University of Southampton

Faculty of Mathematical Sciences

Operational Research

Economic evaluation of interventions for dengue fever and dengue haemorrhagic fever in resource-poor settings, using the example of Thailand

by

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Abstract

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Dengue fever has become a major public health problem. It is considered one of the most important mosquito-borne viral diseases and occurs in >100 countries in tropical and subtropical regions of Asia-Pacific, the Americas, the Middle East, and Africa with >3 billion people at risk. Despite current control interventions against dengue fever in endemic countries, the disease is associated with considerable healthcare utilisation, personal costs to patients and caregivers, productivity loss, and human suffering. Whilst the illness is well understood, there is also recognition that current control efforts focussing predominantly on *Aedes aegypti* control and elimination are less than optimal, although they may still have an important role to play in the short to medium term. In this thesis, the epidemiological and economic impacts of dengue control interventions in Thailand, a geographical setting with a persistent, high level of dengue transmission are investigated, embracing chemical interventions (adulticide and larvicide), environmental control/ public health education and awareness, paediatric vaccination (using dengue vaccine profile[s] broadly consistent with [dengue] vaccines in late-stage development) and, in anticipation of possible new vector-control technologies, *Wolbachia*-infected mosquitoes. The premise that is being examined is not the 'how' of implementation, rather what the possible population impacts of different interventions are (both individually and in combination). Using three different and complementary analyses (epidemiological impact, i.e. effectiveness, cost-effectiveness analysis, and constrained optimisation), our findings show that the most useful method to reduce dengue burden (in terms of cases, cost-effectiveness, and affordability, respectively) would be to combine vaccination with other form(s) of control, e.g. adulticide, environmental control/ public health education and awareness, and *Wolbachia*.

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Author's declaration

I declare that this thesis and the work presented in it is my own and has been generated by me as the result of my own original research. I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. Parts of this work have been published as:

- Knerer G, Currie CS, Brailsford SC. Impact of combined vector-control and vaccination strategies on transmission dynamics of dengue fever: a model-based analysis. Health Care Manag Sci. 2015;18:205-17. Epub: 27 Dec 2013
- Knerer G, Currie CSM, Brailsford SC. The economic impact and cost-effectiveness of combined vector-control and dengue vaccination strategies in Thailand: results from a dynamic transmission model. PLoS Negl Trop Dis 2020;14:e0008805.
- Knerer G, Currie CSM, Brailsford SC. Reducing dengue fever cases at the lowest budget: a constrained optimization approach applied to Thailand. BMC Public Health 2021;21:807.
- Please note that these papers are included in the thesis as published (including UK/US spelling), apart from chapter, table, figure, appendix, and reference numbering, which have been altered to fit within the thesis framework.

Signature:

Acknowledgements

My first exposure to dengue fever was as a newly qualified statistician on a short-term contract at the University of Heidelberg in early 2008. The project that I was employed on was the DENCO Study and was designed to evaluate the perceived limitations of the 1997 dengue criteria, the results of which formed the basis of the revised 2009 WHO dengue classifications system. Little did I know then that this was to be the start of a journey that would take up a good deal of my adult working life as I studied alongside full-time employment. I would like to thank Thomas Jaenisch of the University of Heidelberg and University of Colorado for fostering my nascent interest in dengue fever and vector-borne disease and for giving me the opportunity to be involved in such an important and catalyst project.

I would also like to thank my supervisors – Christine Currie and Sally Brailsford – for their enduring support over the years and their incisive comments as my thesis progressed. I would like to thank my friend Jenny Lloyd for her excellent proof-reading and formatting assistance of this thesis.

Most importantly, I would like to thank my wife and best friend – Julie Roiz Knerer – whose incredible patience, passion for, and knowledge of infectious disease modelling and health economics has been, and will continue to be, an inspiration for me. I would like to dedicate this thesis to her and our wonderful little boy Marius.

Abbreviations

A3	adulticide (3 applications)
ADE	antibody-dependent enhancement
ASEAN	Association of Southeast Asian Nations
Bti	*Bacillus thuringiensis israelensis*
CDC	Centers for Disease Control and Prevention
C_E	temporary cross-enhancement
CEA	cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
CO	constrained optimisation
C_P	temporary cross-protection
D	dominated
DALY	disability-adjusted life year
DEET	N,N-diethyl-meta-toluamide
DENV	dengue virus
DF	dengue fever
DHF	dengue haemorrhagic fever
DSS	dengue shock syndrome
DoI	duration of infectiousness
DoP	duration of vaccine protection
ED	extended dominance
EF	expansion factor
E_h	humans exposed to dengue infection
EIP	extrinsic incubation period
EM	environmental management
E_v	exposed (incubating) mosquitoes (vectors)
E_w	exposed *Wolbachia*-carrying mosquitoes
FDI	foreign direct investment
fsRIDL	female-specific flightless release of insects carrying a dominant lethal
GDP	gross domestic product
HEG	homing endonuclease gene
ICER	incremental cost-effectiveness ratio
I_h	dengue infected and infectious humans
IRS	indoor residual spraying
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
I_v	infected and infectious mosquitoes (vectors)
I_w	infectious *Wolbachia*-carrying mosquitoes

K	carrying capacity
L3	larvicide (3 applications)
N_h	total human population
NICE	National Institute for Health and Care Excellence
OR	operational research
PHEA	public health education and awareness
PP	payer perspective
PSA	probabilistic sensitivity analysis
R	immune humans
R_h	humans recovered from dengue infection
RIDL	release of insects carrying a dominant lethal
SARS	severe acute respiratory syndrome
SDG	Sustainable Development Goal
SEIR	susceptible-exposed-infected-recovered
S_h	humans susceptible to dengue infection
SI	susceptible-infected
SIR	susceptible-infected-recovered
SIS	susceptible-infected-susceptible
SIT	sterile insect technique
S_v	susceptible mosquitoes (vectors)
S_w	susceptible *Wolbachia*-carrying mosquitoes
THB	Thai Baht
μD	dengue-induced mortality
μh	background mortality
UI	uncertainty interval
ULV	ultra-low volume
USD	United States dollars
V80	vaccination with 80% coverage
VMI	Vaccine Modeling Initiative
WHO	World Health Organization

1 Aims and objectives

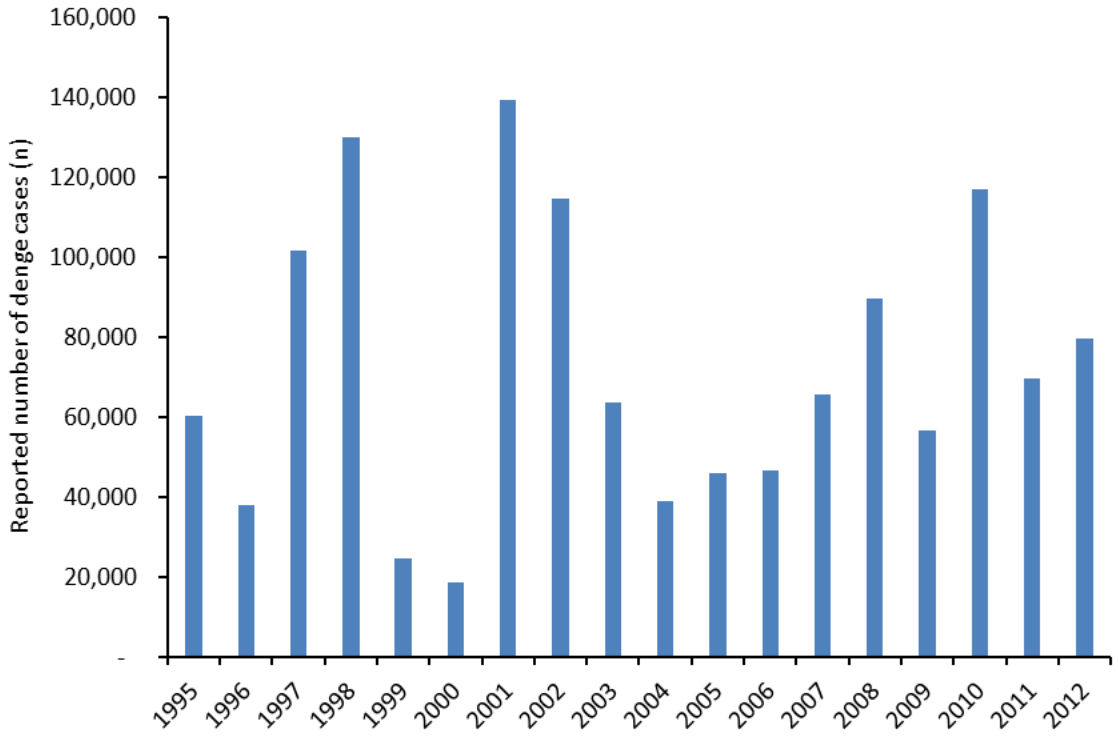
1.1 Background

Dengue is a growing global health priority, with considerable economic and social impacts. It is a major public health problem in low- and middle-income countries across the Americas, Asia, the Middle East, and Africa. Stakeholders and decision-makers in dengue-endemic countries require tools and evidence to assess the optimal strategies to control dengue fever (DF) and guidance in relation to value for money. Predictive models are therefore needed to assess the public health and economic consequences of adopting one, or a combination of, dengue control interventions in a given setting.

Historically, methods to evaluate the public health and economic impacts of interventions against infectious diseases have included randomised controlled trials as well as model-based analyses (primarily static or decision analytic models [also used for non-infectious diseases] [1]). The former tend to capture only relatively short-term impacts whilst the latter do not take account of the dynamics of infectious diseases.

The broad aims of this thesis are to develop mathematical models for predicting the epidemiological and economic effects of dengue control interventions in a geographical setting with a persistent, high level of dengue transmission. The premise that is being examined is not the 'how' of implementation, rather what the possible population impacts of different interventions are in relation to three key factors: effectiveness, cost-effectiveness, and affordability. Thailand acts as an excellent case study in this regard, as an important tropical/ subtropical country in Asia where DF is a major public health priority, having suffered large dengue outbreaks in 1958, 1987, 1998, 2001, 2013, and 2015 (as well as epidemic peaks in 2002, 2008, and 2010) and all four dengue serotypes co-circulate. Moreover, consistent dengue surveillance data for Thailand is publicly available and accessible, detailing dengue case numbers by year, age, mortality, and severity of disease. For example, from 1995 to 2012, the burden of DF in Thailand in the form of reported dengue cases fluctuated between approximately 20,000 and 140,000 cases per year (Figure 1.1), with an annual average of 72,000 cases and 100 deaths [2].

Figure 1.1. Number of reported dengue disease cases and dengue disease incidence, Thailand, 1995–2012



Source: Bureau of Epidemiology [2].

The project combines dynamic transmission models of dengue epidemiology with modelling of the costs and effects of dengue control interventions. These approaches are used to evaluate the epidemiological and cost-effectiveness impact of both individual as well as combined dengue control interventions, but also go beyond cost-effectiveness analysis (CEA) to explicitly consider affordability issues and optimal resource allocation subject to constraints in the form of constrained optimisation (CO).

1.2 Policy context and motivation/ rationale of the thesis

In April 2008, the Paediatric Dengue Vaccine Initiative sponsored an Expert Panel meeting comprising health economists and dengue experts at the University of Antwerp, Belgium, to review the literature on dengue health economics, identify outstanding research imperatives, and provide recommendations on priorities and methodology for conducting further research [3]. The context for that meeting – then as now – lay in the fact that, with dengue vaccines currently in development, policymakers require valid and appropriate economic analyses to determine their potential financial and public health impact. In as much as the Expert Panel chose to be prescriptive in giving advice on suitable methods, it was felt that dynamic transmission models were required and that models should account for elements such as seasonal variations in disease transmission, age-specific differences in disease incidence, and herd immunity. Moreover, the meeting

consensus was that these models should be accompanied by economic analyses to facilitate the choice of the most effective and cost-effective options for intervention [3].

In a similar fashion, a meeting organised and hosted by the World Health Organization (WHO) in August 2010 [4,5] – in collaboration with the Vaccine Modeling Initiative (VMI) of the University of Pittsburgh as well as the Pediatric Dengue Vaccine Initiative – brought together a range of multidisciplinary experts (comprising dengue epidemiologists, clinicians, immunologists, public health officials, vaccine developers, entomologists, and mathematical modelers) to review the current knowledge and future needs with regard to the assessment of the population-wide impacts of a dengue vaccine. The meeting agenda broadly focused on the current state of dengue transmission models and the main scientific challenges facing their future development, as well as approaches to evaluate the impact of vaccination and different vaccination strategies. The summary conclusions of the meeting, or rather the 'recommendations for future action', stated that vaccination was the most important feature to be added to next-generation dengue models and that models should, at a minimum, include: 1) comparisons of standard vaccination strategies across different age groups; 2) consideration of risk for severe disease during secondary infection; and 3) sensitivity analyses in relation to vaccination coverage and vaccine efficacy.

Historically, the impact of vector control on dengue incidence has been subject to some scepticism, if not challenge (e.g. Bowman et al. [6]); therefore, the apparent focus on vaccination in the latter meetings was perhaps warranted in this context. Notwithstanding this, my own presentation at the 2010 meeting [4] focused on optimal resource allocation in the context of a dengue vaccination scenario and seemingly served as a pre-cursor to my doctoral work (reflecting both my personal interests and underlying belief in the importance and merits of multi-faceted [combination] dengue control). Then as now, governments face constraints on resources and control interventions such as (dengue) vaccination need to be both cost-effective and affordable. Using a simple (although not simplistic), excel-based linear-programming model, my analysis sought to consider the impact of a range of existing interventions (larvicide, insecticide-treated bed nets, and indoor residual spraying) alongside dengue vaccination whilst minimising dengue cases and dengue haemorrhagic fever (DHF) hospitalisations within a set of resource constraints.

Under the moniker 'Future Challenges', the meeting report [4] and subsequent meeting publication [5] acknowledged that dengue vaccination would likely occur alongside vector control, educational campaigns, and social outreach, amongst other important factors.

Further, although methodologically challenging, that these 'broader' elements would need to be evaluated in terms of their added population-level benefits to dengue vaccination [4,5].

1.3 Research objectives

This thesis is focused on three specific objectives in relation to effectiveness, cost-effectiveness, and affordability, respectively:

- Objective 1 – Effectiveness: develop a dynamic transmission model to estimate the impact of different DF control strategies, including vaccination, on the epidemiology of DF in Thailand, which has experienced hyperendemic (i.e. persistent, high-level) dengue transmission for many years, with risk present in both urban and rural areas [7];
- Objective 2 – Cost-effectiveness: extend model analyses to estimate the costs of the different (dengue) control options, both individually as well as in combination, encompassing historical forms of vector control as well as possible new ones in the form of vaccination (detailed above) and *Wolbachia* infection; and include formal CEA to determine the best intervention(s) (of the interventions considered) for controlling the spread of dengue from a cost-effectiveness perspective [8].
- Objective 3 – Affordability: having determined 'value for money' in Objective 2, the challenge became one associated with fitting new strategies within potential resources available, in that an assessment of being cost-effective is not the same as being affordable [9]. Accordingly, by combining methods of population epidemiology with CO from the field of mathematical economics, the dynamic transmission model (Objectives 1 and 2) was adapted and extended to estimate the optimal mix of dengue control strategies to maximise public health outcomes subject to affordability constraints, i.e. when real-world fixed budget constraints are explicitly considered (Chapter 5 – Publication 3 [10]). Two separate and complementary objective functions are used, namely number of dengue cases (i.e. incident number of DF cases) and disability-adjusted life years (DALYs) lost with the focus of interventions on *Wolbachia* infection and vaccination.

1.4 Contributions to literature

The main contributions of this thesis to the (dengue) literature relate to the following:

1. Development of deterministic vector–host dynamic transmission models simulating a global dengue virus serotype (Chapter 5 – Publication 3 [10]) as well as consecutive dengue infections with all four dengue virus serotypes. In the latter case(s), each with an incubation period and including cross-protection and immune enhancement, age-structure of (model) population and a climactic factor simulating seasonal influences in

the mosquito population (Chapter 3 – Publication 1 [7] and Chapter 4 – Publication 2 [8]).

2. Reductions in dengue incidence (and corresponding economic impact) attributable to control interventions were determined by comparing the relative differences in dengue incidence in the presence and absence of study interventions with both singular and multivariate impacts being assessed.
3. Models were used to analyse, at the population level, the effectiveness and cost-effectiveness of both orthodox vector control (in the form of larvicide, adulticide, and environmental management/ public health education and analysis [EM/ PHEA]) and new control strategies (including vaccination and *Wolbachia* infection) at reducing the incidence of dengue.
4. The model framework was subsequently extended to examine affordability, in the form of CO to reflect decision-making under explicit real-world budgetary constraints.

1.4.1 Author contributions to thesis

Author contribution to thesis write-up:

Chapter 1 – Aims and objectives: I proposed and delineated the general research questions as well as describing their wider scientific and societal/ health context. Comments from my supervisor were incorporated into the text.

Chapter 2 – Introduction: I reviewed and critically assessed the literature and wrote the chapter as a supplement to the publications. A fore-runner of the text was reviewed as part of the MPhil/ PhD upgrade process with comments and subsequent updates/ reviews (based on this) being incorporated and evolving into the final text.

Chapter 3 – Publication 1 [7]: I developed the manuscript methodology including writing the model code, running the analysis (including model calibration), and presentation and interpretation of the results. I wrote the paper, including all of the constituent manuscript sections: introduction, methods, results, and discussion. I subsequently and solely revised the paper based on peer reviewer comments prior to acceptance.

Chapter 4 – Publication 2 [8]: I developed the manuscript methodology including revising/ updating the model code, running the analysis (including model calibration based on updated data), as well as presentation (including design and construction of the excel-based tool) and interpretation of the results. I wrote the paper, including all of the constituent manuscript sections: introduction, methods, results, and discussion. My supervisors commented on different aspects of the manuscript in development, including

the introduction and methods, with these comments being incorporated into the evolving draft. I subsequently and solely revised the paper based on the journal peer-review comments prior to acceptance.

Chapter 5 – Publication 3 [10]: I developed the manuscript methodology including writing the model code, running the analysis (including model calibration), as well as presentation and interpretation of the results. I wrote the paper, including all of the constituent manuscript sections: introduction, methods, results, and discussion. My supervisors commented on different aspects in development including the introduction, methods, and discussion, with these comments being incorporated into evolving drafts. I subsequently and solely revised the paper based on the journal peer-review comments prior to acceptance.

Chapter 6 – Discussion and Conclusions: I wrote the summary conclusions as well as the key findings of the study. Comments from my supervisor were incorporated into the text.

In brief, Chapter 1 presents the primary motivations and policy context for undertaking this research and underlines the main aims and objectives of the project. Chapter 2 describes why DF is a public health priority, DF epidemiology, and the burden of disease; and highlights the economic consequences of DF. It concludes with a brief methodological background to the choice of model(s) underpinning this work. Chapter 3 presents a dynamic transmission model that simulated the impact of different DF intervention strategies to reflect the consequences of these interventions on the epidemiology of DF in Thailand. Chapter 4 extends the model framework to report the costs of different strategies and includes formal cost-effectiveness analyses of both singular and multiple dengue control strategies in combination. The objective of Chapter 5 is to adapt and evolve the original dynamic transmission models to determine the optimal mix of new strategies for the prevention of DF under budget constraints through the application of CO. Chapter 6 presents the overall conclusions of the project and provides suggestions for future work. It also discusses the implications of these approaches and the ensuing results and limitations.

2 Introduction

DF is a mosquito-borne disease caused by serologically related but antigenically distinct viruses grouped into four serotypes (dengue virus [DENV]-1 to DENV-4). Recovery from infection confers permanent immunity to that serotype, but only short-term cross-immunity to other serotypes [11-14]. All serotypes can cause severe and fatal disease. There is genetic variation within serotypes and some genetic variants within each serotype appear to be more virulent or have greater epidemic potential [15]. In highly endemic regions of the world where all four serotypes co-circulate and the force of infection is high, humans may experience two or more dengue infections over a lifetime due to a primary infection with one serotype, and secondary or subsequent infections with any of the other serotypes [16,17].

Dengue is ranked as the most important mosquito-borne disease [18,19], with historical estimates of 50–100 million symptomatic infections every year [20,21], with approximately 500,000 hospitalisations [11,19,21] and 20,000–25,000 deaths [19,22]. Recent work suggests that the total number of 'true infections' is greater than the dengue burden estimate of the WHO by at least a factor of three, with approximately 390 million dengue infections and 100 million symptomatic (i.e. clinically apparent) infections per year [23,24] in more than 125 countries [20], and varying prevalence of the four dengue serotypes (DENV-1, -2, -3, and -4) [25].

2.1 Transmission of DF

The most common vector responsible for epidemic DF is the infected female of the *Aedes aegypti* mosquito [17,18,26,27], although *Aedes albopictus* is a secondary vector [28]. The adult female mosquito requires blood to produce eggs and the virus is transmitted to susceptible human hosts from the bites of an infected female mosquito. After the virus has incubated in an infected mosquito (known as the extrinsic incubation period [EIP] [29,30], which is temperature dependent and lasts approximately 8–12 days), it is able to transmit the virus for the duration of its natural life expectancy.

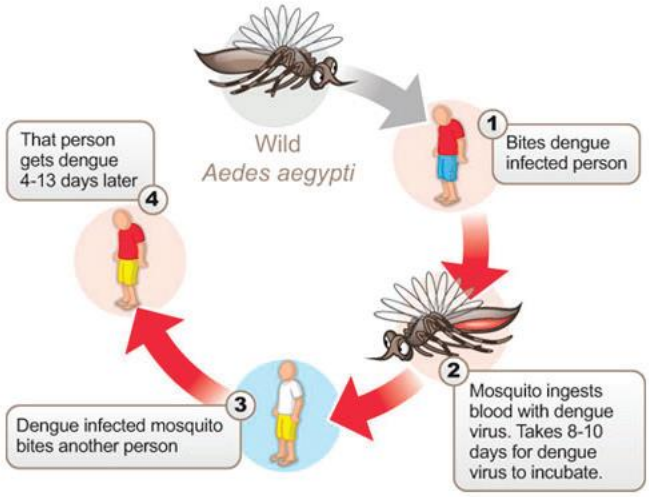
Infected symptomatic humans are the primary carriers and sharers of the dengue virus and act as a source for uninfected mosquitoes [31-33]. It is also posited that people with asymptomatic (i.e. no perceptible symptoms) or inapparent (i.e. symptoms that are sufficiently mild to go undetected by surveillance systems) infections, may additionally contribute a large reservoir of infection that impacts the disease burden [34].

The average incubation period of the virus in humans is 4–6 days (range 3–14 days) and is known as the intrinsic incubation period [35]. Symptoms produced by dengue infection

last approximately 3–12 days, with an average duration of 5–7 days following the onset of symptoms [27,32,36]. The illness persists for several days after the viraemic period (i.e. virus circulating in the blood) has ended [27,37,38]. People who are already infected with the virus are able to transmit the infection through the mosquito vector for 4–5 days (up to a maximum of 12–13 days) after their first symptoms appear [32].

Aedes aegypti are primarily daytime feeders that live in the vicinity of human habitats and lay eggs and produce larvae predominantly in artificial containers [17,39]. Early mornings and evenings before dusk form the peak activity and/ or feeding period for *Aedes aegypti*. The female of the species will bite multiple human hosts during each feeding cycle. Figure 2.1 depicts the transmission lifecycle of the dengue virus infection.

Figure 2.1. Typical lifecycle of a dengue mosquito-borne infection



N.B. Image courtesy of the World Mosquito Program (https://ixc.dfat.gov.au/projects/world-mosquito-program/).

2.2 Dengue characteristics

DF embraces a wide clinical spectrum ranging from asymptomatic infections to more severe manifestations that include DHF and dengue shock syndrome (DSS) [11,36,40,41]. Severe forms of the disease occur rarely, relative to the full spectrum of dengue disease, although they are observed more frequently following a second dengue infection with a different serotype [42-46] and in infants (but not young children) with primary infections [47-52].

It is not entirely clear why only some individuals are predisposed to severe disease; the precise mechanisms leading to the increased risk of severe disease following secondary infection are difficult to investigate due to the many factors that are known to influence disease severity. These include age at which infection occurs, sequence of infecting

serotypes, virus genetics and virulence, underlying disease, co-infection with other pathogens, and time between primary and secondary infections [26,53-61]. One theory advanced for the occurrence of serious forms of the disease relates to immune or antibody-dependent enhancement (ADE), i.e. an immune response to a primary (first) infection with one serotype that enhances (rather than negates) future infections with a different serotype and can increase the likelihood of severe disease [21,62,63]. In this regard, Katzelnick et al. [64] examined data from a long-term study of dengue-exposed Nicaraguan children and showed that ADE (disease) occurs at a relatively precise range of antibody concentrations and that the level of pre-existing dengue antibodies was clearly associated with the severity of secondary dengue disease. For example, higher levels of antibody titres protected against severe disease whilst intermediate and lower levels of antibodies either exacerbated disease or did not enhance disease, respectively [64]. Adults are at risk of death due to late recognition, comorbidities (risk factors for severe disease), self-medication, and failure to self-detect fever [65-67].

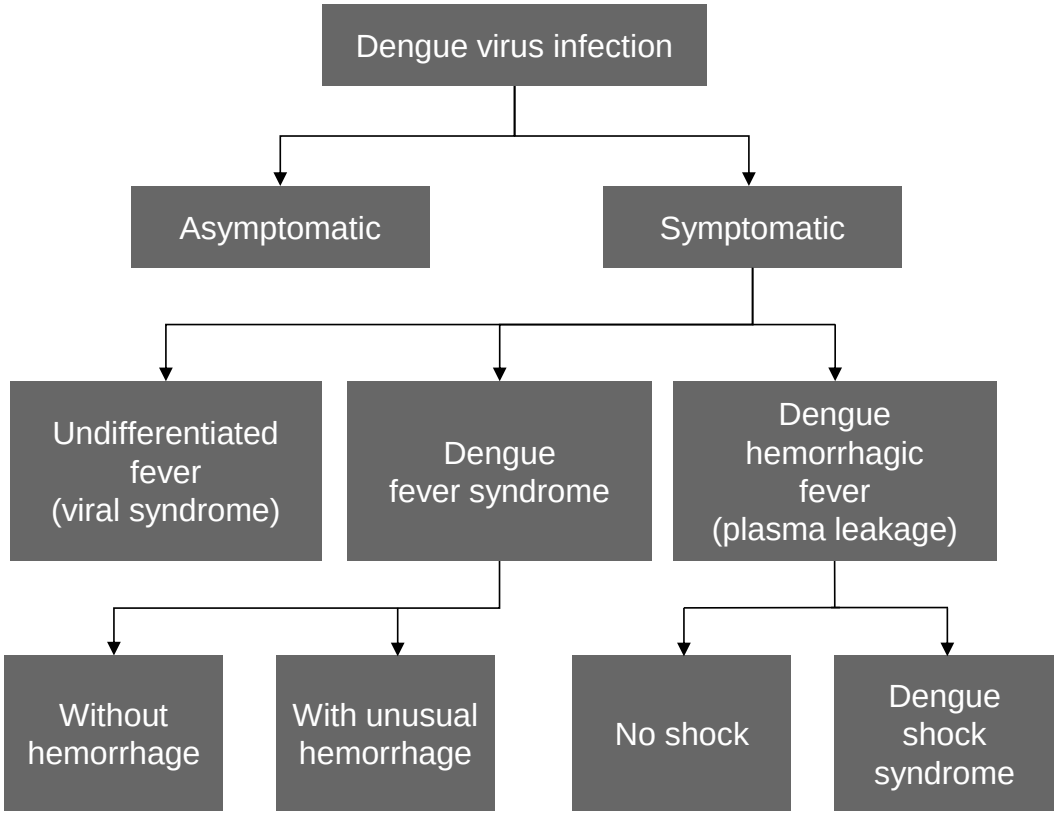
2.3 Clinical description for (dengue) case definitions and diagnosis

Dengue is classified in relation to clinical manifestations, with an assortment of classification systems variously developed to estimate the burden of disease and as an aid to diagnosis and appropriate triage of patients. An important aspect of public health surveillance systems relates to (disease) case definitions to ensure comparability and consistency of data, with the WHO encouraging their use to make surveillance data comparable between countries [68] – see next section.

In the early 1960s and before, dengue was commonly thought of as an incapacitating although not fatal illness. This perception changed in the late 1960s with outbreaks of lethal DHF in children in Southeast Asia [69]. The clinical information gathered from the outbreaks subsequently underpinned the dengue clinical classification published in a WHO guideline in 1975 [70], updated in 1997 [71], and adopted by WHO Southeast Asia Regional Office (SEARO) in 2011 [36]. The WHO classification guidelines (1975 and 1997) described three categorisations of dengue infection encompassing undifferentiated fever, DF, and DHF (Figure 2.2). The first category, undifferentiated fever, is more commonplace than classic DF and defined as being indistinguishable from other viral infections that occur in infants, children, and some adults with primary infection. DF itself is characterised as a febrile illness with at least 2 clinical indicators, which include nausea, vomiting, headache, arthralgia, retro-orbital pain, rash, myalgia, haemorrhagic manifestations, and leukopenia. A diagnosis of DF necessitates epidemiological or laboratory confirmation along with fever and at least 2 clinical symptoms as a result of the lack of precision or specificity in clinical findings and indicators [71]. A differential

diagnosis of DF includes a range of diseases prevalent in the Southeast Asia region [71]. This includes other arborvirus, such as chikungunya, which is often misclassified as dengue in Southeast Asia; other viral diseases, for example, measles, rubella and other viral exanthems, Epstein-Barr Virus, enteroviruses, influenza, hepatitis A, and hantavirus; bacterial diseases, for example, meningococcaemia, leptospirosis, typhoid, melioidosis, rickettsial diseases, scarlet fever; and parasitic diseases such as malaria [36]. For DHF, 4 criteria are required for a diagnosis, namely, i) fever; ii) haemorrhagic indications; iii) thrombocytopenia (i.e. platelet count, ≤100,000 platelets/mm^3); and iv) clinical signs of plasma leakage (i.e. pleural effusion, ascites, etc.). In contrast to DF, a diagnosis of DHF does not need laboratory confirmation of infection due to the specificity of this condition. Importantly, some patients with severe illness and needing medical treatment do not to achieve all of the DHF diagnostic criteria. DHF is further classified by four grades of severity depending on whether there is spontaneous bleeding and how severe any plasma leakage is. The term DSS refers to the third (i.e. III) and fourth (i.e. IV) categories of the DHF grades in which 'shock' is present in addition to all of the four DHF diagnostic criteria where moderate shock equates to grade III DHF and profound shock to grade IV DHF [71].

Figure 2.2. WHO 1997 case classification of symptomatic dengue



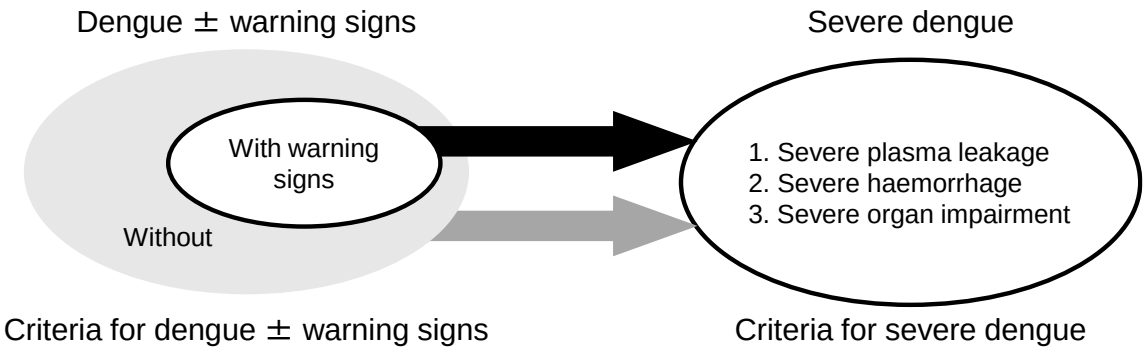
Adapted from Figure 2.1 (Page 12) of WHO [71].

WHO, World Health Organization.

In spite of widespread recognition of the usefulness of the 1997 classification, it has been criticised primarily for not fully capturing the spectrum of dengue disease (i.e. may result in an under-diagnosis of severe dengue cases) as well as not categorising all cases with severe outcomes [69,72]. A number of the weaknesses have been detailed in several studies and summarised in a systematic review comparing the usefulness of the 1997 classification and subsequent 2009 revision [72]. In brief, commentators assert that the 1997 classification using the DF/ DHF/ DSS categorisation of patients is poorly related to disease severity, is complicated to use in practice (e.g. requiring tests that may not be available and/ or difficult to apply), is not terribly helpful for triage in outbreaks, may confuse clinical staff assessing disease severity and, lastly, results in diverse reporting around the world because of difficulties in application [72].

In contrast, the 2009 guidelines [11] (Figure 2.3) are considered to aid clinicians more effectively, with both the triage of dengue cases and their clinical management [72,73]. In the systematic review referred to above [72] comparing the 2 classifications (1997, 2009), the authors found that that the 2009 classification was able to detect disease severity with a high sensitivity; in doing so, assisting in the clinical management of dengue, facilitating surveillance and potentially contributing to a reduction in dengue mortality [72,74]. Notwithstanding this, it is also the case that clinical criteria are less strictly defined in this classification [11,40], leading to potential misclassification and subjective, if not arbitrary clinical interpretation [75-77].

Figure 2.3. Dengue case definition (WHO revision 2009) – abridged

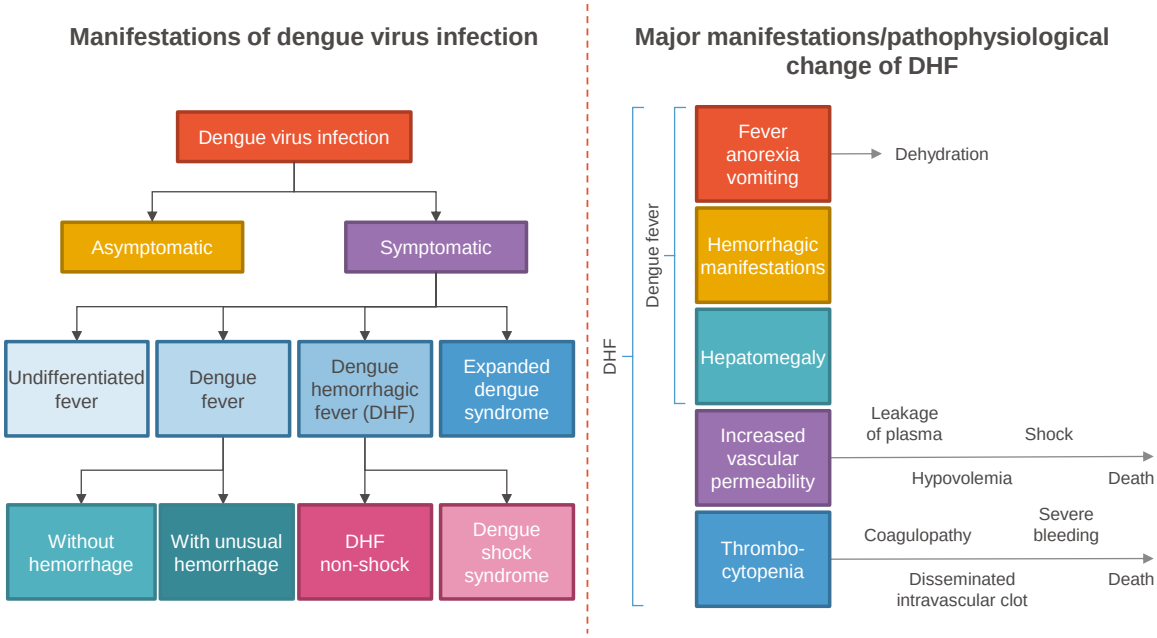


Adapted from Hadinegoro [40] and the WHO [11].
WHO, World Health Organization.

The WHO SEARO 2011 dengue guidelines was a regional update to the 1997 classification and included additional categories of ‘Expanded Dengue Syndrome’ (encompassing unusual manifestations, organ involvement, co-morbidity) and Adult Management (Figure 2.4) based on the WHO SEARO Expert Group, which sought to ameliorate previously identified limitations by reinforcing the dengue classification of (DF/

DHF/ DSS in the previously developed guidelines [36,71]. For example, Hadinegoro [40] had proposed that features from the revised 2009 classification should be integrated into the1997 guidelines, having experienced challenges in the application of the revised guidelines (2009) in Indonesia. It had also previously been highlighted that there should be separate dengue case management guidelines for children and adults [68].

Figure 2.4. WHO SEARO 2011 guidelines



SEARO, Southeast Asia Regional Office.

SEARO guidelines for prevention and control of dengue [36].

When comparing the different guidelines in relation to diagnosing dengue infection, results from a study in an outpatient facility in Indonesia indicated that the sensitivity and specificity of the WHO 1997/ WHO SEARO 2011 was 48.9% and 23.7%, whilst the corresponding figures for WHO 2009 was 78.2% and 68.4% [78]. Two of the 8 secondary infection patients included in the study were in the WHO 1997/ WHO SEARO 2011 grouping while no patients were categorised as severe in the WHO 2009 group. The authors concluded that while the WHO 2009 classification had shown higher sensitivity and specificity, the WHO 1997/ WHO SEARO 2011 classification(s) could potentially diagnose greater numbers of patients who may have experienced severe forms of dengue, but also greater numbers of secondary infection, which have an elevated risk of severe forms of disease compared to WHO 2009.

The WHO 1997/ WHO SEARO 2011 and WHO 2009 dengue guidelines emphasise different aspects in their diagnostic criteria with the respective classifications summarised in brief in Table 2.1.

Table 2.1. Diagnosis of dengue cases

<table>
<tr><th>1997</th><th>2009</th><th>2011</th></tr>
<tr><td>Dengue fever
(no plasma leakage)</td><td>Dengue without warning signs</td><td>Dengue fever (no plasma leakage)</td></tr>
<tr><td>DHF grade I (no shock)</td><td rowspan="2">Dengue with warning signs</td><td>DHF grade I (no shock)</td></tr>
<tr><td>DHF grade II (no shock, spontaneous bleeding)</td><td>DHF grade II (no shock, spontaneous bleeding)</td></tr>
<tr><td>DHF grade III/DSS
(dengue shock syndrome)</td><td rowspan="3">Severe dengue
(severe plasma leakage, hemorrhage, organ involvement)</td><td>DHF grade III /DSS
(dengue shock syndrome)</td></tr>
<tr><td rowspan="2">DHF grade IV (DSS with profound shock)</td><td>DHF grade IV</td></tr>
<tr><td>Expanded dengue syndrome (unusual manifestation, organ involvement, co-morbidity</td></tr>
<tr><td></td><td>Adult management</td><td>Adult management</td></tr>
</table>

Adapted from Hadinegoro 'Forum on Dengue Classification': Asian Dengue Summit 2019 [79].

2.4 Dengue case classification/ surveillance

Table 2.2 presents the case classification and surveillance systems used in the Association of Southeast Asian Nations (ASEAN) countries. Reporting of dengue cases is compulsory in all of the countries listed, although the majority of cases are derived from inpatient reports in public hospitals, with a smaller amount of notifications originating from outpatient facilities, laboratories, private hospitals/ clinics and primary care physicians [73]. In general, surveillance systems are characterised by the lack of consistent reporting practices as both the WHO 1997 [71] and 2009 [11] case definitions and severe disease classifications are often used in dengue endemic countries. Most countries use passive surveillance methods, although a number – including Malaysia, Thailand, Philippines, and Indonesia – have recently taken steps to initiate active surveillance methods at sentinel sites, particularly during outbreaks [73].

Table 2.2. Case classification and surveillance systems used in ASEAN countries

Country	Case definition used 2013	Surveillance system
Brunei	WHO 1997 [71] and 2009 [11]	Passive and active
Cambodia	WHO 1997 [71] adapted	Passive since 1980; active (sentinel) since 2001
Indonesia	WHO 2011 [36]	Current passive; active planned (sentinel)
Malaysia	WHO 1997 [71] and 2009 [11], with laboratory confirmation	Passive and active (sentinel); all cases laboratory confirmed
Myanmar	WHO 1997 [71]	Active (all reports from sentinel hospitals only)
Philippines	WHO 2009 [11]	Passive; some sentinel surveillance
Singapore	WHO 1997 [71] and 2009 [11], with laboratory confirmation	Passive; all reported cases are laboratory confirmed
Thailand	WHO 1997 [71] with modifications	Passive; active; laboratory reports
Vietnam	WHO 2009 [11]	Passive; some sentinel surveillance (non-structural protein 1 testing)

Data are from Thisyakorn et al [73] and Karyanti et al [80].

ASEAN, Association of Southeast Asian Nations; WHO, World Health Organization.

The absence of standardised reporting practices and application of a standard case definition for reporting can make comparisons difficult [25,81,82]. Misdiagnosis may also complicate disease burden estimates, and countries may differ with regard to reporting of probable or confirmed cases [18,83]. For example, whereas mild/ asymptomatic cases may truly be underreported, over-reporting/ misclassification of patients with generalised febrile symptoms during epidemics may also occur. This may arise when hospitals and clinics are overloaded with patients who are concerned that they have dengue but, in reality, do not [83,84].

