Refining baseline estimates of dengue transmissibility and implications for control

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Declaration of originality

I declare this work to be my own, produced under the supervision of Prof. Neil Ferguson, Dr. Simon Cauchemez, and Dr. Ilaria Dorigatti. Any participants involved in collaborative work have been acknowledged in the relevant sections of this thesis.

Natsuko Imai

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Copyright declaration

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Relevant Publications

1. Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating Dengue Transmission Intensity from Sero-Prevalence Surveys in Multiple Countries. *PLoS Negl Trop Dis* 2015; **9**: e0003719.
2. Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating Dengue Transmission Intensity from Case-notification Data from Multiple Countries. *PLoS Negl Trop Dis* 2016; **10**: e0004833.

Presentations

1. Poster presentation: 'Estimating dengue transmission intensity from incidence data in multiple countries'. (2015) American Society of Tropical Medicine and Hygiene 64th Annual Meeting.
2. Oral presentation: 'Underused data: using seroprevalence data to refine global estimates of dengue transmission intensity'. (2014) Imperial College London School of Public Health Annual Symposium.
3. Poster presentation: 'Estimating dengue inter-serotype interactions from age-stratified serotype-specific data'. (2014) American Society of Tropical Medicine and Hygiene 63rd Annual Meeting.
4. Poster presentation: 'Comparison of dengue transmission intensity estimates obtained from different data types'. (2014) American Society of Tropical Medicine and Hygiene 63rd Annual Meeting.
5. Poster presentation: 'Underused data: seroprevalence surveys to estimate dengue transmission intensity'. (2013) EPIDEMICS[4].
6. Poster presentation: 'Defining the Spatio-temporal dynamics of dengue fever'. (2013) Imperial College London School of Public Health Annual Symposium.

Abstract

Climate change, globalisation and increased travel, increasing urban populations, overcrowding, continued poverty, and the breakdown of public health infrastructure are among the factors contributing to the 30-fold increase in total dengue incidence in the past 50 years. Consequently, with an estimated 40% of the world's population at risk of infection, dengue is now the world's most important mosquito-borne viral infection.

However estimates of dengue transmissibility and burden remain ambiguous. Since the majority of infections are asymptomatic, surveillance systems substantially underestimate true rates of infection. With advances in the development of novel control measures and the recent licensing of the Sanofi Dengvaxia® dengue vaccine, obtaining robust estimates of average dengue transmission intensity is key for estimating both the burden of disease from dengue and the likely impact of interventions. Given the highly spatially heterogeneous nature of dengue transmission, future planning, implementation, and evaluation of control programs are likely to require a spatially targeted approach.

Here we collate existing age-stratified seroprevalence and incidence data and develop catalytic models to estimate the burden of dengue as quantified by the force of infection (λ) and basic reproduction number (R_0). We identified a paucity of serotype-specific age-stratified seroprevalence surveys in particular but showed that non-serotype specific data could give robust estimates of baseline transmission. Chapters explore whether estimates derived from different data types are comparable. Using these estimates we mapped the estimated number of dengue cases across the globe at a high spatial resolution allowing us to assess the likely impact of targeted control measures.

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List of abbreviations and acronyms

ADE	antibody-dependent enhancement
BRT	boosted regression tree
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CrI	credible interval
DENV	dengue virus
DF	dengue fever
DHF	dengue haemorrhagic fever
DIC	deviance information criterion
DMN	Dirichlet-multinomial
DSS	dengue shock syndrome
E/M	envelope/membrane
ELISA	enzyme-linked immunosorbent assay
GDP	gross domestic product
GM	genetically modified
GPS	global positioning system
HI	haemagglutination inhibition
IE	inhibition ELISA
IgG	immunoglobulin-G
IgM	immunoglobulin-M
JEV	Japanese encephalitis virus
LnL	log likelihood
MAC-ELISA	IgM antibody capture ELISA
MH MCMC	Metropolis-Hastings Markov Chain Monte Carlo
MLE	maximum likelihood estimate
NS1	non-structural 1
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PO	probability of occurrence
PRNT	plaque reduction neutralisation test
qPCR	quantitative polymerase chain reaction
RBC	red blood cells
RIDL	release of insects carrying a dominant lethal allele
RT-PCR	reverse-transcription PCR
SAGE	Strategic Advisory Group of Experts
SIT	sterile insect technique
TBE	tick-borne encephalitis
UN	United Nations
WHO	World Health Organisation
WNV	West Nile virus
CYD	chimeric yellow fever-dengue
YFV	yellow fever virus

1 Introduction

1.1 Background

Dengue viruses belong to the family *Flaviviridae* which include yellow fever virus (YFV), zika virus, West Nile (WNV), Japanese encephalitis (JEV) and tick-borne encephalitis (TBE) virus among others [1,2]. Dengue exists as four antigenically and genetically distinct serotypes (DENV-1, 2, 3, and 4) which can co-circulate. Infection with any of the four serotypes can result in dengue fever (DF). As a single stranded positive sense RNA arbovirus, they are transmitted primarily by the urban-adapted *Aedes aegypti* mosquito and increasingly by the *Aedes albopictus* mosquito [3–5]. Epidemiology can differ significantly between geographic areas – severe dengue pre-dominantly affects children in Southeast Asia in contrast to the Americas where disease more often manifests in adults as the milder dengue fever [6]. The four serotypes have shared epitopes which can be recognised by antibodies generated against any one of them, resulting in cross-reactive immune responses. A degree of cross-reactivity is also observed between anti-dengue antibodies and other flaviviruses, notably JEV and YF [7].

1.2 Clinical Symptoms and Natural history

After infection by the bite of an infective mosquito, the incubation period generally lasts for 3 – 7 days, followed by development of symptoms which can have up to 3 phases (Table 1.1) [4]. The clinical spectrum of dengue infection is variable, with symptoms also varying with patient age [8,9]. The majority of infections are asymptomatic or result in self-limited acute febrile illness. However a minority of infections can cause severe disease such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) [5].

Table 1.1: Clinical presentation of dengue. Adapted from [4,10].

Phase	Symptoms	Comments
Initial febrile (3 – 7 days)	High temperature, vomiting, myalgias, joint pain, occasional transient maculopapular rash in children.	Children are generally less symptomatic than adults in this phase. Classic dengue fever symptoms are associated with older children and adults.
Critical (coincides with defervescence)	In a small proportion of patients, symptoms of systemic vascular leakage may appear – e.g. bleeding manifestations and thrombocytopenia.	If loss of plasma via leakage becomes critical, dengue shock syndrome can result. This requires urgent and careful fluid resuscitation. Delays can lead to death in 10% of cases.
Spontaneous recovery	Change in vascular permeability is generally transient and is followed by reversion to normal levels after 48-72 hours coinciding with rapid recovery.	Secondary rash may become apparent at this stage and in adults fatigue may persist for weeks after recovery.

All dengue-associated symptoms can be caused by any of the four dengue serotypes. The greatest risk factor for severe dengue is secondary infection by a heterologous serotype. The mechanism underlying this observation is thought to be antibody-dependent enhancement (ADE) [11,12], whereby antibodies against the previous dengue strain will enhance replication of the current strain rather than neutralise it. Upon infection by a second heterologous serotype, the virus-antibody complexes can activate complement resulting in amplification of the immune response which can enhance the infection of monocytic cells. The T-cell mediated lysis of virus infected cells releases cytokines and intracellular enzymes which in turn causes plasma leakage and DSS [13,14]. The observation that dengue-specific T-cells have a higher avidity for previous dengue serotypes compared with the infecting serotype has led to the proposal that original antigenic sin can also play a role in the severity of secondary infections compared to primary infections [15]. The time interval between primary and secondary infections also appears to play an important role in the risk of DHF and DSS [16]. Longer intervals leads to greater decay of dengue antibodies, so upon secondary infection antibodies are present at sub-neutralising titres, facilitating ADE which can cause normally mild infections to become life threatening [10,13,17,18]. The numerous but subtle genotypic variations within the dengue strains have not been conclusively demonstrated to have an impact on severity [4].

1.3 Immunity

Infection with one serotype is thought to be sufficient to confer protective immunity against subsequent infections from the same serotype [4]. However a recent study has suggested that there may be incomplete protection against homologous re-infection [19]. Cross-reactive immunity is short-lived and the waning of antibody levels can facilitate ADE upon secondary heterologous infection increasing the risk of more severe outcomes of dengue such as DHF and DSS [2,4,20]. Estimates of the duration of short-term cross-protection vary widely: 4 months - 9 years [21], 5-12 months [22], 2 years [23], and 1-3 years [24]. However whether this protects against infection or clinically apparent disease is unknown and therefore individuals may still contribute to onward transmission [23,25–27]. The impact of cross-immunity on the risk of tertiary and quaternary infections remains unclear. While there is now evidence that tertiary and quaternary infections occur [25,28], clinically apparent cases are rarely reported and cannot be tested for retrospectively [25]. Wikramaratna *et al.* showed that tertiary and quaternary infections allowed for the high seroprevalence at very young ages observed in Haiti [29] and Nicaragua [30] better than when assuming complete protection after two heterologous infections [25]. However there is little quantitative data on the infectiousness or severity of such infections relative to primary and secondary infections. Therefore the contribution of tertiary and quaternary infections to onward transmission is not fully understood.

1.4 Diagnostic Methods and Limitations

There are several laboratory assays available for the diagnosis of dengue infection. As an acute viral infection, the sensitivity of each assay depends on when patient samples are taken which may affect levels of detectable virus or detectable antibodies. Figure 1.1 summarises the timeline of symptoms and corresponding diagnostic assays that can be used.

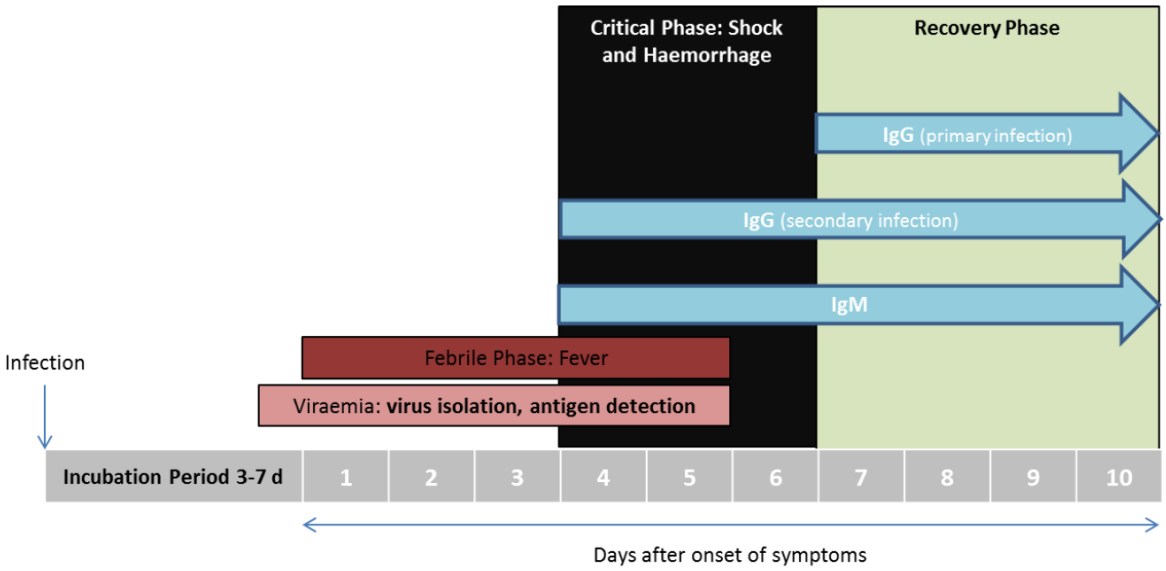

Figure 1.1: Timeline of symptoms and corresponding diagnostic assays. Adapted from [4,20].

Diagnosis is largely based on clinical symptoms, but laboratory confirmation is crucial due to the extremely variable clinical presentation of dengue infection. The most common methods currently employed by diagnostic facilities are: virus isolation, serological assays to detect dengue-specific antibodies and antigens, and genomic detection via reverse-transcription (RT) quantitative polymerase chain reaction (qPCR) [2,10,31]. However, as dengue is an acute infection with a viraemic period of only 2 – 7 days, there is a limited window of opportunity for virological testing [32]. As such, virological assays and case data will only ever identify individuals whose symptoms were severe enough to go to hospital for testing and individuals with poor access to healthcare will be overlooked [18]. Thus serology is the most widely available and utilised diagnostic method as it is less expensive and easy to perform. Serological methods are also not time limited (unlike virus isolation) and can identify individuals with prior asymptomatic infections, presenting a clearer and broader view of dengue epidemiology within the population [33]. However both diagnostic methods

come with their own set of limitations (see chapter 2). However it is important to note that the choice of assay will be dictated by and differ between clinical and research settings.

1.4.1 Virological Assays

Although dengue virus can be detected in plasma, leukocytes, and body tissues, serum is generally used for routine diagnosis. As a RNA virus, dengue is extremely fragile and heat labile, thus virological testing (Table 1.2) can be more difficult than serological methods [10,34]. Given the acute nature of infection, viraemia is short and samples for virological testing must be taken in the first 4 – 5 days of disease. Detection of viral antigens in acute phase serum has proved difficult due to the limited viraemic period and the presence of immune-complexes from previous heterologous infections. Recently assays have been developed that are able to detect dengue E/M antigens and the NS1 protein from the acute phase sera of both patients with primary and secondary infections. However antigen detection tests are still less reliable than other diagnostic methods currently available on the market [35–37].

Table 1.2: Summary of virological methods available for diagnosis (Adapted from [10]).

Assay	Method	Comments
Virus isolation	Mosquito inoculation	The most sensitive method, however extremely time consuming, requiring specialist facilities and training.
	Cell culture	Quicker – preferred for routine diagnosis
Viral antigen detection	ELISA*	Detect viral antigens in serum and PBMCs**. Recent advances detect the NS1 protein on the viral envelope.
Genome detection	One-step RT-PCR, pan-dengue primer PCR, nested-PCR (flavivirus followed by serotype-specific primers)	Direct detection of the viral genome in patient samples. Provides accurate information on serotype and genotype. PCR for routine diagnosis can be difficult due to high costs.

*Enzyme-linked immunosorbent assay, **peripheral blood mononuclear cell.

1.4.2 Serological Assays

In naïve individuals, infection produces a characteristic slow and low titre IgM response followed by low titres of IgG one week after the onset of disease. During a secondary infection, IgG titres rise rapidly and to a high level over two weeks. IgG antibodies are cross-reactive with other flaviviruses and can be detected even in the acute phase of a secondary infection [32,38]. Plaque-reduction neutralisation tests (PRNTs) can be used to determine

the infecting serotype and measure the level of protective antibodies a patient has. However PRNTs are labour intensive and are generally not used for routine diagnosis [2]. The development of IgM enzyme-linked immunosorbent assays (ELISAs) for the detection of anti-dengue antibodies, in particular the MAC-ELISA (IgM antibody capture ELISA) has improved routine diagnosis, with 10% false negatives and 1.7% false positives reported [2]. However, there are numerous commercial kits available (Table 1.3) for detecting anti-dengue antibodies, many of which have not been standardised.

Table 1.3: Summary of available serological assays (Adapted from [10,18]).

Assay	**Method**	**Comments**
Haemagglutination inhibition assay (HI) (Non-serotype specific)	Serial concentrations of patient serum incubated with RBCs* and virus.	Presence of anti-dengue antibodies should inhibit virus from cross-linking RBCs*.
ELISA^ (Non-serotype specific)	Pan-dengue IgM/IgG	Detects the presence of any anti-dengue antibody of any serotype.
	MAC-ELISA	IgM antibody capture ELISA, detects IgM vs. all serotypes.
	IgG	Detects IgG antibodies of all serotypes
Neutralisation tests (Serotype specific)	Plaque reduction neutralisation test (PRNT)	Cells are incubated with patient sera followed by cultured dengue virus at serial concentrations; presence of anti-dengue antibodies should prevent plaque formation.
Other less utilised assays	Indirect immunofluorescent-antibody test, complement fixation.	

*Red blood cells. ^Enzyme-linked immunosorbent assay.

Of the serological assays available, IgM and/or IgG capture ELISAs and HI tests are the most popular. IgM/IgG ELISAs are now replacing the HI test for routine diagnosis due to their high sensitivity and specificity coupled with their simplicity and ease of automation [18]. As the primary response, IgM antibodies can be detected in serum, blood, and saliva samples taken 5 days or more after the onset of fever [4,20]. The MAC-ELISA is a sandwich ELISA where human IgM is captured between anti-human-IgM antibodies and dengue-virus specific antigens. Current IgM ELISAs are not capable of determining the serotype due to the cross-reactive nature of the antibodies. In addition, there is a lack of consensus on the extent of cross-reactivity of dengue with other flaviviruses: whilst the CDC guidelines state that there are issues with cross-reactivity with other flaviviruses where these pathogens co-circulate [39], the WHO guidelines state that cross-reactivity rarely occurs [2]. While detection of dengue-specific IgM antibodies by capture ELISA is indicative of active or recent infection, IgG ELISAs are used for the detection of past infections and use the same viral antigens as

the IgM ELISA. IgG ELISAs are also unable to differentiate between serotypes and are cross-reactive with other flaviviruses [40]. These ELISAs are therefore mainly useful for diagnosing primary and secondary infections in paired serum samples using a simple algorithm (Table 1.4).

Table 1.4: Algorithm for differentiating between primary and secondary infections. Acute (symptomatic phase) and convalescent (post-recovery) serum samples are tested by comparing IgM and IgG ELISAs and their titres (typically the ratio of IgM:IgG) to determine infection type. Adapted from [2,18,39].

Infection Type	IgM Result	IgG Result	IgM/IgG* Titre
Acute Primary	+ (convalescent)		>1 (convalescent)
Acute Secondary	+ (convalescent)		<1 (convalescent)
	− (convalescent)	+ (convalescent), x4 increase in titre acute → convalescent	
Not Acute, Secondary	− (convalescent)	+ (convalescent), but no x4 increase in titre	
Not Infected	− (convalescent)	− (convalescent)	

*ratio differs between different laboratories. + = positive test, - = negative test.

1.4.3 Dengue Virus Serotyping

Although the only truly accurate method of ascertaining dengue serotype requires samples to be taken during periods of acute viraemia, available methods for serotype-specific diagnosis include PRNT, viral isolation with serotype-specific monoclonal antibody immunofluorescence staining, and RT-PCR [33,41–43]. Among the above, PRNT is considered the gold standard for routine serotyping since RT-PCR (the true gold standard for dengue virus serotyping) remains expensive and beyond the resources of most dengue endemic countries [42]. However PRNTs are limited by the cross-reactivity of anti-dengue antibodies to multiple serotypes and other flaviviruses. Because of this, no universal standards have been developed for the interpretation of such PRNT data and the use of PRNTs to determine the infecting secondary and heterotypic serotype is generally discouraged [10]. The serotype with the highest titre is commonly accepted to be the (most recently) infecting serotype. However this may not be definitive due to original antigenic sin. Although attempts have been made to use E/M-specific capture IgM ELISAs to serotype dengue virus infection, the accuracy and reliability of such tests are still questionable [18].

1.5 Current Estimates of Dengue Burden

As of 2012, the World Health Organisation (WHO) listed dengue as the most important mosquito-borne viral infection worldwide. There are now more than 100 endemic countries (Figure 1.2) and an estimated 40% of the world's population at risk of infection [4]. There has been a 30-fold increase in incidence over the past 50 years with an increasing number of countries reporting dengue cases for the first time [44], including in the Florida Keys in September 2009 [45], south-east France in 2010 [46], Madeira, Portugal in 2012 [47], and Tokyo, Japan in 2014 [48].

