprising given the level of investment in the development and implementation of vaccination programmes and that key benefits of vaccination programmes include herd immunity²; a reduction in disease transmission that is best captured using dynamic transmission modelling. The largest share of studies evaluated multiple interventions and intervention combinations rather than single interventions. Transmission models are well suited to incorporating diverse modes of action for various interventions simultaneously. Alternative health economic models such as decision trees are usually developed for a specific intervention and although they can be used for comparing multiple interventions, modifying them to include additional interventions and interactions between interventions can be difficult and cumbersome.

The second stage of the review appraises health economic methods and reporting for set of mosquito-borne disease studies using existing guidelines for reporting economic evaluations (Husereau *et al.*, 2013), explores the handling of parameter uncertainty as well as the use of advanced economic methods and makes recommendations for future DT-EEs.

Comprehensive reporting is key to good quality economic evaluation. In some cases, very few of the CHEERS checklist points were reported well. While this is understandable in that these studies often originate in the discipline of mathematical modelling, which does not share these reporting norms, transmission modelling studies that make comparisons of cost and health impact are *de facto* economic evaluations. This review finds three areas where reporting can be improved: evaluation perspective, costing and model description.

The perspective of the study should be clearly stated and applied equally to costs and effects. Costing methods and data sources should be clearly described including the approach to discounting, currency exchanges and a justification of what resources were costed. Several studies reference previously published work to describe the transmission model. Full reporting of all model and analytical information in the main body of a paper may not be feasible if the journal does not support technical appendices. However, without clear communication of methods to the reader, complex models must be taken on trust; where possible model description should be reported in full. Overall, adherence to the best practices for undertaking and reporting economic evaluation would improve quality and communication in DT-EEs. Publication of these studies is across a wide range of journals with diverse specialisations. If the rate of publication continues to rise, a dedicated journal may help to improve methodology and reporting practices.

Analysis and communication of uncertainty is particularly important in LMIC DT-EEs. A potential risk in layering complex analyses on complex models is that detail and complexity can create a perception of validity. Moreover, in LMICs, data collection systems face considerable challenges and the resulting data sets may be far from robust. Thorough sensitivity or uncertainty analysis is therefore essential. While all studies in this review conducted sensitivity analysis to some degree, in many cases the approach was partial or treated economic and epidemiological parameters separately. This may lead to misinterpretation if confidence or credible intervals are reported for a cost-effectiveness ratio, but only epidemiological uncertainty is included. Pitman *et al.* point out that a comprehensive probabilistic analysis may also be problematic if parameter values cannot be assumed to be independent, that is, if there are unidentified joint parameters (Pitman *et al.*, 2012). However if researchers can address this, then probabilistic analysis is likely to be

²Population health impact arising from mass vaccination is greater than the sum of individual vaccine protection. Unvaccinated individuals also benefit from immunity of the 'herd'.

the best approach to quantifying parameter uncertainty. Indeed, parameter fitting processes more common in transmission modelling methods offer some options for fitting correlated parameters (Li *et al.*, 2010). Otherwise, a univariate analysis that includes both economic and epidemiological parameters can highlight key determinants of model uncertainty, allowing direct comparison of uncertainty or sensitivity for all model parameters. A comprehensive appraisal of parameter uncertainty can be supplemented but not replaced, by further scenario or multivariate sensitivity analysis. This can, for example, elucidate operational decisions such as seasonal timing of vaccination or required vaccine uptake at different assumptions of efficacy.

Box 1: Recommendations for dynamic transmission economic evaluations:

- All epidemiological and economic parameters are fully described and tabulated.
- All studies report a basic description of the model structure and key assumptions. For journals that support web appendices, the transmission model should be described in full including model equations, software platform and all analytical processes involved in parameterisation.
- Economic parameters are included along with epidemiological and other parameters in sensitivity and uncertainty analyses.
- Where appropriate, studies go beyond simple cost-effectiveness ratio or net benefit calculation and employ advanced economic evaluation methods.
- If publications in this area continue to rise, a dedicated journal could improve methodology and reporting standards.