2.5 Epidemiological burden of DF

The incidence of dengue has increased rapidly, with the number of dengue cases being reported to the WHO increasing from approximately 908 cases during 1955–1959 to 2.2 million in 2010 [19] (Table 2.3), 3.2 million in 2015 [85] and over 4 million cases by 2019 [32]. Mortality due to dengue also increased from approximately 960 in 2000 to 4032 in 2015 [32]. Estimates indicate that more than 125 countries across the globe are at risk of

dengue infection [32,86] covering some 3.9 billion people. This includes countries that had formerly been classified as dengue free [86].

Table 2.3. Increase in dengue cases reported to the WHO from 1955 to 2010

Period or year	Number of cases
1955–1959	908
1960–1969	15,497
1970–1979	122,174
1980–1989	295,554
1990–1999	479,848
2000–2007	925,896
2008	1,279,668
2009	1,451,083
2010	2,204,516

Data from Figure 1 of WHO [19].

WHO, World Health Organization.

Table 2.4 presents figures for the global distribution of DF by continent [23]. Of the 96 million apparent dengue infections in 2010, the majority were observed in Asia, equating to some 70% (67 million infections: 95% credible interval 47–94 million) of the disease burden. In comparison, approximately 14% of the global dengue burden was attributable to the Americas, of which Brazil and Mexico were responsible for more than half (and in the case of Brazil, more than 70%). These figures underline the disproportionate nature of the dengue burden suffered in Asia [23].

Table 2.4. Estimated global distribution of dengue (2010)

Region	Apparent infections, millions (95% credible interval)	Non-apparent infections, millions (95% credible interval)
Africa	15.7 (10.5–22.5)	48.4 (34.3–65.2)
Asia	66.8 (47.0–94.4)	204.4 (151.8–273.0)
Americas	13.3 (9.5–18.5)	40.5 (30.5–53.3)
Oceania	0.18 (0.11–0.28)	0.55 (0.35–0.82)
Global	96.0 (67.1–135.6)	293.9 (217.0–392.3)

Data from Bhatt et al. [23].

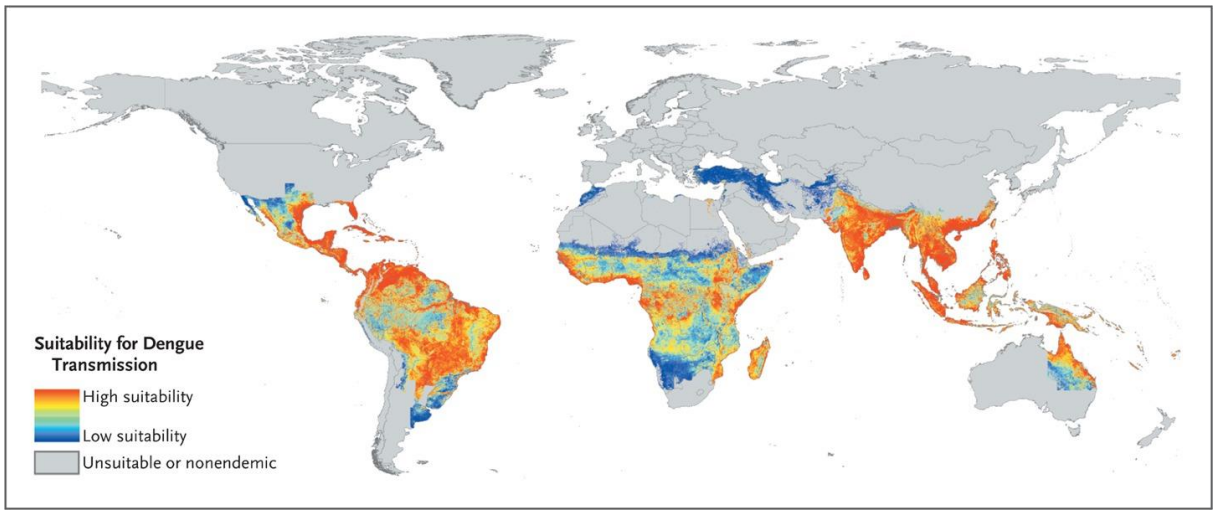
Similarly, the results of a systematic review and meta-analysis of the global epidemiology of dengue outbreaks (1990–2015) showed that Southeast Asia accounted for the largest number of outbreaks (31.3%) of the six WHO regions, followed by the Western Pacific

region (27.4%) and the American region (24.8%) [87]. These three regions were responsible for approximately 83.5% of the total outbreaks in this period [87]. At the country level, India experienced the highest number of outbreaks (22.1%), followed by China (14.5%) and then Brazil (9.2%) [87]. Co-infection with different serotypes was reported in approximately 48% of the dengue outbreaks examined in the review, with circulating serotypes varying across WHO regions and over time.

The data in Table 2.4 also indicate that estimates of dengue incidence from reported cases may be substantively below the real burden of disease. For example, the number of symptomatic cases (i.e. apparent dengue infections sufficient to interfere with daily routine and may be reported) in all geographies is appreciably smaller than the estimated number of asymptomatic cases (i.e. non-apparent or inapparent subclinical infections without symptoms). This is because dengue is often experienced as a very mild flu-like illness and therefore not seen or reported by healthcare workers. However, individuals with this form of the disease may still be capable of contributing to the disease ‘reservoir’ if bitten by a mosquito [34,82,88].

Figure 2.5 presents a map of regions of the world where DF is endemic, as well as highlighting a dengue transmission ‘index of suitability’ in the form of a colour-coded scheme [25]. For example, red and blue areas of the map indicate particularly high and low suitability, respectively, for DF transmission, whereas grey areas indicate unsuitability for dengue transmission and non-endemic regions of the world [25]. Variables that are most strongly associated with elevated dengue risk include high levels of precipitation and a suitable local temperature for dengue transmission. Proximity to low-income urban and peri-urban centres was also linked to greater risk, particularly in highly contiguous areas, indicating that human movement between population centres is an important facilitator of dengue spread [25]. This correlates clearly with the number of reported dengue infections (Table 2.4) in regions of the world, with the red areas of Brazil and Southeast Asia accounting for the majority of the dengue burden in the Americas and globally, respectively [23].

Figure 2.5. Regions at risk of DF transmission



Reproduced from Simmons et al. [25]. Distribution of global dengue risk (determination of risk status based on combined reports from the WHO, the US CDC, Gideon online, ProMED, DengueMap, Eurosurveillance, and published literature.

CDC, Centers for Disease Control and Prevention; DF, dengue fever; US, United States, WHO, World Health Organization.

The reasons for the growth in dengue as a major public health challenge are multi-factorial, including: 1) demographic changes leading to rapid population growth and urbanisation; 2) increase in non-biodegradable containers and difficulty of disposing of tyres, which both act as potential breeding sites of *Aedes aegypti*; 3) rapid increase in overseas air travel, particularly to tropical regions of the world; 4) deterioration in public health infrastructure that is able to deal with vector-borne diseases, due to a lack of political will, but often due to a lack of money and inadequate resource allocation to controlling the disease [89,90]. Other factors include changes in diagnosis and reporting practices (e.g. Thailand, Malaysia, and Singapore) and increasing numbers of countries reporting dengue cases [19].

DF is a global problem, but its effects on populations in Southeast Asia are particularly evident, following a number of social, environmental, and demographic changes in the region [17-19,91,92]. The region is characterised by dense population centres and correspondingly high suitability for dengue transmission [23,25].

Countries in the region can be classified into four different climate categories with corresponding dengue transmission potential [11]. This encompasses tropical monsoon and equatorial zones (Indonesia, Myanmar, Sri Lanka, Thailand, and Timor-Leste), in which *Aedes aegypti* proliferates in rural and urban areas and where multiple virus serotypes circulate [93]; deciduous dry and wet climatic zone (Bangladesh, India, and Maldives), where cyclic epidemics are increasing and multiple virus serotypes similarly

circulate; and sub-Himalayan foothills (Bhutan and Nepal), where epidemic dengue activity has also been recorded [11].

Particular dengue 'hotspots' in Asia include the Philippines, Thailand, Indonesia, Vietnam, Malaysia, and Singapore. Wartel et al. [94] presented a summary historical analysis and enumeration of dengue disease burden and epidemiological trends (1980–2010) in five Southeast Asian countries (Indonesia, Thailand, Malaysia, Philippines, and Vietnam), which included four of the above countries (Thailand, Malaysia, Philippines, Vietnam). Data sources included DengueNet and the WHO. Findings suggested that dengue incidence had increased in all countries over the 30-year period of the analysis, with epidemic (i.e. outbreak) years contributing a greater number of cases (1–3 times more) compared to non-epidemic years, although forming less than one third of the total observation period [94]. Mortality increased during the period in Indonesia, Malaysia, and Philippines, but decreased in Thailand and Vietnam. The authors cautioned that results may be subject to reporting and/ or ascertainment bias in some countries due to the changing nature of surveillance methods over the course of the study period and an increase in the sensitivity of the methods [94].

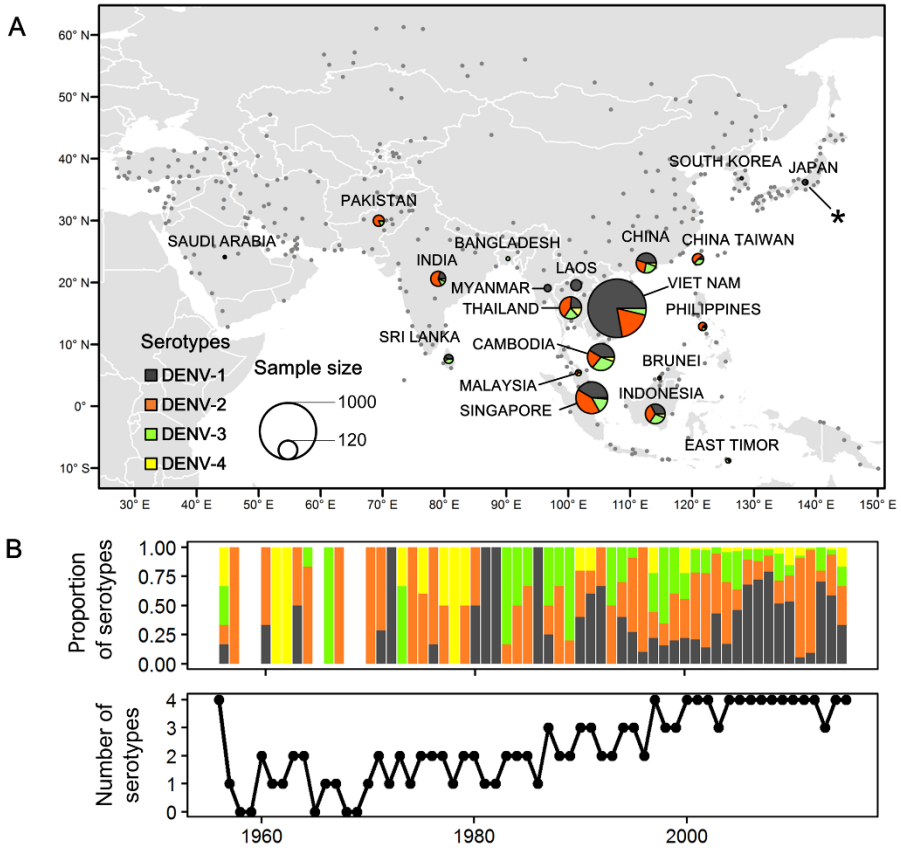
As highlighted above, inconsistent case definitions and reporting standards limit comparability between countries [25,81,82]. Additionally, countries differ with regard to reporting of probable or confirmed cases [32] and by severity [95]. In this regard, commentators suggest that the range of manifestations across the dengue disease spectrum are best captured using prospective methods [96,97]. Prospective cohort studies of 'DF' provide more information about the true incidence of DF and enable estimation of expansion factors, i.e. the difference between the numbers of reported cases and the true incidence [98-101]. Nealon et al. [96] compared dengue incidence rates from passive surveillance data with incidence rates from re-analysis of the vaccine trial control arm (i.e. a controlled clinical trial environment) in five Asian countries (active surveillance and virological confirmation). Results indicated that case definition was an important determinant of disease burden and that dengue burden was significantly under-reported, i.e. not captured by the existing case definitions and diagnostic practices, with only approximately 29% of virologically confirmed dengue in the trial being diagnosed by investigators as dengue [96]. The five countries in the study were Indonesia, Malaysia, Philippines, Thailand, and Vietnam, with the magnitude of under-reporting varying considerably across countries and by case definition, giving rise to a range of expansion factors, from 0.5 to 31.7 [96]. By way of comparison, a similar re-analysis of vaccine trial control arm data from five Latin American countries (Brazil, Colombia, Honduras, Mexico, and Puerto Rico) has been conducted [102]. In brief, results demonstrated: 1) that there is

substantial under-reporting of dengue to national surveillance systems; 2) that the level of underreporting varies considerably by country; and 3) that the number of dengue cases is estimated to be 3.5–19 times higher than reported.

These findings (highlighted above) are important, if not critical, to the determination of the economic and public health (i.e. estimates of burden of disease) impacts of the disease and efforts to control it. This is examined in detail in the ensuing chapters in the context of expansion factors to adjust for perceived under-reporting of dengue incidence.

In an analysis of co-circulation of dengue virus serotypes in Asia, Tian et al. hypothesised that flight networks had played an instrumental role in the spatial distribution of dengue virus serotypes in Asia, with flight hubs such as Thailand and India acting to 'seed' dengue epidemics and other countries such as China, Cambodia, Indonesia, and Singapore helping to establish 'viral diffusion links' with several Asian countries [93]. Figure 2.6 illustrates this process, with the grey dots in the top panel showing the airports for which passenger transport data were used in the analysis and the lower panel indicating the number of serotypes isolated per year in Asia [93].

Figure 2.6. Co-circulation of dengue virus serotypes in Asia



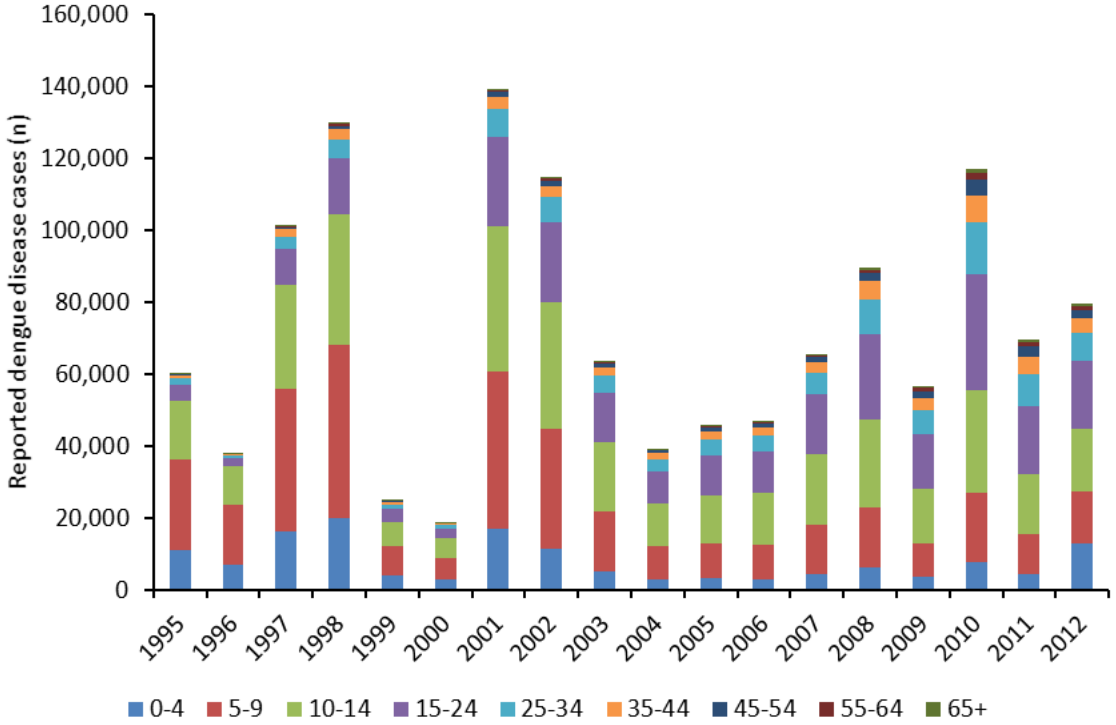
Reproduced from Tian et al. [93].

DENV, dengue virus.

2.5.1 Dengue reports in Thailand

The first cases of dengue disease were documented in Thailand in 1949, with intermittent cases of dengue being recorded during the course of the 1950s [103]. The first major outbreak of DHF was observed in Bangkok in 1958 [104,105], with 2,158 cases and 300 deaths reported [106]. Dengue is a notifiable disease in Thailand and data are collected to differentiate between DF, DHF, and DSS. From 1995 to 2012, the number of reported dengue cases fluctuated between 20,000 and 140,000 cases per year, with an annual average of approximately 72,000 cases and 100 deaths [107] (Figure 2.7).

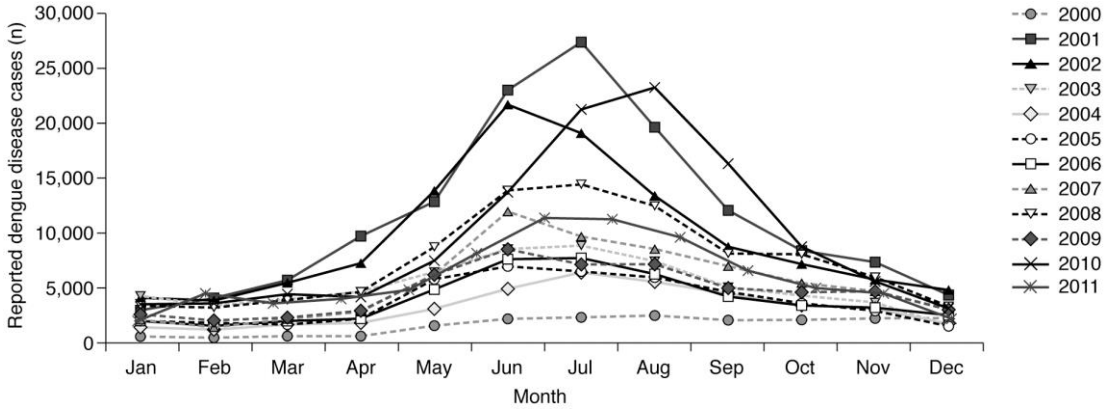
Figure 2.7. Number of reported dengue disease cases, by age group, Thailand, 1995–2012



Source: Bureau of Epidemiology [2].

This period included epidemic years in 1997, 1998, 2001, 2002, 2008, and 2010, when the annual number of reported cases was much higher. A systematic literature survey and analysis of epidemiology of dengue disease in Thailand (2000–2011) indicated that DF tended to increase every year over the survey period, whilst the contribution of DHF and DSS (as a proportion of the overall total reported dengue cases) decreased and stayed relatively stable, respectively [107]. The disease is reported year-long in all regions of Thailand, with a seasonal peak being observed during the hot-wet season (approximately May to September), which is also the period when dengue transmission occurs with the greatest intensity [108-110] (Figure 2.8). By way of comparison, the corresponding seasonal peak in Brazil also occurs in the hot-wet season (October–March) [111-113].

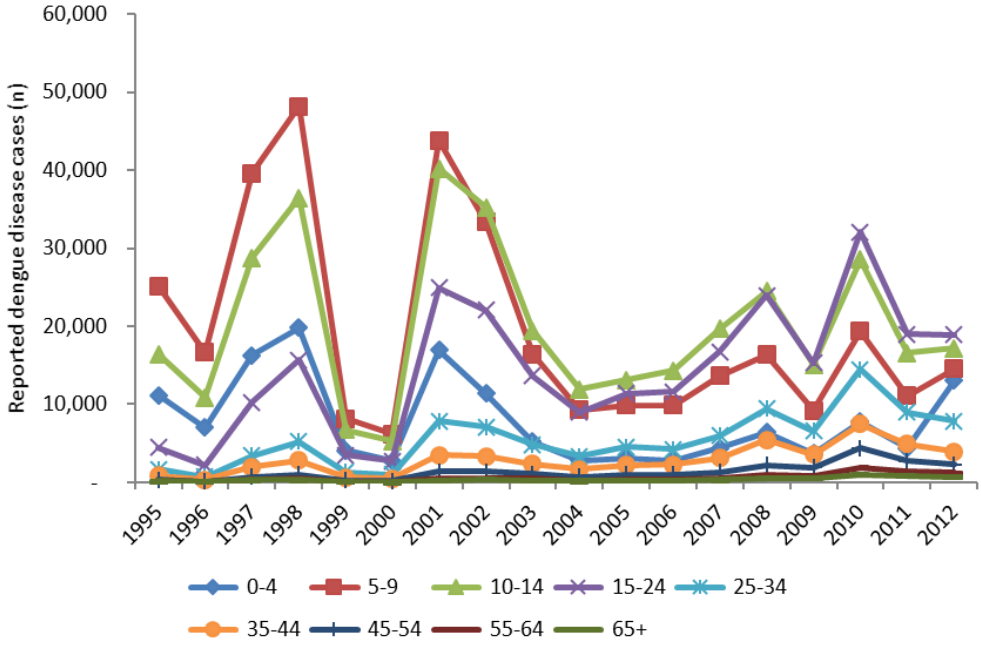
Figure 2.8. Seasonal variation of dengue cases by month (2000–2011)



Reproduced from Limkittikul et al. [107].

Historically, severe dengue illness has predominantly been observed in infants and children in Southeast Asia [114], although an age shift in cases towards older ages has been observed over time [107,115,116]. With respect to Thailand, an examination of long-term epidemiological trends (1995–2012) indicates that the highest numbers of reported cases were in the 5–9-year-old age group, followed by the 10–14-year-old age group, in the period from approximately 1995 to 2001/2002. In subsequent years, the data show that the highest number of reported cases was observed in the 10–14-year-old age group (Figure 2.9), with the trend continuing in the ensuing years [2].

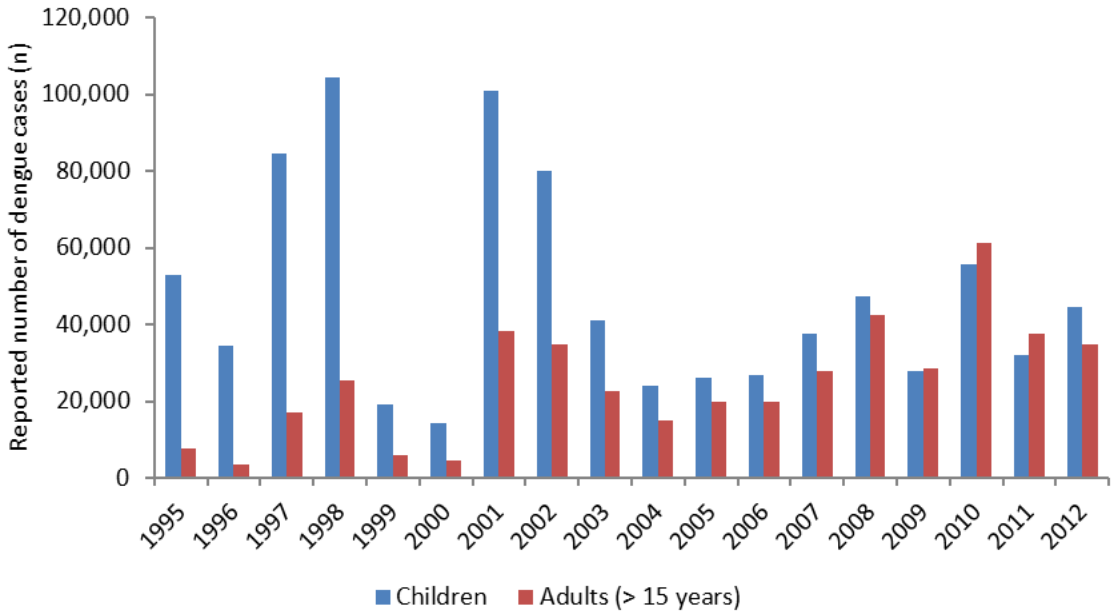
Figure 2.9. Reported cases and incidence of dengue disease, by age group, Thailand, 1995–2012



Source: Bureau of Epidemiology [2].

Figure 2.10 illustrates the changing proportion of dengue cases in children and adults and shows that the proportion of adult and paediatric cases is starting to reverse in Thailand.

Figure 2.10. Increasing age trend in reported dengue cases in Thailand



Data source: Bureau of Epidemiology [2].

The explanation for this ostensible shift in the age distribution of dengue lies in the (reported) decreases in birth and death rates [117]. Researchers investigating the reasons for the observed increases in the average age of dengue cases analysed Thai provincial data (72 provinces) for 1985 to 2005 and found that a reduced birth rate and change in the population age structure could explain the shift in the age distribution of cases, the reduction of the force of infection (the rate at which susceptible individuals become infected), and the increased time between epidemics of DHF [117]. This apparent age shift – indicating an epidemiological change in dengue infection – is also clearly observed in other Southeast Asian countries where DF has been epidemic for several years [115,116,118]. This may potentially be explained by an increase in secondary infections and changes in circulating dengue virus serotypes [119]. Age shifts have been reported in Singapore, Indonesia, Nepal, India, and Bangladesh [80,120-124].

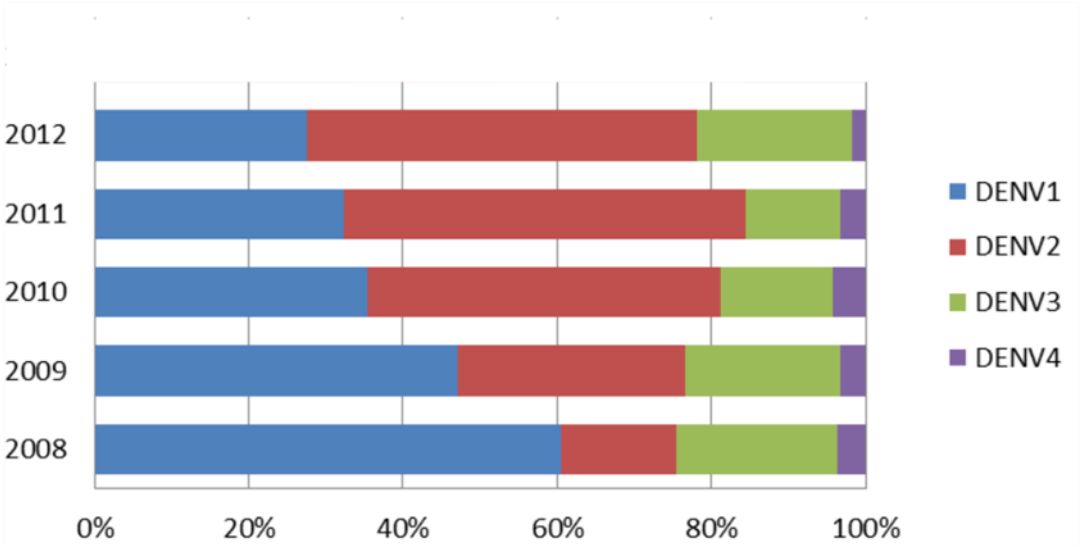
By way of comparison, the predominant dengue clinical manifestation in the Americas has historically been in adolescents and young adults, potentially related to host, epidemiological, and virologic factors [125]. For example, in Venezuela, dengue incidence during 2000–2007 was highest among 10–14-year-old children and adolescents but peaked among 5–9-year-olds in 2007; analogously, in Brazil, the highest incidence of DF during 2000–2007 was among young adults [125]. Despite this, in the epidemic suffered

in Rio de Janeiro in 2008, there was a distinct and rapid increase in the incidence of both DF and DHF among those aged <15 years [126,127]. This apparent age shift had already been observed in Brazil as a whole in hospital admissions since 2007 for DHF [127].

2.5.2 Serotype distribution in Thailand

As highlighted previously in Figure 2.6 above, all four dengue virus serotypes are endemic and circulating in Thailand. In the 5-year period 2008–2012 [128], DENV-1 and DENV-2 were the primary serotypes in Thailand (Figure 2.11). In common with the rest of the region, DENV-4 has not been very prevalent [128]. All four serotypes co-circulated in each of the major outbreaks that occurred in 1958 [129], 1987 [130], 1998 [131], 2001 [132], and 2013 [133].

Figure 2.11. Co-circulation of dengue virus serotypes in Thailand (2008–2012)



Source: Bureau of Epidemiology, Ministry of Public Health, Thailand [128].

2.6 Dengue prevention and treatment

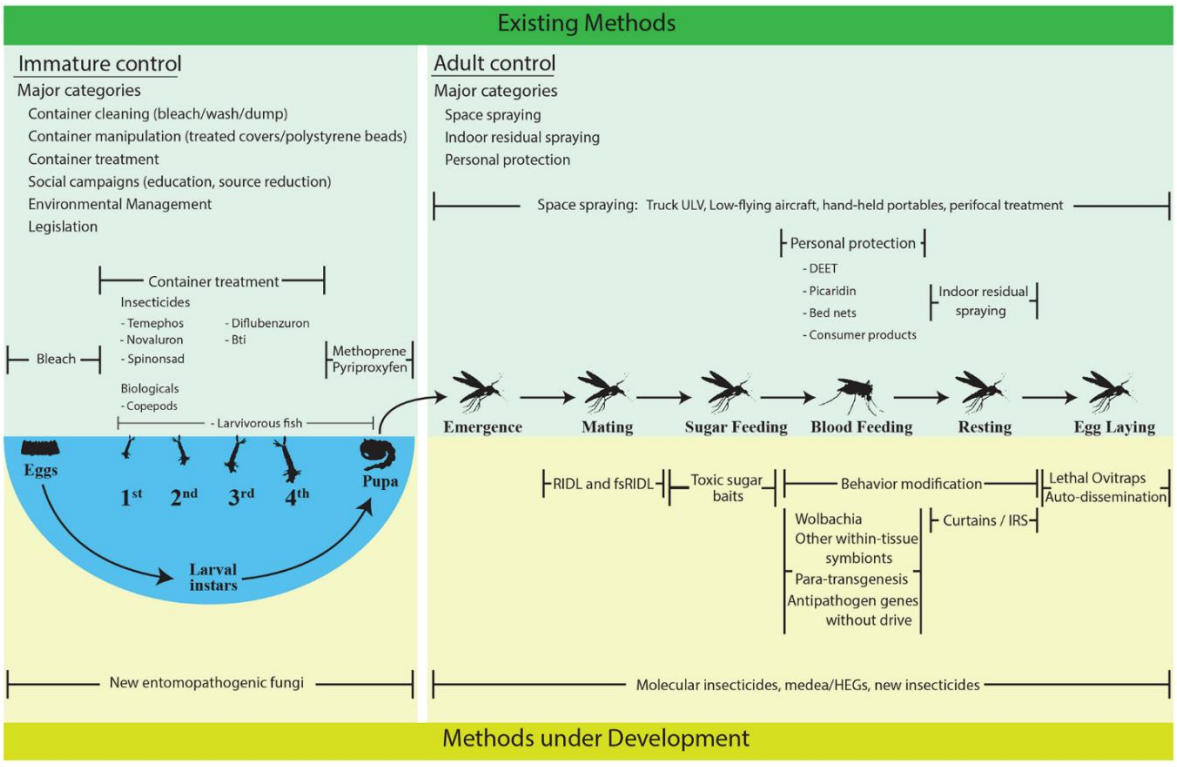
Treatment for DF – in the absence of antiviral prophylactic and/ or therapeutic therapies [36] – consists predominantly of supportive care and alleviation of clinical symptoms (e.g. fluid replacement therapy, blood transfusion, etc.), which may act to significantly reduce morbidity and mortality rates associated with the disease. Hospitalisation may be required in the management of more severe forms of dengue.

The avoidance of mosquito bites (i.e. preventing mosquito contact with human hosts to limit transmission of pathogens), vector-control measures, and community engagement for environmental management initiatives currently form the foundation of prevention and control activities for DF [11,134]. In the case of vector control, the primary objective is to

reduce vector transmission by decreasing and/ or interrupting human/ vector contact. *Aedes* control is linked to many United Nations Sustainable Development Goals (SDGs) including no poverty (SDG 1), good health and well-being (SDG 3), clean water and sanitation (SDG 6), reduced inequalities (SDG 10), sustainable cities and communities (SDG 11), climate action (SDG 13), life on land (SDG 15), and partnership for the goals (SDG 17) [135].

Current and historical vector-control strategies are principally made up of chemical- and non-chemical-based tools and encompass interventions vulnerable to potential insecticide resistance. Vector-control strategies target the different stages of the mosquito lifecycle, embracing immature (i.e. eggs, larvae, and pupae) and adult control stages of the mosquito lifecycle [136]. Figure 2.12 provides a useful summary of both current methods of vector control, as well as those under development.

Figure 2.12. Historical (i.e. 'existing') vector control and methods under development



Reproduced from Figure 1 of Achee et al. [136].

Bti, *Bacillus thuringiensis israelensis*; DEET, N,N-diethyl-meta-toluamide; fsRIDL, female-specific flightless release of insects carrying a dominant lethal; HEG, homing endonuclease gene; IRS, indoor residual spraying; RIDL, release of insects carrying a dominant lethal; ULV, ultra-low volume.

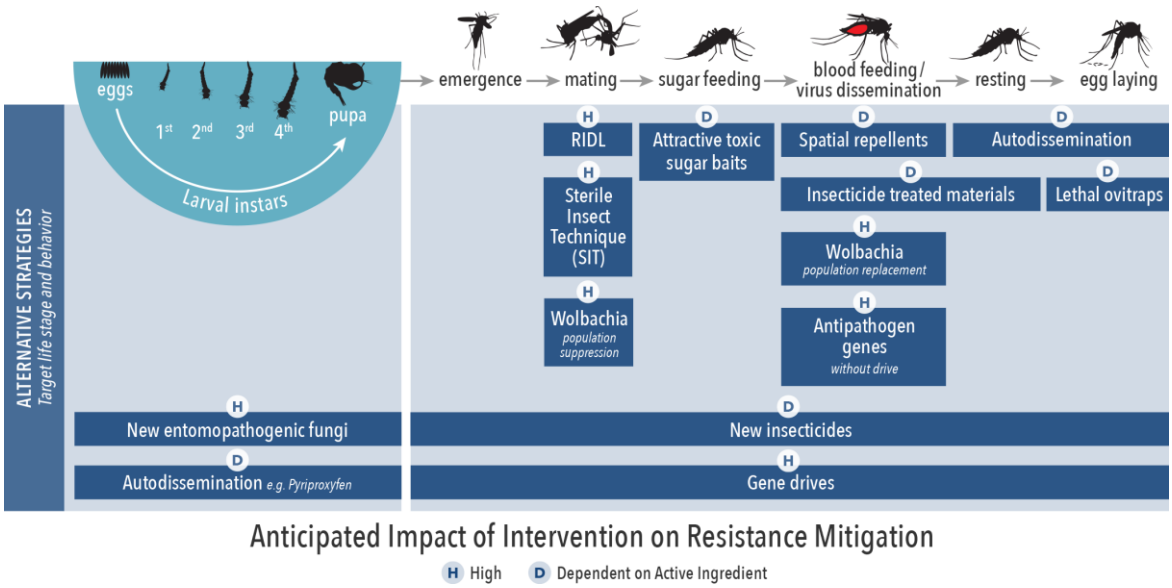
Anecdotal evidence suggests that local vector control 'at best' delays infection and has only a marginal impact on the total burden of disease, whilst large-scale control can have

considerable impact [137]. Notwithstanding this, the evidence base as to the efficacy and effectiveness of vector control is limited, primarily due to the inferior quality of design and conduct of vector-control studies. Several reviews have been conducted in recent years in an attempt to fill the evidence gaps, including Esu et al. [138], Achee et al. [136,139], Bouzid et al. [140], Bowman et al. [6], Horstick et al. [141], and Buhler et al. [142]). This is examined in greater detail in the following chapters.

In terms of real-world observation, a vector-control programme in Sri Lanka reported a 57% reduction in dengue incidence, with approximately 2,200 cases of dengue averted during the 31 months of the intervention [143]. The programme aimed to reduce mosquitoes in high-risk hotspots with large-scale systematic ‘door-to-door’ inspections supplemented by routine mosquito control interventions with insecticides and larvicides, underscoring the importance of the latter. Mixed teams composed of public health officials, police, and military personnel carried out daily inspections in several locations to identify and remove typical mosquito breeding sites, such as containers of stagnant water.

Insecticide-based vector control, usually deployed in the form of a single agent, has generally replaced control interventions that, for the most part, relied on larval control and environmental management and which were formulated on an in-depth understanding of pathogen transmission [134]. Commentators have identified escalating insecticide resistance as a barrier to successful dengue control, as it has the potential to reduce insecticide efficacy [144,145]. There are also environmental concerns related to the impact of insecticide residues [146], underscoring the necessity for alternative/ innovative methods to manage vector populations including *Aedes aegypti* [139,147]. Figure 2.13 provides an overview of a number of alternative strategies, with their anticipated impact on resistance mitigation, including sterile insect techniques (SIT), genetic manipulation, and *Wolbachia* infection [139,148-150].

Figure 2.13. Alternative strategies for vector control



Adapted from Achee et al. [139].

Notwithstanding the developments in vector control highlighted above, it is acknowledged that current (insecticide-based) approaches will likely play a continuing role in vector-control frameworks for the foreseeable future, given the relatively long lead time required for widespread implementation of new control measures [145]. In this regard, current guidance from the WHO '…encourages affected countries [in relation to both dengue and zika viruses] and their partners to boost the use of current mosquito control interventions as the most immediate line of defence, and to judiciously test the new approaches that could be applied in future' [151].

Thailand's dengue control strategy is derived from WHO guidelines [11], which consist of three key elements: 1) avoiding transmission by preventing mosquito bites in infected dengue patients; 2) active community detection of non-consulting cases; and 3) vector-control strategies comprising environmental management, source reduction, and chemical interventions (adulticide and/ or larvicide) [152].

In relation to dengue control via vaccination, the WHO has indicated that, ideally, a dengue vaccine should be given in the form of a single dose, protect against all four dengue virus serotypes, provide long-term immunity, and cause no serious adverse effects [19]. At present, only one dengue vaccine has been licensed, although uptake has been relatively low due to safety concerns [153,154]. In 2012, the initial results of a Phase 2b proof-of-concept trial conducted in Thai school children was published [155], indicating vaccine efficacy of 30.2% (95% confidence interval [CI] −13.4 to 56.6). Efficacy results

differed by serotype, but there were no safety signals after 2 years of follow-up after the first dose [155]. The overall estimate was used as the vaccine efficacy in the analyses presented in Chapter 3 [7]. Phase 3 vaccine trials subsequently conducted in both Asia [156] and Latin America [157] demonstrated a pooled rate of efficacy (in children aged 2–16 years in the first 25 months of follow-up) of 60.3% (95% CI 55.7–64.5) [154]. Analysis of long-term follow-up data of trial participants showed that the vaccine may potentially precipitate severe disease in people who had not yet been exposed to dengue [158]. Evidence from systematic reviews of economic evaluations carried out on the vaccine indicate somewhat mixed findings. For example, de Soárez et al. [159] concluded that the reviewed cost-effectiveness results should not be used in other countries due to methodological deficiencies and that local epidemiological and cost studies should be conducted. In contrast, a systematic review of economic evaluations of the vaccine conducted in Southeast Asian countries concluded that the vaccine could reduce the clinical and economic burden from dengue infection in these countries and be considered as cost-effective [160].

A number of other dengue vaccines are also in development, including one with published Phase 3 overall dengue vaccine efficacy results [161,162]. Overall vaccine efficacy results in children aged 4–16 years at 12- and 18-month follow-up, were 80.2% (95% CI 73.3–85.3) and 73.3% (95% CI 66.5–78.8), respectively, with no apparent serious safety signals. Vaccine efficacy varied by serotype, with efficacy against serotypes 1 and 2 being higher than against serotypes 3 and 4 [161,162]. For the purposes of Knerer et al. [8] and Knerer et al. [10], a dengue vaccine profile approximately consistent with (dengue) vaccines in late-stage development was adopted, and certain assumptions were applied in this regard. Further details are provided in Chapters 4 and 5.

2.7 Health economics, economic evaluation, and reporting

Health economics is the study of resource allocation and its distribution to and within the health sector [163]. Pharmacoeconomics is a sub-discipline within health economics that is concerned with allocation/ distribution in the pharmaceutical market [164]. Economic evaluation is a decision-making aid for the optimal societal resource allocation, encompassing the identification, measurement, valuation, and comparison of the costs and consequences of two or more alternative programmes or interventions [165]. Techniques of economic evaluation include cost-minimisation analysis [166], cost-effectiveness analysis [167], cost-utility analysis [168], and cost-benefit analysis [163]. Several guidelines exist to describe the general economic evaluation framework [165,169]. This work has been informed by Drake et al. [170] and best practice recommendations from the International Society for Pharmacoeconomics and Outcomes

Research (ISPOR) [171]. It also adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [172], which aim to provide recommendations in the form of a checklist to facilitate appropriate reporting of health economic evaluations. The CHEERS checklist consists of a 24-item checklist with recommendations in relation to the minimum amount of information to be included in an economic evaluation. The primary audiences for these standards are researchers reporting economic evaluations, editors, and peer reviewers evaluating their publication potential. The full checklist can be found in Husereau et al. [172].