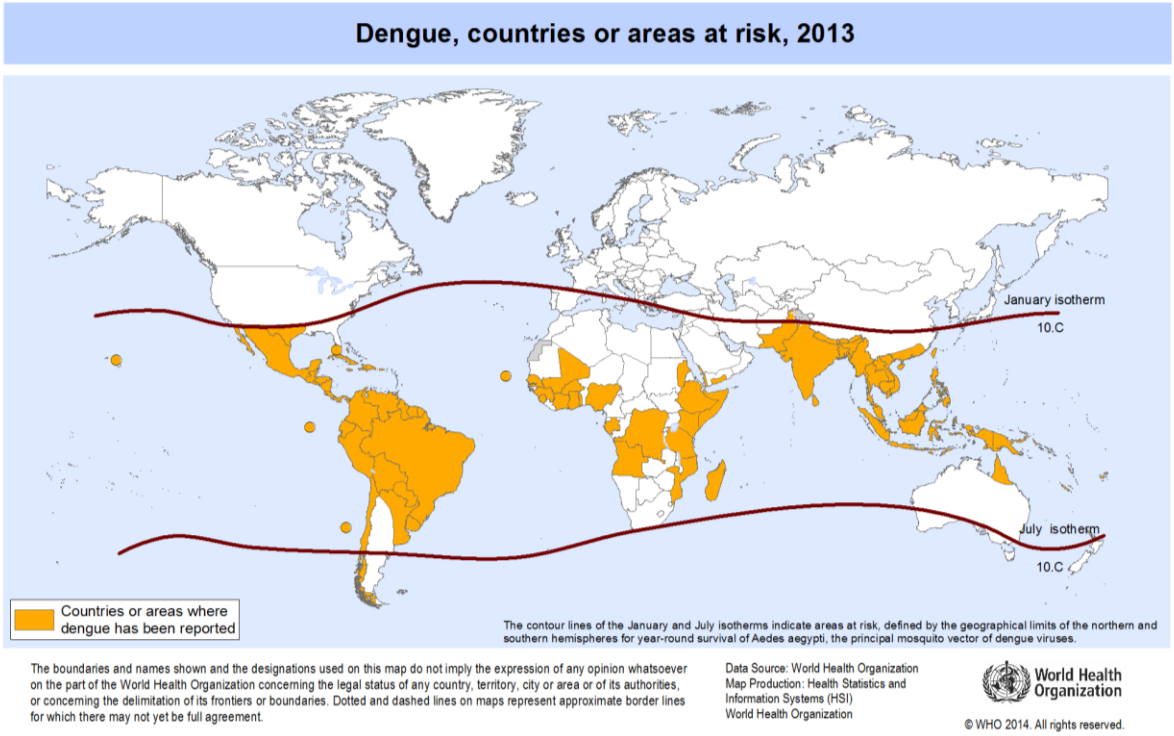

Figure 1.2: Map showing countries at risk of dengue in 2013. Reproduced from [49].

Estimates of the global burden of dengue have ranged widely. Previously the WHO estimated that 2.5 billion people were at risk with 50 – 100 million infections occurring annually [2,50], while Beatty *et al.* estimated that 3.6 billion people were at risk with 34 million DF cases and 2 million DHF cases each year [51]. The most recent estimates by Bhatt *et al.* using cartographic approaches estimated 390 million dengue infections per year (95% credible interval (CrI): 284 – 528), with 96 million (95% CrI: 67-136) apparent infections. This total estimate is more than three times the burden estimate previously quoted by the WHO [2,50].

Accurate burden estimation is difficult, not only due to the aforementioned limitations associated with dengue diagnostics, but also due to differences in surveillance systems leading to underestimation of dengue incidence, the lack of standardised reporting procedures or diagnostic criteria, and the lack of integration between private and public sectors [52]. The WHO collates surveillance data from dengue affected countries via its DengueNet system, but the data are not always updated regularly and there can be inconsistencies with other sources (e.g. WHO regional offices or countries) of national and subnational data [53]. Previous studies have attempted to estimate the burden of dengue and associated economic costs in South East Asia and South America by calculating expansion factors from systematic literature reviews, collation of existing data, and population-based cohorts [54–57]. However, the lack of standardisation also affects the validity of expansion factors (calculated by dividing the cumulative incidence of dengue in cohort studies by that from passive data at both national and local levels) as estimates of underreporting. Due to the wide spectrum of clinical manifestations and the lack of routine laboratory testing, dengue is globally underreported and analyses of officially reported dengue numbers need to take this into account [58].

1.6 Novel Control Methods

In their 2012 report the WHO called for the evaluation and integration of current interventions to achieve a 50% and 25% reduction in dengue mortality and morbidity respectively [44]. As previously mentioned, dengue virus is transmitted between humans primarily by the urban-adapted *Aedes aegypti* mosquito and increasingly by *Aedes albopictus* [3–5]. There are currently no commercially available antiviral drugs, and until the Sanofi dengue vaccine is rolled out in the majority of dengue endemic countries, or other dengue vaccine candidates are successfully developed [59–63], dengue prevention relies heavily on mosquito control [64]. Conventional vector control methods include draining of mosquito breeding-sites, larvicides, and biological control (Figure 1.3). Fumigation with insecticides is particularly common in cities; however it is costly and disruptive [2,64]. Since *Aedes aegypti* mosquitoes are daytime biters, bed nets, which are a particularly effective control measure against malaria are redundant. This makes novel control measures such as genetically modified (GM) and *Wolbachia*-infected mosquitoes even more important.

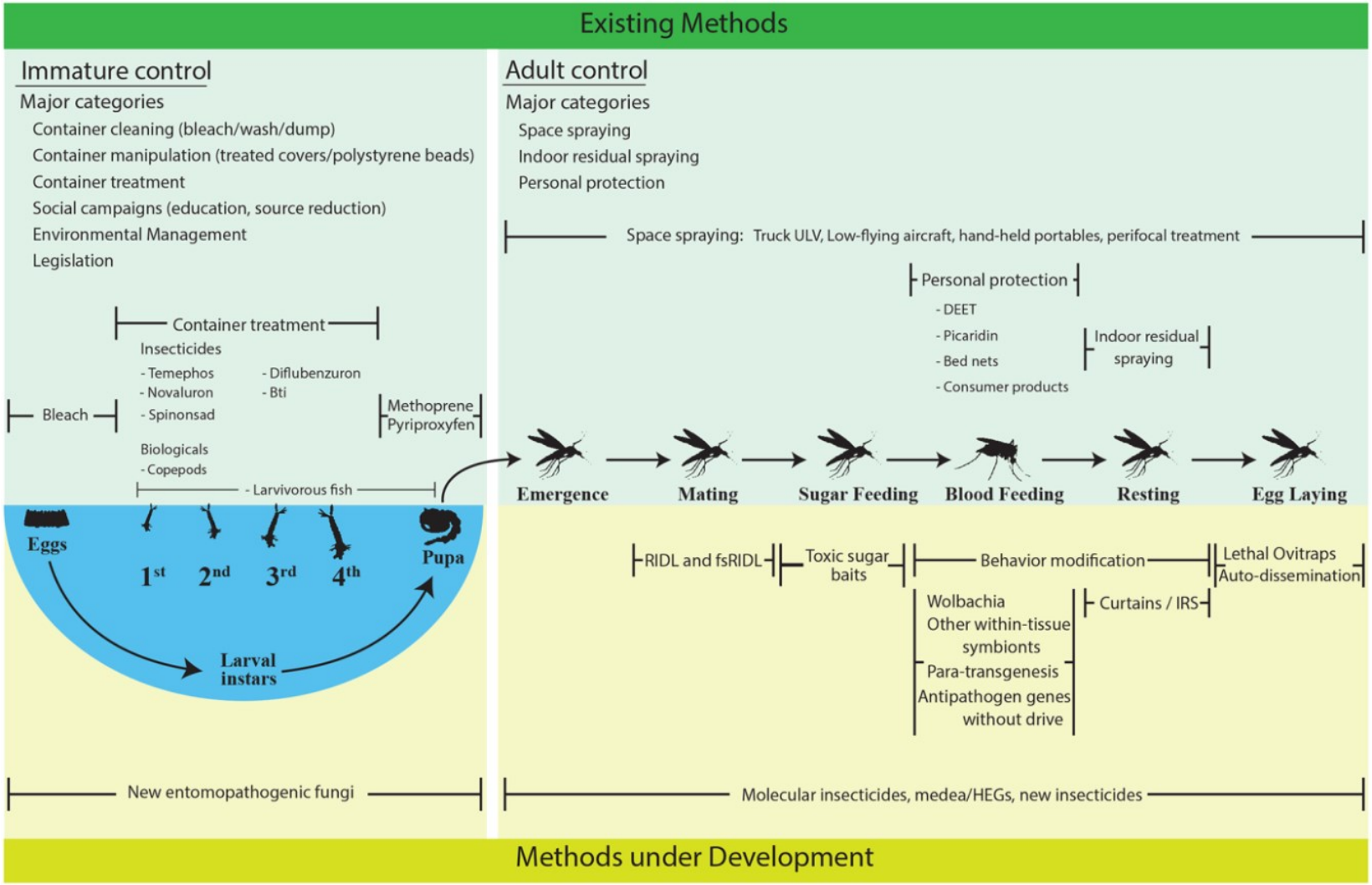

Figure 1.3: New and existing vector control methods. Existing methods (top green region) and methods currently under development (bottom yellow region) are shown in the context of mosquito life cycle. Reproduced from Achee *et al.* [64].

1.6.1 Genetically Modified Mosquitoes

Release of insects carrying a dominant lethal (RIDL) allele is similar to the traditional sterile insect technique (SIT) but in addition to GM males out-competing the wild type males, the male mosquitoes carry female-specific lethal genes. So GM males released into the wild will deliver specific female-acting transgenes into the wild population. The flightless gene results in the reduction of gene expression of a gene usually expressed in the flight muscle. Daughters of RIDL males are thus unable to fly and hence to mate or to find human hosts to feed on (Figure 1.4a). The late-acting lethal gene induces death in both male and female offspring of RIDL males either at the pupal or adult stage (Figure 1.4b). Thus both lethal genes will eventually result in a reduction in the wild type population and of female mosquitoes which are capable of transmitting the dengue virus [65,66]. Currently this RIDL technology has been successfully trialled in Malaysia by Oxitec Ltd. [67] and field trials have demonstrated an 80% and 81-95% suppression of the wild *Ae. aegypti* population in the Cayman Islands and Bahia, Brazil respectively [68,69].

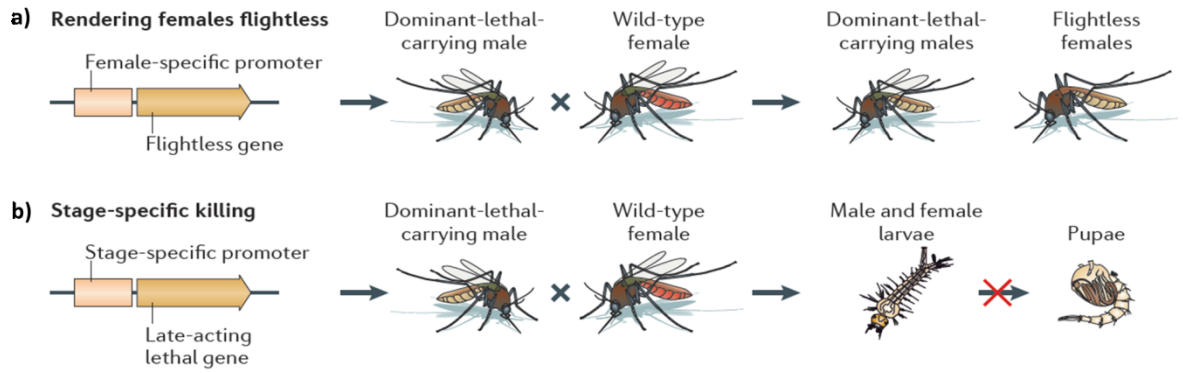

Figure 1.4: Release of insects carrying a dominant-lethal allele (RIDL). Genetically modified males are released and mate with wild-type females. RIDL males carry a) a female-acting transgene. Daughters of the RIDL males carrying this transgene are flightless and thus unable to find human hosts, b) a late-acting lethal gene, which induces death in male and female offspring at the the pupal or at the adult stage. Reproduced in part from [65].

1.6.2 Biological Control: *Wolbachia*

The endosymbiotic bacterium *Wolbachia pipientis* naturally infects up to 65% of all insects. *Wolbachia* infects the gonads of their hosts resulting in trans-ovarial transmission to the next generation and causes reproductive changes in its host including feminisation, parthenogenesis, male killing, and sperm-egg incompatibility [70]. Although *Wolbachia* does not naturally infect *Ae. aegypti* mosquitoes, once introduced into a population by transinfection, the bacterium can spread rapidly due to its maternal transmission route. The three mechanisms currently being trialled for vector control via *Wolbachia* (Figure 1.5) are: a) the release of *Wolbachia*-infected males (similarly to SIT). The offspring of uninfected wild-type females and *Wolbachia*-infected males will die as embryos due to cytoplasmic incompatibility. If the native female mosquitoes harbour a different *Wolbachia* strain to that carried by the males, again any offspring will not be viable, b) the release of *Wolbachia*-infected females that inhibit pathogen (i.e. dengue) growth. All offspring will carry the *Wolbachia* and exhibit dengue-resistant characteristics, and c) the release of females carrying the *w*MelPop strain of *Wolbachia*. This particular strain of *Wolbachia* shortens the lifespan of its insect host in addition to inhibiting viral replication in the mosquito. Reducing lifespan has a disproportionate impact on dengue transmission since only older insects transmit dengue [65]. Currently field trials are on-going in Australia to determine the capacity of *Wolbachia* infected mosquitoes to invade wild *Ae. aegypti* populations [65,71–73]. If successful, this form of biological control could be highly cost-efficient and effective in the long-term given *Wolbachia* is self-propagating.

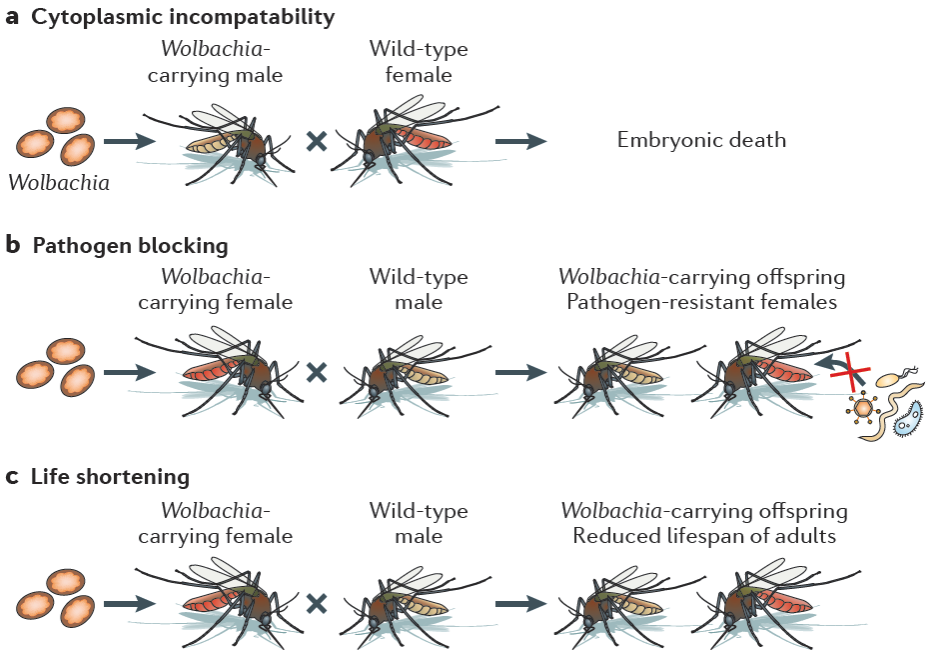

Figure 1.5: Summary of how the release of *Wolbachia*-infected mosquitoes affect the wild type population and subsequent offspring. Release of *Wolbachia*-infected a) males will lead to cytoplasmic incompatibility and embryonic death of all offspring with a wild-type female; b) females carrying the pathogen-blocking stain of *Wolbachia* will result in pathogen-resistant female offspring and both male and female offspring carrying *Wolbachia* from birth; c) females carrying the life-shortening *w*MelPop strain of *Wolbachia* will lead to offspring with reduced lifespans that will not survive to transmit dengue. Reproduced in part from [65].

1.6.3 Sustainability and Scalability of Novel Control Methods

The two methods discussed – RIDL and *Wolbachia* control will require different numbers of mosquitoes to be released. With the RIDL method, multiple and numerous releases will be required over an indeterminate timeframe since the genetic modification cannot be passed on to any of the offspring. Therefore much like the SIT, island settings where elimination of mosquitoes is more feasible will likely benefit the most from this method. In other settings, constant releases may be needed in order to keep the native mosquito population supressed sufficiently [67,73]. In contrast, since *Wolbachia* infections are transmitted transovarially, in theory the bacteria should be able to establish itself in the native mosquito population without constant new releases. However this will be setting dependent since cytoplasmic incompatibility may lead to non-viable offspring. Additionally, after the local mosquito population has been eliminated, wild-type mosquitoes from a different area are

likely to invade the now empty niche which would require the re-release of *Wolbachia*-carrying mosquitoes [70,74]. For both methods, the production of fit and competitive mosquitoes capable of out-competing their wild-type counterparts is crucial. Lab rearing of both RIDL and *Wolbachia*-carrying mosquitoes can quickly lead to in-breeding so the periodic modification or infection of wild-type mosquitoes will be essential in maintaining the fitness of the modified mosquitoes. Crucially, the release of any genetically or biologically modified organisms needs local community acceptance, so good communication and transparency will be vital in the implementation of such novel control methods [75,76].

1.6.4 Dengue Vaccine

The recently licensed Sanofi Pasteur's dengue vaccine (Dengvaxia®) is the first of the dengue vaccines in development (Figure 1.6) to have been licensed for use in a country [59]. Dengvaxia® is a tetravalent live-attenuated chimeric yellow fever-dengue (CYD) vaccine. Phase III trials have shown an overall reduction in dengue cases of 65%, an 81% reduction in hospitalised cases, and a 93% reduction in severe dengue cases [60,77]. However the vaccine is only licensed for use in children 9 years and older, with increased risk of hospitalised cases linked to the use of the vaccine in children under nine years of age [78]. Vaccine efficacy was also significantly lower in dengue naïve individuals [60,77]. However even under these limitations dengue vaccines can have beneficial individual-level and population-level effects by reducing susceptibility to infection given an infectious bite, or by reducing the probability of onward transmission from an infected vaccinated person to a mosquito. High vaccine coverage will also reduce overall transmission within a community. The Strategic Advisory Group of Experts (SAGE) on immunisation recently recommended introduction of the vaccine only in settings with high endemicity (>70% seroprevalence in target age group) and that the vaccine should not be given in low transmission settings (<50% seroprevalence in the target age group) [79].

Although recent studies suggest that neutralising antibody titres correlate with protection from symptomatic infection [80], correlates of protection for an effective dengue vaccine are yet to be well established [81]. Given the importance of dengue immunogenicity at baseline prior to vaccine administration [60,61], it is vital to have robust baseline estimates of dengue transmission intensity and knowledge of prior dengue infections by age.