Most studies did not employ advanced health economic methods and went no further with economic analysis than calculating disaggregated costs and effects, a cost-effectiveness ratio or net benefit. Those that did (Luz *et al.*, 2011; Maire *et al.*, 2011) illustrate some of the advantages of probabilistic decision analysis, including cost-effectiveness acceptability curves (CEACs), and value of information analysis. For example, the inclusion of CEACs goes some way towards dealing with the uncertainty related to the fact that cost-effectiveness thresholds for LMICs are usually not well defined. Studies that rely on a single threshold value undermine efforts made to produce more precise estimates of costs and effects through dynamic transmission modelling, by introducing considerable unquantified uncertainty in the cost-effectiveness threshold chosen (Drake, 2014; Lubell, 2014; Marseille *et al.*, 2015; Revill *et al.*, 2014). The presentation of CEACs helps to illustrate the impact of cost-effectiveness threshold choice.

Value of information analysis can indicate the potential value of further research into a decision problem. The key piece of information provided by value of information analyses is typically an estimate of the monetary value of completely reducing uncertainty in the decision problem, known as the expected value of perfect information (EVPI). If the cost of further research to reduce this uncertainty is greater than this value, then the research is not warranted, and conversely, if the value of information is much greater than the cost of research, then further research could be of benefit, depending on the extent to which the uncertainty could be resolved (Briggs *et al.*, 2006). Maire *et al.* estimate the EVPI, of a pre-erythrocytic malaria vaccine to be \$ 1.9 billion, suggesting that further research to better inform the decisions could be worth investment. This type of analysis can be extended to estimate the expected value of perfect parameter information, the value of reducing uncertainty in a specific parameter, providing more detailed information on the value of uncertainty relating to specific parameter, for example, the potential value of reduced uncertainty in vaccine effectiveness. In general, the application of advanced economic evaluation methods in more DT-EEs could yield useful results.

The two studies by Laxminarayan *et al.* are worth noting in that they tackle the critical question of antimicrobial resistance (Laxminarayan, 2004; Laxminarayan *et al.*, 2006). Dynamic transmission models are an important tool in modelling the spread of antimicrobial resistance, and the incorporation of costs into these models has the potential to quantify the economic impact in addition to the health impact. This is a critical component

in the evaluation of diagnostics and other interventions that can mitigate the emergence and spread of resistance. The capacity to incorporate the impact of interventions on the dynamics of drug resistance is a further example of the flexibility of dynamic transmission modelling.

This review has several limitations. The set of studies identified was reviewed with the aim of describing the scope, methods and reporting practices of DT-EEs from the perspective of a health economist. An evaluation of transmission modelling methods was beyond the scope of this review. Correctly identifying DT-EEs is a challenge as there is no specific or succinct label for this type of study. Studies can originate from mathematical modelling or economic evaluation disciplines, and each has its own standards and reporting norms. Studies that are a combination of both transmission modelling and economic evaluation methods often do not signpost this clearly in the abstract, and it was frequently necessary to refer to the full text. Even then, eligibility for inclusion in the review was not always clear as economic evaluations that do not dynamically model disease transmission also use terms such as ‘dynamic’ and ‘transmission’ (not incorrectly) to describe aspects of their models. The full all-disease review is therefore limited in its time period because of the challenges of the search and screening processes. Despite the challenges in the search, this study identifies two literature sets representing a powerful yet relatively uncommon combination of methods. To the authors’ knowledge, this the first review of this literature base.

DT-EE is an emerging field at the intersection of two disciplines and is particularly relevant to LMICs, where infectious diseases constitute an enormous burden on human health. This review outlines the current landscape in this field and identifies priority areas to improve the implementation of methodology and reporting.

CONFLICT OF INTEREST

The authors declare that they are aware of no potential conflicts.

ORIGINAL PUBLICATION

This review is original work and has not been submitted for publication elsewhere.

ETHICS STATEMENT

This is a desk-based literature review using only publicly available sources. No specific ethical review was obtained for this study.

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