2.8 Economic and disease burden of DF

DF presents a large and increasing disease burden in terms of frequency, cost, and quality of life [173]. Commentators suggest that current estimates are likely conservative due to underreporting of dengue episodes (highlighted in section 2.5) and have considerable uncertainty, particularly in Africa and South Asia [95]. The primary methods for quantifying and comparing country-specific and global burdens of DF include:

1. DALYs
2. Economic impact of DF. This can be stratified into:
   - Costs of illness (estimated from total symptomatic episodes multiplied by the average costs per episode)
   - Other impacts of DF (e.g. impact on tourism and foreign direct investment [FDI]).
   - Costs of dengue prevention and control strategies

2.8.1 DALYs

Similar to quality-adjusted life years, DALYs are an age-weighted measure of the estimated years of life lost from premature death, and years of life lived in less than full health (years lived with disability) [174]. DALYs concern only mortality and disability; healthcare disorganisation, productivity losses, and broader economic impacts also characterise the burden of dengue illness but are not taken into account in DALYs.

Earlier estimates of the worldwide burden associated with a range of diseases showed that approximately 825,000 DALYs annually were reported for dengue in 2010 [18], an increase of 15.9% since 1990, which was not the case for the majority of communicable diseases. Dengue burden was ranked ninth out of 16 diseases in the ‘neglected tropical diseases and malaria’ category. Only 19 of 82 infectious diseases saw their number of DALYs increase [18]. Estimates of the burden of dengue as part of the Global Burden of Disease 2013 study indicated that the disease was responsible for approximately 1.14 million (95% uncertainty interval [UI] 0.73 million to 1.98 million) DALYs globally [20]. This

figure subsequently increased to 2.92 million (95% UI 1.63 million to 3.97 million) DALYs globally in a 2017 update [175]. Regional estimates from the 2013 study [20] suggested that approximately 596,700 (95% UI 342,300–952,000) DALYs in Southeast Asia and 74,100 (95% UI 40,100–141,900) DALYs in Latin America were attributable to DF, with the former having the highest rate of DALYs lost due to dengue illness, followed by Latin America. The disparity in numbers between the two regions may be partially explained by the higher incidence rates of severe dengue (i.e. DHF and DSS) in Southeast Asia compared to the Americas, as well as the higher case fatality rate [114] in the former. DALY estimates specific to Thailand include 427 (range 393–1046), 465.3 (range 76.5–954), and 471 (UI 286–827) DALYs per million population per year [20,176,177].

2.8.2 Economic costs of DF

When assessing the economic impact associated with dengue, estimates of the annual cost of illness range from approximately 1 billion United States dollars (USD) [178] at the regional level to approximately 8.9 billion USD (UI 3.7–19.7 billion) globally in 2013, with 18% of cases being admitted to hospital and the remaining 48% and 34% of cases classified as ambulatory and non-medical, respectively [179]. Research suggests that almost 1 billion USD [178] was spent each year in Southeast Asia to treat dengue illness during 2000–2010, with Indonesia and Thailand responsible for 34% and 31% of the total, respectively [178]. Approximately 451 million USD of these costs were direct costs. Aggregate dengue costs for Thailand were estimated to be approximately 216 million USD per annum (2010). Similarly, and by way of comparison, approximately 2.1 billion USD was spent each year from 2000 to 2007 in the Americas to treat dengue, with Brazil accounting for more than 40% of the total economic burden of dengue (880 million USD) in the region [180]. The methodologies used to derive costs in these two studies were broadly comparable in their use of expansion factors, surveillance data from the WHO, and/ or national and regional case surveillance reports, as well as cost estimation. Ambulatory and hospitalised medical costs, productivity losses, and the cost of premature deaths were included, but vector-control costs were not considered. More recent figures using dengue incidence estimates from the Global Burden of Disease Study 2013 [20] suggest that the aggregate cost of dengue in the Southeast Asia, East Asia, and Oceania super-region was approximately 4.8 billion USD (UI 1.9–10.8 billion) [179]. Analogously, it has been estimated that the corresponding cost of dengue in the Latin America and Caribbean super-region was approximately 1.73 billion USD (UI 0.72–3.90 billion) in 2013, with Brazil accounting for more than 40% of the total economic burden of dengue in the region [179]. Updated aggregate dengue costs specific to Thailand were estimated to be approximately 425 million USD per annum (2013).

2.8.3 Broader economic impacts of dengue

Other important elements should be considered when estimating the economic impact of dengue, e.g. the potential impact of dengue disease on tourism revenues [181-183], possible detrimental effects on FDI resulting from the incidence of dengue [184-187] and persistent dengue cases or sequelae following infection [54,188-190].

2.8.3.1 Tourism

In econometric analyses examining the relationship between monthly tourism data in 13 Brazilian states and monthly reported dengue cases (controlling for calendar year), Bloom [191] suggested that one additional dengue case reduces the number of tourists by 0.36 ($p<0.0001$). Applying this same regression estimate to the average annual estimated expenditure per tourist in Thailand in 2012/2013 ($1,421) yields a potential economic loss of 511.70 USD (2013) per dengue case in Thailand. The validity of this figure is based on the assumption that the statistical relationship between monthly tourism data and monthly dengue cases identified in Brazil also holds true for Thailand.

2.8.3.2 FDI

As highlighted in section 2.9.3, disease incidence can affect the net inflow of FDI into a country [186]. Due to an outbreak of severe acute respiratory syndrome (SARS) in China, analyses showed that there was a reduction of approximately 2.7 billion USD in FDI inflows into mainland China in 2003 and a 62% reduction in FDI into Hong Kong for one quarter; these trends were subsequently quickly reversed on control of the outbreak [192]. Additionally, the authors highlighted that long-term epidemics, such as HIV/ AIDS or malaria could also have severe long-term impacts on FDI [192]. In time series analyses of Brazilian FDI data, Bloom [191] calculated that dengue disease incidence impacted the net inflow of FDI into Brazil to the value of 204 USD per dengue case in 2011.

2.9 Dengue prevention – costs

Dengue control activities form a considerable share of the total dengue economic burden in most dengue-endemic countries, with substantial resources expended on vector control (representing up to approximately half of the total costs of dengue illness) [193,194]. The reported costs of a routine dengue vector-control programme range from 0.2 to 38 USD per inhabitant per year; the median cost being around 2.5 USD per inhabitant per year [195]. At a minimum, this equates to approximately 6.25 billion USD worldwide after adjusting for the approximately 2.5–3.5 billion people living in dengue-endemic countries [195].

Undurraga et al. [196] performed a systematic review to assess the costs of dengue vector-control strategies (Appendix A). Eighteen articles were examined in total, relating to 15 different countries (eight in Latin America and the Caribbean, six in Southeast Asia, and one in Africa), of which nine analysed comprehensive vector-control activities [196]. Their findings indicated that in these nine specific countries, the average per capita cost of dengue vector control was 2.14 USD (2013) [196]. For Thailand in particular, cost estimates varied between 1.15 USD per capita for education, limited use of larvicides, and insecticide [197] and 1.42 USD per capita for insecticides and larvicides [198]. The other nine articles in the review [196] related to the costs of distinct vector-control interventions, e.g. community mobilisation [199,200] or source reduction [201]. Similarly, Fitzpatrick et al. [202] conducted a literature search and data extraction exercise in relation to the costs of 'sustained' vector-control interventions as part of a mathematical modelling analysis. The authors defined vector-control costs to include the cost of both 'sustained' vector control as well as outbreak response interventions. Unit cost estimates used in the study for 'sustained' vector control are presented in Table 2.5 [202].

Table 2.5. Country-specific unit cost vector estimates

Country	**Sustained vector control (2013 USD per capita per year)**		
	Best	**Lower 95% UI**	**Higher 95% UI**
Brazil	0.60	0.31	1.04
Colombia	0.68	0.40	1.09
Mexico	0.65	0.35	1.14
Malaysia	0.72	0.41	1.20
Philippines	0.50	0.26	0.89
Thailand	0.66	0.40	1.06

Adapted from Fitzpatrick et al. [202].

USD, United States dollars; UI, uncertainty interval.

Respective costs per capita per year are perhaps not directly comparable due to differences in methodology and definition. Notwithstanding this, it is clear that the total annual budget outlay on vector control varies considerably by country, with considerable resources expended in countries in Southeast Asia as well as in Latin America [196,202]. Although expenditure linked to vector-control activities still forms a key element of vector-borne disease control programme budgets, programme capacity has declined markedly from the highpoint of eradication programmes for malaria and *Aedes aegypti* in the 1960s and 1970s. For example, complete vector eradication was achieved in 21 countries of the Americas following military-like campaigns to eliminate *Aedes aegypti* between 1948 and 1972 [203]. The combination of reasons for this include the gradual scaling back and

abandonment of vector-control programmes over many years coupled with the trend for decentralisation of many programmes within countries [204].

2.10 Operational research (OR) in healthcare, global health, and infectious diseases

With the challenges (encompassing epidemiological and economic burden) that DF poses to healthcare systems and societies at large, public health officials must determine where to allocate resources appropriately to manage these problems and response(s). OR has a long history in this regard, using modelling and related analytical techniques to investigate resource allocation problems in healthcare, global health, and infectious diseases; and has been successfully applied to a variety of optimisation problems. Rais and Viana [205] carried out a comprehensive survey (>200 studies) of CO and simulation studies in healthcare, with the authors highlighting research activities focusing on a variety of optimisation problems as well as techniques used for solving them. In a similar vein, Batun and Begen [206] have provided an overview of several practical optimisation applications in healthcare operations management, including appointment scheduling, operating room scheduling, organ allocation and transplantation, disease screening, and vaccine design. In global health, Royston [207] and Bradley [208] have detailed the extent and applicability of OR in global health, with the former documenting the utility of quantitative and computational tools (including system dynamics, discrete event/ agent simulation, and mathematical modelling) and the latter presenting a global summary overview of the geographic distribution of OR studies and documenting key drivers for success in bridging the gap between OR and global health policy. In infectious diseases, Brandeau [209] has presented a review of different OR-based methods that have been applied to the allocation of resources to control infectious diseases. The author highlighted how OR-based models can help determine the allocation of resources that maximise health benefits, providing important input into decision-making processes. This has been further elucidated in several follow-up articles within the prevailing theme of facilitating good decision-making through OR-based modelling to evaluate the potential impact of alternative public health programmes and the assessment of the likely costs and health consequences and highlighting her work in hepatitis B control, HIV control, and bioterrorism preparedness and response [210]. The author drew the distinction between applied and theoretical practices and the importance, or rather the centrality, of the former in her work.

In an overview of OR in infectious diseases and the lessons that could be applied to non-communicable diseases, Bosu [211] sought to extract learnings from a variety of examples drawn from OR in infectious diseases. The areas of focus included priority

setting for research and routine service delivery, modelling, and the process of turning findings into policy/ practice. Also, in the particular case of malaria, detailing the systematic approach to the assessment of insecticide-treated-nets, including real-world effectiveness studies (vs. untreated nets) and cost-effectiveness studies of insecticide-treated-nets compared with other malaria control interventions [211].

Similar to malaria, as referred to above, DF is a complex disease with vector/ human interaction and efficient vector survival strategies. As with malaria, mathematical models of, for example, DF transmission have been developed to gain insights into disease transmission, predict outbreaks, and to test and compare different intervention strategies that might be useful in controlling disease and suggest the optimal course of action, which is particularly important in resource-constrained contexts. In the following sections, dengue models are detailed in greater depth, beginning with a background to infectious disease models.

2.11 Characteristics of infectious disease mathematical models

Mathematical models have been widely used to analyse and quantify the transmission of various infectious diseases [212-221]. Brauer [222] presents an excellent overview of mathematical models and outlines some of the important aspects in the history and development of infectious disease mathematical modelling. Importantly, and particularly relevant in the context of the current COVID pandemic, the author details the historical variance between mathematicians and public health professionals in the development of infectious disease mathematical methods, with the former aiming for broad understanding and the latter, practical measures for infectious disease management. He rightly states that whilst mathematical modelling has informed both transformative and practical measures in, for example, the control of smallpox by vaccination and the management of malaria by vector population control, practical implementation is perhaps (considerably) more challenging than projections from (simple) mathematical models [222]. One may debate, perhaps at length, his sentiments as to whether efforts to encourage better communication have been realised so that '…public health professionals can better understand the situations in which simple models may be useful and mathematicians can recognize that real-life public health questions are much more complicated than simple models' [222].

Epidemic disease models, as such, can be traced back to Bernoulli in the eighteenth century and his model of smallpox [223,224]. On smallpox inoculation: 'I simply wish that, in a matter which so closely concerns the well-being of mankind, no decision shall be made without all the knowledge which a little analysis and calculation can provide' (Daniel

Bernoulli 1700–1782).

In the early part of the twentieth century, a methodology for the underlying structure of population dynamics was proposed by Ross [225,226], with the author being awarded the second Nobel Prize in Medicine for the demonstration of mosquitoes as the vehicle of transmission for malaria. This was subsequently formalised by Kermack and McKendrick in 1927 [227]. The early models, as well as subsequent revisions and improvements, were predicated on the principle that individuals could be classified by their epidemiological status [222,225,228-231] and employ deterministic (i.e. the number of newly infected people is always the same for a given number of susceptible people and infectious people [232,233]) ordinary differential equations. In these models, the total population is divided into respective ‘compartments’ (categories) according to the biological properties of different states (e.g. states of infection), for example: ‘susceptible’ (i.e. persons who have no immunity to the infectious agent, and might become infectious if exposed), ‘exposed’ (i.e. exposed/ latent phase but not yet infectious), ‘infected’ (i.e. those persons who are capable of spreading the disease), and ‘recovered’ (i.e. persons who have cleared the infection) in the susceptible-exposed-infected-recovered (SEIR) model [232]. The people in a compartment or category in the model are assumed to have similar characteristics, which are consistent with features of people in the ‘real’ world. Each flow rate between compartments is comprised of the number of individuals entering or leaving a compartment per unit time. Key features of these deterministic transmission models are that the force of infection and rates act on groups in categories and that the same answer is obtained every time [230,232].

Although mathematical models should ideally be parsimonious, they should also attempt to capture the essential details of the disease. Accordingly, additional compartments may often be inserted into the model to reflect further complexity, with any supplementary details to be included dependent on the questions to be addressed by the model, as well as the availability of data (e.g. Anderson et al. [212]; Brauer [234]; Brauer and Castillo-Chavez [235]; Brauer and Kribs [236]; Brauer et al. [237]; Keeling and Rohani [230]; Martcheva [238]; Vynnycky and White [239]; and Tang et al. [240]). Different combinations of disease states can be used to represent the biology of disease and infection in models, for example, susceptible–infected (SI) models to represent lifelong infections without recovery (e.g. herpes simplex virus), susceptible-infected-susceptible (SIS) to represent transient infections that do not confer natural immunity (e.g. gonorrhoea), and susceptible-infected-recovered (SIR) for childhood infections that confer natural immunity.

Other model types include:

- Stochastic and compartmental: the number of infections per day is drawn from the binomial distribution, with probability of infection equal to the contact rate multiplied by the probability that each contact is infectious multiplied by the probability that transmission occurs
- Stochastic and individual-based: everyone makes a certain number of contacts per day. If that contact is infectious, there is a certain probability that transmission will occur. Analogous to the compartmental model described above, individual-based models also group individuals with similar characteristics. However, the transmission (flow) between states, such as healthy and infectious, is determined by the behaviour of the individual, not the group as a whole. For example, an individual-based model can show how a virtual person might behave in a simulated community. During an epidemic, each person has the chance of catching or spreading an infection through encounters with others at home, work, school, and elsewhere. How the disease spreads through the population depends on whether and when individuals encounter each other, as well as what their characteristics are at the time of the encounter [241,242].

2.12 Mathematical models specific to DF

A summary of the approaches used in DF modelling from 1964 to 2006 has been presented by Nishiura [243]. Most of the studies cited used differential equation compartmental models in their analyses, with a small number of studies reporting some form of statistical model. The author showed that, despite different objectives and assumptions evident in the 37 publications under review, the studies revealed a common methodology underlying the structure of population dynamics. A critical appraisal of DF models has also been carried out by Johansson et al. [244], who reviewed models used to assess the impact of future dengue vaccination programmes as well as approaches used to validate and parameterise models. The authors noted the importance of short-term cross-protection as a key feature to be included in mathematical models of DF transmission, as well as the fact that force of infection may be significantly underestimated given the absence of cross-protection in much of the dengue modelling literature reviewed [244]. They further highlighted the evolving consensus related to secondary infections as a potentially important determinant of long-term dynamics via enhancement of susceptibility or infectiousness. Notwithstanding this, they also acknowledge that increased morbidity and mortality associated with secondary infections, in itself, does not really have a large impact on the dynamics of dengue virus transmission at the population scale [244].

Andraud et al. [245] undertook a systematic review of structural approaches in the modelling of dengue transmission. The authors searched and screened all the dengue models published up to March 2012 and included 42 studies. They reviewed deterministic models of dengue transmission to identify important characteristics for future model development, as well as to summarise what is termed 'the evolution of insights' provided by such models. They explicitly acknowledged parallels with the Johansson et al. [244] review in terms of model designs appraised, but sought to draw distinctions relating to both the level of detail offered and the linkages with the underlying assumptions based on epidemiological and entomological studies [245]. A table of model descriptions was presented, or what is termed the 'phylogenetic tree', representing the relationships between selected articles and the main assumptions for each article. The 'phylogenetic tree' has arms detailing single- and multi-serotype models. Each sub-division reflects the main epidemiological and/ or entomological characteristics of the models. The authors advocated the use of combined vector-host transmission models as being the most relevant for health policy in terms of providing projections of combined vaccination and vector-control interventions.

In this thesis, deterministic compartmental models (consistent with the dengue modelling literature), rather than an individual-based stochastic model, are developed. Examples of agent-based models include Focks et al. [246], Chao et al. [247], Perkins et al. [248], and Mahmood et al. [249]. Compartmental dengue models tend to be more common than agent-based models (e.g. Coudeville et al. [250]; Rodriguez-Barraquer et al. [251]; Bartley et al. [109]; Fischer et al. [252]; Feng et al. [253]; Nagao and Koelle [254]; Wearing et al. [12]; Adams et al. [255]; Cummings et al. [256]; Esteva et al. [257]; Ferguson et al. [258,259]; Recker et al. [260]; Chikaki et al. [261]; Pongsumpun et al. [262].

Several reasons inform this choice. First, stochastic and individual-based models may be appropriate when modelling the course of a new outbreak, with the majority of the population still in susceptible states, and only small proportions infected and/ or infectious. In this case, further transmission of the disease will strongly depend on individual behaviour patterns (such as personal contacts, relocations, etc.). Accordingly, stochastic (i.e. random) effects should be considered in order to account for these effects.

In the case of DF, the impact of individual choices appears to be minimal. The disease is well established, even when accounting for certain seasonal patterns. Observed fluctuations and outbreaks appear to be more related to seasonality, vector life cycles, and eradication policies than to individual behaviours. Andraud et al. [245] excluded spatial and stochastic models in their systematic review of dengue models. According to

the authors, ‘non-spatial deterministic approaches provide a good mean-field approximation of the system behaviour and preserve the time series pattern of infected hosts, even while ignoring the stochastic features of the dynamics.’

Furthermore, according to the WHO guides for the standardisation of economic evaluations of immunisation programmes [263,264], stochastic models are considered to be more suitable for modelling small populations (e.g. small islands) or simulating the rise of an emerging infection or the demise of a rare infection close to elimination, because the importance of random transmission events in these particular situations is taken into account [263,264]. In contrast, it is apparent that these situations are not representative of DF incidence in Thailand. Therefore, the choice of a deterministic compartmental model in this study is consistent with WHO recommendations [263,264].

Lastly, a deterministic compartmental model would appear to be a better fit with the overall aims and objectives of this project. For example, deterministic models provide a greater degree of flexibility to test the impact of various assumptions and scenarios as they require fewer inputs and less time to run (although the latter is still an issue). It is also possible to run a large range of sensitivity analyses, which may be impractical to conduct with a stochastic (microsimulation) model. The latter may require fewer approximations, and in theory, the resulting estimates may be more precise and subject to less error than a compartmental model, but it is felt that a comparatively simpler differential equation model will be able to capture the main dynamics at work in this disease.

Accordingly, the underlying structure of a disease transmission model from Bartley et al. [109] was adapted. This is one of the pivotal models in the dengue modelling literature, including immunological interactions between the serotypes (cross-protection and cross-enhancement), seasonality, and explicit modelling of the vector population.

2.13 Data

The dengue incidence data used in this study originated from the Bureau of Epidemiology, Ministry of Public Health, Thailand. The country has a countrywide passive surveillance system for DF, which is an important source of consistent data in relation to age, severity of disease, and serotype. The surveillance reporting system for DF was instituted in 1958, with a national (surveillance) system for DHF subsequently being introduced by the Thailand Bureau of Epidemiology in 1972 [107,265]. In 1994, DF was incorporated into the surveillance system [107].

Suspected cases of dengue are reported at physicians’ discretion, with a mandatory

stipulation to report confirmed cases of the disease. Medically trained doctors provide the diagnoses of all reported dengue disease cases in Thailand using WHO case criteria that classify cases as DF, DHF, or DSS [69]. Nationwide health facilities report hospital in-patient [69] and out-patient diagnoses for dengue disease, with notifications being collected from all government hospitals and a minority of private hospitals and clinics.

Dengue surveillance data for the years 2008–2012 [266-270] were used in this study, encompassing the annual numbers of reported dengue cases (DF, DHF, DSS) and deaths, stratified by age group. Furthermore, classifications of reported dengue cases as outpatient and/ or inpatient (cases) were used in the calculation of economic costs. The data are published by the Bureau of Epidemiology, Ministry of Public Health, Thailand in the form of Annual Epidemiological Surveillance Reports, which are available online on the Ministry of Public Health website [266-270].

In the first instance, surveillance data for the year 2008 [266] was used to calibrate the first epidemiological transmission model [7]. The full dataset covering the years 2008–2012 was subsequently used to calibrate models as detailed in Knerer et al. [8] and Knerer et al. [10] and presented in Chapters 4 and 5, respectively. The average annual number of dengue cases for the years 2008–2012 was calculated to generate a stable estimate of the total projected annual number of dengue cases due to the observed variability in the number of dengue cases between respective years (2008 being considered a peak year in terms of the number of dengue cases [107]).

2.14 Software

The dynamic transmission models presented in Chapters 3 and 4 were implemented in Berkeley Madonna and were used to code the differential equations. For the model analyses conducted in Chapter 5, the software programme Matlab was used to code the differential equation and optimisation code.

3 Impact of combined vector-control and vaccination strategies on transmission dynamics of dengue fever: a model-based analysis

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3.1 Abstract

Dengue fever is a vector-borne disease prevalent in tropical and subtropical regions. It is an important public health problem with a considerable and often under-valued disease burden in terms of frequency, cost and quality-of-life. Recent literature reviews have documented the development of mathematical models of dengue fever both to identify important characteristics for future model development as well as to assess the impact of dengue control interventions. Such reviews highlight the importance of short-term cross-protection; antibody-dependent enhancement; and seasonality (in terms of both favourable and unfavourable conditions for mosquitoes). The compartmental model extends work by Bartley [109] and combines the following factors: seasonality, age-structure, consecutive infection by all four serotypes, cross-protection and immune enhancement, as well as combined vector-host transmission. The model is used to represent dengue transmission dynamics using parameters appropriate for Thailand and to assess the potential impact of combined vector-control and vaccination strategies including routine and catch-up vaccination strategies on disease dynamics. When seasonality and temporary cross-protection between serotypes are included, the model is able to approximate the observed incidence of dengue fever in Thailand. We find

vaccination to be the most effective single intervention, albeit with imperfect efficacy (30.2%) and limited duration of protection. However, in combination, control interventions and vaccination exhibit a marked impact on dengue fever transmission. This study shows that an imperfect vaccine can be a useful weapon in reducing disease spread within the community, although it will be most effective when promoted as one of several strategies for combating dengue fever transmission.

Keywords Dengue fever · Multi-strain model · Seasonality · Vector control · Vaccination

3.2 Introduction

Dengue fever is associated with severe urban epidemics and has become a major public health problem, with considerable economic, political, and social impacts. The WHO currently ranks dengue fever as the most important mosquito-borne viral disease in the world [271]. Dengue fever occurs in more than 100 countries in the tropical and subtropical regions of Asia-Pacific, the Americas, the Middle East, and Africa with an estimated 3 billion people at-risk [271]. Persons living in areas where dengue fever is endemic can often be infected with three and quite often four dengue serotypes in their lifetime [17]. The reason for this is that whilst the circulation of multiple serotypes was geographically relatively restricted in 1970 for example, it is now apparent that most regions (e.g. Central and South America, central Africa etc.) are prone to the circulation of multiple dengue serotypes [16].

Dengue is a mosquito-borne disease, caused by serologically related but antigenically distinct viruses grouped into four serotypes (DENV-1 to DENV-4). Recovery from infection confers permanent immunity to that serotype, but only short-term cross-immunity to other serotypes [11-13]. All serotypes can cause severe and fatal disease with clinical cases being classified into two groups: dengue fever (DF) and dengue hemorrhagic fever (DHF). Symptoms produced by dengue infection last approximately 3 to 12 days, with an average duration of 5–7 days following the onset of symptoms [36]. The illness persists for several days after the viraemic period (i.e. virus circulating in the blood) has ended [36,272]. The symptoms of dengue hemorrhagic fever are more severe than dengue fever symptoms and can lead to death. Dengue hemorrhagic fever may in turn subsequently develop into an acute form of the disease known as dengue shock syndrome (DSS). Risk factors for the incidence of the more serious forms of the disease (Dengue hemorrhagic fever or Dengue shock syndrome) tend to be associated with people who have had past infections with one or more dengue serotypes [21,62,63]. The theory behind this relates to immune or antibody-dependent enhancement (ADE), i.e. an immune response to one serotype which enhances (rather than negates) future infections and can increase the likelihood of

severe disease [21,62,63].

Dengue embraces a wide clinical spectrum from asymptomatic infections to severe manifestations resulting in large numbers of both unreported and asymptomatic infections. It is estimated that approximately 50–100 million individuals are infected every year [272] with 500,000 cases of dengue hemorrhagic fever and 22,000 deaths [32]. Recent work suggests that the number of 'true infections' is considerably greater than the dengue burden estimate of WHO by at least a factor of three [23]. Using advanced mapping techniques, the authors estimate that there are approximately 390 million dengue infections per year with a credible interval of 284–528 million. Furthermore, it is estimated that approximately 96 million of these infections (credible interval 67–136 million) are evident (i.e. any level of disease severity) [23]. The reasons for the growth in dengue fever and dengue hemorrhagic fever as a leading public health challenge tend to be multi-factorial. This includes relatively ineffectual mosquito control, rapid population growth and increase in overseas air travel, an increase in non-biodegradable packaging as well as deteriorations in public health infrastructure [16,273].

The incidence of dengue fever is shown to exhibit a clear dependence on seasonal variation [274-277]. As can generally be observed, the number of cases is correlated with seasonal patterns with the peak of cases in June and July when environmental conditions are more conducive to mosquito development, i.e. humidity and precipitation are much higher compared with periods of low temperature [274-276].

The most common vector responsible for epidemic dengue is the infected female of the *Aedes aegypti* mosquito [26]. These predominantly daytime-biting insects live in the vicinity of human habitats and usually lay eggs and produce larvae in artificial containers. In the absence of a vaccine with proven efficacy against all four serotypes or of any drugs for its treatment [36,155], the control of dengue is currently limited to decreasing *Aedes aegypti* population densities or preventing their contact with human hosts [278]. Major vector control strategies include environmental management and source reduction (i.e. locating and removing mosquito breeding sites, improved sanitation etc.), use of larvicides (i.e. targeting the larvae forms of mosquitoes by spreading chemical larvicide in breeding sites) and insecticide spray targeting adult mosquitoes (adulticide) [36]. Additional prevention methods include the biological control of vectors and the use of repellents that reduce the contact between infected humans and susceptible mosquitoes in the form of sprays for personal protection, impregnated clothing and curtains, screens on windows and mosquito nets [36].

Mathematical models of dengue fever have been developed to gain insights into disease transmission [12,109,246,254,257,261,279-281], predict outbreaks as well as simulate the impact of interventions for disease control [247,250,277,282-291]. Historically, studies tend to be divided into those that consider mechanical and chemical interventions on the one hand [282,283,285-291], and those that consider vaccination on the other [247,250,284]. On the whole, few have begun to consider the combined effects of a range of different interventions including vaccination [292]. A summary of the approaches used in dengue fever modelling from 1964 to 2006 is presented by Nishiura (2006) [243]. The majority of studies cited use differential equation compartmental models in their analyses with a small number of studies reporting some form of statistical model. A critical appraisal of dengue fever models was also conducted by Johansson (2011) [244], who noted the importance of short-term cross-protection as well as the fact that force of infection may be significantly underestimated given the absence of cross-protection in many dengue fever models [244]. Analogously, Andraud (2012) [245] carried out a review seeking to identify important characteristics for future model development. The authors advocated the use of combined vector-host transmission models as being the most relevant for health policy in terms of providing projections of combined vaccination and vector control interventions. The broad aim of this study is to assess the effectiveness of historical forms of vector control in relation to other forms of disease management including a partially effective vaccine. A dynamic compartmental transmission model is developed simulating the impact of different control strategies, in order to reflect the consequences of these interventions on the epidemiology of dengue in Thailand and determine the optimal combination of approaches to disease control based on the subsequent reduction in incidence. The main contributions of this paper to the dengue modelling literature are the inclusion of the impact of combined vector-control and vaccination strategies on the transmission of dengue fever, age-structure of the model population, seasonality, consecutive infection with all four serotypes as well as considerations of cross-protection and immune-enhancement. In the next section, the model is described, followed by a presentation of results, a brief discussion and ending with conclusions and next steps.

3.3 Methods

3.3.1 Mathematical model

The model extends work by Bartley (2002) [109] and includes the following elements: consecutive infections with all four serotypes, age-structure of the population, seasonality, cross-protection and immune enhancement and the impact of combined vector-control and vaccination strategies on the transmission of dengue fever.

Bartley (2002) [109] developed a multi-serotype deterministic compartmental model

(SEIR: SEI) incorporating vector-host transmission, seasonality and secondary infection. The influence of seasonality worked through vector parameters including recruitment, mortality, biting rates and duration of extrinsic incubation period (EIP) which were estimated from entomological studies in Bangkok. Antibody-dependent enhancement was explored in the model by the inclusion of a scaling factor in which ADE may lead to increased infectiousness of the individual (by a factor of φ_{he}) infected for a second time. Sensitivity analyses indicated that duration of infectiousness in the host, vector latent period as well as biting and vector mortality rates were key model parameters. Although the model did not calibrate well with observed data (based on goodness-of-fit tests), the authors concluded that strong correlations provided enough evidence for the necessary inclusion of the main determinants of seasonality. Subsequent work carried out by Wearing and Rohani (2006) [12] and building on the work of Bartley (2002) [109], reinforced the importance of seasonality as well as temporary cross-immunity to explain intra-annual and inter-epidemic dynamics observed in dengue endemic areas.
The epidemiological literature and previous modelling studies are used to inform parameter values in the model comparing the effects of different interventions. In this regard, we draw heavily on inputs from published models of dengue fever developed by Bartley (2002) and Burattini (2008) [109,283] where the model calibrates well with actual data from Singapore. It is assumed that Singapore is not qualitatively different from Thailand in terms of the manifestation of dengue fever. The sensitivity of the results to changes in parameter values and assumptions are subsequently examined in scenario and sensitivity analyses.

3.3.2 Dengue surveillance data

Data from National Epidemiological Surveillance in Thailand [266] indicate that there were approximately 90,000 reported cases of dengue fever/dengue hemorrhagic fever in Thailand in 2008 including 51,355, 1626 and 36,645 dengue hemorrhagic fever, dengue shock syndrome and dengue fever infections respectively. There were also 102 deaths reported in 2008 with the great majority (70%) due to dengue shock syndrome with the remainder attributable to dengue hemorrhagic fever. The highest number of cases were in the 10–14 years age group (*n* =24,480) closely followed by the 15–24 years age group (*n* =23,966).

3.3.3 Magnitude of potential under-reporting of dengue fever infections

Wichmann (2011) [99] states that total and inpatient dengue cases in Thailand may have been under-reported by as much as 8.7 and 2.6 times respectively in the period 2003–2007. Moreover, they estimate that greater than 340,000 (median) symptomatic dengue infections occurred annually in these years in children less than 15 years of age, the

extent of which is not assessed or reflected in national surveillance figures. Their assessment was based on the numbers of nationally reported inpatient dengue cases as well as average multiplication factors which were generated by comparing Thai provincial reporting data with data from prospective cohort studies in the same province [99]. Any potential under-identification of dengue infections is further corroborated by Undurraga (2013) [293]. The authors estimate average annual dengue fever episodes and under-reporting rates for 12 countries in Southeast Asia (2001–2010) stratified by hospital and ambulatory treatment. Their results suggest average reporting rates of 13.2% of total symptomatic dengue episodes in the region, implying an expansion factor of 7.6 for converting reported cases into estimated actual cases.

The issue of under-reporting of dengue cases, akin to missing data, has implications for the development of mathematical models seeking to estimate the burden of disease. Our model seeks to calculate the 'true' epidemiological burden of dengue fever in Thailand by incorporating an adjustment for estimated under-reporting. Model estimates are therefore calibrated with figures reported by National Epidemiological Surveillance in Thailand in 2008 [266] multiplied by an expansion factor of 7.6 [293]. We use the more recent and lower estimate of Undurraga (2013) [293] to adjust for under-reporting to be conservative in our calculations although both the estimates of Wichmann (2011) and Undurraga (2013) [99,293] are relatively comparable and consistent with each other.

3.3.4 Dynamic transmission model

We develop a compartmental transmission model based on SEIR-type of models (Susceptible, Exposed, Infected, and Removed). The epidemiological dynamic transmission model represents the host population as residing in compartments (e.g., susceptibility or disease states) and moving between compartments over time. The movement of the population between compartments is stated mathematically and the system is described by a set of differential equations that represent the flow in and out of each compartment with respect to time. Solving the differential equations allows prediction of the distribution of the population across compartments at given time points, changes over time (e.g., incidence of disease), as well as identification of the equilibrium state. Each flow rate between compartments is dependent upon the value of the input parameters of the transition equations. Parameter values along with data sources are listed in Appendix B. Rates are estimated as the inverse of the average time spent in the compartment. Initial conditions were derived by running the model to equilibrium steady-state without any control interventions. The transmission model is used to estimate epidemiological outcomes including the incidence of dengue fever.

Model compartments comprise those for both human and vector populations. The human population (N_h) is divided into susceptible to dengue infection (S_h); exposed but not yet infectious (i.e. incubating the virus) (E_h); infected and infectious (I_h); temporary cross-protection (C_P); temporary cross-enhancement (C_E) and immune (R) compartments. Temporary cross-protection to recurrent infections (C_P) lasts for approximately 6 months in the base case whilst cross-enhancement (C_E) (i.e. enhancement of viral infectiousness caused by antibodies that do not neutralise [21,62,63]) lasts for approximately 3 months. The final recovery state R imparts permanent immunity to that serotype, but only temporary immunity to other serotypes.

The model assumes that the four dengue serotypes have comparable infectiousness and prevalence as a simple proxy for complex dengue virus circulation dynamics. This is consistent with other modelling studies in this field [12,109,279,280,283,289]. For example, hosts can experience a primary infection with one serotype followed by the possibility of subsequent infections with other serotypes. Accordingly, exposed, infectious and immune states are further stratified by the number of infections suffered (i.e. primary, secondary, tertiary etc.) in the form E_h, E_{h2}, E_{h3} and E_{h4}.

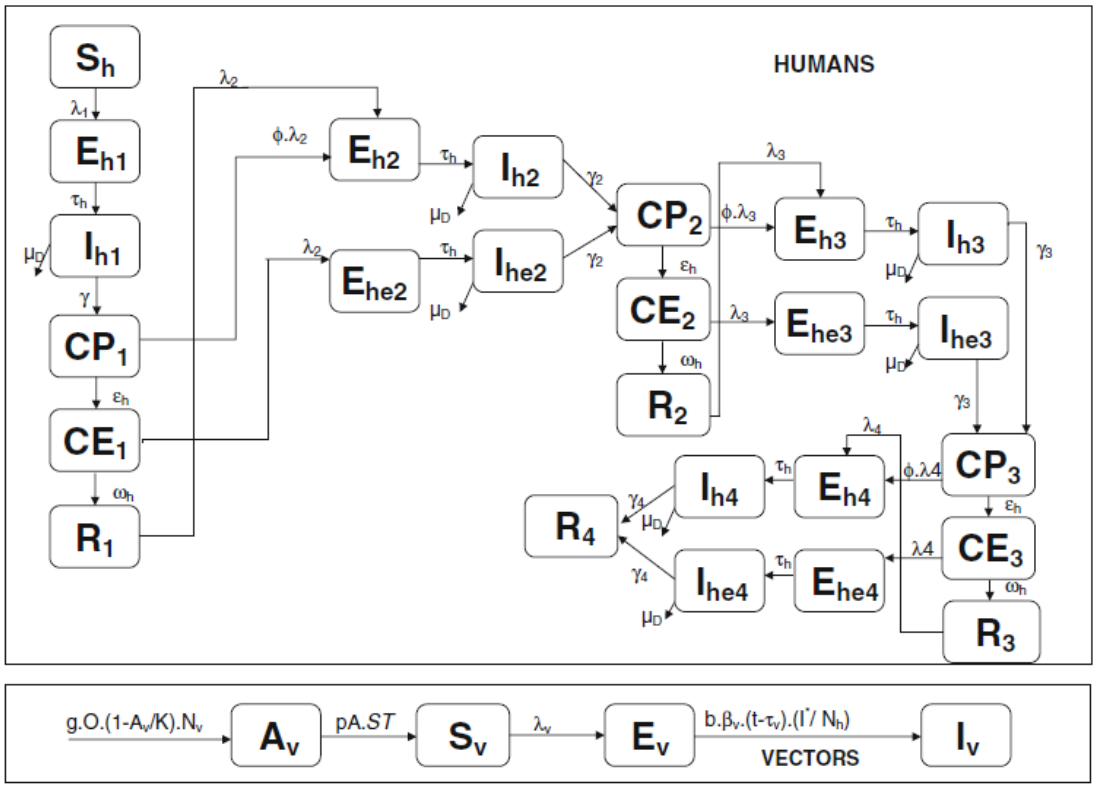
In contrast, it is assumed that mosquitoes will be infected by one serotype only and that they will remain infectious until death. The life cycle of the mosquito is represented in the model by two developmental phases. The aquatic phase comprising egg, larva and pupa stages is denoted by A_v. The adult stage is divided into three compartments: number of susceptible mosquitoes (S_v); number of exposed but not yet infectious mosquitoes (i.e. incubating the virus) (E_v), and infected and infectious mosquitoes (I_v). The total mosquito population is N_v (i.e. $N_v=S_v+E_v+I_v$).

The force of infection $\lambda_{[1...4]}$ is equal to $b\beta_h (I_v/N_h)$ where b is the average number of bites per mosquito per day, β_h is the age-specific transmission probability, and I_v as well as N_h are defined as above (i.e. number of infected and infectious mosquitoes and the total human population respectively). The probability of acquiring the dengue virus is likewise differentiated by infection, which is fixed at 1.0, 0.75, 0.50, and 0.25 for each respective dengue infection. Accordingly, primary, secondary, tertiary and quaternary infections occur at rates of λ_1, λ_2, λ_3 and λ_4 respectively where λ_2 for example, is equal to $b\beta_h (0.75I_v/N_h)$ and λ_3 is equal to $b\beta_h (0.50I_v/N_h)$. These rates are less than λ_1 $[b\beta_h (I_v/N_h)]$ because fewer mosquitoes are assumed to be infected and infectious (I_v) with the serotype to which humans with temporary cross-protection remain susceptible [289]. Similarly, the force of infection or per-capita incidence rate amongst mosquitoes is $b\beta_v (I_{h1}+I_{h2}+I_{h3}+I_{h4}+ ((I_{he2}\varphi_{he})+(I_{he3}\varphi_{he})+(I_{he4}\varphi_{he}))/N_h)$ where b is as above; β_v is the probability of

transmission from human to vector and ($I_{h1}+I_{h2}+I_{h3}+I_{h4}+((I_{he2}\varphi_{he})+(I_{he3}\varphi_{he})+(I_{he4}\varphi_{he}))/N_h$) is the proportion of infectious individuals where N_h is the total human population. The disease dependent death rate α is similarly stratified by infection, in that secondary infections have the potential to be more severe [21,62,63,294]. The flow diagram of the infection process is presented in Figure 3.1. Additional model assumptions relate to the following:

- The population is homogeneous, which means that every individual in a compartment is homogenously mixed with the other individuals;
- Mosquito bites are homogeneously distributed amongst all human hosts; this means that each mosquito bite has an equal probability of being taken from any particular human host.
- The total size of the mosquito population is allowed to vary over time.
- There is no natural protection, i.e. humans and mosquitoes are assumed to be born susceptible and losses of immunity are not considered, nor are maternally derived antibodies.
- The mosquito has no resistant phase due to its relatively short life expectancy.

Figure 3.1. Flow diagram of the infection process. Due to space constraints, the following expression ($I_{h1} + I_{h2} + I_{h3} + I_{h4} + ((I_{he2}\varphi_{he}) + (I_{he3}\varphi_{he}) + (I_{he4}\varphi_{he}))$) is signified by I*



Underlying background mortality (μ_h) is applied to all compartments but not shown on the figure. Only dengue-induced mortality (μD) is displayed.