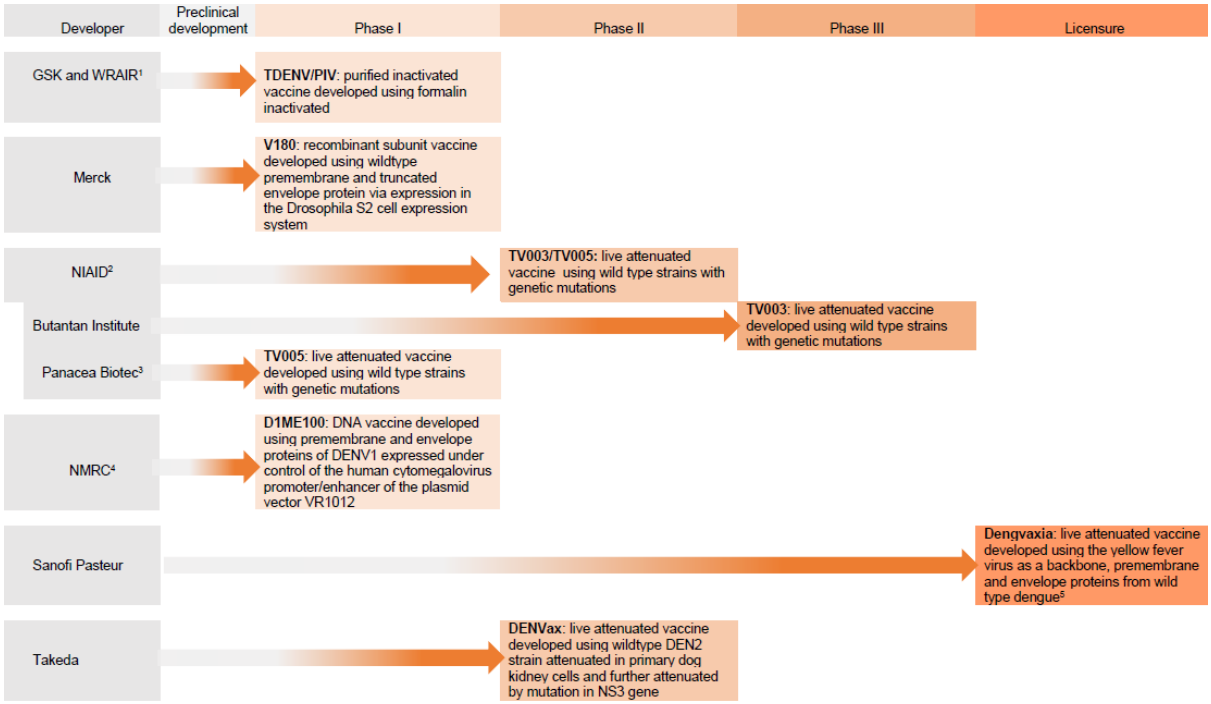

Figure 1.6: Summary of dengue vaccine candidates currently in development. Reproduced from [82]. [1]GlaxoSmithKline and Walter Reed Army Institute Research. [2]National Institute of Allergy and Infectious Diseases, US NIH: National Institutes of Health. NIAID licensed its strains to several developing country manufacturers on a non-exclusive basis. [3]Both Butantan Institute and Panacea Biotech use NIAID vaccine formulation. [4]US Navy Medical Research and Development. [5]Dengvaxia has been approved by Mexico, the Philippines and Brazil for 9 to 45 year olds living in dengue endemic areas.

1.7 Catalytic Models and Estimating the Force of Infection

Transmission intensity or the force of infection (λ) is defined as the per capita rate that susceptible individuals acquire infection [83] and is an important indicator of the burden of dengue fever (or indeed any infectious disease), and a key parameter in dengue transmission dynamics [84]. Dengue is geographically highly heterogeneous in transmission intensity [85–87], so improved estimates of λ are of real value in informing the efficient implementation of control strategies and their subsequent evaluation and adaptation.

The force of infection has been estimated from age-stratified case and serological data using catalytic models for many pathogens, most notably by Muench (1934) [83], Griffiths (1974) [84], Grenfell & Anderson (1985) [88], and Farrington (1990) [89]. Age-stratified data are important in terms of the epidemiology and transmission dynamics of infectious diseases as age-related changes can reveal temporal changes in the intensity of disease transmission within a population. Such data can generally be obtained from two sources [88]:

1) Age-stratified case-notification data over a certain time-period.
   In countries where dengue fever is notifiable, patients at hospital with clinically diagnosed or laboratory confirmed dengue fever will be reported to the national surveillance system [90–94]. Hospital databases will also hold records of suspected or confirmed dengue.

   Limitations: Reporting bias with age. Cases involving young children are more likely to be reported than adults with the same disease. However, if notifications are representative of the true age-distribution class, under-reporting (if age-constant, i.e. age-independent) should not influence the use of proportional case reports. For dengue, since the majority of infections are asymptomatic, notification data will only detect severe cases requiring healthcare. It has been suggested that such data should be considered the incidence of secondary and heterotypic infections [95]. Access to healthcare may also bias the population that is detected by case notifications and this should be taken into account in developing countries where this may be more of an issue. Finally, the quality of such data will also be highly dependent on the country's or region's surveillance system and may not be generalizable [52].

2) Age-stratified seroprevalence surveys.

   These surveys (cohorts or cross-sectional) provide information on the proportion of the population that has been previously infected. If serum samples are drawn randomly from a population, rather than, for example: hospital outpatients, schools, or blood banks, seroprevalence data will provide a far more reliable source of data than case data as they can detect all past infections and will not be affected by biased reporting or surveillance systems.

   Limitations: In addition to the aforementioned problems associated with dengue diagnostics – as a measure of past exposure, serological data are sensitive to past changes in disease incidence and can vary as a result of chance variation and sample size. As monotypic dengue antibodies are thought to be life-long [13], the variability in antibody levels between older age groups will inevitably be small [96]. This may mask or change actual age-related changes in the data making accurate serological testing over a wide age range crucial. Additionally there will be issues associated with cross-reactivity between dengue serotypes and other flaviviruses [2,39].

Muench was the first to propose the use of 'summation data' in conjunction with a simple catalytic model to estimate the force of infection (λ) stating that limitations with notification data meant that estimations can only ever be approximations [83]. He used summation data to calculate the exposure rate that would effectively produce the sum of all effective exposures observed. He argued that by averaging the lifetime exposure rate in the same way that exposure rates are averaged and compared between epidemic and inter-epidemic years, different diseases and populations could be compared effectively [83,97]. His simple catalytic model assumes that the force of infection is constant i.e. both age and time independent. He applied this model to yellow fever data in Brazil, to compare whooping cough and chicken pox, and to estimate infection rates of tuberculosis [83,97]. Here he introduced the concept of how the effective exposure rate is based on the proportion of the population who may show traces of past infection. However the assumption of a constant force of infection only holds true if the population in question were homogeneous with respect to susceptibility, exposure to the pathogen, and if the infection was endemic with a constant incidence rate. Griffiths extended Muench's simple catalytic model and suggested a catalytic linear infection model for measles notification data where the force of infection

was assumed to increase linearly with age between 0 – 10 years [84]. He also noted that 95% of measles infections occur by 10 years of age, after which the force of infection decreases. Grenfell and Anderson further extended Muench's and Griffith's models using measles case notifications and serological data and developed a model where λ was modelled using a polynomial function, but allowed the data to determine the order of the polynomial to estimate an age-dependent force of infection assuming time-homogeneity [88]. Here the authors stressed that the key determinant of the type of model chosen should be the quality and type of data available. For case-notification data, quality is dependent on the surveillance system used and the associated inherent biases. For serological data, whether the samples are representative of the general population is a major limitation in addition to the time/age homogeneity that must be assumed since cross-sectional serological surveys will only provide a picture of who was previously infected at one point in time [98].

Catalytic polynomial models allow us to examine the age-dependence of the force of infection and allow a fair degree of flexibility. However, although polynomials are sufficient to model the general characteristics of age-dependence, there are some aspects of λ that cannot be accurately described. For example, where seroprevalence may vary from age-to-age due to diagnostic or sampling reasons, the non-monotonicity will result in negative values of λ. Furthermore, estimates of λ may increase unrealistically at older ages requiring λ to be estimated over certain age groups. Farrington thus imposed constraints, such as a positive λ, on a generalised non-linear model based on prior knowledge of the pathogens of interest (measles, mumps, and rubella) in order to mitigate these problems [89,99]. Finally, Keiding *et al.* developed a non-parametric model with a two-step process. The prevalence was first estimated using isotonic regression, then the force of infection was calculated by using a kernel smoother [100]. He further developed this model by replacing the kernel smoother with a spline-based model [101].

It should be noted that all the catalytic models described above can be regarded as different types of survival analysis models if placed within a broader statistical context [102]. All have certain limitations. With cross-sectional seroprevalence data, models are being fitted to data from a specific time point giving limited ability to distinguish temporal changes in incidence of infection from age-related changes in exposure [97]. Importantly, age-stratified

data provide information on age and time-dependent changes in infectious disease dynamics. One is usually assumed to be constant over time in order to make conclusions about the other [103]. However in many infections, both factors will play a part in determining patterns of transmission within a population. Therefore age and time-structured data - ideally age-stratified seroprevalence data at regular intervals are required to make stronger conclusions about the force of infection and gives more power to resolve age and time effects. Given the importance of age-related changes in the force of infection to the design of vaccination and disease control, it is crucial to collect finely age-stratified data.

Although the main catalytic models introduced above assume that susceptible individuals can only be infected once in their lifetime, this condition does not hold for multi-strain pathogens like dengue where individuals can be infected sequentially with heterogeneous serotypes [20]. Ferguson *et al.* developed a multi-strain survival model to estimate strain-specific forces of infection which allowed for both age and time-dependent changes in λ and assumed a level of varying susceptibility upon secondary infection dependent on prior infection history [104]. Many subsequent dengue models developed since are similar to Muench's original model [83], or an adaptation of the multi-strain model by Ferguson *et al.* [104].

Dengue dynamics are difficult to disentangle due to the complex immunological responses infection can trigger. Infection with each of the four serotypes will result in protective immunity against the homologous strain but also a transient period of cross-protection against heterologous strains [105]. However as levels of antibodies decay, sub-neutralising antibody levels can then result in ADE upon secondary infection with a different serotype which may enhance transmission as well as the risk of disease [11,106,107]. This potentially needs to be accounted for in estimating forces of infection from serological data [104].

1.8 Thesis outline

The aim of this thesis is to refine baseline estimates of dengue transmissibility from currently available data, and to use the methods developed to generate new estimates of the global burden of dengue infection and disease. This thesis is divided into 6 chapters. Following this introductory chapter:

1) Chapter 2: in this chapter I collate age-stratified seroprevalence data from the literature and estimate the dengue transmission intensity as quantified by the force of infection (λ) and the basic reproduction number (R_0) from non-serotype specific serological data.
2) Chapter 3: following on from chapter 2, I estimate λ and R_0 from serotype-specific PRNT data and ascertain whether non-serotype- and serotype-specific data can give comparable baseline estimates of dengue transmissibility.
3) Chapter 4: in this chapter I collate age-stratified incidence or case-notification data from the literature and estimate λ and R_0. I then compare estimates obtained from seroprevalence data to incidence data and assess whether the two types of data give similar estimates.
4) Chapter 5: in this chapter I use the model developed in chapter 4 in conjunction with the force of infection estimates from chapters 2 and 3, and the probability of dengue occurrence data (University of Oxford) to calculate and map the burden of dengue disease globally.
5) Chapter 6: a discussion chapter summarising the key findings of this thesis and placing them in the context of the challenges of dengue surveillance, control, and evaluation as a whole.

2 Estimating Dengue Transmission Intensity from Non-serotype Specific Seroprevalence Surveys

Work in this chapter formed the basis of: Imai N, Dorigatti I, Cauchemez S, Ferguson NM (2015) Estimating Dengue Transmission Intensity from Sero-Prevalence Surveys in Multiple Countries. PLoS Negl Trop Dis 9(4): e0003719. doi: 10.1371/journal.pntd.0003719

In this chapter I begin with collecting age-stratified seroprevalence data in the literature. The following chapter (chapter 3) also uses these collated data. Here, models are developed to estimate the force of infection from cross-sectional non-serotype specific seroprevalence surveys.

2.1 Introduction

Although recent estimates of the global distribution of dengue and the resulting disease burden have refined our understanding, estimates of global dengue distribution and transmission intensity (as quantified by either the force of infection (λ) - the per capita rate at which susceptible individuals acquire infection, or the basic reproduction number, (R_0)) remain ambiguous [108]. In particular, Bhatt et al.'s estimate of 390 million dengue infections per year is three times higher than previous official WHO estimates, with India accounting for 34% of that total [108]. Motivated by previous work on malaria, the Bhatt et al. analysis relied on correlating their geographic niche-modelling based estimates of dengue presence with burden estimates derived from serological surveys. While an improvement on previous approaches, the fact that dengue infection induces serotype-specific neutralising immunity weakens the parallels with malaria, in that the maximum number of dengue infections an individual can experience is strictly limited (while a person can experience dozens of malaria infections in their lifetime). Here we argue that obtaining robust estimates of the geographic variation in average dengue transmission intensity – as quantified by R_0 (the average number of secondary cases resulting from the introduction of a single infectious individual into a large susceptible population [109]), of each serotype – is key to improving the reliability of burden estimates. In addition, a quantitative understanding of variation in transmission intensity is essential in assessing the likely impact of interventions such as vaccine [60,61] or novel vector control measures [70,74,110].

However, with no standardised diagnostic method, challenging clinical diagnosis (Box 1) and highly variable surveillance systems, there is no consistent way to estimate global dengue transmission [39,111,112]. Dengue transmission is geographically highly heterogeneous, even down to very fine spatial scales [87], however it can also be driven by temperature fluctuations at larger scales leading to similar patterns of transmission across wider regions [113]. Most model-based estimates of dengue transmission intensity and reproduction number have utilised case-notification data, which heavily depend on the quality of the surveillance system and the health infrastructure of the country in question [114–121]. Additionally, since the majority of dengue infections generate only mild symptoms, are asymptomatic, or are clinically diagnosed as a viral infection, even sensitive healthcare-based surveillance systems substantially underestimate true rates of infection [122,123]. Serological data are therefore invaluable in quantifying dengue transmission, in being able to identify both symptomatic and asymptomatic past infections and thus quantify infection prevalence and incidence in the population as a whole.

Here we utilise published age-stratified non-serotype specific seroprevalence surveys and estimate λ and R_0 for dengue in a variety of settings.

Box 2.1: Main issues associated with current diagnostic methods

- Although highly accurate and sensitive, virus isolation and PCR can be time consuming and expensive and relies on sampling (and therefore detection) of symptomatic cases.
- Routinely used serological methods - IgM and IgG ELISAs - are unable to differentiate between the 4 dengue serotypes and are affected by cross-reactivity with other flaviviruses (e.g. yellow fever or Japanese encephalitis).
- IgG ELISAs are unable to differentiate between past, recent, and current infection [2].
- IgM ELISAs can be confounded by false positives and are only useful for a limited time post-infection [124].
- In secondary or later infections, serological diagnosis of the most recent infecting dengue serotype is difficult due to the presence of pre-existing cross-neutralising and cross-reactive antibodies [15,125].
- Serological assay protocols (e.g. thresholds used to define seropositivity) are not standardised across laboratories [112].
- Laboratory capacity and general public health infrastructure and surveillance systems vary widely within and between countries.

2.2 Methods

2.2.1 Literature Search

We searched MEDLINE, EMBASE, and Web of Knowledge for publications reporting age-stratified dengue serological surveys. Figure 2.1 describes the search process and search terms used. Studies published before 1980 were not included in the analysis as we were interested in contemporary dengue transmission. Studies reporting age-specific seroprevalence for at least 5 age groups were included and categorised according to the assay type used. Studies reporting fewer than 5 age groups were excluded as these studies tended to have wide age groups where the mean seroprevalence did not accurately reflect the variability in seroprevalence within that age group (i.e. variability in dengue transmission over time as a reflection of age). Data were extracted from published datasets where age-specific seroprevalence was tested by IgG enzyme-linked immunosorbent assays (ELISAs), inhibition ELISAs (IEs) or PRNTs (used in chapter 3). IgG and IE data are both non-serotype specific and we refer to them interchangeably.

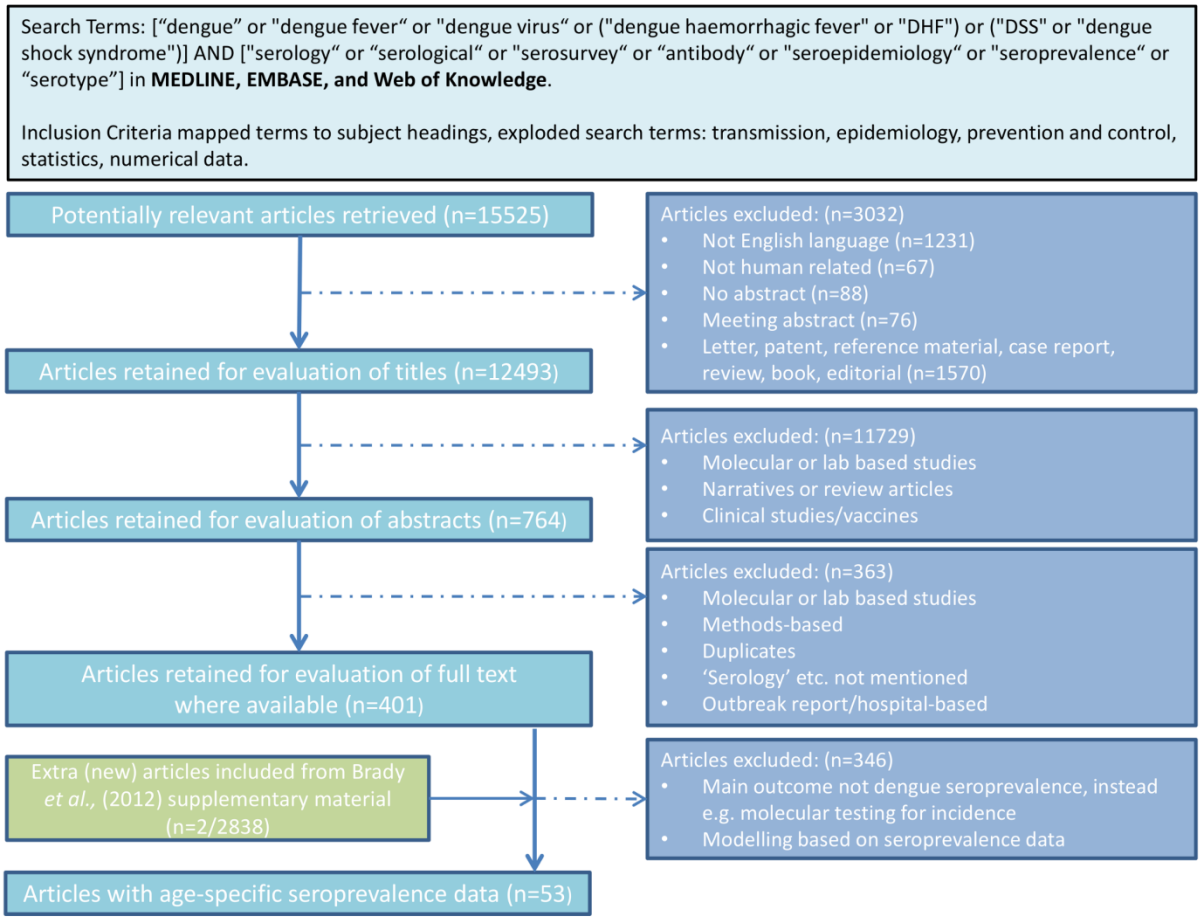

Figure 2.1: Flowchart describing the literature search process for dengue seroprevalence surveys.

2.2.2 Catalytic Models

Data type: Single cross-sectional non-serotype specific surveys

In the context of dengue, seroprevalence measures obtained with non-serotype specific assays such as IgG ELISAs only give an indication of whether an individual has 'ever' been infected and do not differentiate between infecting serotypes or identify the number of past infections. We assume that upon infection, individuals in age group i move from being seronegative to seropositive. We denote the force of infection (also called the infection hazard) by λ; the proportions of the population of age a which are seronegative and seropositive as $x(a_i)$ and $z(a_i)$, respectively (Figure 2.2). Since infection with one serotype only provides homologous immunity, a seropositive individual may still be susceptible to secondary heterotypic infection [15].

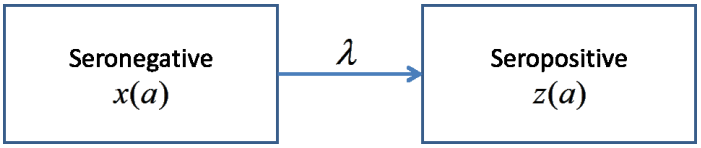

Figure 2.2: Compartmental model showing the flow of individuals in a catalytic model.

Model A: Constant force of infection

A simple catalytic model (model A) was fitted to the single cross-sectional IgG datasets. The model assumes a constant infection hazard λ, with infection causing individuals of age a to move from a seronegative $x(a)$ to a seropositive $z(a)$ state [109]. The proportion seropositive (IgG positive) in age group i at age a, $z(a_i)$ is given by:

$$z(a_i) = 1 - \exp[-\lambda a], \tag{2.1}$$

where λ is the force of infection and a is the age in years.

Model B: Constant force of infection and antibody decay

Since some datasets appeared to have declining seroprevalence with age, the constant force of infection model (model A) was extended by assuming that antibodies could decay with age at a rate α (Figure 2.3), moving people back to the seronegative class (model B).