3.3.5 Age stratification

The model population includes the entire population for the country (i.e. Thailand) where the model is applied and reflects current demographic characteristics such as age, based on recent census data and population projections from national statistics for 2008. For simplicity, the model assumes that population size is constant. Hence, births are equal to deaths and possible migration of infected individuals into the human population is not considered. Individuals survive until 70 years of age (life expectancy) and then die (known as Type I survivorship) [295].

The model is age-stratified with the total population divided into six age cohorts: 0–11 months; 1–4 years; 5–9 years; 10–14 years; 15–24 years and 25 years and over. At each time lag, individuals age and therefore move to the next age class.

We assumed uniform aging over time. Thus, each differential equation includes the addition of a 1/L (where L denotes the width of the age class) proportion of individuals from the previous age class, and the withdrawal of the same proportion of individuals in the age class considered.

3.3.6 Seasonality

Seasonality terms adapted from Coutinho (2005, 2006) [296,297] and Burattini (2008) [283] are incorporated into the aquatic maturation rate and transition rate to adult mosquitoes using the following expression:

$$ST \rightarrow (c - d(\sin(2\Pi f t + \sigma)))\theta(c - d(\sin(2\Pi f t + \sigma)))$$

The assumption is that the vector population fluctuates seasonally with rainfall and other climactic factors affecting the availability of breeding sites and therefore recruitment into the vector population. This is a sinusoidal function with a period of 365 days and where π is equal to 3.1416. The parameters c and d are climactic factors adjusting winters and summers. Accordingly, the length and severity of winters can be simulated with the variation in c and d; if c<d, the winter is relatively severe and of a longer duration. Conversely, if c>d the winter is comparatively mild and short. The Heaviside θ-function [$\theta(c - d\ (\sin(2\pi ft + \sigma)))$] prevents the expression from becoming negative; it is equal to zero when the argument is negative (i.e. <0) and one when the argument is ≥0. The parameter $f(365^{-1})$ represents the frequency with which high and low transmission seasons vary and equates to one reproductive cycle per year. The phase parameter σ is used to synchronise the adult mosquito population at a minimum when the aquatic maturation/progression rate is similarly at a minimum [282,296,297].

3.3.7 Control Interventions

Building on previous scholarship in this area [277,282,283,285,286,289,290,294], we assess the following control interventions individually and in combination:

i. No control
ii. Larvicides
iii. Adulticides
iv. Environmental management embracing source reduction, i.e. elimination of breeding sites and 'clean-up' campaigns, improvements in sanitation as well as health educational measures using the Government of Singapore's 2005 '10-Minute Mozzie Wipe-out' initiative as one such example
v. Vaccination

We simulate the impact of chemical adulticide and larvicide interventions on the incidence of disease by increasing mortality rates for both adult mosquito and aquatic life forms. Using the square pulse function in Berkeley Madonna [298], adulticide and larvicide are administered in condensed intermittent bursts (analogous to a 'clean-up' campaign of 1 day per week for 5 weeks) at the beginning of the dengue season. This is done for 1 year only as well as each year for 5 years at the same time each year, i.e. at the beginning of the dengue season. Conversely, the aquatic carrying capacity (K) is decreased to simulate environmental management and associated activities as defined above. Reflecting the on-going nature of this package of interventions, the aquatic carrying capacity is reduced by 40%, 50%, 60% and 70% for the duration of the dengue season, approximately day 100–170 in the calendar year equating to higher temperatures and rainfall. This is done for 1 year only and the effects are evaluated over 5 and 10 years.

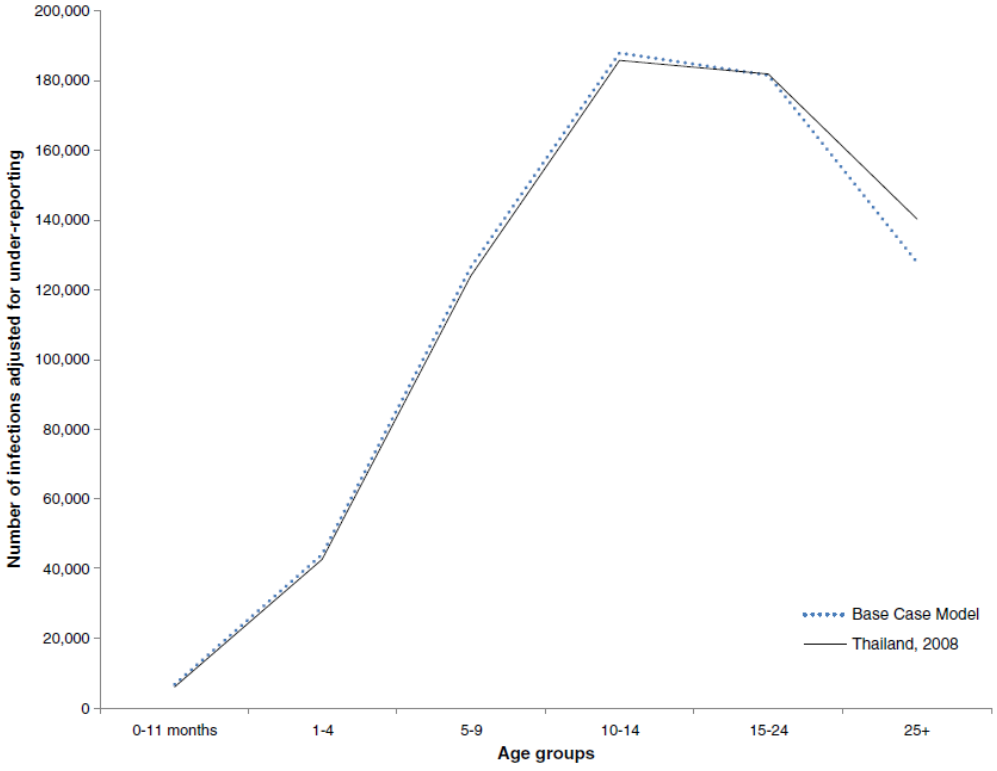
The balance between vaccination coverage, vaccine efficacy, and the waning of vaccine-induced protection determine the relative impact of vaccination on the epidemiology of dengue fever. In the model, infants aged 0–11 months are not vaccinated; rather vaccination takes place at 1 year of age with 70% coverage. There is also catch-up vaccination for those more than 1 year and less than 5 years of age with 30% coverage. Given the uncertainty associated with the uptake of an imperfect vaccine, we have adopted conservation assumptions related to coverage and explored alternatives in scenario analyses. Efficacy is assumed to be 30.2% [155]. Vaccine-acquired protection is assumed to wane over time to take into consideration imperfect vaccine-induced immunity. For the purposes of the current model under consideration, it is assumed that vaccination consists of one dose only.

3.4 Results

3.4.1 Comparison of predicted with observed rates of infection adjusting for under-reporting

Without vector control, the model predicts approximately 675,000 dengue infections per year at steady state in Thailand, all age groups combined. This compares to the number of reported dengue fever/dengue hemorrhagic fever infections in Thailand in 2008 [266] adjusted for under-reporting [293], all age groups combined (*n* = 681,158). Figure 3.2 presents the results of the baseline epidemiological model without any control interventions compared to observed dengue infections using the best fitting combination of parameter values. It can be seen that model output compares well with observed data with the exception of the 25 years and over age group which underestimates the data slightly. Given that the main burden of disease is located in the younger age groups, primarily in the teenage and young adult age groups, this is not considered to be a major source of bias. The best fit was obtained for a model with cross-protection only and without the inclusion of cross-enhancement. Although various levels of cross-enhancement ranging from a 2-fold to 5-fold increase in infectiousness were tested and compared, none provided a better fit than the base model with cross-protection only.

Figure 3.2. Comparison of predicted with observed rates of infection adjusting for under-reporting



3.4.2 Evaluation of single interventions

To evaluate the impact of the different control strategies, we compared the base case steady state without interventions, as shown in Figure 3.2, to the average annual number of cases during the years that follow the introduction of controls. Vaccination being a continuous intervention, its effects are accumulated over the years that follow introduction. Conversely, environmental management, larvicide or adulticide are one-off or relatively short-term interventions, therefore their effects are evident much sooner.

Beginning first with vaccination, Table 3.1 presents the baseline estimates by age at infection and the impact of vaccination over 5, 10 and 20 year periods. Base case characteristics comprise the following: vaccination of 1 year olds with 70% coverage, catch-up vaccination for those more than 1 year and less than 5 years of age with 30% coverage, efficacy of 30.2% and vaccine waning over 10 years. Some vaccines may take longer than others, potentially years, to realise the full benefit of the vaccine and one may observe this outcome to some extent in the simulated results. For example, in the first 5 years after vaccination, the impact of vaccination across age groups is relatively marginal and amounts to a 9–16% decrease in incidence of dengue infections. The most pronounced effect is in the 1–4 years age group reflecting the fact that catch-up vaccination took place in this age-group initially. In contrast, the reduction in incidence 10 years post-vaccination jumps to approximately 35–42%. In the same way, reductions in incidence 20 years post-vaccination range from between 58 and 63% across age groups illustrating that the full benefits of vaccination are often derived in the longer term.

Table 3.1. Baseline estimates by age at infection and the impact of vaccination over 5, 10 and 20 years

Estimates by age-group	0–11 months	1–4 years	5–9 years	10–14 years	15–24 years	≥25 years
Steady state - 674,715	6,653	44,115	126,546	187,853	181,782	127,766
5 years after intervention	6,057	37,225	113,338	170,812	165,662	116,300
10 years after intervention	4,301	25,699	79,216	121,216	118,158	82,612
20 years after intervention	2,739	16,159	50,032	77,547	76,204	52,745

We also carried out sensitivity and scenario analyses to explore different model assumptions. For example, we examined different waning periods including 5 and 20 years, different coverage levels, using both 50% and 90%; an alternative estimate of efficacy using the upper limit of the 95% confidence interval (56.6%) from the recently published dengue vaccine trial [155] and finally, different assumptions around the level of coverage attached to catch-up vaccination; 50% and 70%. Assumptions were tested

univariately, i.e. one value at a time rather than being examined multivariately.

Table 3.2 presents the results of these scenario analyses. Once again, one may observe that the short-term impacts of vaccination, in the realm of 5 years post-vaccination, are relatively marginal, with the exception being when efficacy is increased to 56.6%. One then observes marked gains in the reduction of disease. A similar pattern as above is witnessed in the 10 year and 20 year post-vaccination scenarios. Namely, the full benefits of vaccination become much more evident in the long term particularly when the estimate of efficacy is meaningfully increased.

Table 3.2. Impact of vaccination on dengue burden

Scenario	**5 years after intervention**	**Reduction from steady state (674,715)**	**10 years after intervention**	**Reduction from steady state (674,715)**	**20 years after intervention**	**Reduction from steady state (674,715)**
Vaccination 5-year waning	619,468	8.2%	472,701	29.9%	436,823	35.3%
Vaccination 10-year waning	612,060	9.3%	432,830	35.8%	276,293	59.1%
Vaccination 20-year waning	607,979	9.9%	412,318	38.9%	224,131	66.8%
Vaccination 50% coverage	627,150	7.0%	473,753	29.8%	369,506	45.2%
Vaccination 90% coverage	597,789	11.4%	399,359	40.8%	222,727	67.0%
Catch-up 50% coverage	600,130	11.1%	409,344	39.3%	254,759	62.2%
Catch-up 70% coverage	588,993	12.7%	388,959	42.4%	235,412	65.1%
Efficacy - 56.6%	564,021	16.4%	340,155	49.6%	173,492	74.29%

Table 3.3 presents the results of analyses examining the impact of chemical and environmental management strategies on the incidence of dengue. Depending on the time horizons of the treatment intervention, results are reported either in the years when

the control strategy is active or the 5 years following the end of the intervention or a combination of both. For example, when larvicide and adulticide are administered 1 day per week for 5 weeks at the start of the dengue season, we report results in the active year and the subsequent 4 years. When larvicide and adulticide treatments are administered at the start of the dengue season 1 day per week for 5 weeks for 5 consecutive years, we report the reductions in incidence during these years of active treatment but also the reductions in incidence in the 5 years following the end of treatment. Results indicate that in the most conservative circumstances, i.e. insecticide spraying for 1 day per week for 5 weeks for 1 year only and a reduction in egg-carrying capacity of 40%, adulticide and environmental management are the most effective interventions. In contrast, larvicide, again in the most conservative circumstances, performs relatively poorly when compared to the latter. As the duration of each intervention increases, every year for 5 years in the case of adulticide or an increase in effectiveness in the case of environment management, a corresponding reduction in the disease burden is observed.

Table 3.3. Impact of chemical and environmental management interventions on dengue burden

Scenario	5 years after intervention	Reduction from steady state (674,715)	10 years after intervention	Reduction from steady state (674,715)
Adulticide - pulses of limited duration (1 day) every 5 weeks during dengue season for 1 year	477,200	29.3%	613,954	9.0%
Adulticide - pulses of limited duration (1 day) every 5 weeks during dengue season for 5 years	332,632	50.7%	215,598	68.0%
Larvicide - pulses of limited duration (1 day) every 5 weeks during dengue season for 1 year	635,312	5.8%	677,445	−0.4%
Larvicide - pulses of limited duration (1 day) every 5 weeks during dengue season for 5 years	561,490	16.8%	573,592	15.0%
Environmental management (40% reduction in egg-carrying capacity	461,709	31.6%	605,047	10.3%
Environmental management (50% reduction in egg-carrying capacity	410,894	39.1%	569,923	15.5%
Environmental management (60% reduction in egg-carrying capacity	364,337	46.0%	526,061	22.0%
Environmental management (70% reduction in egg-carrying capacity	322,647	52.2%	470,709	30.2%

3.4.3 Evaluation of multiple interventions

When we examine the impact of combination interventions on the incidence of dengue fever, results are reported for 5, 10 and 20 years post-intervention to ensure that the full benefits of vaccination are captured. Table 3.4 presents the results of these analyses. For adulticide, we assess the contribution of insecticide spraying in the form of 1 day per week for 5 weeks over 5 consecutive years. For environmental management, a reduction in egg-carrying capacity of 40% is used. For vaccination, we adopt the base case characteristics. When vaccination is used in combination with environmental management, model projections suggest annual reductions in incidence of 45%, 57% and 62% for 5, 10 and 20 years post-vaccination respectively. Similarly, when vaccination is used in conjunction with adulticide, model projections indicate annual reductions in

incidence of 53%, 75% and 81% for 5, 10 and 20 years post-vaccination respectively. Finally, when all three interventions are used in combination, model projections show annual reductions in the dengue disease burden of 62%, 81% and 86% for 5, 10 and 20 years post-vaccination.

Table 3.4. Impact of combined interventions on dengue burden

Scenario	5 years after intervention	Reduction from steady state (674,715)	10 years after intervention	Reduction from steady state (674,715)	20 years after intervention	Reduction from steady state (674,715)
Vaccination and environmental management	371,489	44.9%	289,705	57.1%	259,041	61.61%
Vaccination and adulticide	319,973	52.6%	168,484	75.0%	131,869	80.46%
Vaccination/ environmental management/ adulticide	253,987	62.4%	130,826	80.6%	97,288	85.58%

3.5 Discussion

This paper describes the results of using mathematical modelling to compare a range of dengue control strategies and their impact on the epidemiology of dengue fever in Thailand. The interventions under consideration include chemical (i.e. larvicides, adulticides), environmental management and vaccination. The base age-structured epidemiological model (i.e. without any control interventions) is shown to calibrate well with reported dengue fever/dengue hemorrhagic fever cases in Thailand in different age-groups from the year 2008 [243] adjusted for under-reporting [245]. This suggests that the inputs and initial values used to populate the mathematical model are consistent with the decision problem.

As highlighted by Undurraga (2012) [293], estimating the degree of under-reporting in dengue cases with sufficient accuracy is very challenging. The authors stress that generating more rigorous estimates is conditional on having greater insights into the epidemiology of dengue fever. It is suggested that greater accuracy could be achieved with long-term nationally representative cohort studies albeit with considerably more investment in both time and resources. In the absence of the above, researchers must

necessarily rely on regional/local cohort studies, capture-recapture studies, Delphi panels and similar such designs with the attendant uncertainty in estimates that this entails [293]. In the context of the present study, one may hypothesise that using a single standardised value (7.6) to adjust for under-reporting across heterogeneous age-groups exposes a potential weakness in EF calculations. For example, the majority of study inputs underpinning EF calculations are based on children and young adults rather than being taken from a range of age groups in that the majority of cases occur in these age groups. Consequently, there is considerable uncertainty surrounding the appropriate adjustment for under-reporting in older age groups. If the 95% confidence intervals accompanying the point estimate of 7.6 (95% CI: 7–8.6) are used in the adjustment calculations, the discrepancy between model estimates and observed data may be less than 1,000 or as large as 30,000 cases. Hence, variability in estimates is driven by the appropriate choice of EFs in older age groups rather than model structure.

Seasonality in the form of a sinusoidal variation fitted to the aquatic maturation rate was incorporated to provide a degree of ecological and biological veracity. Similarly, temporary cross-protection was included for the same reasons as well as being consistent with recommended good practice in the modelling of dengue fever [244,245]. Finally, sensitivity and scenario analyses were conducted to assess the impact on model fit and results when additional parameters were added or underlying assumptions changed. The results of our simulations indicate that singular interventions can make useful inroads into dengue fever transmission, particularly adulticide in the short term and vaccination in the medium to long term. These interventions subsequently come into their own when used in combination with a 75–85% reduction in the incidence of dengue fever infections when vaccination is combined with either environmental management or adulticide or when all three interventions are combined.

Chemical and environmental management interventions have formed the basis of efforts to control dengue fever over the last 50 years in spite of acknowledged limitations in terms of effectiveness, mode of delivery, cost, and duration of sustainability [299,300] but may still have an important role to play in the short to medium term. Each form of control has their merits as well as drawbacks [300,301]. For example, ‘environmental management’ and all that this encompasses, whether in the form of government driven (top-down) campaigns or community-based (bottom-up) initiatives are predicated to a great extent on the level of local community compliance as well as health educational and inter-agency collaborative enforcement of these schemes. Expert commentators point out that effectiveness could be substantially improved if, for example, efforts were redirected towards eliminating the most ‘productive’ breeding sites rather than all potential sites

using surveys to measure ‘pupal productivity’ and ‘key container’ or ‘key premise’ indices to facilitate identification [302-305]. Likewise with adulticides or larvicides, poor compliance as well as a growing lack of acceptance for the widespread use of chemicals is an important factor limiting the effectiveness of these interventions. For example, residents in areas where insecticide spraying is taking place may keep their doors and windows shut hampering the effective dissemination of the agent to access indoor populations of mosquitoes. This is compounded by pragmatic considerations surrounding correct dosing, functionality of sprayers as well as concerns around sustainability and growing mosquito resistance to insecticides [300]. Studies in Asia and the Americas have shown that resistance is becoming an issue of escalating importance [144,306]. Consequently, many commentators state that insecticide fogging or spraying should only be used in clearly delineated geographical areas and for a limited time only [36].
As highlighted previously, few mathematical modelling studies have explored the combined effects of different interventions including vaccination and their impact on the epidemiology of dengue transmission. A number of reasons necessitate a wider consideration. Firstly, recently published efficacy results of a dengue vaccine were relatively low and differed by serotype [155]. Secondly, even if the reported efficacy had been very high, i.e. in the range 80–90%, there is still a case for some form of mixed strategy incorporating vaccination as well as environmental management and appropriate chemical control. For example, the vaccine is still not 100% effective and there may be occurrences of primary and secondary vaccine failure in the periods both pre- and post-vaccination. Moreover, if we consider the analogous vector-borne disease yellow fever, the vaccine is recognised as being safe and very effective in preventing yellow fever in different age groups with durable protection. Nonetheless, the number of yellow fever cases continues to expand in spite of this. Estimates from WHO indicate that there are approximately 200, 000 cases and 30, 000 deaths linked to yellow fever annually worldwide [307]. Reasons put forward include increasing deforestation, urbanisation, and climate change as well as waning population immunity leading to greater mosquito/virus contact [307]. Mosquito control is advocated using breeding site destruction and larvicides as well as insecticide spraying to kill adult mosquitoes during outbreaks [307]. This would suggest that there is a still place for other forms of vector control in addition to vaccination for the control of yellow fever and by extension dengue fever and mathematical modelling studies can aid in these policy debates.

Given this background, we conducted an assessment of the relative impact of different dengue control interventions incorporating learning from previous studies. The premise being that it is generally not viable to eliminate dengue fever in Thailand using current technologies and their corresponding effectiveness, rather the aim is to control the

transmission of dengue fever. The follow-up question then becomes one of identifying the optimal mix of control interventions again using the tools currently available to us today including an imperfect vaccine.

This study is subject to a number of limitations. Firstly, a number of potentially effective interventions are not included in our evaluation. In a recent analysis, Amaku (2013) [290] highlighted the effectiveness of strategies that reduce contact between humans and vectors through the use of, for example, insect repellents or insecticide-treated clothes. Other interventions not considered relate to biological control including predatory copepods and larvivorous (larvae-eating) fish as well as genetically modified mosquitoes. Evidence from Vietnam indicates that the copepod *Mesocyclops* is very effective at eradicating *Aedes aegypti* when introduced into water receptacles where mosquitoes breed [308-310]. Potential caveats relate to the practical necessity for continual replacement of these organisms in containers as householders regularly empty and clean the water containers. Moreover, additional concerns relate to cultural sensitivities and objections to putting living things in household water receptacles. For example, it is considered unacceptable in Thailand to wash and bathe in water that contains living creatures including small fish [311]. This may prevent the widespread adoption of these interventions.

An additional limitation relates to the absence of heterogeneity in the model with the exception of age. Spatial/ geographical heterogeneity is not considered; dengue fever may vary widely across the country but be more homogeneous within cites but the model does not take this into account. Heterogeneities in host-vector contact are also not considered, for example, in hosts getting bitten or biting by mosquitoes [312]. Woolhouse (1997) [313] identifies the 80/20 ‘rule’ in which 80% of all transmission is due to 20% of all individuals. The authors maintain that the rule is applicable to a variety of disease systems. Similarly, de Benedictis (2003) [314] used polymerase chain reaction to identify human DNA from blood meals in *Aedes aegypti* collected in 22 homes and found that only 3 people accounted for 56% of the meals, thus showing feeding is non-random, with a bias towards young adults and males. The implications of heterogeneity imply that as with ‘pupal’ surveys and ‘key container’ or ‘key premise’ indices, interventions that can be focused on key groups can potentially be hugely effective. Conversely, strategies that fail to reach their target groups will tend to be less successful than perhaps anticipated in reducing population-level disease burden [304,313].

Whilst compartmental models have their strengths as evidenced by their relative popularity, they also have important shortcomings related to the lack of spatial capabilities

and their fixed deterministic status [315]. In contrast to dynamic models, individual-based or agent-based models take a ‘bottom-up’ rather than ‘top-down’ approach to specify how individuals and even vectors interact with each other according to an explicit set of rules [247,281,316]. Moreover, geographic and/or spatially explicit capabilities are integral to these approaches. With increased computing power, these new mathematical methodologies offer great potential in capturing improved realism although an accompanying caveat concerns data availability as the new model formulations tend to be data hungry [315]. This project forms the first step in a body of work examining the impact of different dengue fever intervention strategies on the epidemiology of dengue fever in Thailand. Subsequent steps will in turn examine both the cost-effectiveness of these multiple intervention strategies as well as determine the optimal mix of strategies for the prevention of dengue fever under constraints. Cost-effectiveness does not directly address the problem that ‘decision-makers are increasingly constrained by a fixed-budget and may not be able to fund new more expensive interventions, even if they have been shown to represent good value for money’ [317]. In this regard, quantitative methods applied to the optimal allocation of fixed resources in order to obtain maximum of benefits may be of assistance [318].

4 The economic impact and cost-effectiveness of combined vector-control and dengue vaccination strategies in Thailand: results from a dynamic transmission model

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4.1 Abstract

Background and aims

Dengue fever is a major public health problem in tropical/subtropical regions. Prior economic analyses have predominantly evaluated either vaccination or vector-control programmes in isolation and do not really consider the incremental benefits and cost-effectiveness of mixed strategies and combination control. We estimated the cost-effectiveness of single and combined approaches in Thailand.

Methods

The impacts of different control interventions were analysed using a previously published mathematical model of dengue epidemiology and control incorporating seasonality, age structure, consecutive infection, cross protection, immune enhancement and combined vector-host transmission. An economic model was applied to simulation results to estimate the cost-effectiveness of 4 interventions and their various combinations (6 strategies): i) routine vaccination of 1-year olds; ii) chemical vector control strategies targeting adult and larval stages separately; iii) environmental management/ public health education and awareness [EM/ PHEA]). Payer and societal perspectives were considered. The health burden of dengue fever was assessed using disability-adjusted life-years (DALYs) lost. Costs and effects were assessed for 10 years. Costs were discounted at 3% annually and updated to 2013 United States Dollars. Incremental cost-effectiveness

analysis was carried out after strategies were rank-ordered by cost, with results presented in a table of incremental analysis. Sensitivity and scenario analyses were undertaken; and the impact and cost-effectiveness of *Wolbachia* was evaluated in exploratory scenario analyses.

Results

From the payer and societal perspectives, 2 combination strategies were considered optimal, as all other control strategies were dominated. Vaccination plus adulticide plus EM/ PHEA was deemed cost-effective according to multiple cost-effectiveness criteria. From the societal perspective, incremental differences vs. adulticide and EM/ PHEA resulted in costs of $157.6 million and DALYs lost of 12,599, giving an expected ICER of $12,508 per DALY averted. Exploratory scenario analyses showed *Wolbachia* to be highly cost-effective ($343 per DALY averted) vs. other single control measures.

Conclusions

Our model shows that individual interventions can be cost-effective, but that important epidemiological reductions and economic impacts are demonstrated when interventions are combined as part of an integrated approach to combating dengue fever. Exploratory scenario analyses demonstrated the potential epidemiological and cost-effective impact of *Wolbachia* when deployed at scale on a nationwide basis. Our findings were robust in the face of sensitivity analyses.

4.2 Author summary

Dengue fever has become a major public health problem. It is considered one of the most important mosquito-borne viral diseases and occurs in >100 countries in tropical and subtropical regions of Asia-Pacific, the Americas, the Middle East, and Africa with >3 billion people at risk. Despite current control interventions against dengue fever in endemic countries, the disease is associated with considerable healthcare utilisation, personal costs to patients and caregivers, productivity loss and human suffering. Whilst the illness is well understood, there is also recognition that current control efforts focussing predominantly on *Aedes aegypti* control and elimination are less than optimal although may still have an important role to play in the short to medium term. In this study, we consider the cost-effectiveness of individual as well as mixed dengue control strategies in Thailand, embracing chemical interventions, public health education/ environmental control and paediatric vaccination using a dengue vaccine profile broadly consistent with (dengue) vaccines in late stage development. To anticipate the transition to possible new vector control technologies, we also carry out exploratory scenario analyses of the impact and cost-effectiveness of the release of *Wolbachia*-infected

mosquitoes (which are less capable of spreading viruses). Our findings indicate that single dengue control interventions can be cost-effective weapons in reducing dengue infections, although their effectiveness may be additionally enhanced when combined.

4.3 Introduction

Dengue fever is a mosquito-borne disease caused by serologically related, but distinct, viruses grouped into four serotypes (DENV-1 to DENV-4). The disease is an important public health problem in more than 100 countries in tropical and sub-tropical regions of Asia-Pacific, the Americas, the Middle East, and Africa with a considerable burden in terms of disease incidence, cost and impact on quality of life. *Aedes aegypti* mosquitoes are the primary vector of transmission for dengue fever and, to a lesser extent, *Aedes albopictus*. These mosquitoes are also responsible for the transmission of other vector-borne diseases including zika virus, chikungunya and yellow fever. It is estimated that 3–4 billion people are at risk of dengue with approximately 390 million dengue infections (95% credible interval: 284–528 million) occurring every year, of which 96 million (95% credible interval: 67–136 million) are symptomatic [23]. The reasons for the growth in dengue fever and severe dengue as leading public health challenges tend to be multi-factorial [18]. These include rapid population growth, increasing unplanned urbanisation, overseas air travel and deteriorations in public health infrastructure [16,273,319].

When assessing the economic impact associated with dengue, estimates of the annual cost of illness range from approximately $1 billion [178] at the regional level to approximately US$8.9 billion (95% uncertainty interval $3.7–19.7 billion) globally in 2013, with 18% of cases being admitted to hospital and the remaining 48% and 34% of cases classified as ambulatory and non-medical, respectively [179]. Research suggests that almost US$1 billion [178] was spent each year in South-East Asia to treat dengue illness during 2000–2010, with Indonesia and Thailand responsible for 34% and 31% of the total, respectively. Approximately US$451 million of these costs were direct costs [178]. More recent figures using dengue incidence estimates from the Global Burden of Disease Study 2013 [20] suggest that the aggregate cost of dengue in the Southeast Asia, East Asia, and Oceania super-region was approximately $4.8 billion (95% uncertainty interval $1.9–10.8 billion) [179]. Analogously, it has been estimated that the corresponding cost of dengue in the Latin America and Caribbean super-region was approximately US$1.73 billion (95% uncertainty interval $0.72–3.90 billion) in 2013, with Brazil accounting for more than 40% of the total economic burden of dengue in the region [179]. In addition to costs specific to dengue disease, the reported costs of routine (dengue) vector control programmes range from approximately US$0.20 to $38 per inhabitant per year; the median cost being around US$2.50 per inhabitant per year [320].

Estimates of the burden of dengue as part of the Global Burden of Disease 2013 study indicated that the disease was responsible for approximately 1.14 million disability-adjusted life years (DALYs) globally [20,175]. This figure subsequently increased to 2.92 million DALYs globally in a 2017 update [175]. Regional estimates from the 2013 study [20] suggested that approximately 596,700 DALYs and 74,100 DALYs in South-East Asia and Latin America, respectively, were attributable to dengue fever, with the former having the highest rate of DALYs lost due to dengue illness followed by Latin America. The disparity in numbers between the two regions may be partially explained by the higher incidence rates of severe dengue (i.e. dengue haemorrhagic fever [DHF] and dengue shock syndrome [DSS]) in South-East Asia compared to the Americas, as well as the higher case fatality rate [114] in the former. DALY estimates specific to Thailand range from 427 to 471 DALYs per million population [20,176,177].

Other important elements should also be considered in order to estimate the broader economic burden of dengue; for example, possible detrimental effects on foreign direct investment resulting from the incidence of disease and dengue in particular [185-187,191], as well as the potential impact of dengue disease on tourism revenues [181,182,321].

At present, the widespread prevention and control of dengue fever is limited to the avoidance of mosquito bites, vector control measures and community engagement for environmental management initiatives [11]. Treatment is made up of supportive care, in the absence of licensed anti-viral prophylactic and/ or therapeutic therapies. Thailand's dengue control strategy is derived from WHO guidelines [11], which consist of 3 key elements: 1) avoiding transmission by preventing mosquito bites in infected dengue patients; 2) active community detection of non-consulting cases; and 3) vector control strategies comprising environmental management, source reduction, and chemical interventions (adulticide and/ or larvicide) [152]. Carbamates, pyrethroids, organochlorides and organophosphates form some of the most common agents used in insecticide mosquito control, primarily by treatment of water storage containers through larviciding and/ or perio-domestic space spraying, with the mechanism of action targeting the nervous system of the mosquito [11,147,322]. Anecdotal evidence suggests that local vector control 'at best' delays infection and has only a marginal impact on the total burden of disease, whilst large-scale control can have a considerable impact [137]. Oft cited and successful examples of systematic vector control campaigns include breeding site elimination during the construction of the Panama Canal and *Aedes aegypti* eradication in Central and Latin America during the 1950s and 1960s [323]. It has been asserted that if appropriately carried out, the suppression of *Aedes aegypti* (i.e. reduced to levels below

which epidemics cannot be sustained) can be a pragmatic way to control urban dengue, yellow fever and chikungunya [278]. In addition to the more traditional methods of vector control referred to above, innovative 'technologies' are also undergoing evaluation, including *Wolbachia* infection, in which mosquitoes that carry *Wolbachia* bacteria (which is harmless to humans) are released. These mosquitoes and their offspring are less able to carry and spread viruses as the *Wolbachia* bacteria compete with the viruses. There is growing evidence of the effectiveness of large-scale deployments of *Wolbachia*-infected mosquitoes across different geographies, including Yogyakarta, Indonesia (76% reduction in dengue transmission [324]), Niteroi, Brazil (73% reduction in notified dengue incidence [324]), Nha Trang, Vietnam (86% reduction in dengue incidence [324]) and Kuala Lumpur, Malaysia (40% reduction in dengue incidence [325]). Notwithstanding this, commentators have suggested that current (insecticide-based) approaches will likely play a continuing role in vector control frameworks for the foreseeable future, given the relatively long lead time required for widespread implementation of new control measures [145]. Current guidance from the World Health Organization (WHO) '…..encourages affected countries [in relation to both dengue and zika viruses] and their partners to boost the use of current mosquito control interventions as the most immediate line of defence, and to judiciously test the new approaches that could be applied in future' [151]. Undoubtedly, effective (and widespread) vector control has been problematic to achieve due to resourcing constraints (outside of outbreaks), poor planning, high costs and a lack of a community engagement and acceptance to name but a few [278]. Insecticide resistance is also a growing problem [144]. In this regard, data on mechanisms and prevalence of resistance at specific geographic locations is relatively scarce, although such knowledge may be pertinent to guide national vector control programmes as to the most effective agents to employ in each resistance setting [145].

With respect to dengue control by means of vaccination, the WHO has indicated that ideally, a dengue vaccine should be given in the form of a single dose, protect against all four (dengue) virus serotypes, provide long-term immunity and cause no serious adverse effects [19]. At present, only one dengue vaccine has been licensed although uptake has been relatively low [32]. A number of other dengue vaccines are also in development, including one that has Phase 3 overall dengue vaccine efficacy results [161,162]. Real-world regulatory experiences to date attest to the critical and almost unique complexities that (dengue) vaccine manufacturers face in relation, but not limited, to differential impacts on dengue 'sero-negatives' vs. 'sero-positives' as well as varying vaccine efficacy against dengue serotypes.

In examining the cost-effectiveness of dengue control strategies, evaluations to date have

tended to consider vaccination [180,326-336] or vector-control programmes [143,199,201,294,337-340] singularly and not really considered the costs and benefits of mixed strategies as part of combination control. This state of affairs is changing to some extent with recent papers examining, for example, the epidemiological impact of vector control methods in Brazil [341], mathematical modelling of dengue spread with different interventions, including vaccination, larvicide, insecticide and mechanical control [342] and a recent economic evaluation of vector control in the context of a licensed dengue vaccine in different countries [202]. Notwithstanding the evident merits of vaccination in general, arguments exist for the continued importance of vector control in the management of dengue fever [136,139,143]. Its dependence on the *Aedes aegypti* mosquito for transmission [151] means that vector control strategies are likely to also reduce the incidence of the zika virus, yellow fever and chikungunya. Accordingly, vector control tools can play a wider role in controlling and eliminating vector-borne diseases other than dengue. Indeed, one commentator appropriately captured this sentiment: '…even if commercial dengue vaccines are available soon after a successful licensure process, vector control is critical to disrupting the epidemiologic triad of dengue and other emergent/resurgent mosquito-borne viruses that *Aedes aegypti* can also transmit. Thus, an integrated approach focusing on the mosquito vector cannot be disputed' [322].

If we accept the premise that an easy solution for dengue control does not exist and that multiple strategies are likely be more effective than a stand-alone strategy, the pertinent question then becomes what the cost-effective options are from a priority setting and decision-making perspective. In this regard, we consider a number of dengue control options, both individually as well as in combination, encompassing historical forms of vector control as well as possible new ones in the form of vaccination and *Wolbachia*, to determine the best intervention(s) for controlling the spread of dengue from a cost-effectiveness perspective. We treat orthodox vector control as the foundation of dengue prevention before introducing vaccination over time in the form of a staggered (national) ramp-up to examine the costs and effects of different combined control strategies. We then anticipate the possible transition to a new control context in the form of *Wolbachia* in subsequent exploratory scenario analyses.

We carried out exhaustive experiments to determine the impact of varying factors including the costs of interventions, vaccination coverage, intensity of vector control, disutility weights and discount rates amongst others. In the next section, the model is briefly described, followed by a presentation of results, discussion and ending with conclusions and next steps.

4.4 Methods

We assessed the impact of different control interventions in Thailand using our previously published dengue dynamic transmission model [7] and incorporating updated data inputs and interventions. The model provided the epidemiological base for economic analyses, where we assumed an epidemiology that was representative of average Thailand dengue epidemiology in the years 2008–2012, linking dengue incidence to costs and outcomes, and predicted the number of dengue cases at steady state and under each control strategy. This was subsequently combined with economic inputs to report the costs and consequences of different strategies and included formal cost-effectiveness analysis. As vaccination is a continuous intervention, its effects accumulate over the years that follow introduction. Conversely, environmental management/ public health education and awareness (EM/ PHEA), larvicide or adulticide tend to be relatively short-term interventions, therefore their effects are evident much sooner. To ensure equivalence of comparison, the impact of all interventions in the form of cumulative costs and consequences were estimated over 10 years following intervention initiation. This follow-up period was considered to correspond to reasonable timescales for public health decision-makers [343,344]. In exploratory scenario analyses, we considered the impact of *Wolbachia* individually and in combination with vaccination and took time frames longer than 10 years into account.

4.4.1 Epidemiology model structure

In brief, the transmission model simulated the population-wide transmission dynamics of symptomatic dengue fever in Thailand, focusing on consecutive dengue infections and the overall impact of control interventions on dengue incidence. The model assumed that the four dengue serotypes have comparable infectiousness and prevalence (as a simple proxy for complex dengue virus circulation dynamics) as opposed to modelling the behaviour of individual dengue serotypes. This is consistent with other modelling studies in the field [12,279,280,289]. The model incorporated the age structure of the population, cross-protection, combined vector-host transmission and a climatic factor simulating seasonal influences in the mosquito population. Further information including the flow diagram of the infection process is provided in Appendix C (Methods – Additional Details).

4.4.2 Data

The model [7] was calibrated using dengue national surveillance data [2] stratified by type of management (inpatient vs. outpatient), and age group (0–4, 5–9, 10–14, 15–24, ≥25 years) assuming steady state and adjustment for under-reporting [293]. Further details concerning data, expansion factors and calibration are contained in Appendix C (Methods – Additional Details).

4.4.3 Interventions

Health and economic outcomes were evaluated for combinations of the following interventions.

4.4.3.1 Chemical control (insecticide and larvicide applications)

The evidence base as to the effectiveness of vector control is somewhat undeveloped with a relative deficit of randomised controlled trials measuring epidemiological (as opposed to entomological) impact. For example, a cluster randomised trial evaluating community mobilisation for dengue prevention showed a lower risk of infection with dengue virus in children (relative risk reduction 29.5% [95% confidence interval: 3.8%–55.3%]) and lower reports of dengue illness (relative risk reduction 24.7% [95% confidence interval: 1.8%–51.2%]) [345]. A meta-review [140] – comprised of thirteen systematic reviews investigating the effectiveness of *Aedes* control interventions or protective measures against *Aedes*-transmitted diseases – determined the strength of the evidence to be consistently low or very low and recommended that future evaluative research efforts employ a randomized controlled trial paradigm with longer durations of follow-up and accompanying disease-related metrics. Specifically, a systematic review of the effectiveness of periodomestic space spraying (pyrethroids, pyrethrins or organophosphates) demonstrated reductions in different entomological measures, but the effects disappeared within days or weeks [138]. The authors concluded that more research was needed. Similarly, a systematic literature review of the effectiveness of a commonly used larvicide (temephos) found that larvae were controlled for approximately 2–3 months in the context of a single community-based intervention dependent on an array of factors including study design, local circumstances, water turnover rates and season [346].

Consistent with other authors (e.g. Burattini et al. [283], Luz et al. [285,294] and Fitzpatrick et al. [202]), we modelled the effect of vector control as a reduction in the vector population (as the means of dengue transmission). In this regard, the impact of chemical larvicide and adulticide interventions was simulated by increasing mortality rates for both aquatic life forms (egg, larval and pupal stages) and adult mosquitoes using the square pulse function in Berkeley Madonna [298]. The incidence of insecticide has increased greatly in recent years [145] and evidence indicates that continuous use of chemical control increases the potential for insecticide resistance with clear negative externalities for other animal species, as well as the natural environment due to toxicity of such compounds [322]. Moreover, mathematical modelling simulations suggest that increased applications of insecticide lead to decreasing reductions in mosquito abundance

with a tipping point identified in the frequency of insecticide applications after which there are diminishing returns [285,294]. Luz et al. additionally report that continuous chemical-based vector control may subsequently worsen epidemics due to the evolution of insecticide resistance [285,294]. Analogously, and in reference to sterile insect release techniques (SIT), White et al. [347] state that ‘‘….models that assume a constant release strategy will tend to over-estimate the true level of population control’’. We did not include SIT interventions in the present study but suggest that such over-estimation (referred to above) is as relevant for chemical interventions as for genetically modified insect interventions. Accordingly, in the current study, chemical control was modelled as discrete periodic interventions, rather than continuous, targeted 1 day per week over 3 weeks at the beginning of the annual dengue season. We used mortality rates of 30% to simulate low-efficacy adulticide and larvicide consistent with the low-efficacy chemicals frequently used in real-world conditions [277,283,348]. We evaluated the impact of 3 applications of larvicide/ adulticide (i.e. separate applications 1 day per week for 3 weeks each year over 5 years) as part of combined dengue control strategies. This was informed by both empirical field trials, which found that approximately 2–4 insecticide applications annually were optimal [349] and the results of mathematical modelling, which suggested that combined vector control was superior to single interventions [285,294].