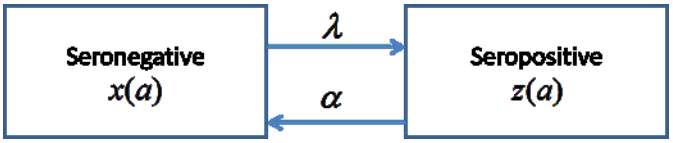

Figure 2.3: Compartmental model showing the flow of individuals in a catalytic model where individuals may lose seropositivity/antibodies.

The proportion of IgG seropositive individuals in age group i at age a (in years) is then given by:

$$\begin{aligned}\frac{dz}{da} &= \lambda(1-z)-\alpha z \\ &= \lambda-(\lambda+\alpha)z.\end{aligned} \tag{2.2}$$

Assuming λ and α are constant, integrating (2.2) gives:

$$\begin{aligned}z(a) &= 1-\exp\left[-\int_0^a(\lambda+\alpha)\,da'\right]-\alpha\int_0^a\exp\left[-\int_{a'}^a(\lambda+\alpha)\,da''\right]da' \\ &= \left[1-\exp\left[-a(\lambda+\alpha)\right]\right]\left[\frac{\lambda}{\lambda+\alpha}\right].\end{aligned} \tag{2.3}$$

Data type: Yearly cross-sectional IgG ELISA surveys

Model C: Time-varying force of infection with interannual variability

Whenever yearly cross-sectional IgG data were available from the same location, a time-varying catalytic model (model C) where the force of infection was allowed to vary over time was fitted to these data. Assuming the force of infection λ has a constant component λ_0 and a time-varying component given by a sinusoidal function with periodicity T, amplitude δ and phase θ:

$$\lambda(t) = \lambda_0\left[1+\delta\sin\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right)\right] \quad . \tag{2.4}$$

Exposure was also allowed to change with age, by introducing a critical age A_{crit} at which exposure levels change. Below that age, exposure is reduced or increased by a scaling factor S relative to individuals over that age. For individuals younger than the critical age $(a < A_{crit})$ the seroprevalence at age a and time t is given by:

$$\begin{aligned} z(a,t) &= 1-\exp\left[-\int_0^a S\lambda_0\left[1+\delta\sin\left(2\pi\left\{\frac{(t-u)}{T}+\theta\right\}\right)\right]du\right] \\ &= 1-\exp\left[-\left[S\lambda_0 a-\frac{S\lambda_0\delta T}{2\pi}\left(\begin{array}{l}-cos\left(2\pi\left\{\frac{(t-a)}{T}+\theta\right\}\right)\\ +cos\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right)\end{array}\right)\right]\right]. \end{aligned} \tag{2.5}$$

For individuals aged equal to or above the critical age $(a \geq A_{crit})$, seroprevalence is given by:

$$\begin{aligned} z(a,t) &= 1-\exp\left[-\left\{\begin{array}{l}\int_0^{A_{crit}} S\lambda_0\left[1+\delta\sin\left(2\pi\left\{\frac{(t-u)}{T}+\theta\right\}\right)\right]du+\\ \int_{A_{crit}}^{a}\lambda_0\left[1+\delta\sin\left(2\pi\left\{\frac{(t-u)}{T}+\theta\right\}\right)\right]du\end{array}\right\}\right] \\ &= 1-\exp\left[-\left[\begin{array}{l}S\lambda_0 A_{crit}-\frac{S\lambda_0\delta T}{2\pi}\left(\begin{array}{l}-cos\left(2\pi\left\{\frac{(t-A_{crit})}{T}+\theta\right\}\right)\\ +cos\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right)\end{array}\right)\\ +\lambda_0 a-\lambda_0 A_{crit}-\frac{\lambda_0\delta T}{2\pi}\left(\begin{array}{l}-cos\left(2\pi\left\{\frac{(t-a)}{T}+\theta\right\}\right)\\ +cos\left(2\pi\left\{\frac{(t-A_{crit})}{T}+\theta\right\}\right)\end{array}\right)\end{array}\right]\right]. \end{aligned} \tag{2.6}$$

We estimated the force of infection (λ_0), the periodicity (T), amplitude (δ) and phase (θ) of dengue outbreaks, and the critical age (A_{crit}) and scale (S) at which exposure levels change.

Estimation Procedure

The constant force of infection (A), antibody decay (B), and time-varying force of infection models (C) were fitted to the IgG data from each available dataset using a Metropolis-Hastings Markov Chain Monte-Carlo (MH MCMC) algorithm with a beta-binomial likelihood. Uniform priors were assigned to all parameters. We assumed that the probability of testing seropositive in each age group was beta-binomially distributed:

$$X_i \sim BetaBinomial\left(N_i, p_i, \psi\right)$$

where N_i is the total number of individuals in age group i, p_i is the probability of testing seropositive (or the proportion in that age group seropositive), and ψ represents over-dispersion. The likelihood is given by:

$$L\left(p_i\right) = \binom{N_i}{X_i} \frac{B\left(X_i + a, N_i - X_i + b\right)}{B\left(a,b\right)},$$

where B is the beta function with standard arguments a and b. We re-parameterised the beta distribution in terms of its mean (m) and variance (v): $m = a/\left(a+b\right)$ and $v = ab/\left[\left(a+b\right)^2\left(a+b+1\right)\right]$ respectively. The over-dispersion parameter ψ was then defined as: $\psi = v/\left[m\left(1-m\right)\right]$.

The beta arguments then become:

$$a = m\left(1/\psi - 1\right) \text{ and } b = \left(1-m\right)\left[1/\psi - 1\right].$$

Here we assign $m = p_i$ from equations (2.1) and (2.3) for models A and B respectively, and equations (2.5) and (2.6) for model C, and estimate ψ. Substituting the above into the likelihood this becomes:

$$L(p_i) = \binom{N_i}{X_i} \frac{B\left(X_i + m(1/\psi - 1), N_i - X_i + (1-m)[1/\psi - 1]\right)}{B\left(m(1/\psi - 1), (1-m)[1/\psi - 1]\right)}.$$

Ignoring the constant, the log-likelihood for one age group is:

$$LnL(p_i) = \log\left\{B\left(X_i + m_i(1/\psi - 1), N_i - X_i + (1-m_i)[1/\psi - 1]\right)\right\} - \log\left\{B\left(m_i(1/\psi - 1), (1-m_i)[1/\psi - 1]\right)\right\}.$$

So total log-likelihood across all age groups is:

$$LnL(p) = \sum_i \begin{matrix} \log\left\{B\left(X_i + m_i(1/\gamma - 1), N_i - X_i + (1-m_i)[1/\gamma - 1]\right)\right\} \\ -\log\left\{B\left(m_i(1/\gamma - 1), (1-m_i)[1/\gamma - 1]\right)\right\} \end{matrix}, \quad (2.7)$$

where X_i is the number of individuals testing positive among those tested in age group *i*, N_i is the total number of individuals tested in age group i, ψ represents the degree of over-dispersion, and m is the predicted proportion of seropositive individuals in that age group. The predicted proportion of seropositive individuals in each age group is calculated by taking the average seroprevalence within each age group. For example for age group 5-9 years, seroprevalence at each age 5, 6, 7 etc. would be computed and the mean value taken as the seroprevalence for that age group.

<u>Confidence Intervals around the Observed Seroprevalence</u>

Binomial proportion 95% confidence intervals (CI) were calculated for the reported seroprevalence in each age group i by:

$$CI = \frac{X_i}{N_i} \pm 1.96 \times se,$$

where $se = \sqrt{\frac{[X_i/N_i](1-[X_i/N_i])}{N_i}}$.

Here X_i is the number of individuals testing positive among those tested in age group i and N_i is the total number of individuals tested in age group i.

2.2.3 Estimating the Basic Reproduction Number

For each model, the strain-specific basic reproduction number R_{0i} was estimated under two different assumptions:

1) Tertiary and quaternary infections possible – here we can only analytically derive an expression for R_{0i} in the case that there is no cross-immunity mediated interactions between serotypes.
2) Individuals develop complete immunity to all dengue serotypes after secondary infection – in this case we can explore the different assumptions about cross-immunity.

Assumption 1: Tertiary and quaternary infection possible.

When tertiary and quaternary infections are possible, we can only estimate R_{0i} assuming there are no cross-immunity mediated interactions between serotypes. Following Ferguson *et al*. [104], the serotype–specific basic reproduction number under assumption 1 is given by:

$$R_{0i} = \frac{(d\lambda_i(t)/dt)/(\sigma\lambda_i(t))+1}{1-\int_0^\infty f(a')z_i(a',t)da'} \quad , \tag{2.8}$$

where σ is the reciprocal of the infectious period (1/6 days) [126,127], $f(a)$ is the probability density function of the age distribution of the population and $z_i(a)$ is the proportion seropositive to serotype i at age a.

For model C where the force of infection varies with time $\lambda(t)$ is given by:

$$\lambda(t) = \lambda_0\left[1+\delta\sin\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right)\right] \quad . \tag{2.9}$$

Assuming temporal changes in the force of infection are relatively small ($d\lambda/dt << \sigma\lambda$), for models A and B equation (2.8) reduces to:

$$R_{0i} = \frac{1}{1-\int_0^\infty f(a')z_i(a')da'}. \tag{2.10}$$

Assuming that the serotypes are equally transmissible and equally prevalent (and thus that the force of infection for each serotype is a quarter of the overall force of infection for dengue when four serotypes are in circulation, λ), the serotype-specific proportion of seropositive individuals of age a, $z_i(a)$, is given by equations (2.11)–(2.14) for models A – C respectively:

Constant force of infection model (model A):

$$z_i(a) = 1 - \exp\left[-\frac{\lambda}{4}a\right]. \tag{2.11}$$

Antibody decay model (model B):

$$z_i(a) = \left[1 - \exp\left[-a\left(\frac{\lambda}{4} + \alpha\right)\right]\right]\left[\frac{\frac{\lambda}{4}}{\frac{\lambda}{4} + \alpha}\right]. \tag{2.12}$$

Time-varying force of infection model (model C):

For $a < A_{crit}$:

$$z_i(a,t) = 1 - \exp\left[-\left[\frac{S\lambda_0 a}{4} - \frac{S\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{\frac{(t-a)}{T} + \theta\right\}\right) \\ +cos\left(2\pi\left\{\frac{t}{T} + \theta\right\}\right) \end{array}\right)\right]\right]. \tag{2.13}$$

For $a \geq A_{crit}$:

$$z_i(a,t) = 1 - \exp\left[-\left[\begin{array}{l} \dfrac{S\lambda_0 A_{crit}}{4} - \dfrac{S\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{ \dfrac{(t - A_{crit})}{T} + \theta \right\} \right) \\ +cos\left(2\pi\left\{ \dfrac{t}{T} + \theta \right\} \right) \end{array} \right) \\ +\dfrac{\lambda_0 a}{4} - \dfrac{\lambda_0 A_{crit}}{4} - \dfrac{\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{ \dfrac{(t-a)}{T} + \theta \right\} \right) \\ +cos\left(2\pi\left\{ \dfrac{(t - A_{crit})}{T} + \theta \right\} \right) \end{array} \right) \end{array} \right] \right]. \quad (2.14)$$

Assumption 2: Complete immunity after secondary infection

If only primary and secondary infections can occur, the assumption of no cross-immunity between serotypes can be relaxed. Following Ferguson et al.[104], the serotype–specific basic reproduction number for models A – C is then given by:

$$R_{0i} = \frac{(d\lambda_i(t)/dt)/\sigma\lambda_i(t)) + 1}{\int_0^\infty f(a')\left[x(a',t) + \sum_{j \neq i} \phi_{ji}\varphi_{ji} z_j(a',t) \right] da'}. \quad (2.15)$$

Here $x(a,t)$ is the proportion seronegative at age a and time t, φ_{ji} is the relative susceptibility to infection of someone infected with serotype j following infection with serotype i, and ϕ_{ji} is the relative infectiousness of someone infected with serotype j following infection with serotype i (relative to a primary infection), and other terms are as defined previously. We set $\varphi_{\mathrm{ji}} = 1$, and also set ϕ_{ji} = 1 since this parameter cannot be estimated from serological data alone. $\lambda(t)$ is given in equation (2.9) for model C where the force of infection varies with time. Assuming temporal changes in the force of infection are relatively small ($d\lambda/dt << \sigma\lambda$), for models A-B, (2.15) reduces to:

$$R_{0i} = \frac{1}{\int_0^\infty f(a')\left[x(a') + \sum_{j \neq i} \phi_{ji}\varphi_{ji} z_j(a') \right] da'}. \quad (2.16)$$

Expressions for $z_j(a)$ for models A and C are given in equations (2.17) and (2.18)-(2.19) respectively below:

Constant force of infection model (model A):

$$z_j = \left[1-\exp\left[-\frac{\lambda}{4}a\right]\right]\left[\exp\left[-\frac{3\lambda}{4}a\right]\right]. \tag{2.17}$$

Time-varying force of infection model (model C):

For $a < A_{crit}$:

$$z_j(a,t) = \left[1-\exp\left[-\left[\frac{S\lambda_0 a}{4}-\frac{S\lambda_0\delta T}{8\pi}\left(\begin{array}{l}-cos\left(2\pi\left\{\frac{(t-a)}{T}+\theta\right\}\right)\\+cos\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right)\end{array}\right)\right]\right]\right] \times\left[\exp\left[-\left[\frac{3S\lambda_0 a}{4}-\frac{3S\lambda_0\delta T}{8\pi}\left(\begin{array}{l}-cos\left(2\pi\left\{\frac{(t-a)}{T}+\theta\right\}\right)\\+cos\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right)\end{array}\right)\right]\right]\right]. \tag{2.18}$$

For $a \geq A_{critical}$:

$$z_j(a,t) = \left[1 - \exp\left[-\left[\begin{array}{l} \frac{S\lambda_0 A_{crit}}{4} - \frac{S\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{\frac{(t-A_{crit})}{T}+\theta\right\}\right) \\ +cos\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right) \end{array}\right) \\ +\frac{\lambda_0 a}{4} - \frac{\lambda_0 A_{crit}}{4} - \frac{\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{\frac{(t-a)}{T}+\theta\right\}\right) \\ +cos\left(2\pi\left\{\frac{(t-A_{crit})}{T}+\theta\right\}\right) \end{array}\right) \end{array}\right]\right]\right]\right] \times \left[\exp\left[-\left[\begin{array}{l} \frac{3S\lambda_0 A_{crit}}{4} - \frac{3S\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{\frac{(t-A_{crit})}{T}+\theta\right\}\right) \\ +cos\left(2\pi\left\{\frac{t}{T}+\theta\right\}\right) \end{array}\right) \\ +\frac{3\lambda_0 a}{4} - \frac{3\lambda_0 A_{crit}}{4} - \frac{3\lambda_0 \delta T}{8\pi}\left(\begin{array}{l} -cos\left(2\pi\left\{\frac{(t-a)}{T}+\theta\right\}\right) \\ +cos\left(2\pi\left\{\frac{(t-A_{crit})}{T}+\theta\right\}\right) \end{array}\right) \end{array}\right]\right]\right]. \quad (2.19)$$

We did not consider models combining both antibody decay (model B) and serotype interactions, as derivation of closed-form expressions for R_{0i} proved intractable in this case.

For all calculations, $f(a)$ or the probability density function of the age distribution of the population was calculated from demography data corresponding to each study year – either from the United Nations population estimates [128], or where available the national census data of the corresponding study region.

2.3 Results

Fifty-three studies reporting age-specific seroprevalence were identified from a total of 15,525 potentially relevant papers (Figure 2.1). Of these, 38 used non-serotype specific assays including IgG and IEs. Only nine studies used PRNTs and five studies reported results from multiple assays. Excluding studies with less than 5 reported age groups from further analysis left a total of 30 surveys from 18 countries for IgG data, and 7 studies from 5 countries for PRNT data. 28 (out of 30) surveys from 17 countries were cross-sectional IgG seroprevalence surveys from a single year. The remaining 2 (out of 30) surveys were conducted in Nicaragua and combined provided 7 years' worth of cross-sectional non-serotype specific data. Most IgG surveys identified were conducted in 2000 – 2010 (23/30), while most PRNT surveys were conducted in the 1990s (4/7). Although recent serosurveys used commercial diagnostics, many studies used in-house assays. Table 2.1 summarises the study and demographics of the datasets retained for analysis from the corresponding or closest year. All studies summarised in Table 2.1 were fitted using model A and B, and model C was also fitted to the two Nicaraguan datasets. Only an overall force of infection could be estimated from non-serotype specific IgG data. As expected, estimates of the force of infection varied widely between countries and, to a lesser extent, within countries. Table 2.2 and Figure 2.4a show parameter estimates derived from the constant force of infection model (A), and Figure 2.5 show the model fits. The combined log-likelihood score for this model across the 28 datasets was -13206.8, while the combined log-likelihood score for the antibody decay model (model B) was -13086.8. Southeast Asian such as Vietnam and Thailand, had a higher force of infection compared with most sites in the Americas [6]. Corresponding estimates of R_{0i} varied according to the assumptions made regarding host immunity (Figure 2.4b). Assuming that two heterologous infections are sufficient for complete immunity (Assumption 2) produced up to two-fold higher estimates of R_{0i} compared to when we assumed that quaternary infections are required for complete immunity (Assumption 1). However, R_{0i} estimates under these two assumptions converge as the estimated force of infection decreases.

The joint antibody decay rate (model B) was low when estimated across all non-serotype specific datasets at 0.020 (95% CrI: 0.014 – 0.030). Allowing for antibody decay slightly

increased the estimated force of infection for each dataset (Table 2.3). Of the non-serotype specific datasets examined, all 17 countries had more than one serotype in circulation in the past. Figure 2.6 shows model B fits.

Table 2.1: Summary of cross-sectional non-serotype specific datasets identified and associated demographics.

Country	Author	Survey Year	Region	Assay Type[+]	# Serotypes circulating	Participant Ages	N	Population size of study region (thousands)	Rural/Urban	% <15 years old	Models used
Brazil	Braga [129]	2005/06	Recife	PanBio	4	5 - 65	2817	40	Urban	28	A and B
Costa Rica	Iturrino-Monge [130]	2002/03	Puntarenas, San Jose	PanBio	4	1 - 10	206	358/1373	Urban	31.5	A and B
Dominican Republic	Yamashiro [131]	2002	Santo Domingo	Focus Tech	4	0 - 60	1209	1887	Urban	35	A and B
El Salvador	Hayes [132]	2000/01	Las Pampitas	CDC	NA	0 - 69	371	944	Rural	38	A and B
French Polynesia	Deparis [133]	1996	Teroma	In-house	4	0 - 21	169	16	Urban	34	A and B
India	Padbidri [134]	1988/89	Andaman	HI/N	NA	0 - 40	2401	356	Rural	38	A and B
Laos	Vallée [135]	2006	Vientiane	In-house	4	0 - 6	143	277	Urban	40	A and B
	Hiscox [136]	2007/08	Khammouane	HI	4	0 - 90	1708	337	Rural		A and B
Mayotte	Sissoko [137]	2006	Mayotte	Focus Tech	NA	2 - 55	1154	175	Whole island	41	A and B
Mexico	Brunkard [138]	2004	Matamoros	PanBio	4	15 - 75	600	412	Urban	32	A and B
	Ramos [139]	2005	Matamoros	Quantitative	4	5 – 65	131	412	Urban		A and B
Nicaragua[-]	Balmaseda [140]	2001-03	Managua	IE	4	5 – 16	1971	2101	Urban	41	A and C
	Balmaseda [30]	2004-07	Managua	IE	4	2 - 9	14182	2101	Urban	38	A and C
Pakistan	Ali [141]	Pre-2003^	Khyber Pakhtunkhawa	Cortez	NA	0 - 60	613	20000	Urban/rural	42	A and B
	Mahmood [142]	2012	Lahore	NovaTech	NA	15 - 55	274	7566	Urban	35	A and B
Papua New Guinea	Senn [143]	2007/08	Madang Province	PanBio	NA	0 - 25	577	493	Urban/rural	39	A and B
Peru	Hayes [144]	1992	Loreto	In-house	2	0 - 60	1608	9	Urban/Rural/Jungle	38	A and B
	Reiskind [145]	1996	Santa Clara	In-house	2	5 - 87	1225	2.4	Suburban	36	A and B
Singapore	Goh [146]	1984	National	HI	4	0 - 40	425	2709	Urban	24	A and B
	Yew [147]	2004	National	PanBio	4	18 - 74	4152	2709	Urban	19	A and B
	Yap [148]	2007	National	PanBio	4	7 - 85	3939	2709	Urban	17	A and B
Sri Lanka	Malavige [149]	Pre-2006^	Colombo district	PanBio	4	6 – 18	313	2309	Urban	25	A and B
	Tissera [150]	2008	Colombo City	In-house	4	0 – 12	797	647	Urban	25	A and B
	Tam [151]	2008	Colombo City	In-house	4	0 - 12	797	647	Urban	25	A and B
Thailand	Perret [152]	2000	Bangkok	In-house	4	5 – 12	283	6355	Urban	24	A and B
	Tuntaprasart [153]	2000	Ratchaburi	In-house	4	15 - 40	245	842	Urban	21	A and B
USA	Brunkard [138]	2004	Brownsville	PanBio	NA	15 – 75	600	139	Urban		A and B
	Ramos [139]	2005	Brownsville	Quantitative	NA	5 – 65	139	139	Urban	36	A and B
Vietnam	Bartley [154]	1996/97	Dong Thap Province	PanBio	4	0 – 20	308	309	Urban/Rural	32	A and B
	Thai [155]	Pre-2005^	Binh Thuan Province	MRL	4	7 - 14	961	1100	Rural	27	A and B

^ Survey date not given, noted as 'pre-year of publication'. [+]All assays were IgG or HI ELISAs .[-]Cross-sectional surveys from multiple years (2001 – 2007).