4.4.3.2 Environmental management/ public health education & awareness

Embracing mechanical control, breeding site/ source reduction and associated educational campaigns (focused on training/ awareness of the local populace with the aim of reduction/ elimination of breeding sites – ‘clean-up’ campaigns). Whilst such initiatives are rarely used as the sole control measure, they are nevertheless considered essential to reducing breeding sites and disrupting disease transmission [140].

Notwithstanding this, the evidence base is relatively scarce, although there is a meta-review which included 4 reviews (5 study arms) that reported on educational and awareness campaigns [140]. Only 1 of the studies/ study arms reported dengue incidence as the main outcome measure and was considered low quality. The remainder reported entomological indices as the main outcomes measures and were deemed very low quality [140]. A more recent systematic review and meta-analysis for the effectiveness of environmental dengue vector control methods [142] focused on (i) container covers with and without insecticides; (ii) waste management and clean-up campaigns and (iii) elimination of breeding sites by removal and/ or making unusable potential mosquito breeding sites. The authors indicated that the great majority, if not all, of the dengue vector control interventions under study showed some form of effectiveness in reducing larval/ pupal densities of *Aedes* mosquitoes, although they strongly advocated for

additional and comparable high-quality studies to strengthen the evidence base, ongoing engagement of communities and public health experts and information on cost-effectiveness and long-term sustainability [142].

In terms of real-world observation, results from a recently published mosquito control programme in Sri Lanka attest to the importance of such interventions and indicate that approximately 2,200 cases of dengue were averted during the 31 months of the intervention, resulting in a 57% reduction in dengue incidence [143]. The programme aimed to reduce mosquitoes in high-risk hotspots with large-scale systematic 'door-to-door' inspections. Mixed teams comprising public health officials, police and military personnel carried out daily inspections in numerous locations to identify and remove typical mosquito breeding sites, such as containers of stagnant water. The programme supplemented routine mosquito control interventions with insecticides and larvicides.

In the present study, EM/ PHEA was represented in model simulations by reductions in carrying capacity (K), the assumption being that reducing environments favourable to the breeding of *Aedes aegypti* vectors reduces the population. Previous simulations of the impact of breeding source reduction on vector-borne disease have used 40–70% reductions in carrying capacity [7,286,348]. For example, in simulations of the impact of analogous control on the burden of chikungunya, Dumont and Chiroleu [348] showed that the best results were obtained with a 66% reduction in carrying capacity. However, they felt that this figure was unrealistic and a decrease of 25% was more plausible under real-world conditions [348]. Consequently, we used the more conservative figure of a 25% decline in carrying capacity to simulate the impact of EM/ PHEA. Reflecting the ongoing nature of this package of interventions, the aquatic carrying capacity was reduced for the duration of the dengue season and beyond, approximately days 100–250 in the calendar year equating to higher temperatures and rainfall. This was done for 1 year only and the effects were evaluated over 10 years [286,348].

4.4.3.3 Vaccination

This acts on susceptible persons with the numbers governed by the balance between vaccine efficacy, vaccination coverage and waning of protection. We adopted a dengue vaccine profile approximately consistent with (dengue) vaccines in late stage development and applied certain assumptions in this regard. Namely, that the vaccine has an overall protective efficacy of 80% (falling to 73% at 18 months post-vaccination and assumed constant at this level until the end of study follow-up) in all populations and against all grades of dengue fever (i.e. vaccine efficacy is not a function of age or severity) and with a duration of protection of 10 years. Additionally, it was assumed that the vaccine is

effective after a course of vaccination, does not distinguish between seronegatives and seropositives (i.e. protects both) and has no adverse events nor serious adverse events (breakthrough infections). Consistent with analyses undertaken in our previous publication [7], we assumed that dengue vaccination would form part of routine paediatric vaccination and fit into existing child immunisation schedules at 1 year and under (in the model, vaccination was administered at 12 months of age). In the base case, we applied vaccination coverage of 80% with roll-out staggered over 4 years, i.e. 20% coverage in the first year, 40% coverage in the second year, 60% coverage in the third year and 80% coverage at the beginning of the fourth year post roll-out. When considering vaccination in combination with *Wolbachia* as part of the exploratory scenario analyses, it was assumed that vaccination coverage had arrived at steady state with no delay in implementation, i.e. there was no ramp-up period. We also examined different population vaccination coverages of 40% and 60%.

4.4.3.4 *Wolbachia*

This is a potential intervention for arbovirus control that has demonstrated the ability to circulate amongst wild *Aedes aegypti* populations in field trials [148,149]. Whilst primarily intended as a means to control dengue virus transmission, it also has applications to chikungunya and zika virus, which share the same vector of transmission [150]. Potential outcomes of wild-type mosquitoes being infected with *Wolbachia* may include reduced egg-laying rates, reduced mosquito population, shorter (mosquito) lifespan and reduced transmission capabilities, which can greatly decrease the potential to spread mosquito-borne viral diseases (such as referred to above). A *Wolbachia* replacement strategy and mechanism of action involves the release of *Wolbachia*-infected mosquitoes into the natural mosquito environment, which subsequently mix and breed with the native wild mosquitoes. *Wolbachia* infection takes place during reproduction resulting in the transformation of wild-type mosquito environments into *Wolbachia*-infected environments as the process replicates itself over generations of mosquitoes. Researchers have captured relevant differences between mosquitoes (*Wolbachia*-infected/ non-*Wolbachia* infected) both explicitly (i.e. modelling *Wolbachia*-infected mosquitoes) and/ or implicitly (i.e. focusing on parameters affected by *Wolbachia*) in assorted models of differing complexity (e.g. Dorigatti et al. [350], Ndii et al. [351], Xue et al. [352], Shen [353], Bañuelos et al. [354], O'Reilly et al. [355]). The authors variously employed scaling factors to reflect the evidence of, for example, changes in birth/ reproduction/ maturation (from aquatic to adult mosquito stage) rates, mortality and biting rates and human vector transmissibility [351,352] due to *Wolbachia* infection. In this regard, mortality rates of *Wolbachia*-infected mosquitoes (wMel strain) are higher than non-*Wolbachia* vectors (scaling factor >1 × μv) as evidence shows that *Wolbachia* infection reduces the mosquito

lifespan [350-353]. Similarly, *Wolbachia* infection is thought to hinder mosquito feeding and decrease the (successful) biting rate (scaling factor <1 × b) [351,352] due to a condition known as bendy proboscis. In turn, a reduced biting rate also means that the overall human-to-vector transmission rate is reduced as some *Wolbachia*-infected mosquitoes may not be infected with dengue virus due to a process known as 'viral replication inhibition' (scaling factor <1 × βv) [351,352,354].

In exploratory scenario analyses, we considered the predicted impact and cost-effectiveness of a country wide *Wolbachia* programme (wMel strain), singularly and in combination with vaccination. Given the exploratory nature of these analyses, we made a number of simplifying assumptions and compared long-term epidemiological projections with previous authors [350] as a basic validation check. We focused only on the situation where *Wolbachia*-infected mosquitoes arrive to steady-state/ fixation in the (mosquito) population after a period of release and the possibility to reduce or eliminate the disease in the human population. Therefore, we were not interested in such factors as the necessary and sufficient conditions for *Wolbachia* penetration and propagation in the *Aedes aegypti* population nor the optimal release strategy. For example, we did not model *Wolbachia*-infected mosquitoes explicitly, rather, model parameters impacted by *Wolbachia*, including mosquito death and biting rates and transmissibility of infection were modified (using scaling factor estimates derived from the literature), to convert non-*Wolbachia* parameters to *Wolbachia*-infected parameters [351,352]. The scaling factors used in our analyses are presented in Table 4.1.

Table 4.1. Scaling factors to convert non-*Wolbachia* vector parameters to *Wolbachia*-infected vector parameters

***Wolbachia* Strain**	**Decreased birth/ reproductive/ maturation rate**	**Increased mortality rate**	**Decreased biting rate**	**Decreased transmission rate**
Wolbachia free	1.00	1.00	1.00	1.00
wMel	0.95	1.10	0.95	0.50

4.4.3.5 Combination interventions

Descriptions of the 5 combination dengue control strategies are presented in Table 4.2.

Table 4.2. Combined dengue control strategies – glossary

Strategy	Combination dengue control
A	No intervention (steady state)[a]
B	Adulticide[b] (3 applications); larvicide[b] (3 applications)
C	Adulticide[b] (3 applications); EM/ PHEA[c]
D	Adulticide[b] (3 applications); larvicide[b] (3 applications); EM/ PHEA[c]
E	High-coverage (80%) vaccination; adulticide[b] (3 applications); EM/ PHEA[c]
F	High-coverage (80%) vaccination; adulticide[b] (3 applications); larvicide[b] (3 applications); EM/ PHEA[c]

[a] Number of infections at steady state in Thailand, all ages combined

[b] Discrete applications of limited duration (1 day) at start of and/ or during dengue season over 5 years; 3 applications per dengue season for 5 years

[c] 25% reduction in carrying capacity, *K*, of immature stages over 1 year

EM/ PHEA = environmental management/ public health education and awareness

4.4.4 Dengue severity

The presence and severity of symptoms determine the associated costs and impact on quality of life. The severity of infection was not introduced directly into the epidemiological transmission model; rather the transmission model generated the overall number of infections and the probability of different manifestations of dengue (symptomatic – dengue fever/ severe – DHF and DSS) were subsequently applied in the economic model to derive costs of dengue by severity.

4.4.5 Outcomes

The humanistic burden of dengue fever was assessed by calculating DALYs lost to disease using the methodology described by Murray and Lopez [356,357]. The duration of symptoms was different for symptomatic (dengue fever) and severe (DHF/ DSS) disease to take into account the difference in their impact on quality of life.

To enable comparison with DALYs lost to dengue presented in other studies [113,176,328,358], we applied comparable values for discounting functions (C, b and r) derived from the Global Burden of Disease study [357]. We did not consider age weighting in the base case but examined the impact of this in sensitivity analyses. Disability weights, D, were obtained from Carrasco et al. [328], Durham et al. [329] and Lee et al. [327]; these studies also considered the cost effectiveness of a potential dengue vaccine.

We adopted the approach of Clark et al. [176] and assumed that unreported cases are likely less severe than reported cases, although they may still hinder usual daily activities, but for a shorter length of time. Consistent with this, we assigned similar disability weights

to unreported cases as to reported cases of dengue fever, but for a shorter duration (4 days for unreported; 10 days for reported).

Inputs used to calculate DALYS lost are presented in Appendix C Table 7.3.

4.4.6 Perspective

Both payer and societal perspectives were considered.

4.4.7 Costs

We used cost estimates of a dengue fever episode obtained from Shepard et al. [178]. These values were based on a study by Kongsin et al. [197], which used the same cost data as Suaya et al. [359]. Kongsin et al. [197] assessed the costs of dengue fever to Thai society and included direct medical costs incurred within the government public health system and borne by patients and households, direct non-medical costs and productivity loss (i.e. indirect costs to households for loss of income and absence from school including caregiver and patient days lost other than for school or work).

Additional studies with applicable unit costs [177,360] that have been used by other researchers – for example, Lee et al. [327] – were not considered in the present study due to their reliance on expert opinion, secondary data or being considered somewhat outdated, leading to potential under-estimation of costs [178]. Accordingly, unit costs (per dengue fever episode) derived from Shepard et al. [178] were used to estimate the following costs:

i. Payer perspective:
   - direct medical costs for inpatient and outpatient dengue cases

ii. Societal perspective:
   - direct medical costs for inpatient and outpatient dengue cases
   - direct non-medical costs for inpatient and outpatient dengue cases
   - indirect costs for inpatient and outpatient dengue cases.

Total costs were comprised of direct medical costs and intervention costs (detailed below) from the payer perspective and direct medical costs, direct non-medical costs and indirect costs in addition to intervention costs from the societal perspective.

As part of sensitivity and scenario analyses, we substituted unit costs with other sets of unit costs referred to above, as well as others. For example, healthcare unit costs (excluding vaccine costs and/ or vector control costs) reported in Lee et al. [361],

Fitzpatrick et al. [202] and Flasche et al. [330]. Cost inputs are presented in Table 4.3.

Table 4.3. Input values

Input	Base case	Sensitivity analysis
Duration of vaccine protection	10 years	5 years and lifetime perspective of the first vaccinated cohort
Vaccine efficacy	80% (falling to 73% at 18 months)	73–85% (falling to 67–79% at 18 months)
Vaccine coverage	Routine vaccination at 1 year of age (80% coverage)	• Routine vaccination at 1 year of age (40% coverage) • Catch-up vaccination for those children aged <1 year and <5 years; different levels of catch-up vaccination coverage scenarios: – moderate (50%) – low (30%)
Discount rates	3% for costs and effects	3% for costs, 1.5% for effects; undiscounted results
Time horizon	10 years	5 years
DALY utility weights, D	0.211 and 0.5 for symptomatic cases of DF and DHF/ DSS, respectively [328]	• 0.197 and 0.545 for symptomatic cases of DF and DHF/ DSS, respectively [327,329] • 0.37 and 0.52 (children) and 0.42 and 0.53 (adults) for symptomatic cases of DF and DHF/ DSS, respectively[a] [328]
DALY age-weighting parameter, β	No age weights	Age weights
Vaccine price per course	$40 plus $4 vaccine administration costs	$20 and $60 plus $4 vaccine administration costs
Cost of 'un-reported' cases	$12.12 for clinic visit [327]	$0 and $40 for clinic visit [330]

Inpatient costs	• $266 DF inpatient direct medical costs [359] • $566.43 DHF inpatient direct medical costs [178] • $72.77 inpatient direct non-medical costs [178] • $54.59 inpatient indirect costs [178]	Unit cost profiles from Fitzpatrick et al. [202], Lee et al. [361] and Flasche et al. [330] in scenario analyses
Outpatient costs	• $141.61 outpatient direct medical costs [178] • $82.20 outpatient direct non-medical costs [178] • $13.65 outpatient indirect costs [178]	Unit cost profile from Fitzpatrick et al. [202], Lee et al. [361] and Flasche et al. [330] in scenario analyses
Number of vector control interventions	• 3 (1 day per week over 3 weeks at beginning of annual dengue season)	2 (1 day per week over 2 weeks at the beginning of annual dengue season)
Vector control unit costs	• $354,098 for 3 applications of larvicide or adulticide per million persons per annum [294] • $382,482 for EM/ PHEA programmes per 1 million persons [362,363]	$277,724 for 2 applications of larvicide or adulticide per million persons per annum [294]

[a] Values are mean disability weights for symptomatic ambulatory and hospitalised children and adults but were applied in this study as a proxy for disability weights of symptomatic cases of DF and DHF/ DSS

DALY = disability-adjusted life-year; DF = dengue fever; DHF = dengue haemorrhagic fever; DSS = dengue shock syndrome; EM/ PHEA = environmental management/ public health education and awareness

4.4.7.1 Costs of unreported cases

Where costs were ascribed to unreported cases for type of treatment, it was assumed that these were on an outpatient basis only in line with the likely less severe nature of these cases [176]. Unreported hospitalisations and deaths have been documented and some estimations for hospitalisations exist for Thailand [178]. Notwithstanding this, we employed a conservative approach in the estimation of these costs. Consequently, we assumed that there were no hospitalisations or deaths associated with unreported cases.

4.4.7.2 Intervention costs

For chemical vector control, we employed a similar cost structure to Luz et al. [294], who assumed annual costs of $201,350 and $277,724 per million persons for 1 and 2 applications of larvicide or adulticide, respectively, inflated to USD 2013. The authors assumed that the cost of a third application of larvicide or adulticide per million population was the same as the incremental cost of going from one to two applications (i.e. an additional $76,374) [294] for a total cost of $354,098 (USD 2013) for 3 applications of larvicide or adulticide per million population. To derive the costs of a Thai-wide vector control programme comprising 3 applications of larvicide or adulticide, the latter cost was then multiplied by the Thai population index. This equates to approximately $0.0295 per capita per month ($0.354 per capita per annum) and compares to other vector control estimates documented in the literature, for example, Undurraga et al. [196] and Fitzpatrick et al. [202]. The latter presented estimates of sustained vector control for Thailand of 2013 USD 0.055 (range 0.033–0.088) per capita per month ($0.66 per capita per annum).

For the costs of environmental management – embracing source reduction, sanitation improvements and health education and awareness measures – we derived cost estimates from Packierisamy et al. [362,363]. They collected information on capital and recurrent expenditure for dengue vector control activities in Malaysia. Data were recorded by line item and function; line items consisted of personnel, administrative and storage buildings, vehicles, fumigation equipment, pesticides, personal protective equipment and out-sourcing of fumigation services to private companies. Functions included a breakdown of costs by inspection, entomological surveillance, fumigation, larviciding and health education. We used the per capita costs of health education ($0.35) to derive the costs of environmental management (embracing source reduction, sanitation improvements and health education measures) per million persons ($350,000). Cost estimates were then updated to USD 2013.

For vaccination, we use a cost of $40 per vaccination course and assumed vaccine administration costs of $4.

Due to uncertainty in the costs of a *Wolbachia* intervention and in line with the exploratory nature of these analyses, we used 2 different cost estimates to evaluate the potential cost-effectiveness of *Wolbachia*: firstly, a cost per dengue case averted of $1 (which we then used to back-calculate a cost per person of $4.45) and secondly, a cost per person of $1 (the latter being an aspirational cost of the World Mosquito Programme *Wolbachia* method). These costs were assigned over 4 years to simulate accelerated *Wolbachia* implementation to the point where *Wolbachia*-infected mosquitoes have reached steady

state/ fixation in the population.

4.4.7.3 Productivity costs due to death

The economic costs of premature mortality (in terms of productivity loss and lifetime earnings foregone) were not included in the cost-effectiveness analyses due to concerns over the risk of double counting benefits associated with averted deaths [165,364].

4.4.8 Discount rate

Costs were discounted at 3% per annum as suggested by Thailand's Health Technology Assessment guidance and the WHO [365,366].

4.4.9 Cost-effectiveness analysis

The cost-effectiveness of different dengue control strategies was evaluated in terms of the incremental cost per DALY averted. In the first instance, dengue control strategies were rank-ordered by increasing cost with all strategies that were both costlier and less effective than alternative strategies (i.e. 'strongly dominated') subsequently eliminated. The incremental cost-effectiveness ratio (ICER) was then calculated for the remaining strategies compared to the next least expensive strategy by dividing the additional cost by the additional benefit to derive the incremental cost per DALY averted. Next, all strategies that were 'weakly dominated' (i.e. the ICER for this strategy was higher than that of the next more effective alternative) were eliminated and the ICER for the remaining strategies was then re-calculated. Results are presented in the form of a table of incremental analyses, i.e. the set of potentially cost-effective options.

Frequently cited cost-effectiveness thresholds [367-369] relate to a country's per capita gross domestic product (GDP) suggesting that 'interventions that avert one DALY for less than average per capita income for a given country or region are considered very cost-effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost-effective; and those that exceed this level are considered not cost-effective [368]'. Whilst not designed to be applied mechanistically, these categories act to provide useful guidance alongside additional contextual information such as affordability, budget impact, fairness, feasibility and other criteria appropriate to the local context [370]. Notwithstanding this, Thailand is one of the few middle-income countries to have a locally established threshold to guide decision-making. In this regard, the threshold criteria for cost-effective health interventions in Thailand was approximately 120,000 Thai Baht [THB] (from 2012 onwards [371], equivalent to $3,860 in 2013 USD with a conversion rate of $1US = 31.0914 THB as of 30 June 2013). This threshold was subsequently increased to the current level of 160,000 THB (equivalent to $5,146 in 2013 USD with a conversion rate of $1US = 31.0914 THB as of 30 June 2013).

4.4.10 Sensitivity analysis

In this study, probabilistic sensitivity analysis was not carried out for practical reasons related to model run-time and complexity. Rather, the sensitivity of interventions in the table of incremental analyses to changing assumptions was explored by univariate variation of key parameters and then iteratively recalculating incremental analyses for the control strategies under evaluation. Both economic and epidemiological parameters were considered. Sensitivity analysis for epidemiological parameters was restricted to those variables shown to be potentially influential in model analyses reported in previous research. For example, vector mortality, duration of infectious period in host, latent period in vector and biting rate were identified as particularly impactful variables when subject to variation in Bartley et al. [109], from which the current model was adapted. In a similar vein, Amaku et al. [290] found that model parameters related to control (i.e. vector mortality rate, biting rate and immature stage carrying capacity) also proved influential to the relative amount of variation if these parameters were varied by ±1%. Therefore, we examined the relative amount of variation in incremental analyses if epidemiological variables including vector mortality rate, biting rate and carrying capacity of immature stages were modified by ±5%. Duration of infectiousness in host and the latent period in vector were varied by ±1 day. Greater levels of variation in key epidemiological parameters were not possible due to problems in model convergence. The variables under consideration in the epidemiological sensitivity analyses formed part of the calibrated transmission model. However, the model was not re-calibrated after each change in parameter.

Table 4.3 presents inputs used for the economic model and univariate sensitivity analysis.

4.5 Results

To evaluate the impact of different control interventions, we compared the base-case steady state (without intervention) to the number of dengue cases, outpatient visits, hospitalisations, DALYs lost and deaths over a 10-year period following the introduction of single and combined dengue control interventions before subsequently carrying out cost-effectiveness analyses. Model results are available in Appendix D.

4.5.1 Outcomes

At steady state, the simulation model predicted approximately 7 million symptomatic dengue infections for all age groups combined in Thailand over a 10-year period adjusting for under-reporting [99,293] (Table 4.4). Most cases (94%) were attributable to dengue fever, with the balance of cases classified as severe dengue fever cases (combined DHF/

DSS). This translated into approximately 890 dengue-related deaths with a cumulative total of approximately 67,595 DALYs lost over 10 years. For the entire period of follow-up, this equated to an expected dengue burden of 1064 DALYs lost per million persons (average annual dengue burden of 106 DALYs lost per million persons). Additionally, the model predicted approximately 6.5 million outpatient consultations and 625,000 hospitalisations over 10 years.

Table 4.4. Baseline estimates and impact of single vector control interventions and vaccination on dengue burden over a 10-year period (number of cases, outpatient consultations, hospitalisations, deaths and DALYs lost)

Category	**No intervention (steady state)[a]**	**Adulticide[b] (× 3)**	**Larvicide[b] (× 3)**	**EM/ PHEA[c]**	**Vaccination: (80% coverage)**
Total dengue cases (millions)	7.147	4.412	6.321	5.462	3.400
Symptomatic	6.684	4.126	5.912	5.108	3.180
Severe	0.463	0.286	0.410	0.354	0.220
Total outpatient consultations (millions)	6.523	4.026	5.769	4.985	3.103
Total hospitalisations (millions)	0.625	0.386	0.552	0.477	0.297
Total deaths	890	549	787	680	423
Total DALYs lost	67,595	41,731	59,788	51,670	32,132
Total DALYs lost per million population	1064	657	942	814	506

[a] Number of infections at steady state in Thailand, all ages combined

[b] Discrete applications of limited duration (1 day) at start of and during dengue season over 5 years; 3 applications per dengue season for 5 years

[c] 25% reduction in carrying capacity of immature stages, *K* over 1 year

DALY = disability-adjusted life-year; EM/ PHEA = environmental management/ public health education and awareness

4.5.2 Outcomes – Single interventions

Results for single interventions (Table 4.4) showed that vaccination was projected to result in the lowest burden of disease over 10 years with 32,132 DALYs lost (approximately 506 DALYs lost per million population), representing a 52% reduction from steady state. Of the more orthodox and routine vector control measures, adulticide (administered in 3 discrete applications per dengue season) demonstrated the lowest burden of disease over 10 years (41,731 DALYs lost [–38%] and 657 DALYs lost per

million population). The low-efficacy larval control modelled in this study had little impact on the dengue health burden and performed the worst of the single control interventions under this metric.

4.5.3 Outcomes – Combined interventions

Combined control strategies that included vaccination were projected to have the greatest bearing on disease burden, in terms of dengue infections prevented and DALYs lost (Table 4.5). When considering the impact of combined vector control strategies, these were observed to be largely additive and targeted distinct stages in the vector lifecycle, represented by different entry points in the model (aquatic larvae, adult mosquitoes and carrying capacity). For example, as single interventions, adulticide and EM/ PHEA reduced the disease burden by approximately 38% and 24%, respectively, and in combination, the reduction was approximately 61% (Table 4.5). However, when vaccination formed part of a mixed control strategy, the combined benefit was less than the sum of the components. For example, vaccination alone led to an approximate 52% reduction in disease burden, but when combined with adulticide (38% reduction alone) and EM/ PHEA (24% reduction alone), only resulted in an overall 79% reduction in disease burden. One potential explanation for this is that routine vector control targeting different channels reduced the force of infection to such an extent that the added impact of vaccination was moderated. This has implications for demonstrating cost-effectiveness as will be seen in the following section. Adding larvicide to this combination resulted in very marginal incremental benefits only.

Table 4.5. Baseline estimates and impact of combined vector control and vaccination interventions on dengue burden over a 10-year period (number of cases, outpatient consultations, hospitalisations, deaths and DALYs lost).

Category	No intervention (steady state)[a]	A3[b]L3[b]	A3[b] EM/ PHEA[c]	A3[b]L3[b] EM/ PHEA[c]	V80A3[b] EM/ PHEA[c]	V80A3[b] L3[b]EM/ PHEA[c]
Total dengue cases (millions)	7.147	3.618	2.814	2.263	1.483	1.390
Symptomatic	6.684	3.383	2.632	2.116	1.387	1.304
Severe	0.463	0.234	0.182	0.147	0.096	0.090
Total outpatient consultations (millions)	6.523	3.302	2.568	2.065	1.354	1.272
Total hospitalisations (millions)	0.625	0.316	0.246	0.198	0.130	0.122
Total deaths	890	450	350	282	185	174
Total DALYs lost	67,595	34,223	26,621	21,404	14,022	13,182
Total DALYs lost per million population.	1,064	539	419	337	221	208

[a] Number of infections at steady state in Thailand, all ages combined

[b] Discrete applications of limited duration (1 day) at start of and during dengue season over 5 years

[c] 25% reduction in carrying capacity of immature stages, *K* over 1 year

A3 = adulticide (3 applications); DALY = disability-adjusted life-year; EM/ PHEA = environmental management/ public health education and awareness; L3 = larvicide (3 applications); V80 = vaccination with 80% coverage

4.5.4 Cost-effectiveness analyses – single interventions

From a societal perspective, total costs for different control programmes, inclusive of intervention costs, ranged from approximately $333 million (EM/ PHEA) to $470 million (larvicide – 3 applications) (Table 4.6). Larval control exhibited the highest total costs over 10 years, with major cost drivers being associated with the number of severe cases and hospitalisations.

EM/ PHEA was the least costly intervention from a societal perspective and therefore formed the reference intervention. Only adulticide (3 applications) and vaccination were not dominated interventions, with ICERs of $3,026 and $7,616 per DALY averted, respectively. When restricting the analysis to the payer perspective (i.e. including only direct medical costs for inpatient and outpatient dengue cases), EM/ PHEA remained the reference intervention as it had the lowest costs (inclusive of intervention costs), with

larvicide exhibiting the highest total costs (approximately $403 million). Adulticide and vaccination remained the only non-dominated interventions, with ICERs of $3,986 and $8,540 per DALY averted, respectively.

Therefore, our results indicate that, from both payer and societal perspectives, an adulticide programme made up of 3 discrete applications per dengue season or vaccination (80% coverage) can potentially be considered as cost-effective (if not highly cost-effective) interventions in Thailand according to broader criteria of cost-effectiveness.

Table 4.6. Cost-effectiveness analysis of single vector-control strategies (societal perspective)[a]

Strategy	Intervention costs (millions)	Discounted total		Incremental		ICER $/ DALY Averted[b]
		Intervention + societal costs (millions)	DALYs lost	Intervention + societal costs (millions)	DALYs lost	
EM/ PHEA[c]	$24.288	$332.598	51,670	–	–	–
Adulticide[d] (×3)	$106.065	$362.673	41,731	$30.076	9,940	$3,026
No intervention[e]	$0.00	$412.265	67,595	–	–	D
Vaccination (80%)	$227.329	$435.780	32,132	$73.106	9,599	$7,616
Larvicide[d] (×3)	$106.065	$470.216	59,788	–	–	D

[a] All costs were measured in 2013 USD; costs and DALYs were discounted at 3%

[b] Compared with the preceding non-dominated strategy; small differences due to rounding error

[c] 25% reduction in carrying capacity of immature stages, *K* over 1 year

[d] Discrete applications of limited duration (1 day) at start of and/ or during dengue season over 5 years; 3 applications per dengue season for 5 years

[e] Steady state.

D = dominated; DALY = disability-adjusted life-year; EM/ PHEA = environmental management/ public health education and awareness

4.5.5 Cost-effectiveness analyses – combined interventions

From the societal perspective, discounted total costs for different combined control strategies ranged from approximately $295 to $554 million over 10 years (Table 4.7). Adulticide in combination with EM/ PHEA (Strategy C) was the least costly control strategy, whilst Strategy F (vaccination, adulticide, larvicide and EM/ PHEA) was associated with the highest costs but the lowest number of DALYs lost, with the major

cost driver being vaccination. Similar to the predicted reductions in disease burden highlighted earlier, decreases in total costs (without vaccination) were observed to be broadly additive in nature. For example, whilst the total costs of EM/ PHEA and adulticide in isolation were $333 million (–19% vs. no intervention) and $363 million (–12% vs. no intervention), respectively, total costs for EM/ PHEA and adulticide in combination were $295 million (–28% vs. no intervention), i.e. less disease burden equates to reduced total costs. Strategies E (vaccination, adulticide and EM/ PHEA) and F (vaccination, adulticide, larvicide and EM/ PHEA) were the only non-dominated strategies with expected ICERs of $12,508 (vs. Strategy C – adulticide and EM/ PHEA) and $120,028 (vs. Strategy E: vaccination, adulticide and EM/ PHEA) per DALY averted, respectively (Table 4.7). The incremental impact of incorporating larvicide into combined control strategies was not justified by the additional resultant costs. All other combined control interventions were dominated strategies.

Table 4.7. Cost-effectiveness analysis of combined dengue control strategies (societal perspective)[a]

Strategy	Interventions	Intervention costs (millions)	Discounted Total		Incremental		$/ DALY averted[b]
			Intervention + societal costs (millions)	DALYs lost (thousands)	Intervention + societal costs (millions)	DALYs lost (thousands)	
C	A3[c]EM/ PHEA[d]	$130.353	$295.056	26,621	–	–	–
D	A3[c]L3[c]EM/ PHEA[d]	$236.418	$371.576	21,404	–	–	ED
A	No intervention[e]	$0.00	$412.265	67,595	–	–	D
B	A3[c]L3[c]	$212.130	$424.679	34,223	–	–	D
E	V80A3[c]EM/ PHEA[d]	$358.174	$452.639	14,022	$157.583	12,599	$12,508
F	V80A3[c]L3[c]EM/ PHEA[d]	$464.261	$553.511	13,182	$100.872	840	$120,028

[a] Assumes cost of vaccination series was USD 40 and duration of protection was 10 years. All costs were measured in 2013 USD. DALYs were discounted at 3%

[b] Compared with the preceding non-dominated strategy; small differences due to rounding error

[c] Discrete applications of limited duration (1 day) at start of and during dengue season over 5 years

[d] 25% reduction in carrying capacity of immature stages, *K* over 1 year

[e] No intervention – steady state in Thailand, all ages combined

A3 = adulticide (3 applications); D = dominated; DALY = disability-adjusted life-year; ED = extended dominance; L3 = larvicide (3 applications); USD = United States Dollars; V80 = vaccination with 80% coverage

Accordingly, the expected ICER for Strategy E was the only combined control strategy that could be considered cost-effective under the criteria of 3 × GDP per capita, although not under alternative threshold criteria for cost-effective interventions in Thailand [371].

When considering the payer perspective, similarly, only Strategy E was deemed cost-effective ($13,254 vs. Strategy C – adulticide and EM/ PHEA) under the metric of 3 × GDP per capita.

4.5.6 Scenario analyses – Outcomes

In this section, we broaden our analyses to consider the impact of *Wolbachia* alone and, subsequently, in combination with vaccination. It was assumed that *Wolbachia*-infected mosquitoes have arrived to fixation in the (mosquito) population and that vaccine coverage has arrived at steady state, i.e. there was no ramp-up period.

A decrease of approximately 84% in disease burden (67,595 to 10,623 DALYs lost) was observed compared to the expected burden of dengue disease over 10 years (DALYs lost) in the base-case steady state without interventions. When *Wolbachia* was combined with vaccination (low coverage [40%] scenario – Strategy WV40), medium coverage [60%] scenario – Strategy WV60 or high coverage [80%] scenario – Strategy WV80), only relatively modest incremental reductions in disease burden were predicted (Table 4.8). As alluded to previously, one potential explanation for this is that vector control, in this case *Wolbachia,* has reduced the force of infection to such an extent that the additional impact of vaccination may only be marginal.

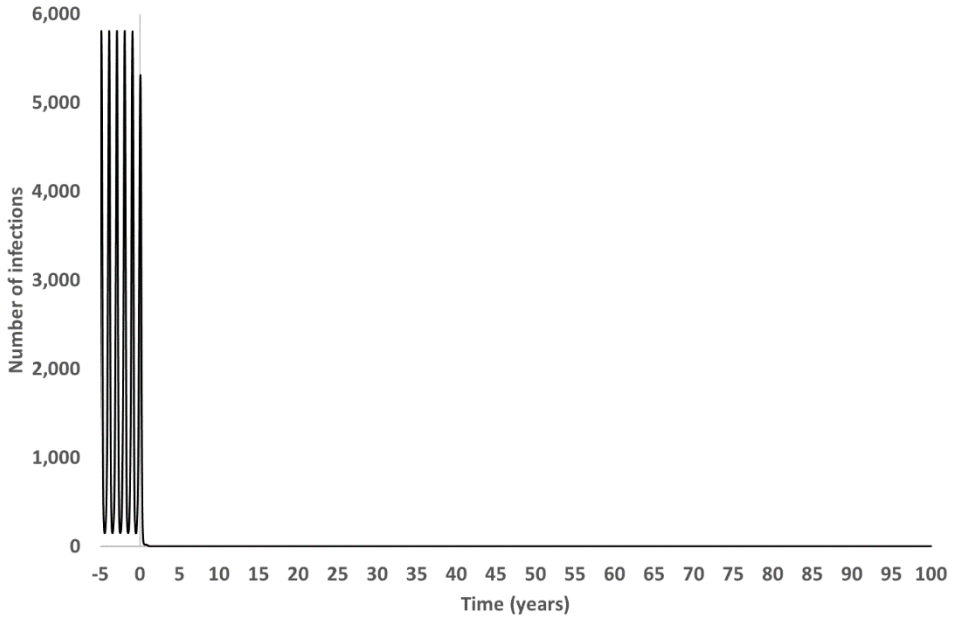
Table 4.8. Impact of *Wolbachia* and combined *Wolbachia* vaccination on dengue burden over a 10-year period (number of cases, outpatient consultations, hospitalisations, deaths and DALYs lost)

Category	*Wolbachia* W	*Wolbachia* / vaccination (low – WV40)[a]	*Wolbachia* / vaccination (medium – WV60)[a]	*Wolbachia* / vaccination (high – WV80)[a]
Total dengue cases (millions)	1.123	1.094	1.080	1.066
Symptomatic	1.050	1.023	1.010	0.997
Severe	0.073	0.071	0.070	0.069
Total outpatient consultations (millions)	1.025	0.999	0.986	0.973
Total hospitalisations (millions)	0.098	0.096	0.094	0.093
Total deaths	140	136	134	133
Total DALYs lost	10,623	10,346	10,213	10,081
Total DALYs lost per million population	167	163	161	159

[a] *Wolbachia* combined with vaccination (40% vaccination coverage, 60% vaccination coverage, 80% vaccination coverage for Strategies WV40, WV60 and WV80 respectively). Vaccination and *Wolbachia* assumed to have arrived at steady state/ fixation. DALY = disability-adjusted life-year

If we considered a longer timeframe and extended the period of follow-up to approximately 100 years, model simulations predicted that with *Wolbachia* alone, dengue disease was suppressed for more than 25 years before any meaningful rebound in incidence was observed. When *Wolbachia* was combined with targeted vaccination (i.e. low coverage vaccination scenario – Strategy WV40), this period was approximately doubled to just over 50 years. Correspondingly, when combined with broader vaccination coverage (e.g. in the range 60–80% of target vaccine population), the period of dengue disease suppression was extended to approximately 100 years (Figure 4.1).

Figure 4.1. Long term impact of combined *Wolbachia vaccination* on dengue burden (number of cases)



Wolbachia combined with high-coverage vaccination (80% vaccination coverage). Vaccination and *Wolbachia* assumed to have arrived at steady state/ fixation.

4.5.7 Scenario analyses – cost-effectiveness analysis

In this section, we extended cost-effectiveness analyses to also include *Wolbachia* and vaccination combinations. In the first instance, we evaluated the cost-effectiveness of *Wolbachia*, alone and in combination with vaccination using a *Wolbachia* cost of $1 per dengue case averted and subsequently using a *Wolbachia* cost of $1 per person. As mentioned previously, it was assumed that *Wolbachia*-infected mosquitoes had arrived to fixation in the (mosquito) population and that vaccine coverage had arrived at steady state, i.e. there was no ramp-up period.

Initially, we examined the cost-effectiveness of *Wolbachia* singularly compared to the other interventions in our analyses. From the societal perspective, EM/ PHEA formed the reference control as it was the least costly intervention. Total discounted costs (10 years) for *Wolbachia* amounted to approximately $347 million, of which 79% ($274 million) comprised intervention costs. *Wolbachia* was the only non-dominated intervention, with an ICER of $343 per DALY averted; all other singular interventions were dominated (Table 4.9). When restricting the analysis to the payer perspective (i.e. including only direct medical costs for inpatient and outpatient dengue cases), EM/ PHEA similarly formed the reference intervention with *Wolbachia* being the only non-dominated control with an ICER of $1,399 per DALY averted.

Accordingly, our results suggest that from both the payer and societal perspectives, a *Wolbachia* programme (wMel) can be considered a potentially cost-effective (if not highly cost-effective) intervention in the setting of Thailand.

Table 4.9. Cost-effectiveness analysis of single dengue control strategies including *Wolbachia* (societal perspective)[a]

Strategy	Intervention costs (millions)	Discounted total		Incremental		$/ DALY averted[b]
		Intervention + societal costs (millions)	DALYs lost	Intervention + societal costs (millions)	DALYs lost	
EM/ PHEA[c]	$24.288	$332.598	51,670			
Wolbachia	$273.744	$346.696	10,623	$14.099	41,048	$343
Adulticide[d] (× 3)	$106.065	$362.673	41,731	-	-	D
No intervention[e]	$0.000	$412.265	67,595	-	-	D
Vaccination (80%)	$273.135	$427.314	23,372	-	-	D
Larvicide[d] (× 3)	$106.065	$470.216	59,788	-	-	D

[a] All costs were measured in 2013 USD; costs and DALYs were discounted at 3%

[b] Compared with the preceding non-dominated strategy; small differences due to rounding error

[c] 25% reduction in carrying capacity of immature stages, *K* over 1 year

[d] Discrete applications of limited duration (1 day) at start of and/ or during dengue season over 5 years; 3 applications per dengue season for 5 years

[e] Steady state

D = dominated; DALY = disability-adjusted life-year; EM/ PHEA = environmental management/ public health education and awareness

In this section, we present cost-effectiveness results for the simultaneous comparison of multiple dengue control strategies including *Wolbachia* (Table 4.10).

When considering *Wolbachia* combined with vaccination, total (10-year) societal costs were estimated at $482 million, $549 million and $617 million for *Wolbachia and* low (Strategy WV40), medium (Strategy WV60) and high (Strategy WV80) vaccination coverage scenarios, respectively. The main cost drivers were the costs of *Wolbachia* ($274 million) and vaccination ($137 million, $205 million and $274 million for low, medium and high vaccination coverage respectively).

Strategy C (adulticide and EM/ PHEA) was the least costly strategy and therefore acted as the reference. Only *Wolbachia* and vaccination combination strategies were non-

dominated, with all other combined control strategies under evaluation (i.e. B, D, E and F) being dominated. The expected ICER for Strategy WV40 was the only control strategy that met wider criteria to be considered potentially cost-effectiveness from both the societal ($11,462 per DALY averted vs. Strategy C) and payer ($12,520 per DALY averted vs. Strategy C) perspectives.

Table 4.10. Cost-effectiveness analysis of alternative combined dengue control strategies including *Wolbachia* (societal perspective)[a]

Strategy	Interventions	Intervention Costs (millions)	Discounted Total		Incremental		$/ DALY averted[b]
			Intervention + societal costs (millions)	DALYs lost (thousands)	Intervention + societal costs (millions)	DALYs lost (thousands)	
C	A3[c]EM/ PHEA[d]	$130.353	$295.056	26,621	–	–	–
D	A3[c]L3[c]EM/ PHEA[d]	$236.418	$371.576	21,404	–	–	ED
A	No intervention[e]	$0.000	$412.265	67,595	–	–	D
B	A3[c]L3[c]	$212.130	$424.679	34,223	–	–	D
WV40	WolVacc40[f]	$410.504	$481.592	10,346	$186.536	16,275	$11,462
E	V80A3[c]EM/ PHEA[d]	$403.817	$487.143	12,256	–	–	ED
WV60	WolVacc60[f]	$478.888	$549.071	10,213	$67.478	134	$503,966
F	V80A3[c]L3[c]EM/ PHEA[d]	$509.895	$590.420	11,814	–	–	D
WV80	WolVacc80[f]	$547.272	$616.568	10,081	$67.498	131	$514,432

[a] Assumes cost of vaccination series was USD 40 and duration of protection was 10 years. All costs were measured in 2013 USD; costs and DALYs were discounted at 3%

[b] Compared with the preceding non-dominated strategy; small differences due to rounding error

[c] Discrete applications of limited duration (1 day) at start of and during dengue season over 5 years

[d] 25% reduction in carrying capacity of immature stages, *K* over 1 year

[e] No intervention – steady state in Thailand, all ages combined

[f] *Wolbachia* combined with vaccination (40% vaccination coverage, 60% vaccination coverage, 80% vaccination coverage for Strategies WV40, WV60 and WV80 respectively). Vaccination and *Wolbachia* assumed to have arrived at steady state/ fixation

A3 = adulticide (3 applications); D = dominated; DALY = disability-adjusted life-year; ED = extended dominance; L3 = larvicide (3 applications); V80 = vaccination with 80% coverage

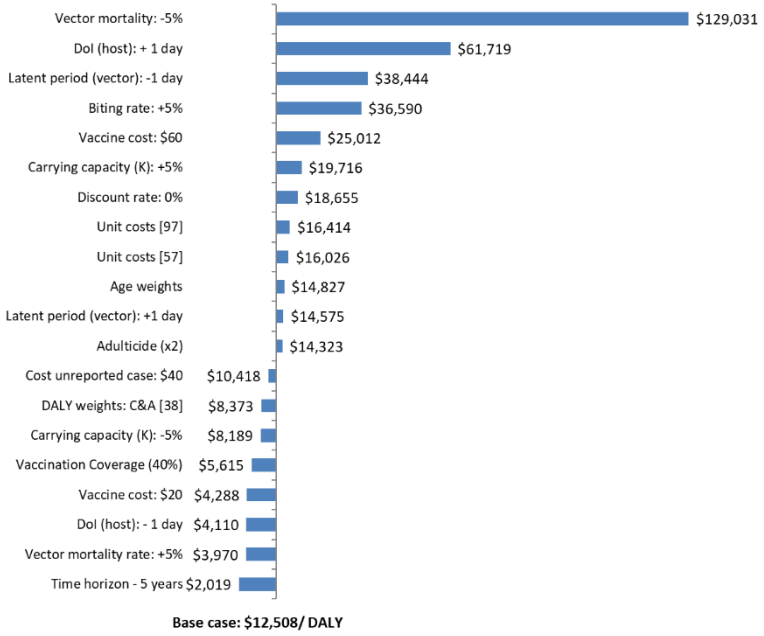
Considering the cost-effectiveness of *Wolbachia*, singularly and in combination with

vaccination, using a *Wolbachia* cost of $1 per person, total (10-year) discounted costs from the societal perspective (inclusive of intervention costs) were estimated at approximately $134 million, $333 million, $431 million and $530 million for single *Wolbachia* and combined with low, medium and high coverage vaccination scenarios, respectively. As a single intervention, *Wolbachia* was the most economical option from both the societal and payer perspectives, with all other single dengue control strategies being dominated. In combination with a low coverage vaccination scenario, *Wolbachia* (Strategy WV40) was the least costly strategy from the societal perspective and acted as the reference. All other control strategies were dominated except for Strategies WV60 and WV80.

4.5.8 Sensitivity analysis

Figure 4.2 summarises the univariate deterministic sensitivity analysis performed on our model. The tornado diagram is shown for Strategy E (vaccination [80% coverage]/ adulticide [3 interventions] and EM/ PHEA) vs. Strategy C (adulticide [3 interventions] and EM/ PHEA]) only as it was not possible to present a tornado diagram for other ICERs in the table of incremental analyses. The model was most sensitive to key epidemiological parameters, particularly vector mortality rate (–5%: $129,031 per DALY averted) and duration of host infectiousness (+1 day: $61,719 per DALY averted) and led to corresponding rises in dengue cases and DALYs lost. The next two most influential parameters were again epidemiological variables, vector latent period (+1 day) and biting rate (+5%) and similarly, also led to rises in dengue cases and DALYs lost. This resulted in analogous increases in the baseline ICER to $38,444 and $36,590 per DALY averted, respectively. All of the latter ICERs were in excess of threshold criteria for cost-effectiveness. With the exception of vaccine cost of $60 ($25,012 per DALY averted), increase (+5%) in carrying capacity (K) ($19,716 per DALY averted) and 0% discount rate ($18,655 per DALY averted), the rest of the parameters under examination (amounting to 24 scenarios in total) and predominantly consisting of economic variables, yielded ICERs within the broader criteria for cost-effectiveness (i.e. 1 ×, 2 × or 3 × GDP per capita). At the lower end of the scale, a number of scenarios led to a reduction in the base-case cost-effectiveness ratio from cost-effective to highly cost-effective (i.e. 1 × GDP per capita) including 5-year time horizon (in that vaccine coverage was still in the ramping-up stage at 5-year follow-up), vector mortality rate (+5%) and vaccine costs of $20 ($4,288).

Figure 4.2. Deterministic sensitivity analysis (societal perspective)



DoI = duration of infectiousness (host); DoP = duration of vaccine protection.

4.6 Discussion

In this study, we assessed the epidemiological and economic impact of a range of possible dengue control interventions, both singularly and in combination, using a previously developed mathematical model [7]. We used cost-effectiveness analysis to identify the dengue disease control strategies (of the options considered) that have the potential to generate the greatest improvements in disease reduction for the least resources. We focused primarily on historical forms of vector control including adulticide, larvicide and EM/ PHEA before introducing dengue vaccination in the fashion of staggered roll-out over time (consistent with Integrated Dengue Management [136,372,373]). We additionally examined the potential impact and cost-effectiveness of *Wolbachia* as a vector control strategy in exploratory scenario analyses.

The base age-structured epidemiological model was shown to calibrate well at steady state with reported symptomatic and severe dengue cases in different age groups in Thailand from the years 2008–2012 [2] adjusted for under-reporting [99,293]. Additionally, the model predicted outpatient consultations and hospitalisations over 10 years that were consistent with observed data when adjusted for under-reporting. We estimated 1064 DALYs lost per million persons over 10 years (average annual dengue burden of 106 DALYs lost per million persons). This would appear to be on the lower side of other published estimates. For example, Clark et al. [176] estimated a total of 427 DALYs lost per million persons in 2001. The difference is primarily due to both the greater number of cases (124,409) and deaths (209) reported in the 2001 Thailand dengue surveillance data

used in their study as well as the inflation factor (10) employed to account for under-reporting.

Our base-case model simulations predicted that single control strategies (adulticide or vaccination) and a combined strategy in the form of vaccination/ adulticide/ EM/ PHEA would be highly cost-effective and cost-effective control measures, respectively, consistent with guidance (threshold) criteria for cost-effective health interventions. Exploratory scenario analyses also showed *Wolbachia* (in isolation) to be highly cost-effective vs. other single control measures and exhibited marked decreases in dengue burden, enhanced by the addition of vaccination. Whilst the incremental impact of broader vaccination coverage in addition to *Wolbachia* was relatively limited, it considerably influenced both the costs and cost-effectiveness of a combined control strategy according to cost-effectiveness threshold criteria referred to above.

Base-case findings were robust to variations in assumptions in sensitivity analyses under which ICERs (compared with the preceding non-dominated strategy) were iteratively re-calculated for each change in parameterisation. As expected, epidemiological parameters forming the calibrated dynamic transmission model were most sensitive to variation. Notwithstanding this, cost-effectiveness ratios demonstrated remarkable consistency with base-case analyses. Whilst the ICERs were subject to variation in each re-iterative calculation, the conclusions did not manifestly alter after performing extensive sensitivity analyses.

Our study results are broadly consistent with previous research, although methodological differences would perhaps suggest that it is unlikely that the findings of different studies are directly comparable. Methodological differences that have the potential to impact results include, for example, comparators, the specified efficacy or mortality rate for vector control, duration and intensity of vector control interventions (i.e. continuous, monthly etc.), unit costs, vaccine price, perspective and timeframe, amongst others. For example, with respect to efficacy/ mortality rates, Luz et al. [294] employed mortality rates of 30%, 60% and 90% to characterise low, medium and high efficacy insecticide-based vector control, respectively, whilst Fitzpatrick et al. [202] used only high or medium efficacy vector control strategies in their simulations. This contrasts with the low efficacy profiles for (chemical) vector control used in the current study, which would likely impact the ICERs and perhaps explain some of the elements contributing to their higher nature compared with other authors [202,294]. With respect to unit costs, we used dengue-related costs derived from Shepard et al. [178], although they subsequently updated these estimates in 2016 [179]. Whilst there are differences between the two sets of unit costs, it

is unlikely that the current results would change markedly, or that any bias would be introduced, given the broad consistency between the estimates (as long as either Shepard et al. [178] or Shepard et al. [179] costs – not a mixture – were applied to all comparators under evaluation). When substituting unit costs in the current study for those reported (excluding vaccine costs and/ or vector control costs) in Fitzpatrick et al. [202], Lee et al. [361] and Flasche et al. [330] as part of sensitivity and scenario analyses, the broad order of interventions under evaluation remained unchanged from the base case in all three instances. Specifically, using healthcare unit cost estimates from Fitzpatrick et al. [202], the expected baseline ICER of Strategy E (vaccination, adulticide, EM/ PHEA) vs. Strategy C (adulticide, EM/ PHEA) increased from $12,508 to $16,026 per DALY averted. Similarly, using healthcare unit costs from Lee et al. [361], the resulting ICER for Strategy E vs. Strategy C increased to $16,414 per DALY averted while the same ICER (i.e. Strategy E vs. Strategy C) decreased to $11,271 per DALY averted when using healthcare unit costs presented in Flasche et al. [330]. Notwithstanding these differences, the general direction of study results suggests an inherent consistency across study designs and geographies.

As highlighted previously, comparatively few (although increasing) mathematical modelling studies have historically explored the combined effects of assorted interventions and their impact on the epidemiology of dengue transmission as well as cost-effectiveness. A number of reasons suggest a wider consideration. Firstly, dengue efficacy estimates published to date are variable, with remaining areas of uncertainty. Secondly, it could be argued that even if reported efficacies had been very high, i.e. 80–90%, there would still be a case for some form of mixed strategy that incorporates, but does not rely solely on, vaccination. Yellow fever provides an important reference in this regard in that vaccination is the primary tool for the prevention of yellow fever, with the vaccine recognised as being safe and effective in preventing the disease in different age groups with durable protection. Nevertheless, despite this, estimates from different bodies suggest that there are approximately 200,000 cases and 30,000 deaths linked to yellow fever annually [307] with urban outbreaks leading to the international transmission of yellow fever beyond its historical borders. Vector control embracing public education, surveillance, larva and adult mosquito control are advocated as important aspects in the prevention and control of vector-borne diseases including yellow fever [374]. This would suggest that there is a still place for other forms of vector control in addition to vaccination for the control of yellow fever and, by extension, dengue fever, and mathematical modelling studies can aid in these policy debates.

In considering the scope and potential of mixed dengue control strategies, mathematical

modelling can be valuable in exploring ‘what-if’ control scenarios. Such analyses have the potential to assist relevant stakeholders in considering the addition of new interventions and/ or changing the implementation of existing ones as well as assist in characterising what could be expected from implementation of combination interventions. Moreover, the inclusion of cost-effectiveness information seeks to address decision-maker and policy-maker needs in lower-income and middle-income countries, which are increasingly focused on developing evidence-based priority-setting frameworks that incorporate value for money criteria [370,375,376].

The outputs from mathematical model simulations, whilst both informative and necessary, are not sufficient for decision-making purposes and should not be the only gauge to provide the basis for recommendations and/ or changes in policy. A range of criteria as part of a wider evidence generation and synthesis framework also influences the choices and determinations in the allocation of scarce healthcare resources. Whilst cost-effectiveness analyses can assist in the assessment of value for money, they must be considered alongside other health system goals. This includes, but is not limited to, for example, affordability and overall budget impact, equity and feasibility as well as considerations of community participation and acceptance amongst others [370,377].

This study is subject to a number of limitations. Firstly, our transmission model did not account for asymptomatic infections, rather focussed on clinically apparent infections. Asymptomatic infections are thought to form an important element of the dengue burden with some 75% of dengue cases being asymptomatic [23,34,42,82]. Additionally, asymptomatic cases may also play a role in dengue transmission, potentially acting as a pool of infection, although commentators highlight the absence of ‘clear’ data with respect to viremia in inapparent infections as well as the effect of the latter on dengue transmission [34,88]. Notwithstanding this, the focus of this paper is on the economic impact of symptomatic dengue infections and their abeyance. Hence, we do not believe that this omission fundamentally undermines the broad conclusions of our analyses. We did not adjust for, nor take into consideration, any positive externalities of vector control programmes on the burden of disease and costs of illness associated with other vector-borne diseases (e.g. zika virus, chikungunya, malaria, etc.) in Thailand. This omission would most likely under-estimate the cost-effectiveness of vector control combinations in our analyses. The vaccine profile used in this study was informed by real-world overall efficacy data [161,162]. For simplicity, we did not account explicitly for individual serotypes (i.e. DENV-1, DENV-2, DENV-3 and DENV-4) in our model, rather we simulated consecutive dengue infections. In the use of reported efficacy data [161,162], we applied this to a paediatric cohort rather than the age demographic specified in the trial on the

assumption that an age-based indication would subsequently be extended to include younger age cohorts and include paediatric vaccination at 1 year of age and under. We ignored any apparent reported imbalances in vaccine immune response between different serotypes and thus any potential negative implications that may follow from this. Moreover, we assumed reported overall vaccine efficacy was constant post-18 months follow-up and did not lessen over time. This could possibly have led to overestimates of the impact of dengue vaccination in the longer term, although it is felt that general conclusions concerning possible enhancements of vector control programmes from simultaneous vaccination strategies (and vice versa) remain unchanged. Our analyses used short-term intervention horizons (1 and 5 years) for traditional vector control measures under evaluation. As a result, this may have induced the so-called 'divorce effect' following the introduction and cessation of non-immunising vector control measures [344,378]. In reality, and as highlighted by previous commentators [379], successful vector control programmes would unlikely be terminated as rapidly or abruptly, although as the authors further indicated, it is not inconceivable that a vector control programme could be interrupted, discontinued and/ or substituted (for another programme) for a variety of reasons. This may plausibly include, for example, funding issues, conflict, natural disasters, insecticide resistance or where an intervention were to be judged ineffective. To mitigate the impact of any divorce effect, it is envisaged that such vector control programmes would continue for an indefinite period and/ or until a mixture of more effective and durable control programmes (e.g. *Wolbachia* and/or the use of irradiated mosquitoes, etc.) would displace and in turn substitute for current vector control practices. To minimise the risk and potential for insecticide resistance as a result of longer-term chemical use associated with vector control, it is recommended that insecticide resistance management strategies are also implemented [380]. These strategies may take the form of insecticide rotation (where frequency of rotation is designed to use different insecticides of different modes of action in order that there is not constant exposure to a single chemical), mosaic (which involves the spatial alternation of 2 or more insecticides with different modes of action) and mixture of insecticides (which involves the simultaneous use of 2 or more insecticides with different modes of action). Qualitative research from Surin, Thailand indicates that most providers actually used a single chemical rather than mixed chemicals (which would be in line with integrated vector management [381]), primarily due to resource constraints [382]. Hence, it would be important to ensure that current protocols are practically implemented before introducing any new initiatives. With reference to exploratory analyses of *Wolbachia* as one element of a dengue control strategy, it is acknowledged that many practical hurdles still exist before a widespread *Wolbachia*-based dengue control strategy can be implemented. These include, for example, the optimal choice of *Wolbachia* strain, appropriate surveillance and monitoring

of environmental and evolutionary changes, as well as community 'buy-in' and acceptance, amongst others [383,384]. The premise that we are examining is not the 'how' of implementation, rather what the possible population impact could be once *Wolbachia*-infected mosquitoes have arrived at equilibrium/ steady state fixation. Although coverage in reality is likely to be limited initially, this exploratory scenario analysis gives some insights into the human population impact of a potential *Wolbachia* programme on a large scale countrywide, both separately but also in combination with vaccination. A further limitation relates to the chosen year of unit costs. Specifically, we used costs for the year 2013 and have not updated these to more recent years, which may suggest that our analyses are slightly out of date. However, it is unlikely that any bias was introduced into our comparative analyses, as the same reference year for costs was applied in all analyses. It also enabled us to compare our results with key published dengue analyses that used 2013 unit costs. Further limitations in relation to the epidemiological transmission model can be found in Knerer et al. [7].

Although much research and discussion has focused on the promise of dengue vaccination, it is now broadly accepted, for various reasons, that even after vaccination roll-out, a multi-faceted approach focused on the integration of control strategies may be warranted [41,322]. Chemical and environmental management interventions have formed the basis of efforts to control dengue fever over the last 50 years in spite of acknowledged limitations in terms of effectiveness, mode of delivery, cost, and duration of sustainability [299,300], but may still have an important role to play in the short to medium term. Accordingly, quantitative analyses presented in this paper are intended to contribute to the wider body of research in this area. In this regard, optimal dengue control strategies – identified through cost-effectiveness analyses – may act to facilitate value for money gains and produce health improvements in the most budget conscious way.

This paper has formed the second part of a three-part series examining the broader impacts of mixed control strategies on the epidemiology of dengue fever in Thailand. In the third part of the series, we will move beyond cost-effectiveness analysis to focus on affordability in the context of constrained optimisation. This is because, the former does not directly address the problem that as Sendi and Briggs [317] have indicated, '…..decision-makers are increasingly constrained by a fixed budget and may not be able to fund new, more expensive interventions, even if they have been shown to represent good value for money'.

5 Reducing dengue fever cases at the lowest budget: a constrained optimization approach applied to Thailand

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5.1 Abstract

Background: With the challenges that dengue fever (DF) presents to healthcare systems and societies, public health officials must determine where best to allocate scarce resources and restricted budgets. Constrained optimization (CO) helps to address some of the acknowledged limitations of conventional health economic analyses and has typically been used to identify the optimal allocation of resources across interventions subject to a variety of constraints.

Methods: A dynamic transmission model was developed to predict the number of dengue cases in Thailand at steady state. A CO was then applied to identify the optimal combination of interventions (release of *Wolbachia*-infected mosquitoes and paediatric vaccination) within the constraints of a fixed budget, set no higher than cost estimates of the current vector control programme, to minimize the number of dengue cases and disability-adjusted
life years (DALYs) lost. Epidemiological, cost, and effectiveness data were informed by national data and the research literature. The time horizon was 10 years. Scenario analyses examined different disease management and intervention costs, budget constraints, vaccine efficacy, and optimization time horizon.

Results: Under base-case budget constraints, the optimal coverage of the two interventions to minimize dengue incidence was predicted to be nearly equal (*Wolbachia* 50%; paediatric vaccination 49%) with corresponding coverages under lower bound (*Wolbachia* 54%; paediatric vaccination 10%) and upper bound (*Wolbachia* 67%; paediatric vaccination 100%) budget ceilings. Scenario analyses indicated that the most impactful situations related to the costs of *Wolbachia* and paediatric vaccination with

decreases/ increases in costs of interventions demonstrating a direct correlation with coverage (increases/ decreases) of the respective control strategies under examination. **Conclusions:** Determining the best investment strategy for dengue control requires the identification of the optimal mix of interventions to implement in order to maximize public health outcomes, often under fixed budget constraints. A CO model was developed with the objective of minimizing dengue cases (and DALYs lost) over a 10-year time horizon, within the constraints of the estimated budgets for vector control in the absence of vaccination and *Wolbachia*. The model provides a tool for developing estimates of optimal coverage of combined dengue control strategies that minimize dengue burden at the lowest budget.

Keywords: Dengue, Vaccination *Wolbachia*, Constrained optimization.

5.2 Background

Dengue fever (DF) is the most common vector-borne disease in Thailand as a result of rising incidence and increasing geographical incursion [385]. The main vectors of transmission for dengue in Thailand are the female mosquitoes of the *Aedes Aegypti* species and, to a lesser extent, *Aedes Albopictus*, with both species prevalent in the country. All four of the dengue virus serotypes (DENV-1, DENV-2, DENV-3, DENV-4) circulate in Thailand [93] and have historically been associated with major dengue outbreaks in the country.

At present, the widespread prevention and control of DF is limited to the avoidance of mosquito bites and vector control measures, primarily based on insecticides and community engagement for environmental management initiatives [11]. Treatment consists primarily of supportive care, in the absence of licensed antiviral prophylactic or therapeutic treatments [66]. The dengue control strategy in Thailand is derived from World Health Organization (WHO) guidelines [11] consisting of three key elements: 1) avoiding transmission by preventing mosquito bites of people infected with dengue; 2) active community detection of non-consulting cases; and 3) vector control strategies comprising environmental management, source reduction, and chemical interventions (adulticide and/or larvicide) [152].

With respect to dengue control by means of vaccination, only one dengue vaccine has been licensed, although uptake to date has been limited [32,386], due in part to complex eligibility requirements amongst other factors [32]. A number of other dengue vaccines are under investigation, although at different stages of the development lifecycle with, for example, Phase 3 overall dengue vaccine efficacy results being recently published (and

publicly presented) [161,162].

In addition to the more traditional methods of vector control highlighted above, innovative 'technologies' are also undergoing evaluation, including the release of *Wolbachia* infection, which reduces the ability of *Aedes Aegypti* mosquitoes to transmit dengue, zika, chikungunya, and yellow fever [387,388]. Female mosquitoes infected with the bacteria can pass this to their progeny and spread *Wolbachia* vertically across the generations. There is growing evidence of the effectiveness of large-scale deployments of *Wolbachia*-infected mosquitoes across different geographies resulting in substantive decreases in dengue incidence [324,325,389].

With the challenges that DF poses to healthcare systems and society at large, public health officials must determine where to allocate scarce resources to manage these problems and response(s). Cost-effectiveness analysis (CEA) is often used for healthcare resource allocation with the optimal allocation of resources achieved by selecting interventions in increasing order of their incremental cost-effectiveness ratios [390]. In a companion piece to the current study [8], a CEA was carried out to assess the impact of different control interventions in Thailand, focusing primarily on historical forms of vector control, but also anticipating new control strategies in the form of vaccination against dengue and *Wolbachia*-infected mosquitoes.

The emphasis of such analyses is on value for money, i.e. whether interventions are worth the ensuing investment, rather than who pays for it. Accordingly, CEAs highlight what decision-makers ideally should do, but not necessarily what they are practically able to do (within the potential budget available). As Sendi et al. [317] indicate, '…decision-makers are increasingly constrained by a fixed-budget and may not be able to fund new more expensive interventions, even if they have been shown to represent good value for money'. CEA does not directly address this challenge, with commentators asserting that for local decision-makers, the criterion for determining how to spend public money (in the form of CEA) should be associated with the budget available for allocation [377].

Constrained optimization (CO) in the field of operational research (OR) assists in addressing some of the limitations of conventional health economic analyses and has been used to identify the optimal allocation of resources across interventions subject to a variety of constraints [391-393]. In two position papers, the International Society for Pharmacoeconomics and Outcomes Research Optimization Methods Good Practices Task Force underlined the facility of CO methods in healthcare when resources are constrained [394,395]. Historically, OR methodologies have successfully been employed

in a variety of optimization problems arising in healthcare [205,396,397]. In the field of infectious diseases, Brandeau [209,210,318,398-401] highlighted how OR-based models can help determine resource allocation that maximizes health benefits, providing important input into decision-making processes. In a similar vein, the identification and evaluation of optimal strategies to minimize infectious disease (subject to constraints) has also been explored by other authors by means of mathematical models, for example, in the determination of the most effective combination of preventive interventions for malaria [402,403], human papillomavirus infection and cervical cancer [404,405], and DF [406-409], amongst others [410,411].

In this paper, we take up where the previous analyses, focused on CEA, concluded [8]. The CO approach applied in this study endeavours to provide decision-makers/ stakeholders with additional practical information when a proposed budget constraint is explicitly considered. The objective is not to make recommendations concerning specific control frameworks and/ or practical implementation for Thailand; rather, as highlighted, to complement CEA evidence as well as provide further insights into prioritizing and combining dengue control strategies.

The paper is organized as follows. First, we present a mathematical model of DF transmission with vaccination and *Wolbachia* as control interventions, economically assess the strategies under examination and propose a CO problem, the aim being to identify the optimal combination of these two interventions, within the constraint of a fixed budget, to minimize the number of dengue cases compared to steady state. We conclude with a discussion and next steps.

5.3 Methods

5.3.1 Resource allocation for infectious disease management

5.3.1.1 Objective function

Two separate and complimentary objective functions were used, namely, number of dengue cases (i.e. incident number of DF cases) and disability-adjusted life years (DALYs) lost. Number of dengue cases formed the primary objective function in base-case analyses, with DALYs lost as secondary.

The impact of interventions (including cumulative costs and effects) was estimated over a 10-year time horizon following intervention initiation. This follow-up period is believed to correspond to a reasonable timescale for public health decision-makers [343,344].

5.3.1.2 Decision variables

Vaccination: acts on susceptible individuals with outputs governed by the balance between vaccine efficacy, vaccination coverage, and waning of protection. Similar to Knerer et al. [8], we used a dengue vaccine profile approximately consistent with (dengue) vaccines in late stage development and applied certain assumptions in this regard. The vaccine was assumed to have an overall protective efficacy of 73% (50 and 80% examined in scenario analysis) in all populations and against all grades of DF and an assumed duration of protection of 10 years. Additionally, it was assumed that the vaccine is effective after a course of vaccination, protects both seronegatives and seropositives, and has no adverse events or serious adverse events (breakthrough cases). Consistent with analyses undertaken in previous studies [7,8], it is assumed that dengue vaccination would form part of routine paediatric vaccination and fit into existing child immunization schedules at age 1 year and under (in the current model, vaccination is administered at birth). When considering vaccination in combination with *Wolbachia*, it was assumed that vaccination coverage had arrived at steady state with no delay in implementation, i.e. there was no ramp-up period.

Wolbachia: This is a potential intervention for arbovirus control, demonstrating the ability to circulate amongst wild *Aedes aegypti* populations in field trials [148,149] and with applications to chikungunya and zika virus as well as to DF, which share the same vector of transmission [150]. Potential outcomes of *Wolbachia* infection may include reduced egg-laying rates, reduced mosquito population, shorter (mosquito) lifespan and reduced transmission capabilities, which can greatly decrease the potential to spread mosquito-borne viral diseases (such as referred to above). A *Wolbachia* replacement strategy and mechanism of action involves the release of *Wolbachia*-infected mosquitoes into the natural mosquito environment, which subsequently mix and breed with native wild mosquitoes. *Wolbachia* infection takes place during reproduction resulting in the transformation of wild-type mosquito environments into *Wolbachia*-infected environments as the process replicates itself over generations of mosquitoes. Researchers have captured relevant differences between mosquitoes (*Wolbachia*-infected/non-*Wolbachia*-infected) both explicitly (i.e. modelling *Wolbachia*-infected mosquitoes) and/or implicitly (i.e. focusing on parameters affected by *Wolbachia*) in assorted models of differing complexity (e.g. Dorigatti et al. [350], Ndii et al. [351], Xue et al. [352], Shen [353], Bañuelos et al. [354], O'Reilly et al. [355]). Scaling factors are variously used to reflect evidence of, for example, changes in birth/reproduction/maturation rates (from aquatic to adult mosquito stage), mortality and biting rates, and human vector transmissibility [351,352] due to *Wolbachia* infection. In this regard, mortality rates of *Wolbachia*-infected mosquitoes (wMel strain) are higher than non-*Wolbachia* vectors, as evidence shows that

Wolbachia infection reduces the mosquito lifespan [350-353]. Similarly, *Wolbachia* infection is thought to hinder mosquito feeding and decrease the (successful) biting rate [351,352] due to a condition known as bendy proboscis. In turn, a reduced biting rate also means that the overall human-to-vector transmission rate is reduced, as some *Wolbachia*-infected mosquitoes may not be infected with dengue virus due to a process known as 'viral replication inhibition' [351,352,354].

Given the somewhat exploratory nature of these analyses, we made a number of simplifying assumptions and compared long-term epidemiological projections with another study [350] as a basic validation check. In the previous analysis, dengue disease was suppressed for approximately 25 years before any meaningful rebound in incidence was observed [350]. We focused only on the situation where *Wolbachia*-infected mosquitoes arrive to steady-state/ fixation in the (mosquito) population after a period of release and the possibility to reduce or eliminate the disease in the human population. Accordingly, factors such as the necessary and sufficient conditions for *Wolbachia* penetration and propagation in the *Aedes aegypti* population or optimal release strategy are not considered. Model parameters impacted by *Wolbachia* infection, including mosquito death and biting rates, and transmissibility of infection, are modified (using scaling factor estimates derived from the literature), to convert non-*Wolbachia* parameters to *Wolbachia*-infected parameters [351,352]. The scaling factors used in the analysis are presented in Table 5.1. In a previous study by the authors [8], a model-based analysis estimated a country wide *Wolbachia* release programme in Thailand would result in a decrease of approximately 84% in disease burden over 10 years (using the same scaling factors referred to above). This is broadly consistent with estimates from the literature referenced above as well as a model-based analysis predicting that a nationwide *Wolbachia* replacement programme instigated in Indonesia (100% coverage) would prevent approximately 86% of cases in the longer term [355].

5.3.1.3 Budget constraints

The purpose of the budget constraint(s) is to approximate real-life settings, where decisions are formulated within a limited budget and very high levels of both vaccination and *Wolbachia* are unlikely to be fully realized. In the current context, the overall (available) budget was constrained to be no higher than cost estimates of the current vector control programme.

Cost estimates of vector control of $0.396, $0.66, and $1.056 per capita per year for sustained vector control in Thailand, representing lower bound, base case, and upper bound estimates, respectively, were derived from Fitzpatrick et al. [202]. This equates to

(discounted) budget constraints of approximately $251, $368, and $589 million (2013 United States Dollars) for lower bound, base case, and upper bound estimates respectively, for Thailand over 10 years.

5.3.1.4 Optimization routine

Simulation output suggests that the output surface for each of the objective functions is an inclined plane, with a small amount of curvature. As a result, we opted to perform a grid search to identify the best combinations of interventions to use that satisfy the budgetary constraints. As the search space is relatively low-dimensional and the simulation model runs moderately quickly, this is a reasonably efficient method for identifying the best mix. If the number of decision variables were to increase, more sophisticated optimization methods would be required.

In the grid search, the parameter space of the respective interventions (i.e. vaccination coverage 0–100% and *Wolbachia* [release] coverage 0–100%) is divided by 100 and then 10,000 simulations (i.e. 100 × 100) are run. The programme eliminates all combinations that exceed the pre-specified budget constraint and retains only those permutations that fall within the programme scope. The process then concludes with the presentation of the optimal combination of the two interventions that minimize the number of dengue cases and DALYs (subject to budget constraints).

5.3.1.5 Dynamic transmission model background

We modelled the transmission of DF in the population of Thailand, using a system of ordinary differential equations adapted and simplified from Knerer et al. [7,8]. In the earlier studies, an age-structured susceptible–exposed–infectious–recovered/ susceptible–exposed–infectious dynamic transmission model combining seasonality, consecutive infection by all four serotypes, cross-protection, and immune enhancement, as well as combined vector-host transmission was developed. The model was used to represent dengue transmission dynamics using parameters appropriate for Thailand and to assess the impact and cost-effectiveness of combined vector-control and vaccination strategies on disease dynamics.

In the current study, we do not model population age structure and assume only one ‘global’ dengue serotype is circulating, as the use of a single serotype/ infection model was considered sufficient to answer the research question under investigation and adhere to the principle of parsimony. The human population is divided into four compartments comprising: humans susceptible to dengue infection (S_h), exposed to infection (E_h), infected and infectious (I_h), and recovered (R_h) compartments. The total human population

(N_h) is equal to the sum of the populations of humans in all human compartments, i.e. $N_h = S_h + E_h + I_h + R_h$. The life cycle of the mosquito is represented by three infection phases, susceptible mosquitoes (vectors) (S_v), exposed (incubating) mosquitoes (E_v), and infected and infectious mosquitoes (I_v). The total vector (mosquito) population is equal to N_v (i.e. $N_v = S_v + E_v + I_v$). The complete model without study interventions is presented in the system of equations below:

$$\frac{dS_h}{dt} = \mu_h N_h - \left(b_v \beta_{hv} \frac{I_v}{N_h}\right) S_h - \mu_h S_h + \theta V_h$$

$$\frac{dE_h}{dt} = \left(b_v \beta_{hv} \frac{I_v}{N_h}\right) S_h - (\mu_h + \tau_h) E_h$$

$$\frac{dI_h}{dt} = \tau_h E_h - (\mu_h + \gamma_h) I_h$$

$$\frac{dR_h}{dt} = \gamma_h I_h - \mu_h R_h$$

$$\frac{dS_v}{dt} = \mu_v N_v - \left(b_v \beta_{vh} S_v \frac{I_h}{N_h}\right) - \mu_v S_v$$

$$\frac{dE_v}{dt} = \left(b_v \beta_{vh} S_v \frac{I_h}{N_h}\right) - (\mu_v + \tau_v) E_v$$

$$\frac{dI_v}{dt} = \tau_v E_v - \mu_v I_v$$

In the presence of *Wolbachia*, the model is extended to include a *Wolbachia*-carrying mosquito population. The population of *Wolbachia*-carrying mosquitoes is divided into subpopulations of susceptible (S_w), exposed (E_w), and infectious (I_w) mosquitoes, where $S_w + E_w + I_w = N_w$. In total, the model comprises 11 compartments; four for the human population three each for the two mosquito populations, and one for vaccination. The complete model with study interventions is presented in the system of equations below:

$$\frac{dS_h}{dt} = (1 - \varepsilon p)\mu_h N_h - \left(\left(b_v \beta_{hv} \frac{I_v}{N_h}\right) + \left(b_w \beta_{hw} \frac{I_w}{N_h}\right)\right) S_h - \mu_h S_h + \theta V_h$$

$$\frac{dV_h}{dt} = (\varepsilon p)\mu_h N_h - (\mu_h + \theta) V_h$$

$$\frac{dE_h}{dt} = \left(\left(b_v \beta_{hv} \frac{I_v}{N_h}\right) + \left(b_w \beta_{hw} \frac{I_w}{N_h}\right)\right) S_h - (\mu_h + \tau_h) E_h$$

$$\frac{dI_h}{dt} = \tau_h E_h - (\mu_h + \gamma_h) I_h$$

$$\frac{dR_h}{dt} = \gamma_h I_h - \mu_h R_h$$

$$\frac{dS_v}{dt} = \mu_v (1 - W) N_v - \left(b_v \beta_{vh} S_v \frac{I_h}{N_h}\right) - \mu_v S_v$$

$$\frac{dE_v}{dt} = \left(b_v \beta_{vh} S_v \frac{I_h}{N_h}\right) - (\mu_v + \tau_v) E_v$$

$$\frac{dI_v}{dt} = \tau_v E_v - \mu_v I_v$$

$$\frac{dS_w}{dt} = \mu_w W N_w Br - \left(b_w \beta_{wh} S_w \frac{I_h}{N_h}\right) - \mu_w S_w$$

$$\frac{dE_w}{dt} = \left(b_w \beta_{wh} S_w \frac{I_h}{N_h}\right) - (\mu_w + \tau_w) E_w$$

$$\frac{dI_w}{dt} = \tau_w E_w - \mu_w I_w$$

Initial conditions were derived by running the model to equilibrium steady state without any control interventions. Key model assumptions are as follows:

- The total human population (N_h) is treated as constant, i.e. births balance deaths at rate μ_h with no immigration of infected individuals into the human populace.
- The mortality rate due to DF is assumed to be negligible (<1% with appropriate medical care [32]) and is therefore not included in the model.
- The population is homogeneous, which means that every individual in a compartment is homogenously mixed with the other individuals.
- Mosquito bites are homogeneously distributed amongst all human hosts, which means that each mosquito can bite any human host with equal probability.
- There is no natural protection, i.e. humans and mosquitoes are assumed to be born susceptible and losses of immunity are not considered, nor are maternally derived antibodies.
- The mosquito has no resistant phase due to its relatively short life expectancy.
- The coefficient of transmission of the disease is fixed and does not vary seasonally in the base case.

Table 5.1 lists the parameter values and their units and sources.

Table 5.1. Parameter notation, values, and sources

Symbol	Definition	Value	Data source
μ_h	Human birth rate = death rate	1/(70 × 365)	[7]
μ_v	Vector mortality rate (non-*Wolbachia*)	12 days^{-1}	[109]
T_v	Average extrinsic incubation rate	9 days^{-1}	[109]
T_h	Average intrinsic incubation rate	7 days^{-1}	[109]
γ_h	Human recovery rate	6 days^{-1}	[283]
β_{hv}	Transmission probability, vector (non-*Wolbachia*) to host	0.186	Modelled
β_{vh}	Transmission probability, host to vector (non-*Wolbachia*)	0.186	Modelled
b_v	Biting rate (non-*Wolbachia*)	[0, 1]	[109]
ε	Vaccine efficacy	73%	Assumed[a]
θ	Waning rate at which temporarily protected individuals with dengue vaccine become partly susceptible to DF	10 years	Assumed
p	Proportion (coverage) of population vaccinated at birth	[0, 1]	Modelled
μ_w	Vector mortality rate (*Wolbachia*)	1.10 × μ_v	[351,352]
T_w	Average extrinsic incubation rate (*Wolbachia*)	T_v	[351,352]
b_w	Biting rate (*Wolbachia*)	0.95 × b_v	[351,352]
β_{hw}	Transmission probability, vector (*Wolbachia*) to host	0.5 × β_{hv}	[351,352]
β_{wh}	Transmission probability, host to vector (*Wolbachia*)	B_{vh}	[351,352]
Br	Scaling factor, vector birth rate (*Wolbachia*)	0.95	[351,352]
W	*Wolbachia* release coverage	[0, 1]	Modelled

[a]Informed by candidate vaccines in development [161,162].

DF dengue fever.

5.3.1.6 Data, expansion factors and calibration

Similar to Knerer et al. [8], epidemiological data from National Epidemiological Surveillance in Thailand [266-270] was used to populate the dynamic transmission model. For the years 2008–2012, there was an average of 82,505 reported cases of dengue per year, including 43,890, 1688 and 36,927 dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS), and DF cases, respectively [266-270]. Approximately 74% of these cases were hospitalized (61,465), with 88 deaths per year (72% due to DSS, with the remainder attributable to DHF).

The average number of reported cases was adjusted by an expansion factor of 8.5 to derive total 'actual' dengue cases. This is consistent with suggested expansion factors in South-East Asia for converting total reported dengue cases into estimated 'actual' cases, ranging from approximately 3.8 in Malaysia, to 8.5 in Thailand and 19 in East Timor [293]. Similarly, expansion factors were also calculated for individual countries based on the active phase of the CYD14 trial, which varied according to case definitions (different laboratory or clinical criteria) [96]. For Thailand, these were 12.0, 8.6, and 8.8 for virologically confirmed dengue, clinically diagnosed and virologically confirmed dengue, and clinically diagnosed dengue, respectively [96].

Model estimates were calibrated with figures reported by the National Epidemiological Surveillance in Thailand in 2008–2012 [266-270] multiplied by an expansion factor to adjust adjusting for under-reporting. The transmission parameters for human (β_{hv}) and vector (β_{vh}) were calibrated using a gradient-based optimization loop that minimized the mean-square difference between the model and recorded observations (adjusted for under-reporting). Model code was written in MATLAB and the optimization function *fminsearch* was used. At steady state, the model predicted an average of approximately 697,000 dengue cases per year in Thailand for all age groups combined. This compares to the average number of reported DF/ DHF cases in Thailand for the period 2008–2012 [266-270] adjusted for underreporting [293], all age groups combined (n = 701,256), which indicates a good fit between observed and predicted data.

5.3.2 Outcomes

DALY estimates were taken from Knerer et al. [8], which were calculated using the methodology described by Murray [356,357]. In the former study, and consistent with the approach of Clark et al. [176], the authors assumed that unreported cases are likely less severe than reported cases, although may still hinder usual daily activities, but for a shorter length of time. Accordingly, similar disability weights had been assigned for both unreported and reported cases of DF, but for a shorter duration of time (4 and 10 days for unreported and reported cases, respectively).

5.3.3 Costs

As with the outcomes described above, we derived disease as well as intervention costs from our earlier paper [8] and highlight salient details in the following sections.