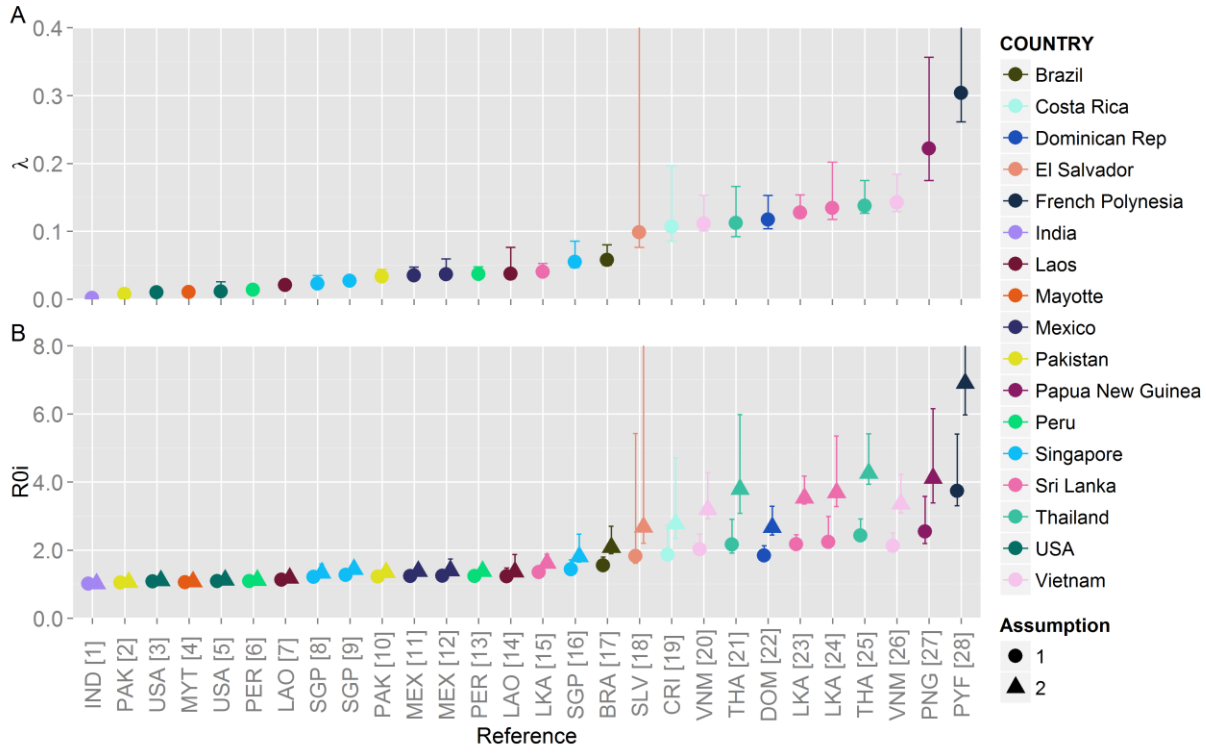

Figure 2.4: A) Force of infection and B) corresponding R_{0i} estimates from constant force of infection model (model A) fitted to cross-sectional non-serotype specific datasets. Posterior median and 95% credible intervals (CrI) shown. Assumption 1 = individuals can be infected four times, assumption 2 = individuals develop protective immunity after two infections. See end of chapter for figure references and ISO country abbreviations.

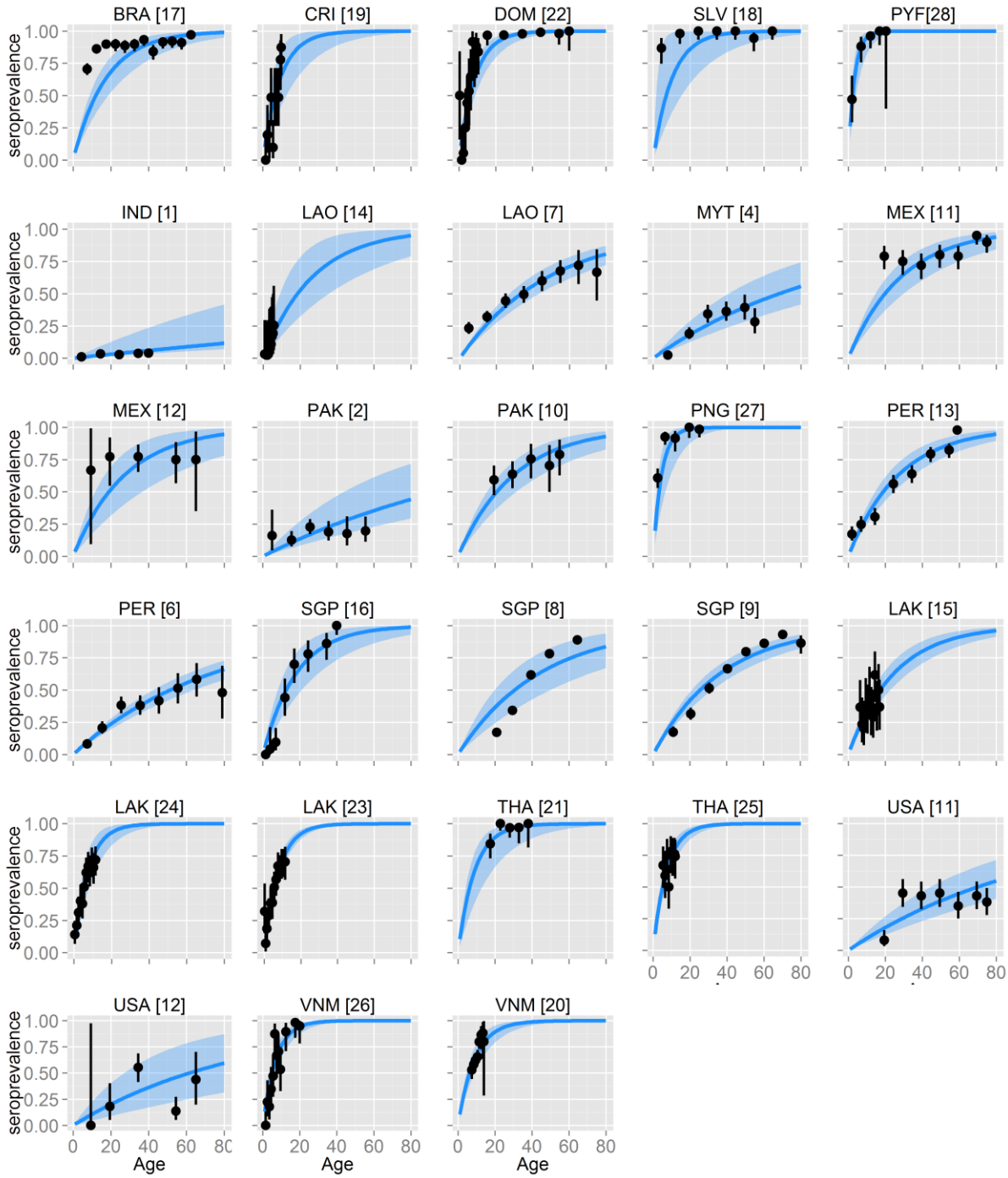

Figure 2.5: Model fits from the constant force of infection model (model A) fit to IgG data (points). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown. See end of chapter for figure references and ISO country abbreviations.

Table 2.2: Summary estimates from the fit of cross-sectional non-serotype specific datasets using model A (constant force of infection).

Country	**Author**	**Force of Infection λ**	**Over-dispersion ψ**	**R_{0i} (95% CrI)**		**LnL**
		(95% CrI)	**(95% CrI)**	**Assumption 1**	**Assumption 2**	
Brazil	Braga *et al.*[129]	0.058 (0.050-0.080)	0.155 (0.116-0.346)	1.55 (1.47-1.80)	2.08 (1.90-2.70)	-1056.2
Costa Rica	Iturrino-Monge *et al.*[130]	0.107 (0.086-0.197)	0.329 (0.264-0.555)	1.87 (1.68-2.73)	2.77 (2.35-4.72)	-115.8
Dominican Republic	Yamashiro *et al.*[131]	0.117 (0.104-0.153)	0.087 (0.050-0.264)	1.84 (1.74-2.13)	2.67 (2.44-3.29)	-229.9
El Salvador	Hayes *et al. (2)*[132]	0.099 (0.076-0.430)	0.443 (0.299-0.799)	1.82 (1.62-5.43)	2.67 (2.21-10.66)	-47.6
French Polynesia	Deparis *et al.*[133]	0.304 (0.261-0.463)	0.044 (0.016-0.396)	3.73 (3.30-5.41)	6.90 (5.97-10.42)	-51.6
India	Padbidri *et al.*[134]	0.002 (0.001-0.007)	0.010 (0.004-0.239)	1.01 (1.01-1.04)	1.01 (1.01-1.05)	-336.4
Laos	Vallee *et al.*[135]	0.037 (0.030-0.076)	0.043 (0.018-0.231)	1.23 (1.18-1.48)	1.36 (1.28-1.87)	-46.4
	Hiscox *et al.*[136]	0.021 (0.019-0.026)	0.033 (0.022-0.126)	1.13 (1.12-1.16)	1.18 (1.16-1.23)	-1093.7
Mayotte	Sissoko *et al.*[137]	0.010 (0.009-0.017)	0.056 (0.033-0.241)	1.06 (1.05-1.09)	1.07 (1.06-1.12)	-544.6
Mexico	Brunkard *et al.*[138]	0.035 (0.031-0.047)	0.093 (0.061-0.300)	1.23 (1.21-1.32)	1.37 (1.32-1.55)	-286.3
	Ramos *et al.*[139]	0.037 (0.030-0.059)	0.133 (0.073-0.439)	1.24 (1.20-1.41)	1.40 (1.31-1.74)	-78.2
Pakistan	Ali *et al.*[141]	0.007 (0.006-0.016)	0.063 (0.035-0.308)	1.05 (1.04-1.10)	1.05 (1.05-1.14)	-302.0
	Mahmood *et al.*[142]	0.033 (0.030-0.044)	0.040 (0.018-0.253)	1.22 (1.19-1.29)	1.34 (1.30-1.49)	-174.7
Papua New Guinea	Senn *et al.*[143]	0.222 (0.175-0.357)	0.116 (0.053-0.521)	2.55 (2.19-3.58)	4.11 (3.39-6.15)	-175.7
Peru^	Hayes (1) *et al.*[144]	0.037 (0.034-0.048)	0.061 (0.042-0.189)	1.37 (1.34-1.51)	1.37 (1.34-1.51)	-828.1
	Reiskind *et al.*[145]	0.013 (0.013-0.016)	0.014 (0.007-0.083)	1.11 (1.11-1.14)	1.11 (1.11-1.14)	-675.7
Nicaragua*	Balmaseda *et al.*[30,140]	0.218 (0.214 – 0.223)	0.016 (0.009 – 0.028)	3.22 (3.16 – 3.27)	6.42 (6.27 – 6.58)	-8184.2
Singapore	Goh *et al.*[146]	0.055 (0.047-0.086)	0.229 (0.166-0.507)	1.43 (1.37-1.71)	1.80 (1.65-2.47)	-143.4
	Yew *et al.*[147]	0.023 (0.020-0.035)	0.147 (0.099-0.422)	1.21 (1.18-1.34)	1.33 (1.27-1.59)	-2273.7
	Yap *et al.*[148]	0.027 (0.025-0.033)	0.041 (0.027-0.146)	1.26 (1.25-1.33)	1.44 (1.40-1.57)	-2084.4
Sri Lanka	Malavige *et al.*[149]	0.040 (0.037-0.053)	0.034 (0.018-0.139)	1.35 (1.31-1.47)	1.61 (1.54-1.88)	-206.8
	Tissera *et al.*[150]	0.134 (0.118-0.202)	0.160 (0.124-0.320)	2.24 (2.06-2.99)	3.69 (3.28-5.35)	-509.7
	Tam *et al.*[151]	0.128 (0.120-0.154)	0.026 (0.015-0.089)	2.17 (2.09-2.45)	3.53 (3.35-4.18)	-504.8
Thailand	Perret *et al.*[152]	0.112 (0.092-0.166)	0.120 (0.050-0.607)	2.16 (1.91-2.91)	3.79 (3.08-5.98)	-46.8
	Tuntaprasart *et al.*[153]	0.137 (0.127-0.175)	0.038 (0.019-0.175)	2.43 (2.30-2.92)	4.26 (3.93-5.42)	-175.0
USA (Texas)	Brunkard *et al.*[138]	0.010 (0.009-0.016)	0.086 (0.056-0.279)	1.08 (1.07-1.12)	1.10 (1.09-1.17)	-381.9
	Ramos *et al.*[139]	0.011 (0.009-0.026)	0.226 (0.149-0.578)	1.09 (1.07-1.21)	1.12 (1.08-1.32)	-84.1
Vietnam	Bartley *et al.*[154]	0.142 (0.129-0.184)	0.088 (0.056-0.243)	2.12 (2.02-2.50)	3.36 (3.09-4.23)	-147.0
	Thai *et al.*[155]	0.112 (0.101-0.153)	0.093 (0.063-0.285)	2.02 (1.91-2.45)	3.19 (2.92-4.27)	-606.3

^Only 2 serotypes in circulation, calculation adjusted accordingly, i.e. assuming complete immunity upon secondary infection (assumption 2). Assumption 1: tertiary and quaternary infections possible, assumption 2: complete protection after secondary infection.

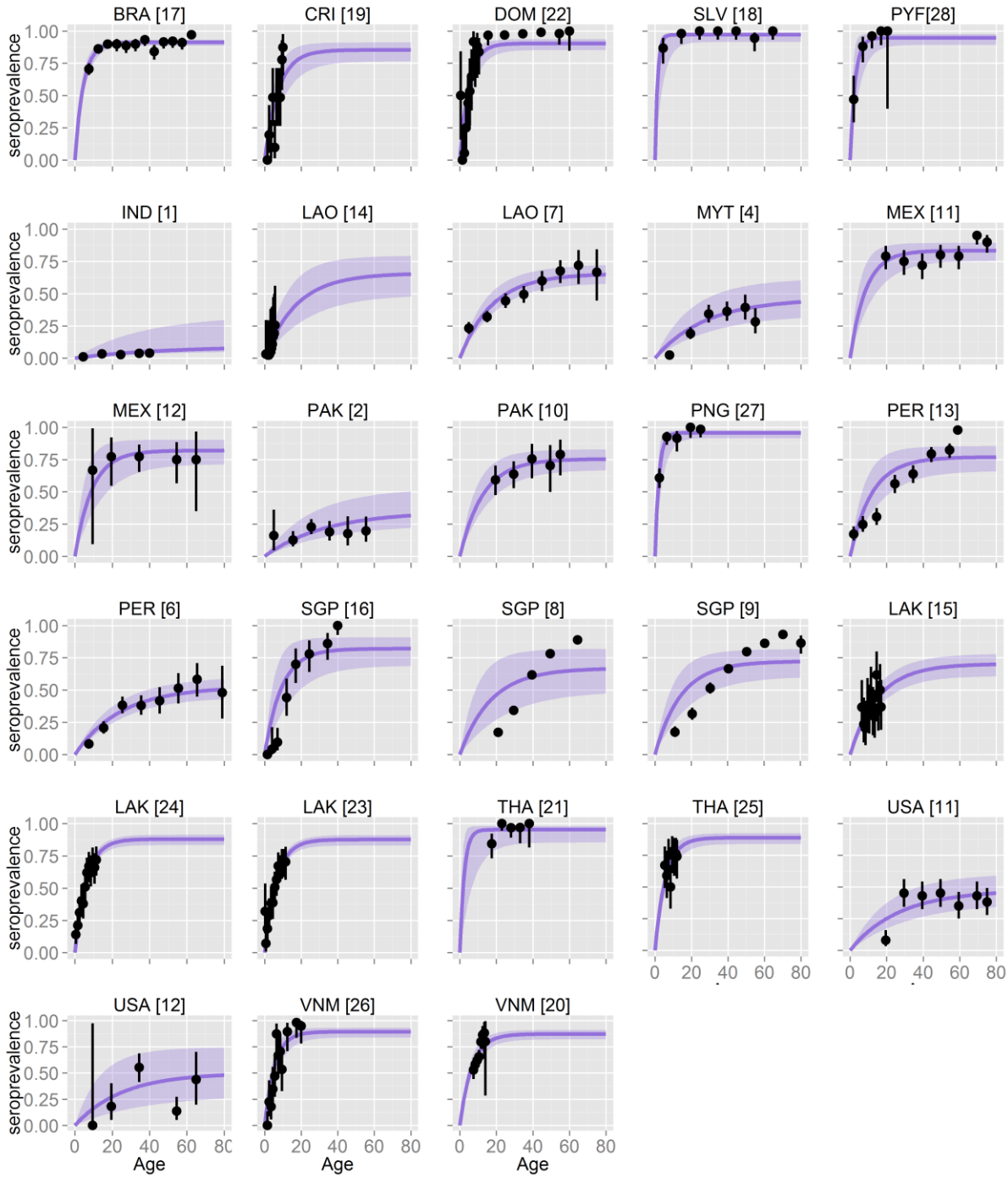

Figure 2.6: Model fits from the antibody decay model (model B) fit to IgG data (points). 95% exact CI around data points, posterior median (line) and 95% CrI (shaded area) shown. See end of chapter for figure references and ISO country abbreviations.

Table 2.3: Summary estimates from the fit of cross-sectional non-serotype specific datasets using model B. All the non-serotype specific datasets were fitted together using the antibody decay model (model B) to estimate an overall shared antibody decay rate.