In brief, unit costs (per DF episode) derived from Shepard et al. [178] were used to calculate the following costs:

i. Payer perspective:

- direct medical costs for inpatient and outpatient dengue cases.

ii. Societal perspective:
    - direct medical costs for inpatient and outpatient dengue cases
    - direct non-medical costs for inpatient and outpatient dengue cases
    - indirect costs for inpatient and outpatient dengue cases.

Total costs are comprised of direct medical costs and intervention costs (detailed below) from the payer perspective; and direct medical costs, direct non-medical costs, and indirect costs, in addition to intervention costs, from the societal perspective.

Studies with applicable unit costs [177,360] and used by other researchers – for example, Lee et al. [327] – were similarly not considered in the present study, for the reasons outlined in Knerer et al. [8]. Namely, their reliance on expert opinion, secondary data, or being considered somewhat outdated, leading to potential under-estimation of costs [178].

Cost inputs and other values are presented in **Table 5.2**. As part of scenario analyses, an alternative unit cost profile (Fitzpatrick et al. [202]) was substituted to determine the impact on the base-case results.

Table 5.2. Base case and scenario analysis values and sources

Input	Base case	Scenario analysis
Vaccination target population	Paediatric population vaccinated at birth (0–100% coverage)	Paediatric population vaccinated at birth (70–100% coverage)
Optimization time horizon	10 years	5 years
Vaccine efficacy	73%	50%, 80%
Time horizon	10 years	5 years
Inpatient costs	– $266 DF inpatient direct medical costs [359] – $566.43 DHF inpatient direct medical costs [178] – $72.77 inpatient direct non-medical costs [178] – $54.59 inpatient indirect costs [178]	Unit cost profiles from Fitzpatrick et al. [202] – $141.55 hospital bed day, primary – $169.24 hospital bed day, specialist
Outpatient costs	– $141.61 outpatient direct medical costs [178] – $82.20 outpatient direct non-medical costs [178] – $13.65 outpatient indirect costs [178]	Unit cost profile from Fitzpatrick et al. [202] – $18.29 ambulatory clinic visit
Cost of 'un-reported' cases	$12.12 for clinic visit [327]	N/ A
Vaccine price per course	$40 plus $4 vaccine administration costs	$20 plus $4 vaccine administration costs; $60 plus $4 vaccine administration costs
Wolbachia	*Wolbachia* cost per dengue case averted of $1 (i.e. cost of release per person covered of $4.45)	*Wolbachia* cost per person covered of $1 [412-414]; *Wolbachia* cost per person covered of $15.05 [412-414] (adjusted to 2013 prices [415])

DF dengue fever; *DHF* dengue haemorrhagic fever.

5.3.3.1 Costs of unreported cases

Where costs were ascribed to unreported cases for type

of treatment, it was assumed that any treatment costs for unreported cases were on an outpatient basis only (i.e. there were no hospitalizations and/ or deaths associated with unreported cases), in line with the likely less severe nature of these cases [8,176]. Unreported hospitalizations and deaths have been documented and some estimations for hospitalizations exist for Thailand [178]. However, a conservative approach was employed in the estimation of these costs.

5.3.3.2 Productivity costs due to death

Any economic costs associated with premature mortality (i.e. productivity loss and lifetime earnings foregone) were not included in calculations due to concerns over the risk of double counting benefits associated with averted deaths [165,364].

5.3.3.3 Intervention costs

In earlier cost-effectiveness analyses that also included exploratory analyses of the cost-effectiveness of large-scale deployment of *Wolbachia* infection [8], two different cost estimates were used to calculate the costs of a *Wolbachia* intervention (due to uncertainty in the costs of such an intervention): firstly, a *Wolbachia* cost per dengue case averted of $1 (which was then used to back-calculate a cost of release per person covered of $4.45) and secondly, a *Wolbachia* cost per person covered of $1 (the latter being an aspirational cost of the World Mosquito Programme *Wolbachia* method [412-414]).

In the current study and continuing with the exploratory nature of analyses, we use similar costs to those above, with a *Wolbachia* cost of $1 per dengue case averted being used in base-case analyses and a *Wolbachia* cost per person covered of $1 being examined in scenario analyses.

As an additional scenario analysis, we also use a cost per person covered of $15.05 (the mean of the accelerated costs in Brady et al. [415]) adjusted to 2013 prices (for consistency). This is the average of the cost per person for an accelerated *Wolbachia* programme ranging from approximately $12 to $21 per person. This includes both urban areas (~$12 per person covered) and rural areas (~$14–21 per person covered). Costs were assigned over 4 years to simulate accelerated *Wolbachia* implementation to the point where *Wolbachia*-infected mosquitoes had reached steady state/fixation in the population.

For vaccination, a cost of $40 per vaccination course and assumed vaccine administration costs of $4 was used [8].

5.3.4 Discount rate

Costs were discounted at 3% per annum as suggested by Thailand's Health Technology Assessment guidance and the WHO [365,366].

5.3.5 Scenario analyses

Scenario analyses were carried out on different features and input data of the model to test the robustness of simulated findings and identify key parameters of influence that may impact base-case findings. Analyses predominantly focused on different budget constraints, disease management costs (i.e., unit cost profile), intervention costs, vaccine efficacy, and time horizon. An additional scenario was examined in which the parameter search space for paediatric vaccination was restricted to 70–100% (rather than 0–100% in the base case). **Table 5.2** details scenario analysis inputs and ranges.

5.4 Results

At steady state, the simulation model predicted approximately 7 million symptomatic dengue cases (7.175 million) in Thailand for all age groups combined over a 10-year period. The estimated total DALYs lost in this period were approximately 67,831 with cumulative disease costs of $338 million from the payer perspective. In the following sections, we detail *Wolbachia* and vaccination coverage, dengue reductions, and associated costs (including disease and intervention costs) stratified by different budgetary constraints.

In the unconstrained case, i.e. absence of budget restrictions or limits on investment (represented by the red section in Figure 5.1), the projected optimal coverage of *Wolbachia* and paediatric vaccination (to minimize dengue incidence) comprised 100% coverage of each intervention. In this situation, a reduction of approximately 6 million dengue cases and 58,000 DALYs with an associated budget of $679 million, was forecast over 10 years (Table 5.3) versus steady state. *Wolbachia*-infected mosquito release costs of $274 million and vaccination costs of $351 million formed the great majority of the budget items.

Table 5.3 also presents the optimal mix of the two interventions when budget constraints are introduced, encompassing base-case (approximately ≤ $368 million), lower bound (≤ $251 million), and upper bound (≤ $589 million) budget limits. Under base case budget constraints, the optimal coverage of the two interventions to minimize dengue cases (and DALYs lost) was predicted to be approximately even (*Wolbachia* 50%; paediatric vaccination 49%) although with different constituent costs (*Wolbachia* $135 million; vaccination $170 million). Corresponding intervention coverages estimated under lower

and upper bound budgetary limits were *Wolbachia* 54% and paediatric vaccination 10% for the lower and *Wolbachia* 67% and paediatric vaccination 100% for the upper budget ceilings respectively. When resources become limited under the lowest budget constraints (≤ $251 million), *Wolbachia* has more impact on the population level of disease (as it becomes more affordable relative to vaccination cost) and vaccination is effectively reduced to a targeted hotspot control strategy.

Table 5.3. Optimal combination of *Wolbachia* and paediatric dengue vaccination coverage to minimize the number of dengue cases (and DALYs lost) by budget constraint

Budget constraint ($ millions)	***Wolbachia* (%)**	**Paediatric vaccination (%)**	**Cases (millions)**	**DALYs lost**	***Wolbachia* costs ($ millions)**	**Vaccination costs ($ millions)**	**Total costs (PP) ($ millions)**
Steady state	**0**	**0**	**7.175**	**67,831**	**–**	**–**	**$337.830[a]**
≥ 590	100	100	1.022	9660	273.744	350.666	$678.674
≤ 589	67	100	1.046	9888	182.496	350.666	$588.677
≤ 368	50	49	1.194	11,288	135.489	170.020	$368.772
≤ 251	54	10	1.296	12,256	147.854	25.331	$251.601

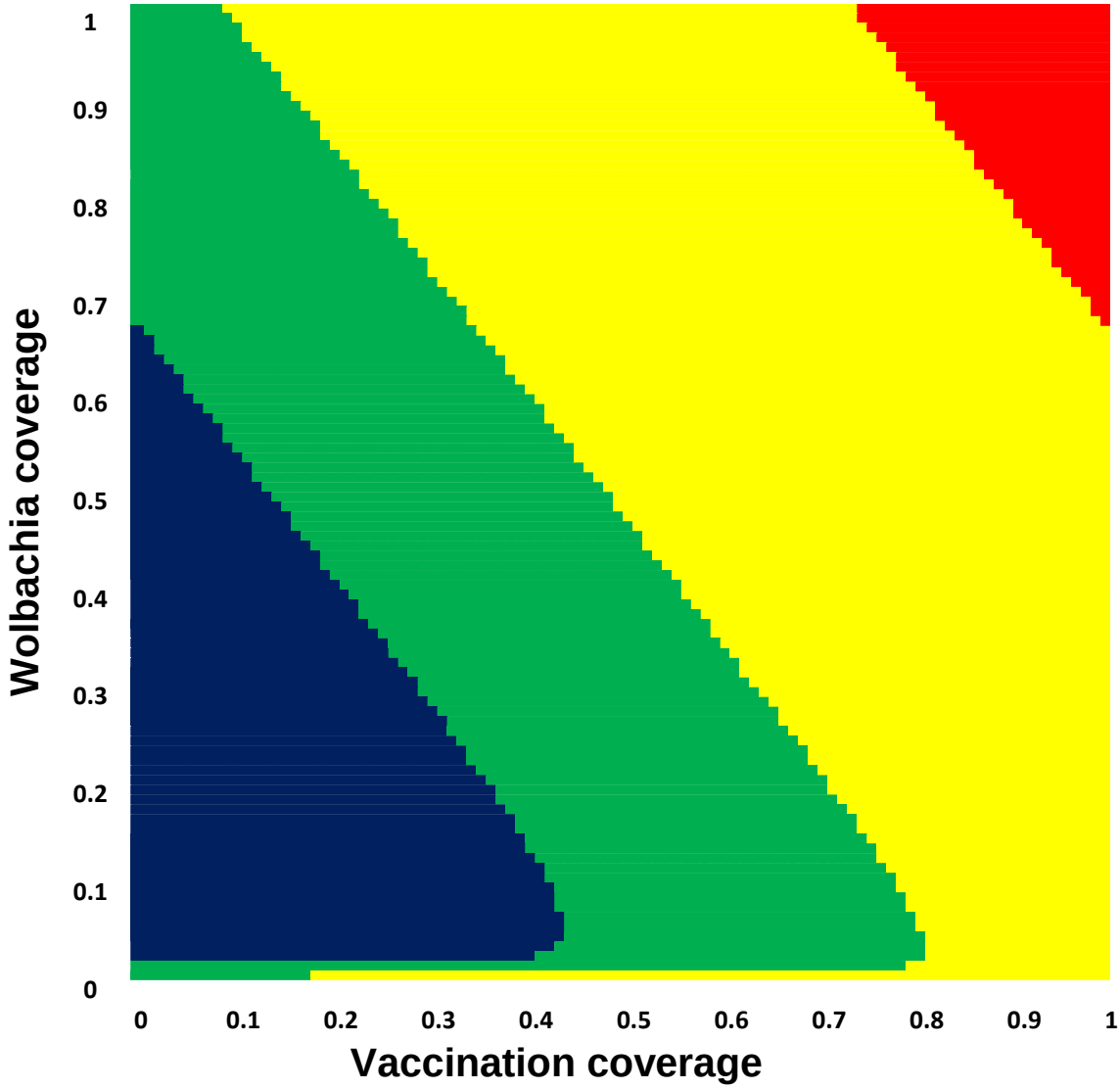
Bold text indicates steady state estimates without control

DALY disability-adjusted life year, *PP* payer perspective

[a]$414 million from a societal perspective

Figure 5.1 presents a heat map of *Wolbachia* coverage and vaccination coverage against budget constraints. In this figure, intervention coverages are varied in the range 0–100% for each control strategy with the respective budget constraints colour coded ranging from the lowest budget constraint (≤ $251 million over 10 years) in blue to the absence of any budget constraint in red.

Figure 5.1. Heatmap of paediatric dengue vaccination coverage and *Wolbachia* coverage against budget constraints.



The heatmap illustrates, for example, the limits of intervention combinations by budgetary ceiling; the chart showing the highest possible combinations of *Wolbachia* and vaccination coverage that are feasible without exceeding upper limit budget constraints (as an example). In practical terms, this could take the form of either, for example, 100% *Wolbachia* coverage combined with approximately 74% paediatric vaccination coverage or approximately 67% *Wolbachia* coverage combined with 100% paediatric vaccination coverage. In effect, this suggests that one or other intervention can have very high coverage (i.e. 100%), but not both interventions without exceeding the budget ceiling. Similarly, from a more restricted budgetary standpoint (i.e. green section [base case] in Figure 5.1), very high coverage of, for example, *Wolbachia*, is compatible with lower coverage of vaccination (or vice versa or midway for both), but high levels of coverage for both interventions together are not compatible within budget constraints. Depending on the public health goal, trade-offs may need to be determined to fulfil the desired objective.

These trade-offs become less urgent as the budget available to fund interventions expands (as observed in the current study when the budget constraint is loosened). Appendix D shows dengue cases and DALYs lost by levels of *Wolbachia* and vaccination coverage.

Table 5.4. Scenario analyses: optimal combination of *Wolbachia* and paediatric dengue vaccination coverage to minimize the number of dengue cases (and DALYs lost) – base-case budget constraint

Scenario	*Wolbachia* (%)	Paediatric vaccination (%)	Cases (millions)	DALYs lost	Total costs (PP) ($millions)
Wolbachia cost (lower bounds)	100	71	1.073	10,143	368.820
Vaccine cost –50%	43	100	1.075	10,167	367.215
Unit cost profile [202]	45	64	1.161	10,979	368.916
80% vaccine efficacy	44	53	1.180	11,158	368.389
Societal perspective	51	43	1.206	11,399	368.846
Vaccine coverage 70–100%	22	70	1.216	11,500	368.680
50% vaccine efficacy	69	33	1.221	11,540	368.630
Vaccine cost +50%	68	23	1.230	11,628	368.925
Wolbachia cost (upper bounds)	21	41	1.326	12,531	366.220
5-year follow-up	33	22	1.317	12,450	202.720

DALY disability-adjusted life year, *PP* payer perspective.

When assessing the impact of alternative situations as part of wider scenario analyses (Table 5.4), approximately half of the scenarios display lower dengue incidence (and DALYs lost), with the remainder demonstrating greater incidence versus base-case projections (all within the budget ceiling of ≤ $368 million discounted over 10 years). The most impactful scenarios relate to the costs of *Wolbachia* and paediatric vaccination with decreases and/or increases in costs of interventions demonstrating a direct correlation with the coverage (increases and/or decreases) of the interventions under examination. For example, a reduction in vaccine acquisition costs results in a corresponding increase in paediatric vaccination coverage (100%) and a smaller reduction in *Wolbachia* coverage (i.e. more resources are directed to the lower-cost vaccination programme). Similarly, a decrease in *Wolbachia* costs gives rise to greater coverage (i.e. a large-scale countrywide *Wolbachia* release programme) as well as an increase in vaccination coverage (i.e. more resources are directed to vaccination). Conversely, as intervention costs increase, more

investment flows to the less costly option and coverage increases as a result. When substituting a different and, in this case, lower unit cost profile [202], more funds are seemingly freed up for vaccination, with higher coverage compared to *Wolbachia,* reflecting the influence of unit costs in this regard. An increase in vaccine efficacy, from 73% to 80% representing the best case, results in greater resources being targeted towards vaccination and less to *Wolbachia (*although the change in coverage and resultant outcomes are relatively small). A decrease in vaccine efficacy, from 73% to 50% representing the worst case, results in the converse with resources directed more to *Wolbachia* and away from vaccination. When paediatric vaccination is restricted to the range 70--100% (in the grid search), left over investment above the minimum vaccination coverage of 70%, flows to *Wolbachia* (22%) and away from vaccination in order to optimally maximise public health outcomes at the lowest cost.

5.5 Discussion

This study aimed to provide further insights into the prioritization and combination of dengue control strategies. The impact of *Wolbachia* infection (wMel strain) and vaccination on the dengue disease burden in Thailand was investigated as part of a constrained optimization problem. The primary goal of the exercise was to identify the best combination of vaccination and *Wolbachia* to minimize the number of dengue cases (and DALYs lost) subject to explicit budgetary constraints. We used a case study of Thailand for the analysis and set the budget constraint to be equal to the estimated current per capita spend on vector control in Thailand [202].

The paper acts as a complement to a CEA conducted by the same authors [8], which investigated both historical methods of dengue control as well as new technologies. For the most part, health economic model analyses are typically unconstrained, the assumption being that resources are available as needed and thus, affordable [394]. In practical terms, the reality may be that funding is absent, as programmes are frequently subject to national and local budget constraints. From a global perspective, many interventions remain under- or even un-funded by countries, although still falling within WHO cost-effectiveness thresholds and considered value for money as a result [377]. In low- and middle-income countries (and increasingly in more developed markets), other considerations beyond cost-effectiveness are likely important for decision-making, including affordability, overall budget impact and sustainability of funding amongst others [377].

The base epidemiological model underpinning the optimization analyses was shown to calibrate well at steady state with average reported symptomatic DF cases in Thailand for

the years 2008–2012 [266-270], adjusted for under-reporting [7,8,293]. As a validation check, predictions were compared with previous model projections presented in Knerer et al. [8], derived using a different model structure and fitted to age-specific data on baseline dengue infection levels (2008–2012) [266-270]. Comparable figures for DALYs lost and cumulative disease costs over 10 years were approximately 67,595 DALYs lost and $336 and $412 million [8] from the payer and societal perspectives, respectively, indicating good concordance between the different model outputs.

Our results suggest that several different combinations of *Wolbachia* and vaccination (paediatric) can produce analogous reductions in the incidence of dengue cases yet have different budget impacts (comparing disease and intervention costs) to achieve the respective coverages. In the base case, the optimal mix between the two study interventions was shown to be approximately equivalent. Conversely, when an alternative (lower) unit cost profile [202] was substituted in scenario analyses, more resources were directed to vaccination with a resulting higher coverage than *Wolbachia*, reflecting the influence of unit costs in this regard. *A priori* hypotheses in relation to the optimal mix and cost of interventions were also borne out. For example, reduced *Wolbachia* costs would lead one to surmise a congruent increase in *Wolbachia* coverage (and decrease in vaccination coverage) whereas an increase in *Wolbachia* costs would lead to the opposite. Similarly, reductions/ increases in both vaccine acquisition costs, and efficacy would have parallel effects.

This study is subject to a number of important limitations. Similar to Knerer et al. [8], the transmission model used in this analysis does not account for asymptomatic cases, rather focussing on the economic impact of clinically apparent (symptomatic) cases and their remission. The vaccine profile employed in this study was informed by real-world overall efficacy data [161,162]. For simplicity, a global serotype transmission model was used that does not explicitly account for individual serotypes (i.e. DENV-1, DENV-2, DENV-3, and DENV-4) nor the potential effects of secondary cases. Hence, any apparent reported imbalances in vaccine immune response between different serotypes and any potential negative implications that may follow from this were not considered. Regarding the use of reported efficacy data [161,162], estimates were applied to the target population under the respective vaccination schedule in the study, rather than the age demographic specified in the original trial. The assumption was that any age-based recommendation would subsequently be extended to include younger children (including those under study). The reported overall vaccine efficacy was also assumed to be constant for the course of study follow-up (10 years) and therefore did not decrease over time. This may have led to possible overestimation in the base case of the impact of vaccination in the longer term.

As a counterbalance, a much lower vaccine efficacy (50%) was examined in scenario analyses to reflect uncertainty in published overall vaccine efficacy results in relation to long-term waning of vaccine protection. Sensitivity analysis was restricted to those parameters that did not form part of the calibrated model. Epidemiological variables including biting rate, vector mortality rate, and transmission rate that were part of the calibrated model were therefore not examined. With respect to vector mortality rate, Ndii [416] reasoned that a maximum 10% reduction in *Wolbachia*-infected vector mortality rate (as used in the current analyses) was appropriate, citing evidence that an increased rate would result in the *Wolbachia*-infected mosquito population dying out and the non-*Wolbachia* infected population dominating the environment. Geographical specificity/heterogeneity was also not considered in the analyses, but would perhaps be of value to help to characterize the optimal split between the two study interventions (to minimize dengue infection) at a finer spatial resolution, for example, north versus south, urban hotspots versus rural locations, etc. *Wolbachia* coverage will have additional benefits to the human population (beyond the dengue mitigation included in the current model), for example, in those areas of Thailand where there is a preponderance of chikungunya and/or Zika virus. Whilst dengue is prevalent throughout Thailand, research on the long-term circulation of Zika virus indicates elevated risks of the disease (relative to the country as a whole) in the northeast and east of Thailand and reduced risks in the south of the country [417]. Conversely, an ongoing outbreak of chikungunya (since October 2018) indicates that cases are concentrated in Southern Thailand [418]. Historically, a large outbreak of Chikungunya in 2008–2010 was also located in the south of Thailand [419], reaching approximately a third of country districts with a subsequent sero-survey in 2014 confirming the extent of chikungunya penetration in this geographical area (estimated seroprevalence of approximately 29.6%) [420]. Notwithstanding the potential benefits of a spatial perspective to such analyses, this does not preclude additional sources of heterogeneity in the local setting, which may affect the feasibility of implementing different strategies and thus the overall results.

As previously highlighted in Knerer et al. [8], it is acknowledged that many practical hurdles still exist before a widespread *Wolbachia*-based dengue control strategy could be implemented. These include, for example, the optimal choice of *Wolbachia* strain, appropriate surveillance, and monitoring of environmental and evolutionary changes, as well as community ‘buy-in’ and acceptance [383,384]. Certainly, the premise that is being examined in this study is not the ‘how’ of implementation, rather what the possible population impact could be once *Wolbachia*-infected mosquitoes have arrived at equilibrium/steady state fixation in areas where they have been released. Although coverage is likely to be limited initially, such analyses provide insights into the human

population impact of a potential *Wolbachia* programme on a large, countrywide scale, both separately and in combination with other control strategies.

5.6 Conclusions

Our model provides a tool for developing estimates of optimal coverage of combined dengue control strategies (*Wolbachia* and paediatric vaccination) that minimize dengue burden at the lowest budget. If proposals/ suggestions are usefully to be put forward in relation to broader vaccine and/or *Wolbachia* introduction for dengue control, policy and decision makers will likely need to determine which dengue interventions to prioritize to optimize the health status of the population, which may necessitate trade-offs depending on the public health goal. As alluded to above, practical operational realities may conceivably be more complicated than the somewhat simplified analyses presented here; in particular, the source of funding budgets for vaccination and/ or *Wolbachia* may be quite distinct, and thus not reflect the trade-offs discussed in this study. Notwithstanding this, commentators suggest that long-term dengue control necessitates increasing investment, complementary control strategies, and intervention programmes across a broad geographic area to minimize cross-border infection [379]. Accordingly, selecting the best investment strategy for dengue control requires the identification of the optimal mix of interventions to implement to maximize public health outcomes. This is often under fixed budgetary constraints and depends on the characteristics of the control strategies in each dengue setting. In this vein, important questions for future work and potential next steps include: (1) Should further investments in dengue interventions focus primarily on reinforcing existing control protocols and/ or increasing the coverage of current interventions and/ or introducing new ones (vector control tools and integrated strategies) and under what circumstances? (2) In what manner should a combination of interventions be further expanded to achieve specified public health objectives at the lowest budget (and potentially in the context of budget cuts in health)?

6 Discussion and Conclusions

Dengue is associated with considerable healthcare utilisation, personal costs to patients and caregivers, productivity loss, and human suffering, despite current control interventions against the disease in endemic countries. With a geographical focus on Thailand, an important location for dengue in Southeast Asia, this thesis builds on, contributes to, and advances on research in relation to the control of DF. It seeks to provide insights into the epidemiological and economic impacts of different dengue control interventions, both individually as well as in combination, in a country with persistent and high levels of dengue transmission. Importantly, whilst defining and examining dengue control interventions, the focus is not on the operational aspects of implementation of these interventions – the 'how' – rather what the possible population impacts of these control strategies are. In this regard, the dengue mathematical models presented in this work have been developed to gain insights into disease transmission and to test and compare different intervention strategies that may be useful in controlling disease and suggest the optimal course of action based on a range of different yet complementary analyses, which is particularly important in resource-constrained contexts.

It is acknowledged that many practical hurdles still exist before some of the interventions and combinations evaluated in this thesis can be implemented. These include, for example, factors in a widespread *Wolbachia*-based dengue control strategy and/ or dengue vaccination programme, such as the optimal choice of *Wolbachia* strain, appropriate surveillance and monitoring of environmental and evolutionary changes, as well as community 'buy-in' and acceptance and feasibility, amongst others [383,384]. Moreover, although (highly) informative and necessary, it is recognised that the outputs from mathematical model simulations are not sufficient for decision-making purposes and should not be the only gauge to provide the basis for recommendations and/ or changes in policy. Certainly, a range of criteria also influence the choices and determinations in, for example, the allocation of scarce healthcare resources, and should be considered alongside other health system goals.

Historically, a number of studies have previously examined the impact of dengue vaccination or vector-control programmes as singular interventions, with less of a focus (if at all) on combination dengue control. This has changed to a degree, during the time I have been working on this thesis, with general recognition that suppression of DF necessitates a combination of preventive and control strategies adapted to the specific conditions and context of each dengue-endemic setting. Moreover, that some form of vector control will continue to form part of control policies to mitigate dengue disease burden and risk even after potential dengue vaccine roll-out. Accordingly, there is a

requirement to assess these wider aspects in terms of their added population-level benefits.

Orthodox forms of vector control, encompassing chemical interventions (adulticide and larvicide) and EM/ PHEA, have been considered, as well as possible new ones in the form of vaccination and *Wolbachia*-infected mosquitoes (which are less capable of spreading viruses). In terms of relevance to current practice and policy, the choice of control interventions under evaluation has been informed by existing dengue control strategies in Thailand as well as WHO guidelines [11], which form much of the basis of country practice and control implementation plans. For Thailand, the dengue control strategy consists of three key elements (derived from WHO guidelines [11]):

i. avoiding transmission by preventing mosquito bites of people infected with dengue
ii. active community detection of non-consulting cases
iii. vector-control strategies comprising environmental management, source reduction, and chemical interventions (adulticide and/ or larvicide [152]).

In the first instance, 'base case'/ status quo analyses (N.B. now and at the time of the first paper being published online in December 2013 [7]) focused on the epidemiological impact of established dengue vector-control strategies, comprising control interventions referenced in point (iii) above (i.e. EM/ PHEA [adulticide and/ or larvicide]). Paediatric vaccination was also considered as part of this analysis in that at the time of writing the manuscript (first half of 2013), the initial results of a Phase 2b proof-of-concept trial conducted in Thai school children had been published [155], indicating vaccine efficacy of 30.2% (95% CI −13.4 to 56.6).

In consideration of 'innovative' control measures (representing the 'future'), for example *Wolbachia* infection or SIT (also known as insect birth control), the WHO indicated in their guidelines [11] (referred to above) that whilst '….some promising new dengue vector-control tools were the subject of operational research, they had not been sufficiently well field-tested under programmatic conditions for recommendations to be made for their use as public health interventions.' Accordingly, the (epidemiological) impact analysis presented in Chapter 3 (Publication 1 [7]) was restricted to the above interventions (see section 3.3.7 Control Interventions for further details). Subsequent guidance from the WHO encouraged '….affected countries [in relation to both dengue and zika viruses] and their partners to boost the use of current mosquito control interventions as the most immediate line of defence, and to judiciously test the new approaches that could be applied in future' [151].

In this regard, the National Environment Agency in Singapore has been conducting a phased pilot study of *Wolbachia* release since 2016 in line with the WHO Vector Control Advisory Group recommendation for careful pilot studies under operational conditions. Moreover, also in the setting of Southeast Asia, the Applying *Wolbachia* to Eliminate Dengue (AWED) trial [421,422] was initiated to assess the efficacy of *Wolbachia*-infected mosquito release to reduce dengue incidence in Yogyakarta, Indonesia. As highlighted in Chapter 4 (Publication 2 [8]), the results of *Wolbachia* pilot operations include Yogyakarta, Indonesia (76% reduction in dengue transmission [324]), Niteroi, Brazil (73% reduction in notified dengue incidence [324]), Nha Trang, Vietnam (86% reduction in dengue incidence [324]) and Kuala Lumpur, Malaysia (40% reduction in dengue incidence [325]).

Accordingly, *Wolbachia* was incorporated into the body of interventions under evaluation in this thesis (Chapter 4 [Publication 2 [8]], Chapter 5 [Publication 3 [10]]) to reflect evolving policy and ongoing progress in technical innovations in vector control, particularly in the Southeast Asia forum. A number of pilot trials of SIT have been conducted in several geographies [423], even though to date, it is often considered more the exception that reports are fully documented in the peer-reviewed literature [10,423,424]. The geographical focus includes, for example, Brazil, Cuba, Italy, Mauritius, Mexico, Germany, the United States, and France. Notwithstanding this, the SIT intervention is not a focus of this thesis and has therefore not been included in any evaluative analyses.

As highlighted earlier, Chapter 1 presents the rationale and primary motivation for undertaking the research as well as describing the policy context and underlining the main aims and objectives of the project.

Chapter 2 then describes why DF is a public health priority, DF epidemiology, and the burden of disease, as well as highlighting the economic impact of DF. It concludes with a brief methodological background to the choice of models underpinning this work, which is subsequently picked up in the discussion section of Chapter 3 (Publication 1 [7]). The subsequent chapters of the thesis present the other two published manuscripts (Chapters 4 and 5 [Publications 2 [8] and 3 [10]]).

Chapter 3 (Publication 1 [7]) presents a dynamic transmission model simulating the impact of different DF intervention strategies (referred to above) to reflect the consequences of these interventions on the epidemiology of DF in Thailand and determine the optimal combination of approaches to disease control based on the subsequent reduction in incidence. The key contributions of Chapter 3 (Publication 1 [7]) to the dengue modelling literature (at the time of publication as well as now) relate to the

inclusion of the impact of combined vector-control and vaccination strategies on the transmission of DF, the age-structure of the model population, seasonality, consecutive infection with all four serotypes, as well as considerations of cross-protection and immune-enhancement. This same dengue transmission model also underpins the analyses presented in Chapter 4 (Publication 2 [8]) as well as providing the framework for adaptation in Chapter 5 (Publication 3 [10]). For both of the first two publications (Chapters 3 and 4), the analyses focused in the first instance, on the impact of individual control interventions and, subsequently, the potential impact of combined dengue control strategies. Vaccination being a continuous intervention, its effects accumulate over the years that follow introduction. Conversely, EM/ PHEA and larvicide and/ or adulticide are one-off or relatively short-term interventions, therefore their effects are evident much sooner. In Chapter 3 (Publication 1 [7]), vaccination was found to be the most effective single intervention, albeit with imperfect efficacy (30.2%) and with a limited duration of protection. Adulticide and environmental management proved to be the most effective of the vector-control interventions. As the duration of each intervention increased, a corresponding reduction in the predicted disease burden was observed. The analyses showed that an imperfect vaccine could potentially be a useful weapon in reducing disease spread within the community, although it will be most effective when promoted as one of several strategies for combating DF transmission. When vaccination was used in combination with environmental management, model projections suggested annual reductions in incidence of 45%, 57%, and 62% for 5, 10, and 20 years post-vaccination respectively. Similarly, when vaccination was used in conjunction with adulticide, model projections indicated annual reductions in incidence of 53%, 75%, and 81% for 5, 10, and 20 years post-vaccination respectively. However, when all three interventions were used in combination, model projections showed annual reductions in the dengue disease burden of 62%, 81% and 86% for 5, 10 and 20 years post-vaccination.

When Chapter 3 (Publication 1 [7]) was first published, there was a relative dearth of studies examining the impact of combined dengue control strategies. In the years prior to online publication in December 2013, Derouich et al. [280], for example, considered the impact of environmental management and a hypothetical vaccine in a two-dengue serotype model (i.e. simulating consecutive dengue epidemics), concluding that environmental management as a method of vector control by itself was not sufficient to control dengue, rather only delay the outbreak of the epidemics and that vaccination against dengue was also necessary. Yang and Ferreira [286] presented a SEIR-SEI compartmental model, incorporating seasonality, to test the impact of different vector-control strategies (insecticide, larvicide, mechanical control [i.e. removal of breeding sites/ containers]). The authors calculated an efficiency index to assess the percentage of

disease averted in humans due to the control intervention(s) with results indicating that all control strategies were efficient in reducing vector population size (efficiency index up to 80%) although the estimated reduction in dengue cases was less than 40% [286]. It was further reported that control strategies could be combined in order to increase efficiency yield(s), dependent on initiation time (i.e. time when intervention[s] were introduced) and available budget. Luz et al. [285,294] analysed the impact of larvicide and adulticide applications, with the effect of these measures introduced by increasing larval and adult vector mortality, respectively. The authors explored the impact of different application frequencies and durations, suggesting that vector-control strategies based on larval (i.e. larvicide) control in isolation may necessitate reassessment and that year-round larvicide control may yield diminishing returns as well as potentially stimulate/ induce insecticide resistance. Coudeville et al. [250] developed an age-structured compartmental model to determine the potential impact of vaccination on dengue burden. Vector control was considered, although the authors did not model any specific interventions. Rather, vector control was introduced by an arbitrary reduction in the vector population size and emergence of new vectors [250] indicating that, in the short term, vector control does reduce disease incidence, but does not alter the long-term dynamics of transmission [250].

Subsequently and post-publication (i.e. after 2013), a series of publications examined the potential impacts of assorted combined dengue control, with findings broadly consistent with the results presented in Chapter 3 (Publication 1 [7]). For example, Christofferson et al. [425] presented a deterministic compartmental model and analyses to suggest that vaccination campaigns characterised by imperfect vaccine efficacy and coverage may be enhanced by simultaneous vector-control strategies. A fundamental assumption in the analyses was that vector control was continuous over the period of simulation (as were efficacy and coverage), although the authors explicitly acknowledged that in reality, this was unlikely to be the case for a number of reasons relating to logistics and costs, etc. Bustamam et al. [342] developed a mathematical model to consider the impact of different dengue control interventions comprising vector control (insecticides, fumigation, and mechanical control enforcement) as well as vaccination of adults and/ or newborns. Their model predictions suggested that insecticide treatment, adult vaccination, and mechanical control enforcement were the most important interventions in reducing dengue disease compared to larvicide treatment and vaccination of newborns. Additionally, the authors proposed that insecticide treatment was the best strategy to control dengue, based on both short- and long-term simulations. Interestingly, their findings indicated little difference between periodic and constant interventions based on the reduced number of the infected human population and concluding that, with resource constraints, a periodic insecticide

control strategy was a beneficial option to reduce dengue disease spread. Outwardly, the authors did not appear to consider the impact of growing insecticide resistance [144,145], which may be induced through continuous vector control (and highlighted in other model-based analyses [285,294]). Polwiang [426] examined the effects of combined dengue vaccination and vector-control strategies using a compartmental transmission model. The impact of vaccination was informed by real-world efficacy reports of the only licensed dengue vaccine [156-158], whilst vector control was represented by a composite measure embracing bed nets and chemical control, as well removal of breeding ground containers (i.e. source reduction). Results indicated that a combination of strategies reduced the number of dengue infections by more than 90%, with vaccine coverage of 50%. The authors therefore affirmed that vector control and vaccination are essential tools of dengue control, and their combination would ultimately lead to a reduction of dengue disease in the community. Using a similar SEIR-SEI compartmental model to Yang and Ferreira [286] (referred to above), Carvalho et al. [341] investigated the impacts of chemical control incorporating insecticide and larvicide as well as mechanical control (i.e. environmental management) and vaccination (based on a hypothetical vaccine profile) in the setting of Brazil. The authors indicated that the dengue epidemics simulated in their analyses were only eliminated with the addition of a vaccine, in that vector-control measures were predicted to be less than sufficient to halt the spread of dengue disease. Specifically, although infected mosquitoes were eliminated from the 'system' (embodied in the series of ordinary differential equations), susceptible mosquitoes remained, with infected humans subsequently leading DF to re-emerge in the human population.

Whilst the above-discussed publications [341,342,425,426] variously focused on the simultaneous impact of combined dengue strategies, Thavara et al. [427], in contrast, drew a distinction in their model-based analyses of the impact of dengue vaccination [428]. The authors indicated that mosquito control, by itself, would have increased the incidences of DF and DHF (as a result of age-related disease manifestation or some form of immunological mechanism) in areas of high mosquito density and that, to combat this, mosquito-control programmes should only be carried out after a vaccination programme with high coverage has been initiated [427]. Similarly to Coudeville and Garnett [250], the authors did not model any specific interventions, rather vector control was also introduced by an arbitrary reduction in the vector population size, with the impact assessed in the basic reproduction number [427].

In Chapter 4 (Publication 2 [8]), the objective of the analyses was to determine what the cost-effective dengue control options were from a priority setting and decision-making perspective. CEA was used to identify which of the considered dengue disease control

strategies had the potential to generate the greatest improvements in disease reduction for the least resources. The dynamic transmission model developed in Chapter 3 (Publication 1 [7]), with updated data inputs, provided the epidemiological base for the economic analyses, where an epidemiology representative of average Thailand dengue epidemiology in the years 2008–2012 was assumed, linking dengue incidence to costs and outcomes, and thus predicting the number of dengue cases at steady state and under each control strategy. This was subsequently combined with economic inputs to report the costs and consequences of different strategies and included formal CEA. The focus of the analyses was primarily on historical forms of vector control (including adulticide, larvicide, and EM/ PHEA) before introducing dengue vaccination in the form of staggered roll-out over time and *Wolbachia* infection in exploratory scenario analyses.

DALYs lost to disease (representing the humanistic burden of dengue) were calculated using the methodology described by Murray and Lopez [356,357]. To account for differences in the impact on quality of life, the duration of symptoms was stratified for symptomatic (DF) and severe (DHF/ DSS) disease as well as by unreported versus reported cases to reflect that unreported cases are likely less severe than reported cases, although may still hinder usual daily activities, but for a shorter length of time. Cost estimates of a DF episode reflecting both the payer and societal perspectives in Chapter 4 (Publication 2 [8]) and Chapter 5 (Publication 3 [10]) were taken from Shepard et al. [178], based on a study by Kongsin et al. [197], who assessed the costs of DF to Thai society and included direct medical costs, direct non-medical costs, and productivity losses.

With respect to sensitivity/ scenario analysis, ISPOR good practice guidelines indicate that probabilistic sensitivity analysis (PSA) tends not to be conducted in dynamic transmission models due to computational complexity [171]. These guidelines also highlight that it may be challenging or inappropriate to conduct this type of analysis in such models. Accordingly, PSA is not formally mandated as part of their best practice recommendations for dynamic transmission models [171]. Ultsch et al. [429] state that “All identifiable sources of uncertainty should be accounted for, if not by PSA then by other analyses”. Similarly, Drake et al. [170] indicated that detailed sensitivity or uncertainty analysis is essential and, whilst PSA is preferable, a univariate analysis including both economic and epidemiological parameters should be an alternative in the event that PSA is not possible. In Chapter 4 (Publication 2) [8], PSA was not carried out for practical reasons related to model run-time and complexity as highlighted previously (Section 4.4.10). Rather, the sensitivity of interventions in the table of incremental analyses to changing assumptions was explored by univariate variation of key parameters and then iteratively recalculating incremental analyses for the control strategies under evaluation. In this sense, sensitivity/

scenario analysis was restricted to those parameters that did not form part of the calibrated model. Notwithstanding this, epidemiological variables including biting rate, vector mortality rate, duration of infectious period in host and latent period in vector that were part of the calibrated model were also examined, the reason being that vector mortality, duration of infectious period in host, latent period in vector, and biting rate were identified as particularly impactful variables when subject to variation in Bartley et al. [109], from which the model (presented in Chapter 3 [Publication 1 [7]] and Chapter 4 [Publication 2] [8]) was adapted. Similarly, Amaku et al. [290] found that model parameters related to control (i.e. vector mortality rate, biting rate, and immature stage carrying capacity) also proved influential to the relative amount of variation if these parameters were varied. The latter authors indicated that other epidemiological variables, for example, degree of cross-protection or larval mortality rate in Bartley et al. [109] and Amaku et al. [290], respectively, were not showing the degree of sensitivity of some of the key epidemiological variables (e.g. vector mortality rate, duration of infectious period in host, and biting rate) highlighted above.

Our results predicted that single control strategies (adulticide or vaccination) and a combined strategy (vaccination/ adulticide/ EM/ PHEA) would be highly cost-effective and cost-effective control measures, respectively, with exploratory scenario analyses also showing that *Wolbachia* (in isolation) was predicted to be highly cost-effective and exhibited marked decreases in dengue burden, enhanced by the addition of vaccination. Importantly, the base-case findings were robust to variations in assumptions in sensitivity analyses under which ICERs (compared with the preceding non-dominated strategy) were iteratively re-calculated for each change in parameterisation. As expected, the epidemiological parameters that formed the calibrated dynamic transmission model were most sensitive to variation.

As highlighted earlier, study results in Chapter 4 (Publication 2 [8]) were broadly consistent with previous research encompassing trial-based evaluations, for example Liyangage et al. [143], as well as model-based analyses, for example, Fitzpatrick et al. [202,294], subject to methodological differences that have the potential to impact results. These include comparators, specified efficacy or mortality rate(s) for vector control, duration and intensity of vector-control interventions (i.e. continuous, monthly etc.), unit costs, vaccine price, perspective, and timeframe, amongst others. For example, with respect to efficacy/ mortality rates for (chemical) vector control, we used low efficacy profiles in our analyses, in contrast to other researchers who had employed high and medium efficacy rates or mortality rates of 30%, 60%, and 90% (i.e. low efficacy, medium efficacy, and high efficacy) for vector control. This would likely impact the ICERs and

perhaps explain some of the elements contributing to the higher nature of the ICERs in our study compared with other authors [202,294]. Moreover, with respect to unit costs, we used dengue-related costs derived from Shepard et al. [178] rather than unit costs that have been used in other studies [177,360], the reason being their reliance on expert opinion, secondary data, or being considered somewhat outdated, leading to potential under-estimation of costs [178]. When we substituted other reported unit costs (excluding vaccine costs and/ or vector-control costs) as part of sensitivity and scenario analyses for those reported in other studies, for example, Fitzpatrick et al. [202], Lee et al. [361], and Flasche et al. [330], the broad order of interventions under evaluation remained unchanged from the base case in all three instances, suggesting an inherent consistency across study designs and geographies.

In the period between resubmission of Publication 2 [8] (Chapter 4) after addressing referee comments and final publication, important studies analysing the cost-effectiveness of *Wolbachia* infection were published, including Brady et al. [415] and Suwantika et al. [430]. In a model-based analysis, Brady et al. [415] used previous estimates of the burden of disease, effectiveness of *Wolbachia* release, and a spatially explicit model of release and surveillance requirements (wMel) [355] to predict the costs and effectiveness of the ongoing (pilot) *Wolbachia* programme in Yogyakarta, Indonesia as well as three hypothetical *Wolbachia*-release programmes. Their findings predicted *Wolbachia* release to be a highly cost-effective and possibly cost-saving dengue control intervention when implemented in dense built-up urban areas*,* with ICERs of less than $1,500 per DALY averted as well as presenting positive cost-benefit ratios.

In a similar fashion, Suwantika et al. [430] carried out a model-based analysis to assess cost-effectiveness using a static age-structured decision tree model. The authors aimed to analyse the cost-effectiveness of a dengue vaccination programme combined firstly with *Wolbachia* and secondly, health education, also in the setting of Indonesia. The three analyses under evaluation – vaccination and *Wolbachia*, vaccination and health education, and vaccination only – were compared to no intervention. Effectiveness estimates for *Wolbachia* infection of 86% derived from O'Reilly et al. [355] were used. Model predictions indicated ICERs of $4,460, $6,399, and $9,995 per QALY gained for vaccination and *Wolbachia*, vaccination and health education, and vaccination, respectively.

These findings compare favourably with the *Wolbachia* results presented in Chapter 4 (Publication 2 [8]) and demonstrate innate consistency between the three separate analyses, with ICERS for a countrywide *Wolbachia* programme of $343 per DALY averted

and *Wolbachia* in combination with targeted vaccination of $11,462 per DALY averted. Differences between ICERs in the respective publications variously relate to cost of interventions, vaccine efficacy, and vaccine coverage, as well as comparators. For example, the *Wolbachia* cost (per person covered) used in Chapter 4 (Publication 2 [8]), was approximately 50% greater than that of Suwantika et al. [430], but only a third of the corresponding cost used in Brady et al. [415]. In their analyses, the former used a cost per vaccine course of $60 plus administration costs together with a vaccine efficacy of 40% and vaccine coverage of 88%. The analogous figures in Chapter 4 (Publication 2 [8]) were $40 plus administration costs with vaccine efficacy of 80% (falling to 73% at 18 months) and vaccine coverage of 40%. In relation to comparators, in Brady et al. [415], *Wolbachia* was compared to existing dengue control measures in all scenarios, which consisted primarily of insecticide-based vector control, whereas in Suwantika et al. [430], the comparator in all scenarios was 'no intervention'. In contrast, in Chapter 4 (Publication 2 [8]), EM/ PHEA acted as the reference comparison to *Wolbachia* release, whereas when combined with vaccination, the comparison was with A3 EM/ PHEA (i.e. adulticide 3 doses + EM/ PHEA) as the reference.

Chapter 5 (Publication 3 [10]) explored affordability via CO, in which different control interventions – *Wolbachia* and vaccination – were combined. CO helps to address some of the acknowledged limitations of conventional health economic analyses (in that being cost-effective is not the same as being affordable) and has typically been used to identify the optimal allocation of resources across interventions, subject to a variety of constraints. We sought to estimate the optimal mix of dengue control strategies to maximise public health outcomes within the constraints of a fixed budget, set no higher than cost estimates of the current vector-control programme in Thailand, to minimize the number of dengue cases and DALYs lost. A dynamic transmission model was developed to predict the number of dengue cases in Thailand at steady state. A CO was then applied to identify the optimal combination of interventions (release of *Wolbachia*-infected mosquitoes and paediatric vaccination) subject to constraints. Epidemiological, cost, and effectiveness data were informed by national data and the research literature and with a follow-up time horizon of 10 years.

Stratifying analyses by different budgetary ceilings (base case [≤ $368 million], lower bound [≤ $251 million] and upper bound [$568 million]), we predicted that the optimal coverage of the two interventions to minimise dengue incidence under base-case budget constraints was approximately equal (*Wolbachia* 50%; paediatric vaccination 49%) with corresponding coverages under lower bound (*Wolbachia* 54%; paediatric vaccination 10%) and upper bound (*Wolbachia* 67%; paediatric vaccination 100%) budget ceilings.

Heatmap analyses showed the limitations and extent of various *Wolbachia* infection and vaccination combinations with, for example, the chart indicating the highest possible combinations of *Wolbachia* and vaccination coverage that were feasible without exceeding respective budget constraints. In general terms, this effectively means that within a resource-constrained budget, very high levels of both vaccination and *Wolbachia* are unlikely to be fully realised and, depending on the public health goal, trade-offs will likely be required to achieve the preferred objective(s).

Sensitivity analysis was restricted to those parameters that did not form part of the calibrated model. Epidemiological variables including biting rate, vector mortality rate, and transmission rate that were part of the calibrated model were therefore not examined. Given the focus in the analyses on budget limitations and optimising within these constraints, sensitivity analyses targeted *a priori* hypotheses in relation to the optimal mix and cost of interventions. For example, reduced *Wolbachia* costs would lead one to surmise a congruent increase in *Wolbachia* coverage (and decrease in vaccination coverage) whereas an increase in *Wolbachia* costs would lead to the opposite. Similarly, reductions/ increases in both vaccine acquisition costs and efficacy would have parallel effects, etc. In this way, scenario analyses focused on different budget constraints, disease management costs (i.e. unit cost profile), intervention costs, as well as vaccine efficacy and time horizon. As highlighted in Chapter 5 (Publication 3 [10]), an additional scenario was examined in which the parameter search space for paediatric vaccination was set to a default of 70–100% (rather than 0–100% in the base case) to explore the extent and impact of *Wolbachia* infection coverage, given the paediatric vaccination programme effectively in place. In this regard, scenario analyses indicated that the most impactful situations related to the costs of *Wolbachia* and paediatric vaccination with decreases/ increases in costs of interventions demonstrating a direct correlation with coverage (increases/ decreases) of the respective control strategies under examination.

Earlier research literature highlighted the identification and evaluation of optimal strategies to minimise infectious disease (subject to constraints) in, for example, the determination of the most effective combination of preventive interventions for malaria [402,403], human papillomavirus infection and cervical cancer [404,405], as well as DF [406-409], amongst others [410,411]. When we focus specifically on *Wolbachia* in relation to DF*,* relatively few mathematical models have considered *Wolbachia* in concert with vaccination against DF. Two studies [416,431] explicitly examined these interventions in combination, although with differing overall objectives, and can be thought of as hypothesis generating in that they are setting neutral and/ or generic analyses. Firstly, Supriatna et al. [431] investigated the optimal strategy of *Wolbachia*-infected mosquito release, focusing on the

interplay between epidemiological and economic factors, using optimal control theory methods, which is a variant of CO. The premise the authors explored is one where sufficient provision exists to support a vaccination programme of susceptible individuals, but with limited support for the release of *Wolbachia*-infected vectors; the purpose being to minimise total costs (comprising intervention and disease costs) by releasing the lowest number of *Wolbachia*-infected mosquitoes that will reduce the peak of dengue outbreaks and prevalence of infections. Cost figures presented were generic in the form of (universal) cost units whilst measures of intervention coverage were not used, rather level of contagiousness in the case of *Wolbachia* [431], which limits generalisability and comparison with the current study. Secondly, Ndii [416], in a short piece, examined the epidemiological impact of *Wolbachia* infection and vaccination, focusing on three scenarios: *Wolbachia* infection, vaccination, and a combination of these. Using estimates of vaccine and *Wolbachia* impact based on the first licensed dengue vaccine [432] and previous work [351], the author concluded that the impact of *Wolbachia* in reducing dengue transmission was greater than that of vaccination if the vaccine efficacy was low and that the majority of reduction in dengue cases could be derived from a stand-alone *Wolbachia* strategy. This finding is consistent with Chapter 4 (Publication 2 [8]) (which informed the current analyses), where it was found that, in a combined *Wolbachia* infection and dengue vaccination control strategy, *Wolbachia* reduced the force of infection to such an extent that the incremental impact of vaccination may only be marginal.

This thesis is subject to some important limitations. Firstly, a number of potentially effective control interventions (including experimental vector control methods) – highlighted in Figure 2.12 and Figure 2.13, namely, insecticide-treated nets/ other materials, biological control including predatory copepods and larvivorous (larvae-eating) fish, classical SIT, release of insects with dominant lethality, and other strategies for mosquito-borne arbovirus control interventions – were not considered. Comprehensive reviews of evidence and potential effectiveness already exist in work such as Achee et al. [136,139] and others [433]. The objective of this thesis was not to provide a systematic review and evaluation of all existing methods to control dengue, rather to evaluate certain interventions commonly in use in dengue endemic and hyperendemic countries such as Thailand with an eye to those interventions also under advanced and/ or late-stage evaluation that may become available in the short to medium term in countries such as Thailand and potentially be adopted at scale. In this regard, the interventions under consideration in this thesis meet the above criteria in that they are either already being widely used or have the potential to be adopted on local regulatory approval.

An additional limitation relates to the absence of heterogeneity in our analyses, except for age. Spatial/ geographical heterogeneity was not considered, although DF may vary widely across (as well as within) countries, but be more homogeneous within cites, although the models used in Chapters 3, 4, and 5 do not take this into account. Notwithstanding this, dengue incidence is relatively homogeneous across regions in Thailand, unlike, for example, in Brazil. Therefore, in this context, the impact of spatial/ geographical heterogeneity is likely to be relatively minimal. Vector-host heterogeneities are also not considered, for example, in hosts getting bitten or biting by mosquitoes [312]. Woolhouse et al. [313] previously identified the 80/20 'rule' where 80% of all transmissions are due to 20% of people, with the authors suggesting that this 'rule' was relevant for a variety of other diseases as well. Additionally, using polymerase chain reaction to identify human DNA from blood meals in *Aedes aegypti*, de Benedictis et al. [314] highlighted that only three people accounted for approximately 56% of the meals in samples collected from 22 homes, indicating the non-random nature of feeding, with an apparent bias towards young adults and males. The importance and main implications of heterogeneity suggest that interventions that can be focused on key groups/ sub-populations can potentially be very effective, whereas strategies that fail to reach their target groups will tend to be less successful in reducing population-level disease burden [304,313] than perhaps originally anticipated. The dynamic transmission models presented in Chapters 3 and 4 (Publications 1 and 2 [7,8]), and Chapter 5 (Publication 3 [10]) do not account for asymptomatic infections, rather they focus on clinically apparent infections (and their adjustment for under-reporting). Whilst asymptomatic infections are considered to form an important element of the dengue burden and potentially play a role in dengue transmission (for example, approximately 75% of dengue cases are asymptomatic [23,34,42,82]), the emphasis in our analyses is on the economic impact of symptomatic dengue infections and their mitigation. Accordingly, we do not believe that such an omission fundamentally undermines the broad conclusions of our analyses. Vector-control interventions (adulticide and/ or larvicide) and EM/ PHEA used short-term intervention horizons (1 and 5 years) to represent traditional vector-control measures under evaluation. This may potentially induce a phenomenon known as the 'divorce effect' (i.e. a greater number of infections in total versus no control, and counting from the time that control started [378]) as a consequence of the introduction and subsequent withdrawal of non-vaccinating vector-control measures [344,378]. Rationally, and as referenced earlier in Chapter 4 (Publication 2 [8]), it is unlikely that successful vector-control programmes would be terminated as rapidly or abruptly, although it may be that such programmes are variously subject to factors such as interruption(s), discontinuation, and/ or substitution (with another programme) for a variety of plausible reasons. These may include, for example, funding and resourcing issues, conflict, natural disasters, insecticide resistance,

or where an intervention is deemed ineffective. In practical terms, it is envisioned that vector-control programmes would either continue indefinitely and/ or until a mixture of more effective and/ or lasting control programmes (e.g. *Wolbachia,* etc.) become the standard. This would effectively act to mitigate the impact of any divorce effect. Lastly, it is important to note that any positive externalities of the vector-control programmes examined in this thesis on the burden of disease and costs of illness associated with other vector-borne diseases (e.g. zika virus, chikungunya, malaria, etc.) in Thailand were not considered or taken account of in this project. To fully capture these inter-dependencies, some form of systems analysis and/ or general equilibrium modelling framework may be required, which is out of the scope of the current project. The implications of this omission would likely impact the estimation of the burden of disease and cost-effectiveness of vector-control combinations in our analyses, leading to potential under-estimation of the cost-effectiveness of vector-control interventions, for example.

Conclusions

Using three different and complementary analyses (epidemiological impact, i.e. effectiveness, CEA, and CO), we predicted the most beneficial approach to reduce dengue burden (in terms of cases, cost-effectiveness, and affordability, respectively) to be the simultaneous application of existing form(s) of control, e.g. adulticide, EM/ PHEA, transitioning to more innovative technologies such as *Wolbachia* (where appropriate/ feasible) and combining with vaccination, thereby amplifying the singular impact of each intervention.

Individually, each publication makes a worthy contribution to the research literature as evidenced by their acceptance and publication in high-quality peer-reviewed journals. For example, and as highlighted earlier, the key contributions of Chapter 3 (Publication 1 [7]) to the dengue modelling literature (at the time of publication as well as now) relate to the inclusion of the impact of combined vector-control and vaccination strategies on the transmission of DF, the age-structure of the model population, seasonality, consecutive infection with all four serotypes, as well as considerations of cross-protection and immune-enhancement. The research contribution of Chapter 4 (Publication 2 [8]) builds on the above and presents comprehensive CEA of vector-control methods as well as providing one of the first attempts to evaluate the cost-effectiveness of a candidate dengue vaccine using recently published efficacy data in the context of current dengue control strategies. It is also, to our knowledge, one of the first published attempts to evaluate the cost-effectiveness of *Wolbachia* release using a dynamic transmission model, again in the context of alternative existing methods of control. Lastly, having determined ‘value for money’ in Chapter 4 (Publication 2 [8]), the original research

contribution of Chapter 5 (Publication 3 [10]) was firstly in the presentation of a mathematical model of DF transmission with vaccination and *Wolbachia* as control interventions, secondly, to economically assess the strategies under examination and lastly, to propose a CO problem, the aim being to identify the optimal combination of these two interventions, within the constraint of a fixed budget in Thailand. Notwithstanding the above, it is in the contribution of the aggregate body of work in relation to three key factors: effectiveness, cost-effectiveness, and affordability, that the innovative nature of the overarching framework can be appreciated and that addresses some of the research gaps identified by commentators, for example, Ogunlade et al. [433]. Moreover, this thesis also talks to the ethos encapsulated in Brandeau's work in relation to the distinction between applied and theoretical practices and the importance of the former in her work [401].

These findings could potentially be of interest to relevant decision-makers/ policymakers/ stakeholders in dengue-endemic countries. They could also be useful when considering the addition of new interventions and/ or changing the implementation of existing ones, as well as characterising what could be expected from implementation of combination interventions. In this regard, our results concur/ correlate with published RCT findings (in the case of mixed vector control [143] or *Wolbachia* [389]) across geographies, which therefore yields practical insights/ implications in addition to academic interest. Additionally, the inclusion of CEA and affordability information seeks to address decision-maker and policymaker needs in lower- and middle-income countries, increasingly focused on developing evidence-based priority-setting frameworks that incorporate value for money and budget impact criteria.

As a result of this work, further research could be conducted into whether, for example, investment in dengue interventions should focus primarily on reinforcing existing control protocols, increasing the coverage of current interventions, or introducing new ones (vector-control tools and integrated strategies). Furthermore, in relation to combination dengue control, what mix of different (control) elements could potentially be most beneficial, under what circumstances, and in what geographies. Lastly, research into how to implement – and then expand – any changes in dengue control could provide insights into how best to maximise public health objectives at the lowest budget.

7 Appendices

7.1 Appendix A

Table 7.1. Cost of vector-control activities based on empirical publications from 2000 through 2014 (2013 USD)

Authors	Setting	Country	Period	Vector-control activities	Unit costs
Comprehensive vector-control activities					
Baly et al. [198]	Trujillo state	Venezuela	2007	Insecticides and larvicides	$0.58[a]
Undurraga et al. [434]	Mexico	Mexico	2010–2011	Surveillance, insecticide, nebulization, indoor spraying, larvicides, educational and awareness campaigns, and community-based participatory control programs	$0.79[b]
Kongsin et al. [197]	Thailand	Thailand	2005	Education, limited use of larvicides, and insecticide	$1.15[a]
Taliberti et al. [435]	Sao Paulo City	Brazil	2005	Active surveillance, inspection, education, larvicide, and insecticide	$1.31
Baly et al. [198]	Laem Chabang Municipality	Thailand	2007	Insecticides and larvicides	$1.42[c]
Armien et al. [436]	Panama Province	Panama	2005	Surveillance, laboratory, and vector-control activities	$1.80[a]
Perez-Guerra et al. [437]	Puerto Rico	Puerto Rico	2002–2007	Surveillance, clean-up campaigns, fumigation, inspection, education and management	$2.31[d]
Packierisamy et al. [362]	Malaysia	Malaysia	2010	Inspection, surveillance, fogging, larviciding, and health education	$2.68[b]
Baly et al. [438]	Guantanamo	Cuba	Jan–Jul 2006	Surveillance, source reduction, larviciding, insecticide, education, and active screening for fever cases	$3.10[e]
Orellano and Pedroni [339]	Clorinda	Argentina	Jan–Apr 2007	Surveillance, source reduction, fogging, larviciding, and education.	$4.32[f]
Baly et al. [438]	Guantanamo	Cuba	Aug–Dec 2006	Surveillance, source reduction, use of larvicide and insecticide, education, and active screening for fever cases	$6.79[e]

Specific vector-control interventions					
Kay et al. [200]	Xuan Phong District	Vietnam	2007	Community-based strategies to control dengue	$0.09
Suaya et al. [201]	Phnom Penh and Kandal Province	Cambodia	2001–2005	Larviciding campaigns against *Ae. aegypti*	$0.24
Kay et al. [200]	Tho Nghiep District	Vietnam	2007	Education, larvicide, insecticide, and community participation	$0.28[g]
Tun-Lin et al. [304]	Vietnam	Vietnam	2004	Mesocyclops in productive containers	$0.32
Tun-Lin et al. [304]	Myanmar	Myanmar	2004	Dragon-fly nymphs, fish	$1.13
Rizzo et al. [439]	Poptun, El Peten	Guatemala	2009–2010	Insecticide-treated curtains	$1.30
Baly et al. [198]	Trujillo State	Venezuela	2007	Long-lasting insecticide-treated curtains	$1.53[h]
Baly et al. [199]	Santiago de Cuba	Cuba	2001–2002	Conventional dengue control plus community participation	$2.22
Tun-Lin et al. [304]	Philippines	Philippines	2004	Tire splitting, drum and dish rack cleaning, waste management	$2.42
Tun-Lin et al. [304]	Mexico	Mexico	2004	Bucket and flower pot management	$2.51[i]
Pepin et al. [340]	Minas Gerais	Brazil	2009–2011	Intelligent dengue monitoring system	$3.10[j]
Tun-Lin et al. [304]	Kenya	Kenya	2004	Temephos in large productive container	$3.24[k]
Baly et al. [198]	Laem Chabang Municipality	Thailand	2007	Long-lasting insecticide-treated curtains	$3.35[l]
Tozan et al. [440]	Plaeng Yao District, Chachoengsao Province	Thailand	2014	Insecticide-treated school uniforms	$5.50[m]
Ditsuwan et al. [441]	Muang District, Songkhla province	Thailand	2009	Standard indoor ultra-low-volume space spraying	$6.03[n]
Lorono-Pino et al. [442]	Merida City	Mexico	2012	Insecticide consumer products	$8.50

Reproduced from Undurraga et al. [196].

[a]Study was done during epidemic year or season.

[b]Study was done during nonepidemic year.

[c]Estimates correspond to the average over 2 years.

[d]Estimates correspond to the average over 5 years.

[e]Results were presented as $1.89 per household January to July 2006, and $2.14 per household in August to December 2006.

[f]January through February are the months with higher DENV transmission in Clorinda, so vector-control costs are most probably not representative of costs during the rest of the year.

[g]Authors used a discount rate of 6% and did not include the costs of buildings.

[h]Cost per capita was obtained assuming an household size of 3.7 (http://geo-mexico.com/?p 5 3162).

[i]Partnership model with supervision, included delivery, training, personnel, amortization capital cost, supplies and materials, and utilities.

[j]Cost per capita was obtained assuming an average household size of 3.2.

[k]Cost derived using factory proprietary method. Their estimate excluded the costs of international shipment, collection of uniforms, and distribution to households.

[l]Partnership and vertical models. Cost estimates included delivery, training, personnel, amortization capital cost, supplies and materials, and utilities.

[m]Cost estimates included microcredit fund and in-kind contribution of health workers and teachers.

[n]Opportunity cost represented 90% of total costs.

Notes: Per capita vector-control costs for specific interventions were not annualized because of variations in dengue season across countries; hence, comparisons between specific interventions or countries must be done with caution.

7.2 Appendix B

Table 7.2. Parameter notation, value and source

Symbol	Definition	Value	Data source
μ_h	Human birth rate=death rate	1/70 years	[443]
μ_D[1.0.4]	Dengue-induced mortality in humans	$\mu_{\alpha[1, 3, 4]}$=0.00002; $\mu_{\alpha[2]}$=0.0003	[294]
μ_v	Vector mortality rate	12 days^{-1}	[109]
μ_A	Aquatic mortality rate	10 days^{-1}	[283]
T_v	Average extrinsic incubation rate	9 days^{-1}	[109]
T_h	Average intrinsic incubation rate	7 days^{-1}	[109]
γ_h	Human recovery rate	7 days^{-1}	[283]
β_v	Transmission probability, host to vector	0.375	[282]
β_h	Transmission probability, vector to host	Age specific	Modelled
b	Biting rate of susceptible or infectious mosquitoes	Variable	[444]
O	Oviposition rate	50 days^{-1}	[283]
K	Aquatic (egg/larvae) carrying capacity	10^{-6}	[296,297]
W	Waning rate at which temporarily protected individuals with dengue vaccine become partly susceptible to dengue fever	10 years	Assumed
ST	Seasonality term	See text	[283,296,297]
c	Climactic factor adjusting winters and summers	0.07	[283]
d	Climactic factors adjusting winters and summers	0.06	[283]
σ	Phase	$\pi/2$	[283]
f	Frequency of seasonal cycles	2.8×10^{-3} days^{-1}	[283]
g	Proportion of infected eggs/larvae	0.50	[283]
pA	Maturation rate from larvae to adult (per day)	0.80	Modelled
ε_h^{-1}	Period of cross−protection	6 months	[109]
ω_h^{-1}	Period of cross-enhancement	3 months	[109]
Φ_h	Proportion of cross-protection	0–1	[109]
φ_{he}	Increase in infectiousness (cross-enhancement)	1–5	[109]

7.3 Appendix C

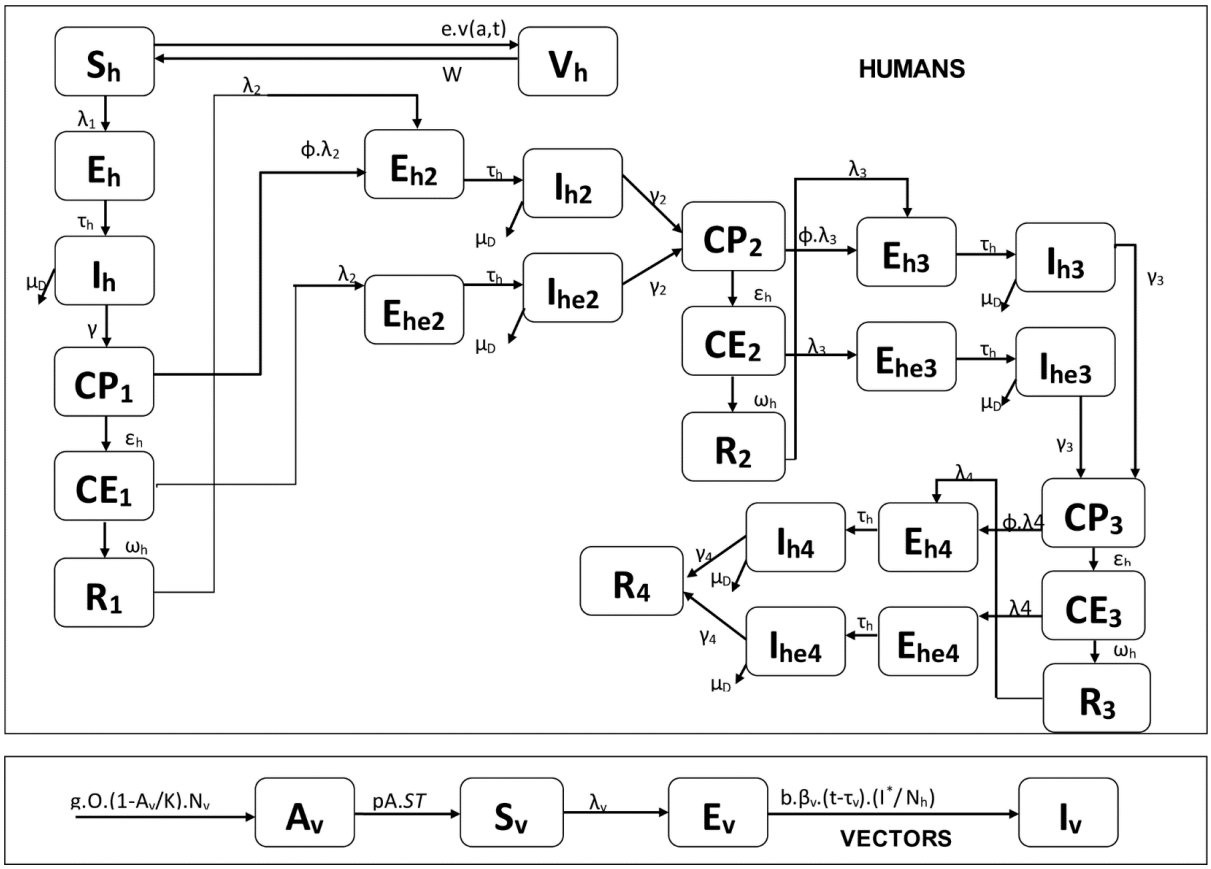
Methods

Epidemiology model structure

The previously published model extends work by Bartley et al. [109] and includes the following elements: consecutive infections with all four serotypes, age-structure of the population, seasonality, cross-protection and cross-enhancement and the impact of combined vector-control and vaccination strategies on the transmission of dengue fever (DF) [7]. Model compartments comprise those for both human and vector populations. The human population (N_h) is divided into susceptible to dengue infection, S_h; exposed but not yet infectious (i.e. incubating the virus), E_h; infected and infectious humans, I_h; temporary cross-protection, C_p; temporary cross-enhancement (C_E) (i.e. enhancement of viral infectiousness caused by antibodies that do not neutralise [21,62,63]) and immune (R) compartments. The final recovery state R imparts permanent immunity to that serotype, but only temporary immunity to other serotypes.

Human hosts can experience a primary infection with one serotype followed by the possibility of subsequent infections with other serotypes. Accordingly, exposed, infectious and immune states are further stratified by the number of infections suffered (i.e. primary, secondary, tertiary etc.) in the form E_h, E_{h2}, E_{h3} and E_{h4}. The life cycle of the mosquito is represented in the model by two developmental phases. The aquatic phase comprising egg, larva and pupa stages is denoted by A_v. The adult stage is divided into three compartments: number of susceptible mosquitoes, S_v; number of exposed but not yet infectious mosquitoes (i.e. incubating the virus), E_v and infected and infectious mosquitoes, I_v. The total mosquito population is N_v (i.e. $N_v = S_v + E_v + I_v$). The epidemiological literature and previous modelling studies that were used to inform parameter values in the model, along with further model details and model inputs, can be found in Knerer et al. [7]. The flow diagram of the infection process is presented in Figure 7.1.

Figure 7.1. Flow diagram of the infection process



Due to space constraints, the following expression (Ih1 + Ih2 + Ih3 + Ih4 + ((Ihe2φhe) + (Ihe3φhe) + (Ihe4φhe))) is signified by I*. Underlying background mortality (μh) is applied to all compartments but not shown on the figure. Only dengue-induced mortality (μD) is displayed.

Data, under-reporting, expansion factors and calibration

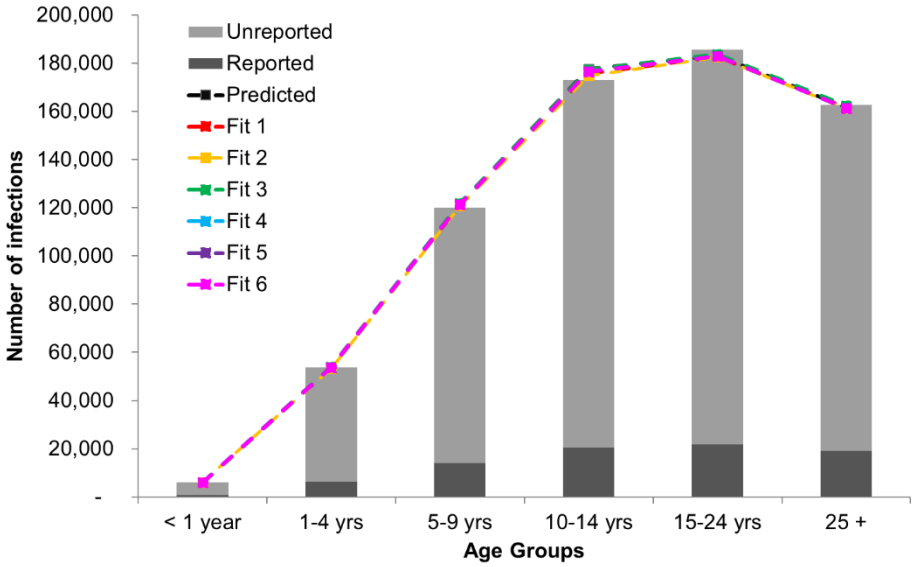
Data. Dengue population level epidemiological data from National Epidemiological Surveillance in Thailand [2] for the years 2008–2012 indicate that there was an average of 82,505 reported cases of dengue per year including 43,890, 1,688 and 36,927 dengue haemorrhagic fever, dengue shock syndrome and DF infections, respectively. An average of 88 deaths per year were reported in the period 2008–2012 with the great majority (72%) due to dengue shock syndrome with the remainder attributable to dengue haemorrhagic fever. The highest number of cases was in the 15–24 years age group (n = 21,840) followed by the 10–14 years age group (n = 20,367).

Under-reporting/ expansion factors. The issue of under-reporting of dengue cases, akin to missing data, has implications for the development of mathematical models seeking to estimate the burden of disease. Our model seeks to calculate the 'true' epidemiological burden of DF in Thailand by incorporating an adjustment for estimated under-reporting. Research indicates potential under-reporting of total cases of symptomatic dengue infections, which are not reflected in national surveillance figures [99,293]. Undurraga et

al. [293] documents an average reporting rate of approximately 13% of total symptomatic dengue episodes in Southeast Asia. This suggests an overall expansion factor (EF) of 7.6 in Southeast Asia to convert reported cases into estimated ‘actual’ cases, i.e. total dengue symptomatic infections [293]. Expansion factors for individual countries in Southeast Asia range from approximately 3.8 in Malaysia to 19 for East Timor with a proposed EF for Thailand of 8.5 [293]. An EF of 2.9 is advised for inpatient dengue cases in Thailand, consistent with Wichmann et al. [99] who recommended EFs of 2.6 and 8.7 for inpatient and total dengue cases in Thailand respectively. More recently, Nealon et al. [96] calculated expansion factors for symptomatic dengue disease in individual countries based on the active phase of the CYD14 trial [156] which varied according to case definitions (different laboratory or clinical criteria). For Thailand, these were 12.0, 8.6 and 8.8 for virologically confirmed dengue, clinically and virologically and confirmed dengue, and clinically diagnosed dengue respectively. Consistent with the above, we adjust the average number of reported cases in the period 2008–2012 (82,505 cases per year stratified by age group) by an expansion factor of 8.5 applied to all age groups to derive total ‘actual’ symptomatic dengue cases.

Calibration. Model estimates were calibrated with figures reported by National Epidemiological Surveillance in Thailand in 2008-2012 [2] multiplied by an expansion factor to adjust for under-reporting. The age specific transmission rate provided the calibration target and the log-likelihood was used as the criterion to evaluate the goodness of fit of candidate models. Starting values for the parameters were based on a focused review of the literature and varied within the ranges of the values identified to determine best fit. Figure 7.2 presents the results of the model calibration and sensitivity analyses, which indicate a good fit between observed and predicted data by age group. It is possible that a better fit may exist in individual age groups but if one considers the total log-likelihood (calculated by summing across age groups for each candidate model), the chosen model proved to be the best fit. The latter was obtained for a model with cross-protection only and without the inclusion of cross-enhancement. We did test and compare various levels of cross-enhancement ranging from a 2-fold to 5-fold increase in infectiousness to reflect the potential impact of antibody-dependent enhancement [21,62,63], but none afforded an improved fit compared to the base model with cross-protection only. We estimate the probabilities of death and of being an ambulatory and/ or inpatient case (inpatient versus outpatient), to replicate the number of deaths and type of treatment reported in national data [2].

Figure 7.2. Predicted vs. observed cases: adjusted for under-reporting



Outcomes

Disability-adjusted life-years (DALYs) lost to disease were calculated using the methodology described by Murray [356,357].

Table 7.3 presents the inputs used to calculate DALYS lost where K is the age weighting modulation factor, D is the disability weight; r is the social discount rate, a is the age at the onset of disability/ average age at death; L is the duration of the disability or the years of life lost due to premature death; C is the age-weighting correction constant and b is the parameter from the age-weighting function, which represents the value of life at different ages. The disability weight reflects the severity of the health state on a scale from 0 (perfect health) to 1 (death). The parameter L represents the duration of the disease (or the years of life lost in the case of dengue death). The remaining years of life were calculated based on the average age of the onset of symptoms in each age group and an average life expectancy of 70 years in Thailand.

Many studies do not incorporate age-weighting as the concept of age-weighted DALYs is often considered controversial. The case where there is no age weighting correspond to the situation where K=0 (no age weights).

Table 7.3. Inputs used to calculate DALYs lost due to dengue in Thailand (2008–2012)

Parameter	Value	Source
Age-weighting modulation factor *K*	1	[356]
Age-corrected constant *C*	0.16243	[357]
Age-weighting parameter *b*	0.04	[357]
Disability weight (death) *D*	1	[357]
Social discount rate r_O	0.03	[357]
Cost discount rate r_C	0.03	[365,366]
Duration of disability in reported dengue fever cases (days) L_{DF}	10	[328]
Duration of disability in reported DHF/ DSS cases (days) L_{DHF}	14	[328]
Duration of disability in unreported cases (days) L_{DFU}	4	[176,328]
Years of life lost in death (0–11 months)	69.5	Assumption
Years of life lost in death (1–4 years)	67	Assumption
Years of life lost in death (5–9 years)	63	Assumption
Years of life lost in death (10–14 years)	58	Assumption
Years of life lost in death (15–24 years)	50	Assumption
Years of life lost in death (25 + years)	22	Assumption
Age at onset of disability (0–11 months)	0.5	Assumption
Age at onset (1–4 years)	3	Assumption
Age at onset (5–9 years)	7	Assumption
Age at onset (10–14 years)	12	Assumption
Age at onset (15–24 years)	20	Assumption
Age at onset (25 + years)	48	Assumption

7.4 Appendix D

xl spreadsheet can be downloaded from

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7654761/#pntd.0008805.s002

7.5 Appendix E

Table 7.4. Dengue cases (DALYs lost) by levels of *Wolbachia* and vaccination coverage[a]

Wolbachia coverage (%)	Vaccination coverage (%) 20%	40%	60%	80%	100%
20%	1,417,931 (13,405)	1,337,095 (12,641)	1,267,332 (11,981)	1,200,286 (11,347)	1,139,607 (10,774)
40%	1,303,028 (12,319)	1,239,815 (11,721)	1,184,649 (11,199)	1,130,722 (10,690)	1,080,824 (10,218)
60%	1,252,812 (11,844)	1,196,744 (11,314)	1,147,228 (10,846)	1,098,567 (10,386)	1,053,175 (9,957)
80%	1,220,827 (11,541)	1,169,162 (11,053)	1,122,875 (10,615)	1,077,378 (10,185)	1,035,018 (9,785)
100%	1,199,360 (11,339)	1,149,906 (11,339)	1,105,994 (10,456)	1,062,461 (10,044)	1,021,832 (9,660)

[a] Total costs from the payer perspective (comprised of direct medical costs and intervention costs) represented by colour coded categories as follows:

≤ $251 M | $252 M ≤ B ≤ $368 M | $369 M ≤ B ≤ $589 M | ≥ $590 M

DALYs, disability-adjusted life years

8 Glossary

List compiled from the National Institute for Health and Care Excellence (NICE) Guide to the processes of technology appraisal [445], the WHO guide for standardization of economic evaluations of immunization programmes [446], and Milwid et al. [447].

Analytic time horizon - the period of time over which the costs and health outcomes that occur as result of the intervention(s) are considered

Comparator - the standard intervention against which the intervention under evaluation is compared. The comparator can be no intervention

Cost-effectiveness analysis - an economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (e.g. life-years gained, deaths avoided, or cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness

Cost-effectiveness model - an explicit mathematical framework which is used to represent clinical decision problems and incorporate evidence from a variety of sources to estimate costs and health outcomes

Deterministic model - mathematical model in which there is no inclusion of chance or random variation in the modelled infectious disease process. Deterministic models can be solved by numerical analysis or computer simulation and give a fixed and exactly reproducible result

Direct medical costs - associated with the service/ programme under consideration. These are organisational and operational costs borne by the health sector (e.g. health professionals' time)

Direct nonmedical costs - incurred by patients/ families in the course of treatment (e.g. transport costs)

Disability adjusted life years (DALYs) - used to generate health-related measures of utility for those living with a disability measured in terms of time lost due to premature death (mortality) and time lived with a disability (morbidity)

Discount rate - the rate at which costs and outcomes are discounted to account for time preference

Dominance - when one intervention is both less costly and more effective than the comparators

Dynamic model - mathematical model in which the force of infection is a function of the proportion of infectious people in the population at each time point. The force of infection can change over time in this type of model

Economic evaluation - compares the costs and outcomes of at least two alternative programmes. There are four different types of economic evaluation: cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis

Effectiveness - the extent to which an intervention produces an overall health benefit, considering beneficial and adverse effects, in routine practice. It is not the same as efficacy

Efficacy - the extent to which an intervention is effective when studied under controlled research conditions

Extended dominance - the incremental cost-effectiveness ratio (ICER) for a given treatment alternative is higher than that of the next, more effective, alternative (that is, it is dominated by the combination of two alternatives and should not be used to calculate appropriate ICERs)

Incremental cost-effectiveness ratio (ICER) - the ratio of the difference in the mean costs of a technology compared with the next best alternative to the differences in the mean outcomes

One-way simple sensitivity analysis (univariate analysis) - each parameter is varied individually to isolate the consequences of the parameter on the results of the study

Perspective (in economic evaluation) - the viewpoint from which an economic evaluation is conducted. The viewpoint may be that of the patient, hospital/ clinic, healthcare system, or society

Probabilistic sensitivity analysis - probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation)

Randomised controlled trial - a comparative study in which people are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups

Systematic review - research that summarises the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select, and appraise relevant studies, and to extract, collate and report their findings are used. Statistical meta-analysis may or may not be used

Two-way sensitivity analysis - analysis in which the sensitivity of the results is tested in relation to simultaneous variation of two parameters

Vaccine efficacy - refers to the percentage reduction in the attack rate of unvaccinated and vaccinated cohorts as observed in a randomised control trial

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