Country	**Author**	α **(95% CrI)**	λ **(95% CrI)**	ψ **(95% CrI)**	R_{0i} **Assumption 1***	**LnL**
Brazil	Braga *et al.*[129]	0.020 (0.014 – 0.030)	0.203 (0.161 – 0.267)	0.010 (0.001-0.039)	2.32 (2.07-2.60)	-1063.0
Costa Rica	Iturrino-Monge *et al.*[130]		0.115 (0.072 – 0.178)	0.158 (0.046-0.375)	1.59 (1.36-1.95)	-116.3
Dominican Republic	Yamashiro *et al.*[131]		0.186 (0.128 – 0.258)	0.164 (0.067-0.326)	1.89 (1.60-2.26)	-306.3
El Salvador	Hayes *et al. (1)*[132]		0.702 (0.217 – 0.986)	0.150 (0.015-0.596)	5.11 (2.20-7.21)	-332.2
French Polynesia	Deparis *et al.*[133]		0.356 (0.172 – 0.811)	0.131 (0.010-0.529)	2.93 (1.89-5.47)	-41.6
India	Padbidri *et al.*[134]		0.002 (0.001 – 0.009)	0.007 (0.000-0.251)	1.01 (1.01-1.04)	-42.2
Laos	Vallee *et al.*[135]		0.038 (0.021 – 0.068)	0.019 (0.001-0.134)	1.16 (1.09-1.30)	-204.6
	Hiscox *et al.*[136]		0.037 (0.028 – 0.053)	0.025 (0.006-0.108)	1.16 (1.13-1.22)	-492.7
Mayotte	Sissoko *et al.*[137]		0.017 (0.010 – 0.031)	0.071 (0.019-0.288)	1.07 (1.04-1.12)	-478.3
Mexico	Brunkard *et al.*[138]		0.098 (0.058 – 0.179)	0.058 (0.013-0.219)	1.47 (1.28-1.82)	-537.9
	Ramos *et al.*[139]		0.090 (0.049 – 0.187)	0.044 (0.001-0.288)	1.43 (1.23-1.88)	-388.8
Pakistan	Ali *et al.*[141]		0.011 (0.007 – 0.021)	0.036 (0.003-0.245)	1.05 (1.03-1.10)	-89.6
	Mahmood *et al.*[142]		0.060 (0.041 – 0.097)	0.022 (0.001-0.200)	1.28 (1.19-1.43)	-296.5
Papua New Guinea	Senn *et al.*[143]		0.451 (0.224 – 0.792)	0.053 (0.002-0.346)	3.11 (2.02-4.69)	-172.9
Peru	Hayes (2) *et al.*[144]		0.065 (0.040 – 0.116)	0.149 (0.062-0.344)	1.58 (1.36-1.99)	-951.6
	Reiskind *et al.*[145]		0.022 (0.017 – 0.030)	0.018 (0.002-0.099)	1.20 (1.16-1.27)	-692.9
Singapore	Goh *et al.*[146]		0.089 (0.046 – 0.185)	0.441 (0.219-0.709)	1.48 (1.24-2.04)	-176.3
	Yew *et al.*[147]		0.040 (0.019 – 0.091)	0.240 (0.099-0.532)	1.24 (1.12-1.56)	-68.5
	Yap *et al.*[148]		0. 051 (0.031 – 0.090)	0.167 (0.072-0.373)	1.32 (1.19-1.56)	-2765.2
Sri Lanka	Malavige *et al.*[149]		0. 046 (0.036 – 0.060)	0.025 (0.001-0.113)	1.26 (1.20-1.35)	-2767.6
	Tissera *et al.*[150]		0. 144 (0.125 – 0.166)	0.006 (0.000-0.0345)	1.81 (1.67-1.96)	-2440.3
	Tam *et al.*[151]		0. 140 (0.127 – 0.160)	0.004 (0.000-0.025)	1.78 (1.65-1.93)	-42.3
Thailand	Perret *et al.*[152]		0.414 (0.116 – 0.942)	0.139 (0.024-0.556)	3.96 (1.72-8.33)	-288.1
	Tuntaprasart *et al.*[153]		0. 157 (0.118 – 0.204)	0.033 (0.002-0.164)	1.96 (1.69-2.28)	-71.9
USA (Texas)	Brunkard *et al.*[138]		0. 018 (0.011 – 0.030)	0.071 (0.017-0.258)	1.09 (1.06-1.15)	-51.1
	Ramos *et al.*[139]		0.020 (0.008 – 0.057)	0.215 (0.055-0.568)	1.10 (1.01-1.30)	-19.8
Vietnam	Bartley *et al.*[154]		0.166 (0.117 – 0.232)	0.120 (0.036-0.293)	1.85 (1.57-2.21)	-158.8
	Thai *et al.*[155]		0.135 (0.105 – 0.176)	0.035 (0.005-0.164)	1.76 (1.58-2.01)	-607.5

*Assumption 1: tertiary and quaternary infections possible. Global log-likelihood = -13086.8.

With age-structured serosurvey data from multiple sequential years (as was available for Nicaragua), it was possible to estimate temporal and age-specific changes in exposure [30,140] (Figure 2.7a). Model C which allowed for the force of infection to vary sinusoidally over time and to change at (fitted) age threshold was fitted to those data. Table 2.4 summarises the estimated parameter values and Figure 2.8 show the model fits. We estimated that exposure increased in individuals over 3.9 years old (95% CrI: 2.7 – 5.4 years), with the estimated force of infection during the study period (2001 – 2007) being 0.323 (95% CrI: 0.261 – 0.377) above 3.9 years and 0.174 (95% CrI: 0.118 – 0.280) below 3.9 years. These estimates represent the average total force of infection for all four serotypes in circulation. The force of infection was estimated to vary with a period of 8.8 years (95% CrI: 1.3 – 12.5 years). Resulting estimates of R_{0i} (Figure 2.7b) showed the same dependence on immunity assumptions as the point estimates derived from single serosurveys (Figure 2.4), but interestingly showed less temporal variation than the force of infection estimates (Figure 2.7a).

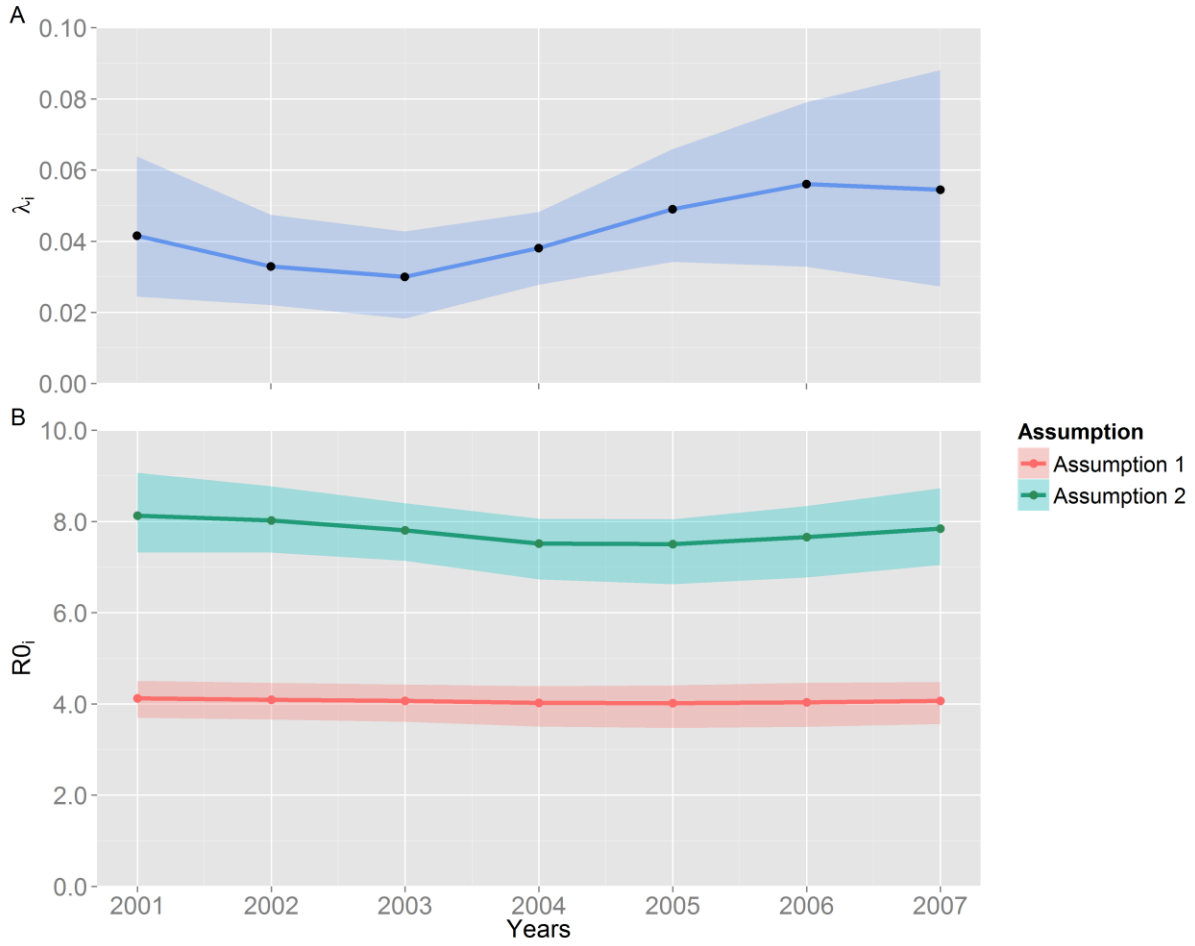

Figure 2.7: Estimated time-varying A) serotype-specific force of infection in individuals under the threshold age and B) R_{0i} derived by fitting the time-varying force of infection model (model C) to Nicaraguan data (2001 – 2007). Posterior median and 95% CrI shown. Assumption 1: individuals can be infected up to four times, assumption 2: individuals develop protective immunity after their second infection.

Table 2.4: Summary parameter estimates where the time-varying force of infection model (model C) was fitted to 7 years' worth of cross-sectional data from Nicaragua.

Parameter	Name	Median Estimate (95% CrI)	LnL
Force of infection	λ	0.323 (0.261 – 0.377)	-7848
Amplitude	δ	0.360 (0.072 – 0.670)	
Phase	θ	0.392 (0.015 – 0.990)	
Periodicity (yrs)	T	8.8 (1.3 – 12.5)	
Scaling of λ for those under critical age threshold relative to those over that threshold	S	0.54 (0.39 – 0.84)	
Critical age (yrs) threshold at which λ assumed to change	$A_{critical}$	3.9 (2.7 – 5.4)	
Over-dispersion	ψ	0.016 (0.009 – 0.028)	

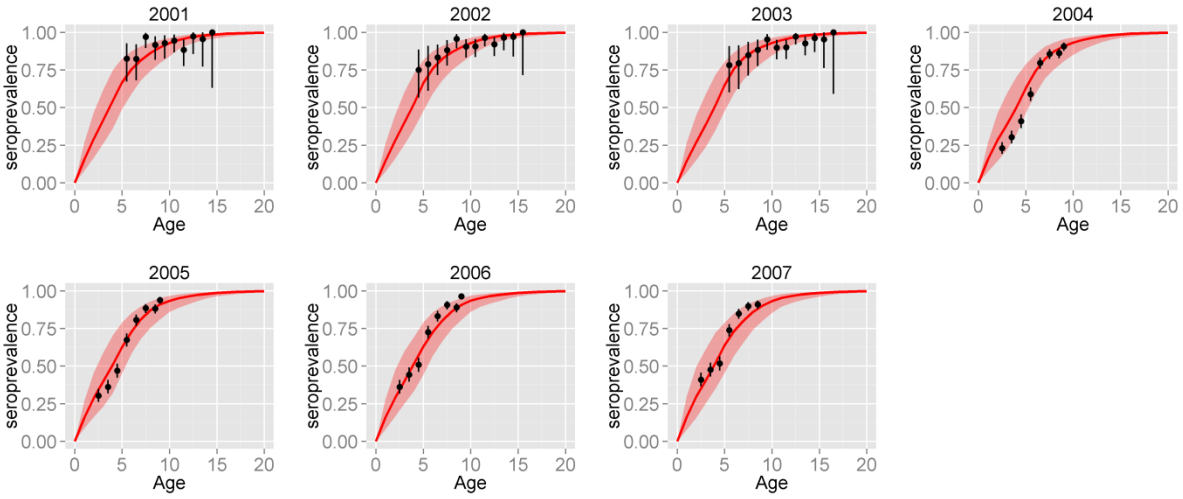

Figure 2.8: Observed (points) and estimated (line) cross-sectional seroprevalence in Nicaragua from 2001 to 2007 using the age-threshold model with time-varying force of infection (model C). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown.

2.4 Discussion

From a literature review, we selected 30 studies reporting age-structured seroprevalence data obtained with IgG/IE assays in 18 different locations from 1980 to 2010. From each dataset, we estimated dengue transmission intensity, quantified by λ and R_{0i}. Overall, our estimates highlight the highly heterogeneous nature of dengue transmission in both space and time. This analysis also highlights how the relationship between the force of infection and R_{0i} is affected by underlying assumptions about serotype interactions and immunity. The majority of our estimates of R_{0i} from 18 countries ranged from 1 – 4 (28 out of 28 and 24 out of 28 from the constant force of infection model (model A) fitted to IgG datasets under assumption 1: individuals can be infected four times, and 2: individuals develop protective immunity after two infections, respectively).

Dengue epidemiology differs between the Americas and Southeast Asia. Severe dengue predominantly affects children in Southeast Asia in contrast to the Americas where disease more often manifests in adults as the milder dengue fever [6]. However the changing demographics in Thailand (lower birth and death rates) have increased the average age of DHF suggesting that the epidemiology will continue to evolve [121]. However with the cross-sectional data used in this analysis it is difficult to determine whether the higher force of infection in South East Asia is a reflection of the length of time dengue has been in circulation. The recent Phase III dengue vaccine trial conducted in several countries in Latin America showed that the forces of infection are highly heterogeneous across Latin America, with some countries comparable to South East Asia (Columbia and Honduras) and others having much lower forces of infection (Mexico and Puerto Rico) [77]. However, multiple cross-sectional surveys or cohort studies would be needed to estimate how forces of infection by age have changed over time. The low R_{0i} estimated in the Indian subcontinent is probably due to the lack of datasets from this region and the spatial heterogeneity of transmission within that large region. The one serosurvey from India used in our study was conducted in Andaman, an island with a low population density where we estimated a very low force of infection. It is likely that the epidemiology of dengue on Andaman is not representative of dengue epidemiology on the mainland.

Seroprevalence surveys have the benefit of not being affected by surveillance system sensitivity or case reporting rates, but still have several limitations (Box 1) [10,31]. A particular issue is the wide variation in the assays used between studies (Table 2.1). Optimally, one would assess the sensitivity of transmission intensity estimates to factors that varied between assays, such as the threshold used to define seronegativity. However, such an analysis requires access to the raw titer data which was not provided in any of the publications reviewed here. Additionally, seroprevalence surveys sometimes use serum samples collected for a different purpose and therefore may not be representative of the population. Six out of the 31 studies used such samples: from blood banks [131], ante-natal clinics [152], hospitals [143,146,156], or residual samples from a different study [154]. Use of convenience samples can increase the volume of serological data produced, but the potential biases such sampling introduces must be taken into account when analysing such data. Cross-reactivity with Japanese encephalitis and other flaviviruses such as zika virus can also be an issue with IgG assays. Of the studies included in this chapter, there were 6 countries where Japanese encephalitis cases had occurred in the past (Laos, Sri Lanka, India, Vietnam, and Singapore). Table 2.5 summarises each author's justification (where available) in their chosen assay in their study context.

Table 2.5: Justification of assay choice in each country where Japanese encephalitis (JE) cases had been previously reported.

Country	Ref	Justification
Singapore	Goh *et al.* Yew *et al.* Yap *et al.* [146–148]	Although the PanBio ELISA can be cross-reactive with JE, the incidence of JE in Singapore is very low in comparison to dengue which is endemic. They therefore concluded that the impact of false positives on the observed dengue seroprevalence would be minimal.
Sri Lanka	Tam *et al.* [151]	Specifically tested how the seropositivity against JE would affect dengue estimates using JE vaccination history as a proxy. They found no evidence for JE having an effect and conclude that the majority of past infections detected by the ELISA were dengue.
	Malavige *et al.* [149]	Cite the high specificity and sensitivity of the PanBio assay making it unlikely that JE was affecting the results, but go on to specify that false positives cannot be completely ruled out.
	Tissera *et al*. [150]	Surveyed in a known dengue area and so state that the impact of JE would be minimal.
India	Padbidri *et al.* [134]	Tested samples in conjunction with neutralizing antibodies and so cross-reactivity with JE can be ruled out.
Thailand	Perret *et al*. [152]	Tested all samples with IgM and IgG ELISAs for JE as well and excluded cross-reactivity in dengue positive samples by calculating the ratio between JE and dengue IgG antibody.
	Tuntaprasart *et al*. [153]	Conducted a post-outbreak survey and therefore contribution of JE is likely to be minimal.
Laos	Vallee *et al*. [135]	Authors differentiate between recent JE and dengue infection. However they are unable to differentiate past infections. However they state that dengue infections appeared to be more frequent than JE.
	Hiscox *et al*. [157]	Authors categorized their results as: if a sample was positive for both JE and dengue this was considered flavivirus positive. If the sample produced a 2-fold higher titre to the homologous virus they were categorized as DENV positive or JEV positive only.

Although we can only estimate a total force of infection across all serotypes from non-serotype specific data (such as surveys using IgG ELISA assays), such data are still sufficient for assessing heterogeneity in overall dengue transmission intensity between different populations. It is not possible to disentangle temporal from any age-dependent variation in exposure from single cross-sectional seroprevalence surveys, requiring broad assumptions to be made about such variation. Hence, for simplicity, we generally assumed constant transmission intensity over time when analysing single cross-sectional surveys. However, for Nicaragua [30,140], data from multiple sequentially conducted serosurveys were available, so we were able to estimate time and age-dependent changes in the force of infection. We found evidence of long term variation in transmission intensity over a timescale of 1-12

years, and that exposure levels changed with age, with children aged 4 or older having twice the exposure of those under that age. We suspect that this may be associated with school attendance, with children spending more time away from home leading to an increase in exposure if the majority of transmission is occurring outside the domestic environment [158]. This school-cohort effect has also been observed in Sri Lanka, conversely with a decrease in exposure, where Tam *et al.* estimated an age-varying force of infection of 0.154 (95% CI: 0.132 – 0.177) for 0.5 – 6 year olds and 0.087 (95% CI: 0.020 – 0.154) for children aged 6 years and above also demonstrating the existence of different transmission environments [151].

In the next chapter (chapter 3) I compare the estimates obtained from IgG data to estimates derived from serotype-specific PRNT data and summarise the issues associated with cross-sectional seroprevalence data and discuss the limitations of this analysis. In addition, a simple regression is used to explore the impact that potential environmental and demographic covariates have on the estimated force of infection.

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2.6 ISO Abbreviations

ISO 3 letter code	Country
BRA	Brazil
CRI	Costa Rica
DOM	Dominican Republic
IND	India
LAO	Laos
LKA	Sri Lanka
MEX	Mexico
MYT	Mayotte
PAK	Pakistan
PER	Peru
PNG	Papua New Guinea
PYF	French Polynesia
SGP	Singapore
SLV	El Salvador
THA	Thailand
USA	United States of America
VNM	Vietnam

3 Estimating Dengue Transmission Intensity from Serotype-specific Seroprevalence Surveys and a Comparison of Data Types

Work in this chapter formed the basis of: Imai N, Dorigatti I, Cauchemez S, Ferguson NM (2015) Estimating Dengue Transmission Intensity from Sero-Prevalence Surveys in Multiple Countries. PLoS Negl Trop Dis 9(4): e0003719. doi: 10.1371/journal.pntd.0003719

In this chapter I use the cross-sectional serotype-specific PRNT data identified in chapter 2 and apply a multistrain model to estimate the serotype-specific force of infection. Re-analysing the PRNT data as non-serotype specific data allows us to compare how useful less expensive assays can be. I then summarise the limitations of analysing seroprevalence data.

3.1 Introduction

In the previous chapter (chapter 2) I analysed data from non-serotype specific IgG ELISAs used in less expensive cross-sectional surveys. In this chapter I use serotype-specific seroprevalence data from PRNTs, which are considered the current gold standard for non-acute routine dengue serotyping (PCR for acute serotyping), to estimate strain-specific forces of infection. Due to the much lower costs, future seroprevalence studies are still likely to depend on IgM or IgG ELISAs rather than the more labour intensive PRNTs. Here I compare the estimates derived from IgG, IE and PRNT data to determine the usefulness of less expensive assays.

3.2 Methods

3.2.1 Literature Search

The literature was searched for age-stratified seroprevalence surveys since 1980 and data were extracted from published datasets where age-specific seroprevalence was tested by PRNTs. The search process is described in detail in chapter 2.

3.2.2 Catalytic Models

Data type: Cross-sectional PRNT surveys

Since dengue viruses exist as four distinct serotypes, individuals may be seropositive for one serotype but seronegative for the other three serotypes. For example an individual may have a primary infection with DENV-1 (DENV-1 seropositive), and then upon secondary

infection with e.g. DENV-2, that individual becomes DENV-2 seropositive, still remaining DENV-1 seropositive. In order to fit serotype-specific PRNT data, we applied the multi-strain catalytic model developed by Ferguson *et al.* [104]. Different model variants (model D1 – D4) were assessed as described below, which explored different assumptions on serotype interactions.

Moreover, for comparison purposes, we fitted the same PRNT data to model A (constant force of infection model described in chapter 2), having defined individuals with PRNT titres below the detection limit for all four dengue serotypes as seronegative and individuals with at least one PRNT titre over the detection limit as seropositive. Since assays differed between surveys, here the detection limit also varied from study to study. The data were fitted to model A as described in chapter 2.

Model D1 (no interaction): No interaction between circulating serotypes

Here we assume complete serotype independence. We assumed absence of antibody-dependent enhancement (ADE), no cross-protection, no change in susceptibility and no change in transmissibility following primary infection.

Under these assumptions the proportion seronegative against all dengue serotypes, $x(a,t)$ is given by:

$$
\begin{aligned}
x(a,t) &= \exp\left[-\int_0^a \sum_j \lambda_j (a-\tau, t-\tau)\, d\tau\right] \\
&= \exp\left[-\int_0^a \sum_j \lambda_j \left[1+\delta \sin\left\{2\pi\left(\frac{t-\tau}{T}+\theta\right)\right\} d\tau\right]\right] \\
&= \exp\left[-\sum_j \left[\lambda_j a - \frac{\lambda_i \delta T}{2\pi}\left(-\cos\left\{2\pi\left[\frac{t-a}{T}+\theta\right]\right\}+\cos\left\{2\pi\left[\frac{t}{T}+\theta\right]\right\}\right)\right]\right].
\end{aligned}
$$

The proportion seropositive against strain i only is given by:

$$\begin{aligned} w_i(a,t) &= \left[\exp\left[-\int_0^a \sum_{j\neq i}\lambda_j(a-\tau,t-\tau)d\tau\right]\right]\left[1-\exp\left[-\int_0^a \lambda_i(a-\tau,t-\tau)d\tau\right]\right] \\ &= x(a,t)\left[\exp\left[\int_0^a \lambda_i\left[1+\delta\sin\left(2\pi\left\{\frac{t-\tau}{T}+\theta\right\}\right)\right]d\tau\right]-1\right] \\ &= x(a,t)\left[\exp\left[\left\{\lambda_i a-\frac{\lambda_i\delta T}{2\pi}\begin{pmatrix}-\cos\left[2\pi\left(\frac{t-a}{T}+\theta\right)\right]+\\ \cos\left[2\pi\left(\frac{t}{T}+\theta\right)\right]\end{pmatrix}\right\}\right]-1\right] \end{aligned} \quad (3.1)$$

where λ_i is the force of infection of strain i, T is the periodicity in years, δ is the amplitude, θ is the phase, t is the chronological time in years and a is the age in years.

Models D2-D4: Assuming interaction between serotypes

The following models assume interaction between serotypes mediated by cross-immunity. We define φ_{ij} to be susceptibility of an individual to infection with serotype *j* following infection with serotype i, relative to the susceptibility of an individual who has never been infected with dengue.

Ferguson *et al.* [104] showed that the proportion of the population at age a and time t, seropositive for strain i and seronegative for each other serotype j in circulation, $(j\neq i)$, $w_i(a,t)$, is given by:

$$w_i(a,t) = x(a,t)\int_0^a \lambda_i(a-\tau,t-\tau)\exp\left[-\int_0^\tau \sum_j(\varphi_{ij}-1)\lambda_j(a-\tau',t-\tau')d\tau'\right]d\tau \quad (3.2)$$

where we assume that the force of infection is given by:

$$\lambda_i(a-\tau,t-\tau) = \lambda_i\left[1+\delta\sin\left(2\pi\left(\frac{t-\tau}{T}+\theta\right)\right)\right]. \quad (3.3)$$

Substituting the definition of the force of infection given in equation (3.3) into equation (3.2) we obtain:

$$
\begin{aligned}
w_i(a,t) &= x(a,t)\int_0^a \lambda_i \left[1+\delta\sin\left(2\pi\left(\frac{t-\tau}{T}+\theta\right)\right)\right] \\
&\quad \exp\left[-\int_0^\tau \left\{\sum_{j\neq i}^{4}(\varphi_{ij}-1)\lambda_j\left[1+\delta\sin\left(2\pi\left(\frac{t-\tau'}{T}+\theta\right)\right)\right]\right\}d\tau'\right]d\tau \\
&= x(a,t)\int_0^a \lambda_j \left[1+\delta\sin\left(2\pi\left(\frac{t-\tau}{T}+\theta\right)\right)\right] \qquad (3.4) \\
&\quad \exp\left[-\left\{\sum_{j\neq i}^{4}(\varphi_{ij}-1)\lambda_j\left[\tau-\frac{\delta T}{2\pi}\begin{pmatrix}-\cos\left(2\pi\left(\frac{t-\tau}{T}+\theta\right)\right)\\ +\cos\left(2\pi\left(\frac{t}{T}+\theta\right)\right)\end{pmatrix}\right]\right\}d\tau\right],
\end{aligned}
$$

where λ_i is the force of infection of strain i, T is the periodicity in years, δ is the amplitude, θ is the phase, t is the chronological time in years and a is the age in years.

Finally, evaluating the integral between 0 and *a* gives:

$$
w_i(a,t) = \frac{x(a,t)\lambda_i}{\left(\sum_{j\neq i}^{4}(\varphi_{ij}-1)\lambda_j\right)}\left[1-\exp-\left\{\left(\sum_{j\neq i}^{4}(\varphi_{ij}-1)\lambda_j\right)\left(a+\frac{\delta T}{2\pi}\begin{pmatrix}\cos\left(2\pi\left(\frac{t-a}{T}+\theta\right)\right)\\ -\cos\left(2\pi\left(\frac{t}{T}+\theta\right)\right)\end{pmatrix}\right)\right\}\right]. \qquad (3.5)
$$

Here $x(a,t)$ is the proportion seronegative (completely unexposed to any strain of dengue), which is explicitly given by:

$$
\begin{aligned}
x(a,t) &= \exp\left[-\int_0^a \sum_j \lambda_j(a-\tau,t-\tau)d\tau\right] \\
&= \exp\left[-\sum_j\left[\lambda_j a-\frac{\lambda_j\delta T}{2\pi}\begin{pmatrix}-\cos\left\{2\pi\left(\frac{t-a}{T}+\theta\right)\right\}\\ +\cos\left\{2\pi\left(\frac{t}{T}+\theta\right)\right\}\end{pmatrix}\right]\right].
\end{aligned}
$$

Model D2 (equal interaction): We assume that susceptibility enhancement-inhibition φ_{ij} is identical for all strain combinations. We estimate 5 parameters: a force of infection for each serotype λ_i $(i=1,...,4)$ and one susceptibility parameter $\varphi=\varphi_{ij}$ for all $i,j=1,...,4$.

Model D3 (primary interaction): We assume that susceptibility enhancement-inhibition is dependent only on the primary infecting strain $(\varphi_{i.})$. We estimate 8 parameters: a force of infection for each serotype λ_i and a susceptibility enhancement-inhibition term for each primary infecting serotype $\varphi_{i.}$.

Model D4 (secondary interaction): We assume that susceptibility enhancement-inhibition is dependent only on the secondary infecting strain $(\varphi_{.j})$. We estimate 8 parameters: a force of infection for each serotype λ_i and a susceptibility enhancement-inhibition term for each secondary infecting serotype $\varphi_{.j}$.

Estimation Procedure

Given a seroprevalence survey of N individuals at time t_0, the N_k individuals in each age class k can be classified into: n_{xk} the number unexposed (seronegative against any strain, PRNT < cut off defined in the study), n_{ik} the number monotypically exposed against serotype i (PRNT for serotype i > cut off defined and PRNT < cut off defined in the study for the remaining serotypes), and $(N_k - n_{xk} - \sum_i n_{ik})$ multi-typically exposed (PRNT > cut off defined in the study for 2 or more serotypes). The multinomial log-likelihood is then given by:

$$L(\lambda_{ik}) = \sum_{k=1}^{m}\begin{bmatrix} n_{xk}\ln[x(a_k,t_0)]+\sum_i n_{ik}\ln[z_i(a_k,t_0)]+\left(N_k+n_{xk}+\sum_i n_{ik}\right) \\ \ln\left[1-x(a_k,t_0)-\sum_i z_i(a_k,t_0)\right] \end{bmatrix}, \quad (3.6)$$

where the proportion seropositive and seronegative in each age group was calculated by taking the average seroprevalence within each age group. For example, for age group 5-9

years, seroprevalence at each age 5, 6, 7 etc. would be computed and the mean value taken as the seroprevalence for that age group.

Models D1 – D4 were fitted to PRNT data using the MH-MCMC algorithm using the multinomial log-likelihood defined in equation (3.6). Since the available PRNT data are all cross-sectional seroprevalence surveys from a single year, we assume no seasonality and set $\delta = 0$. For the constant force of infection model (model A) fitted to the re-defined PRNT data a beta-binomial likelihood was defined as described previously (chapter 2). All models were fitted using the R Statistical Package (version 3.1.0) [159].

Deviance Information Criterion (DIC)

Goodness of fit of each model variant was assessed using the DIC calculated by:

$$DIC = \hat{D} + 2pD,$$

where $\hat{D}$ is the deviance at the posterior mean:

$$\hat{D} = -2\log\left[P\left(data \mid \bar{\theta}\right)\right].$$

pD is the effective number of parameters calculated as the difference between the deviance of the posterior mean $\left(\bar{D}\right)$ and the deviance at the posterior mean $\left(\hat{D}\right)$.

$$pD = \bar{D} - \hat{D},$$

where $\bar{D} = -2\log\left[P\left(data \mid \theta\right)\right]$.

3.2.3 Estimating the Basic Reproduction Number, R_0

For the PRNT data, since we were able to estimate serotype-specific forces of infection, we estimated strain-specific reproduction numbers (R_{0i}) as described by Ferguson *et al.* [104]. For the constant force of infection model (model A) fitted to PRNT data, methods are described in chapter 2. As in chapter 2, for each model we estimated R_{0i} under two different assumptions:

1. Tertiary and quaternary infections possible – here we can only analytically derive an expression for R_{0i} in the case that there are no cross-immunity mediated interactions between serotypes.
2. Individuals develop complete immunity to all dengue serotypes after secondary infection – in this case we can explore different assumptions about cross-immunity.

Assumption 1: Tertiary and quaternary infection possible.

When tertiary and quaternary infections are possible, we can only estimate R_{0i} assuming there are no cross-immunity mediated interactions between serotypes. Thus estimates cannot be derived for models D2-D4 (equal interaction, primary interaction, and secondary interaction models).

Following Ferguson et al. [104], the serotype–specific basic reproduction number under assumption 1 is given by:

$$R_{0i} = \frac{(d\lambda_i(t)/dt)/(\sigma\lambda_i(t))+1}{1-\int_0^\infty f(a')z_i(a',t)da'}, \tag{3.7}$$

where σ is the reciprocal of the infectious period (1/6 days) [126,127], $f(a)$ is the probability density function of the age distribution of the population and $z_i(a)$ is the proportion seropositive to serotype i at age a. Assuming temporal changes in the force of infection are relatively small ($d\lambda/dt << \sigma\lambda$), for model D1 equation (3.7) reduces to:

$$R_{0i} = \frac{1}{1-\int_0^\infty f(a')z_i(a')da'}.$$

The serotype-specific proportion of seropositive individuals of age a, $z_i(a)$, for model D1 (no interaction) is given by:

$$z_i(a) = 1-\exp[-\lambda_i a]. \tag{3.8}$$

Assumption 2: Complete immunity after secondary infection

If only primary and secondary infections can occur, we can relax the assumption of no cross-immunity between serotypes. Following Ferguson et al.[104], the serotype–specific basic reproduction number for the no interaction, equal interaction, primary interaction, and secondary interaction models (D1 – D4) is given by:

$$R_{0i} = \frac{(d\lambda_i(t)/dt)/\sigma\lambda_i(t)) + 1}{\int_0^\infty f(a')\left[x(a',t) + \sum_{j\neq i}\phi_{ji}\varphi_{ji}w_j(a',t)\right]da'}.$$

Here $x(a,t)$ is the proportion seronegative at age a and time t and ϕ_{ji} is the relative infectiousness of someone infected with serotype j following infection with serotype i (relative to a primary infection), and other terms are as defined previously. We set ϕ_{ji} = 1 since this parameter cannot be estimated from serological data alone. Assuming temporal changes in the force of infection are relatively small ($d\lambda/dt << \sigma\lambda$), this reduces to:

$$R_{0i} = \frac{1}{\int_0^\infty f(a')\left[x(a') + \sum_{j\neq i}\phi_{ji}\varphi_{ji}w_j(a')\right]da'}.$$

For model D1 (no interaction) we set $\varphi_{ji} = 1$, while for models D2 (equal interaction), D3 (primary interaction), and D4 (secondary interaction) we estimate the interaction parameters φ_{ji}. For models D1 and D2-D4 the proportion of population seropositive for strain j only are given in equation (3.5).

For all calculations, $f(a)$ or the probability density function of the age distribution of the population was calculated from demography data corresponding to each study year – either from the UN population estimates [128], or where available the national census data of the corresponding study region.

3.2.4 Multiple Linear Regression

A weighted regression analysis was used to explore the relationship between the λ values (estimated from the constant force of infection model (model A) fitted to the non-serotype specific seroprevalence data in chapter 2, and the λ values estimated from model A fit to the serotype-specific PRNT data re-categorised as IgG data) and a number of environmental and demographic covariates (equation (3.9)).

$$\lambda = \beta_0 + \beta_1 Lat_{abs} + \beta_2 T_{\max} + \beta_3 P + \beta_4 N + \beta_5 G + \beta_6 U \quad , \tag{3.9}$$

where λ is the force of infection, Lat_{abs} is the absolute latitude, $T_{\max}$ is the average maximum temperature, P is the population size of the study region, N is the total number of individuals sampled, G is the GDP per capita (USD), and U is whether the study was conducted in an rural or urban area (0=rural, 1=urban). Data on each covariate was extracted from the source publication, United Nations estimates [128], or World Bank estimates [160]. The model was weighted according to the variance of the λ estimates (weights = 1/variance of the posterior distribution). The model was fitted in the R Statistical Package (version 3.1.0) [159].

3.3 Results

3.3.1 Parameter Estimates

Of the 53 studies reporting age-specific seroprevalence identified in chapter 2, only nine studies used PRNTs. Excluding studies with fewer than 5 reported age groups from further analysis left a total of 7 studies from 5 countries, conducted mostly in the 1990s (4 of 7). Table 3.1 summarises the study and demographics of the datasets retained for analysis from the corresponding or closest year. Model A (constant force of infection) and models D1 – D4 (no interaction, equal interaction, primary interaction, and secondary interaction) were fitted to studies summarised in Table 3.1.

PRNT data are serotype-specific, allowing us to estimate the serotype-specific force of infection (λ_i) and basic reproduction number (R_{0i}) for each serotype individually (Figure 3.1). Estimates varied widely between different surveys, again highlighting the heterogeneity of dengue transmission. Within the same survey, serotype-specific differences in transmission intensity were apparent, demonstrating how a certain serotype may be more dominant at any one time point. For example, for model D2 (equal interaction), force of infection estimates for Haiti were 0.046 (95% CrI: 0.010 – 0.179) for DENV-1 but 0.219 (95% CrI: 0.088 – 0.445) for DENV-4.

Table 3.1: Summary of PRNT surveys identified and associated demographics.

Country	Author	Year	Region	Age Range (years)	N	Serotypes^	Population size of study region (thousands)	Rural/Urban	% Aged <15 yrs	Models used
Cuba	Guzman *et al.*[161]	1983	Cerro	0 – 45	1295	2	125.5	Urban	26	A, D1 – D4
	Guzman *et al.*[162]	1997/98	Santiago	0 - 95	1151	2	475.6	Urban	17.3	A, D1 – D4
Haiti	Halstead *et al.*[29]	1996/99	Port au Prince	6 – 14	210	4	2000	Urban	43	A, D1 – D4
Indonesia	Graham *et al.*[163]	1995	Yogyakarta	4 – 10	1837	4	421	Urban	34	A, D1 – D4
Peru	Morrison *et al.*[158]	1999	Iquitos	5 – 60+	2524	2	350	Urban	34	A, D1 – D4
Thailand	Sangkawibha *et al.*[164]	1980	Rayong	0 - 10	1009	4	53	Suburban	39.4	A, D1 – D4
Thailand	Rodriguez-Barraquer *et al.*[165]	2010	Rayong	6 - 19	1647	4	230	Urban	19.3	A, D1 – D4

^Number of serotypes known to have been in circulation.

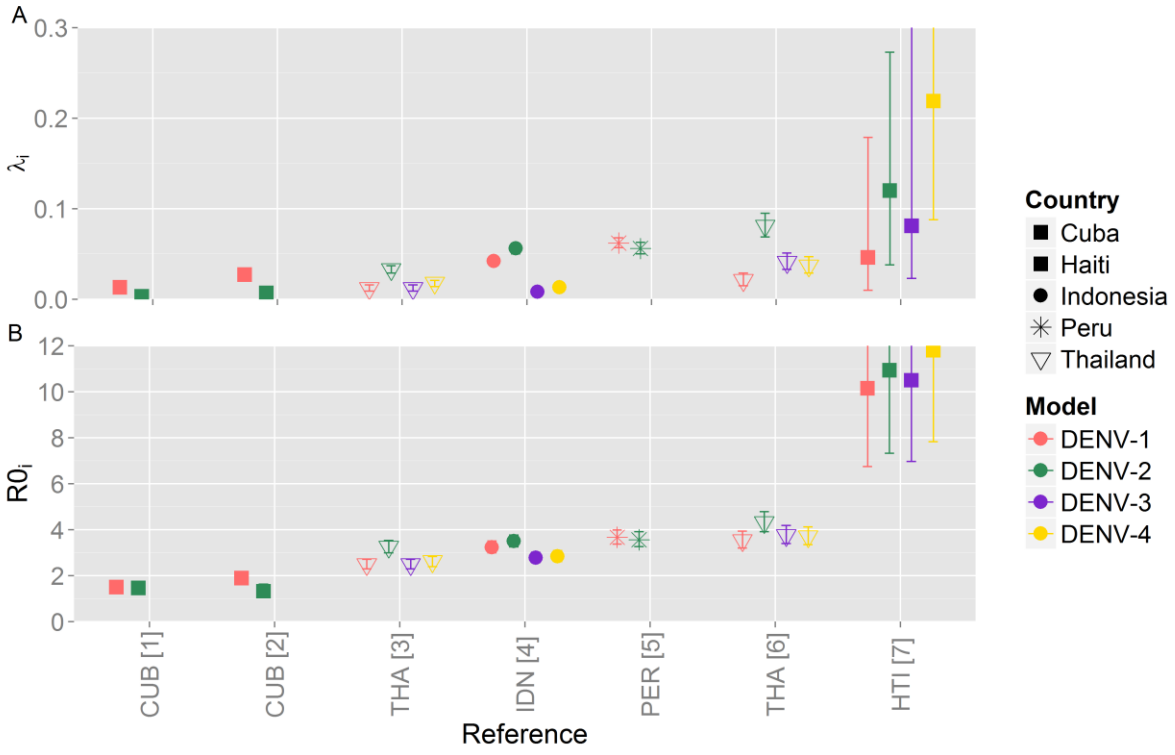

Figure 3.1: Serotype-specific estimates of A) force of infection, λ_i, and B) R_{0i} estimates derived from model D2 (equal interaction) fitted to the PRNT datasets. Posterior median and 95% CrI shown. See end of chapter for references and ISO country codes.

Comparison of cross-protection or enhancement parameters under different assumptions allowed us to estimate the probable serotype causing primary and secondary infections. However, due to the wide credible interval of the estimated parameter, it was difficult to definitively determine the sequence of infections (Table 3.2 - Table 3.5).

For all datasets, the model fit improved when we assumed some level of inter-serotype interaction, demonstrating that inter-serotype interactions play an important role in dengue dynamics. Figure 3.2 – Figure 3.5 show the model fits for each model variant and Table 3.6 compares the DIC for each model variant.

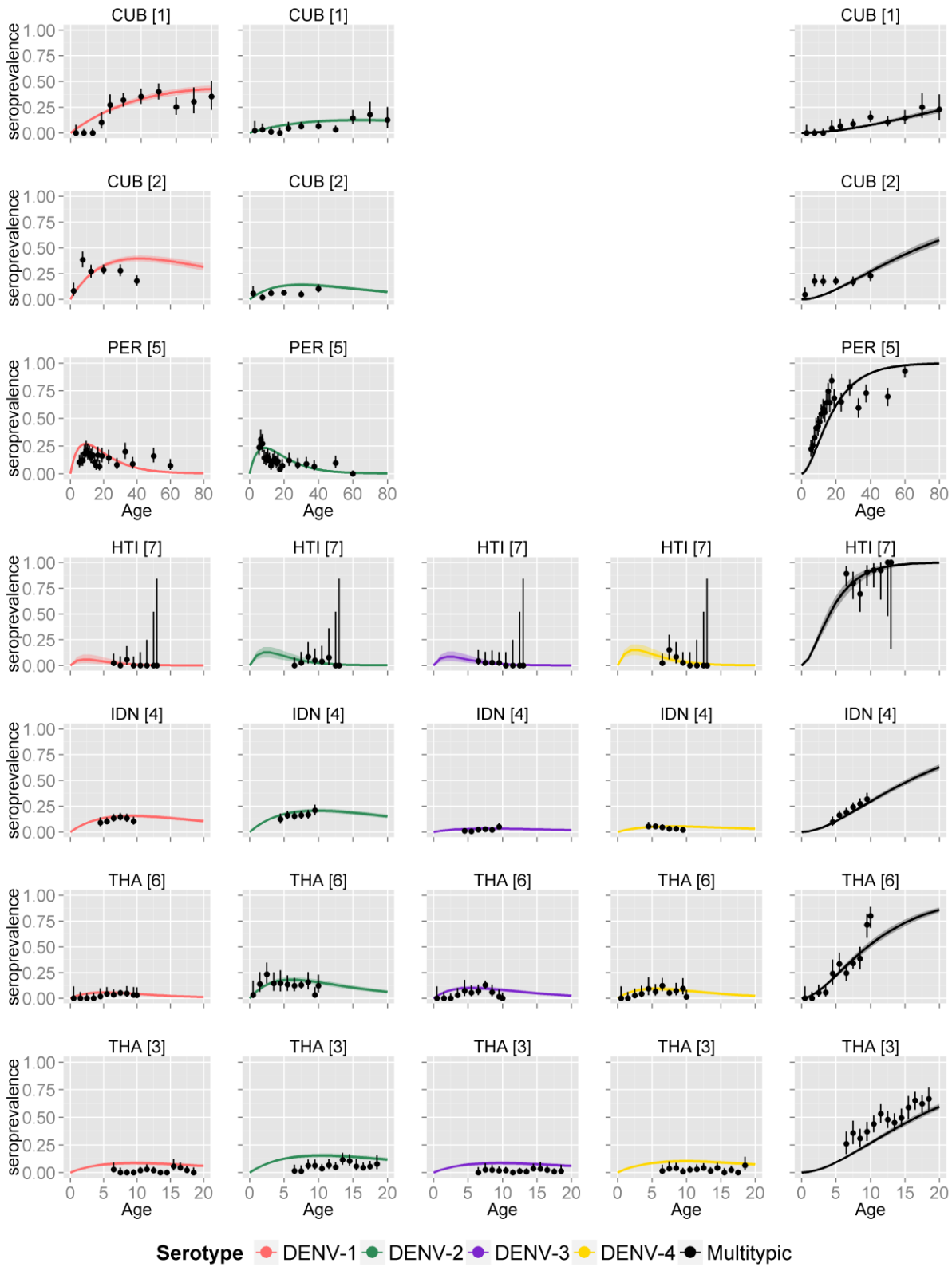

Figure 3.2: Model fits from the multi-serotype no interaction model (D1) fit to PRNT data (points). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown. *Multitypic (right-most column) defined as multi-typically infected with more than one serotype. PRNT > cut-off point for ≥2 serotypes. [Ref] refers to ISO/reference list at end of chapter.

Table 3.2: Summary estimates of the strain-specific forces of infection (λ) and reproduction numbers (R_{0i}) obtained from model D1 fitted to PRNT surveys assuming no inter-serotype interaction. *Assumption 1: individuals can have up to 4 infections, 2: individuals develop immunity after 2 infections.

	Country	**Cuba**		**Haiti**	**Indonesia**	**Peru**	**Thailand**	
	Author	Guzman *et al.*[161]	Guzman *et al.*[162]	Halstead *et al.*[29]	Graham *et al.*[163]	Morrison *et al.*[158]	Sangkawibha *et al.*[164]	Rodriguez-Barraquer *et al.*[165]
λ_i	**DENV-1**	0.027 (0.025 – 0.030)	0.013 (0.012 – 0.014)	0.074 (0.030 – 0.129)	0.046 (0.042 – 0.051)	0.081 (0.077 – 0.085)	0.030 (0.023 – 0.038)	0.024 (0.020 – 0.029)
	DENV-2	0.013 (0.012 – 0.014)	0.005 (0.004 – 0.006)	0.146 (0.094 – 0.204)	0.058 (0.053 – 0.063)	0.073 (0.069 – 0.077)	0.082 (0.072 – 0.093)	0.041 (0.036 – 0.045)
	DENV-3	NA	NA	0.103 (0.055 – 0.159)	0.011 (0.008 – 0.014)	NA	0.051 (0.042 – 0.060)	0.024 (0.020 – 0.029)
	DENV-4	NA	NA	0.167 (0.115 – 0.225)	0.018 (0.015 – 0.022)	NA	0.047 (0.038 – 0.056)	0.029 (0.024 – 0.033)
$\sum_i \lambda_i$		0.040 (0.038 – 0.043)	0.018 (0.017 – 0.020)	0.494 (0.434 – 0.561)	0.134 (0.127 – 0.141)	0.154 (0.148 – 0.160)	0.209 (0.196 – 0.224)	0.118 (0.112 – 0.124)
R_{0i} **Assumption 1**	**DENV-1**	1.93 (1.84 – 2.02)	1.41 (1.37 – 1.2.02)	2.97 (1.74 – 4.53)	2.46 (2.30 – 2.63)	3.70 (3.54 – 3.86)	1.79 (1.58 – 2.03)	2.10 (1.87 – 2.36)
	DENV-2	1.41 (1.36 – 1.46)	1.16 (1.13 – 1.16)	4.99 (3.55 – 6.73)	2.88 (2.70 – 3.08)	3.41 (3.27 – 3.55)	3.36 (3.05 – 3.70)	3.06 (2.79 – 3.36)
	DENV-3	NA	NA	3.77 (2.48 – 5.31)	1.31 (1.23 – 1.40)	NA	2.40 (2.15 – 2.68)	2.10 (1.87 – 2.35)
	DENV-4	NA	NA	5.59 (4.10 – 7.33)	1.52 (1.42 – 1.63)	NA	2.28 (2.04 – 2.56)	2.34 (2.10 – 2.60)
R_{0i} **Assumption 2**	**DENV-1**	1.93 (1.84 – 2.02)	1.41 (1.37 – 1.2.02)	6.91 (6.05 – 7.98)	3.11 (2.96 – 3.28)	3.70 (3.54 – 3.86)	3.56 (3.35 – 3.79)	4.05 (3.82 – 4.31)
	DENV-2	1.41 (1.36 – 1.46)	1.16 (1.13 – 1.16)	7.80 (6.70 – 9.15)	3.45 (3.28 – 3.64)	3.41 (3.27 – 3.55)	4.42 (4.13 – 4.74)	4.64 (4.37 – 4.94)
	DENV-3	NA	NA	7.20 (6.26 – 8.35)	2.59 (2.48 – 2.71)	NA	3.80 (3.56 – 4.07)	4.05 (3.82 – 4.30)
	DENV-4	NA	NA	8.19 (7.01 – 9.64)	2.66 (2.54 – 2.79)	NA	3.75 (3.52 – 4.01)	4.17 (3.93 – 4.43)
	LnL	-1631.9	-1091.3	-137.3	-2632.8	-2898.5	-1320.7	-1785.2

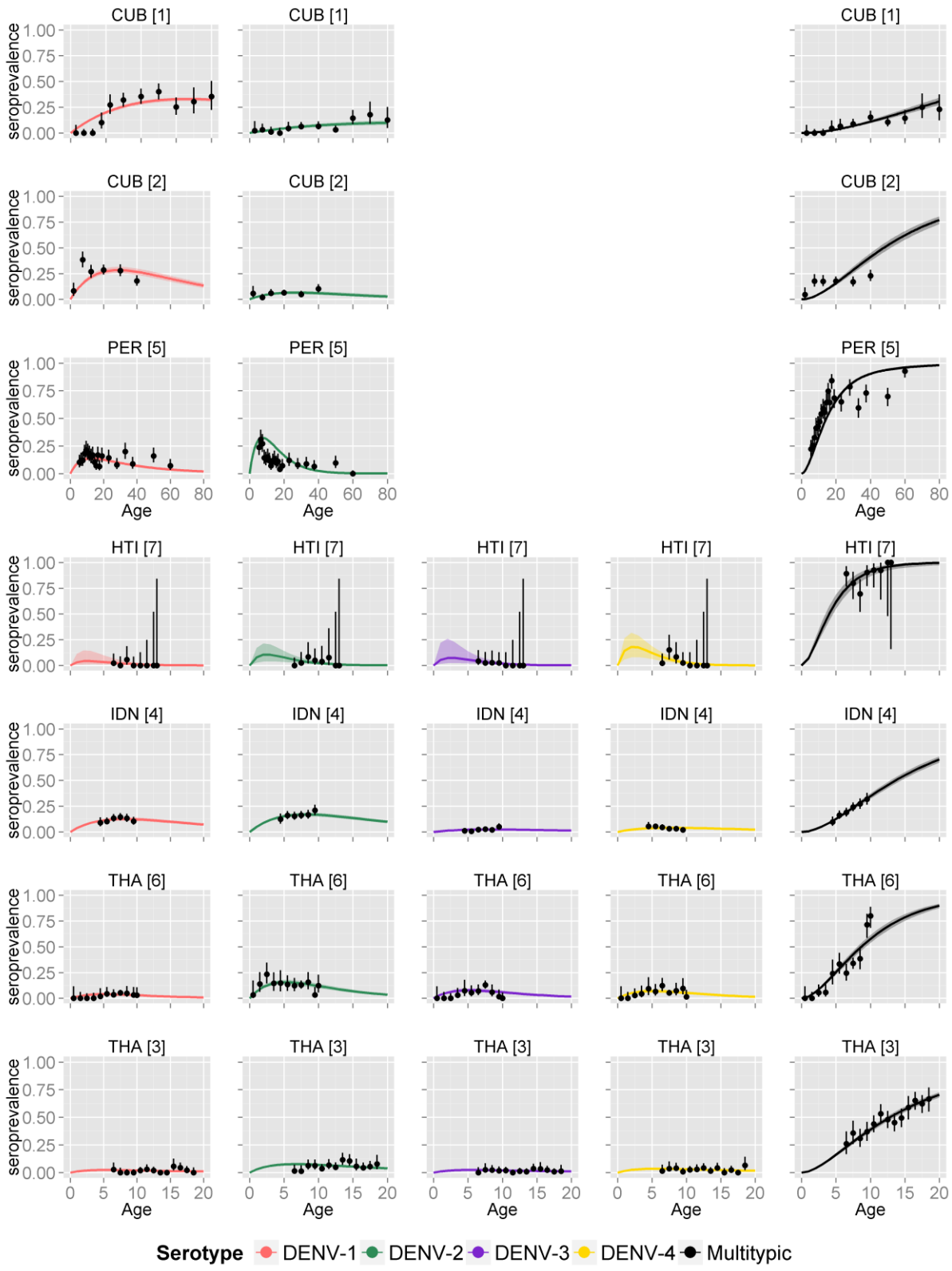

Figure 3.3: Model fits from the multi-serotype equal interaction model (D2) fit to PRNT data (points). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown. *Multitypic (right-most column) defined as multi-typically infected with more than one serotype. PRNT > cut-off point for ≥2 serotypes. [Ref] refers to ISO/reference list at end of chapter.

Table 3.3: Summary estimates of the force of infection (λ) and serotype-specific reproduction number (R_{0i}) assuming inter-serotype interactions are equal for all serotype combinations. Model D2 (equal interaction) fitted to PRNT data.

	Country	**Cuba**		**Haiti**	**Indonesia**	**Peru**	**Thailand**	
	Author	Guzman *et al.*[161]	Guzman *et al.*[162]	Halstead *et al.*[29]	Graham *et al.*[163]	Morrison *et al.*[158]	Sangkawibha *et al.*[164]	Rodriguez-Barraquer *et al.*[165]
λ_i	**DENV-1**	0.027 (0.024 – 0.030)	0.013 (0.012 – 0.015)	0.046 (0.010 – 0.179)	0.042 (0.037 – 0.047)	0.062 (0.057 – 0.068)	0.021 (0.015 – 0.029)	0.012 (0.012 – 0.016)
	DENV-2	0.007 (0.005 – 0.008)	0.003 (0.002 – 0.004)	0.120 (0.038 – 0.176)	0.056 (0.050 – 0.062)	0.056 (0.050 – 0.063)	0.081 (0.069 – 0.095)	0.033 (0.029 – 0.037)
	DENV-3	NA	NA	0.081 (0.023 – 0.373)	0.008 (0.006 – 0.010)	NA	0.041 (0.033 – 0.051)	0.012 (0.009 – 0.016)
	DENV-4	NA	NA	0.219 (0.088 – 0.445)	0.013 (0.011 – 0.017)	NA	0.037 (0.029 – 0.047)	0.018 (0.014 – 0.021)
$\sum_i \lambda_i$		0.033 (0.031 – 0.036)	0.016 (0.015 – 0.018)	0.518 (0.403 – 0.681)	0.119 (0.112 – 0.127)	0.118 (0.112 – 0.125)	0.182 (0.167 – 0.198)	0.075 (0.070 – 0.080)
φ*		1.350 (0.691 – 2.024)	0.128 (0.005 – 0.519)	0.475 (0.107 – 0.994)	1.100 (0.898 – 1.330)	0.898 (0.697 – 1.120)	1.199 (0.935 – 1.493)	5.561 (4.728 – 6.530)
R_{0i}	**DENV-1**	1.89 (1.75 – 2.07)	1.50 (1.43 – 1.56)	10.15 (6.75 – 28.65)	3.23 (2.99 – 3.51)	3.67 (3.38 – 3.99)	3.54 (3.21 – 3.94)	2.49 (2.29 – 2.71)
	DENV-2	1.32 (1.13 – 1.63)	1.46 (1.30 – 1.54)	10.94 (7.33 – 19.03)	3.50 (3.25 – 3.77)	3.56 (3.26 – 3.92)	4.32 (3.92 – 4.79)	3.25 (3.00 – 3.53)
	DENV-3	NA	NA	10.50 (6.97 – 19.55)	2.77 (2.56 – 3.02)	NA	3.76 (3.40 – 4.18)	2.49 (2.29 – 2.71)
	DENV-4	NA	NA	11.81 (7.83 – 19.57)	2.84 (2.62 – 3.09)	NA	3.71 (3.35 – 4.13)	2.62 (2.40 – 2.84)
	LnL	-1631.9	-1091.3	-137.3	-2632.8	-2885.9	-1320.7	-1785.2

*φ is the interaction parameter describing susceptibility enhancement-inhibition estimated using model D2.

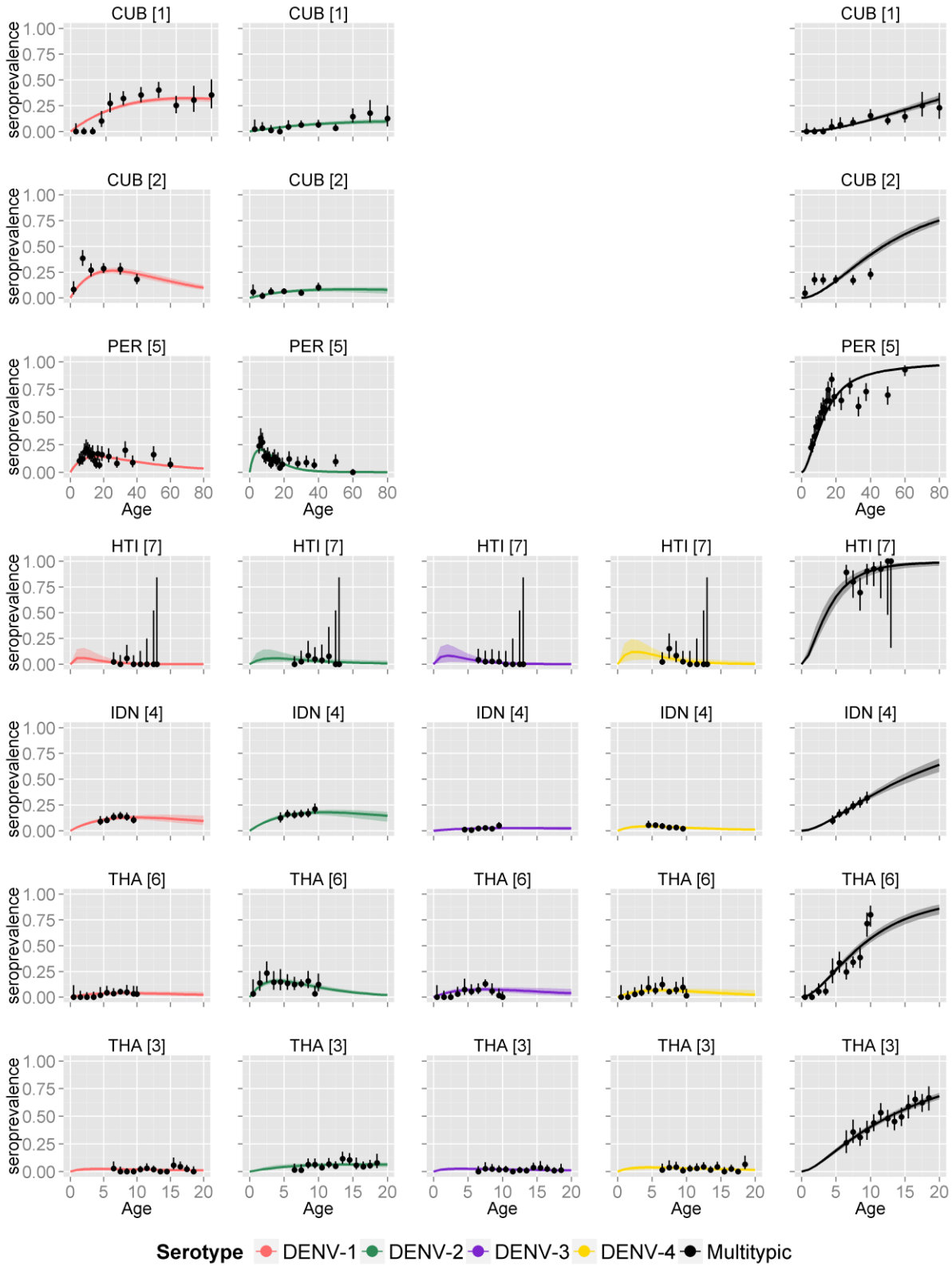

Figure 3.4: Model fits from the multi-serotype primary interaction model (D3) fit to PRNT data (points). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown. *Multitypic (right-most column) defined as multi-typically infected with more than one serotype. PRNT > cut-off point for ≥2 serotypes. [Ref] refers to ISO/reference list at end of chapter.

Table 3.4: Summary estimates of the force of infection (λ) and serotype-specific reproduction number (R_{0i}) assuming inter-serotype interactions are dependent only on the primary infecting serotype. Model D3 (primary interaction) fitted to PRNT data.

		Cuba		**Haiti**	**Indonesia**	**Peru**	**Thailand**	
	Author	Guzman *et al.*[161]	Guzman *et al.*[162]	Halstead *et al.*[29]	Graham *et al.*[163]	Morrison *et al.*[158]	Sangkawibha *et al.*[164]	Rodriguez-Barraquer *et al.*[165]
λ_i	**DENV-1**	0.028 (0.026 – 0.031)	0.013 (0.012 - 0.015)	0.116 (0.013 – 0.312)	0.036 (0.027 – 0.048)	0.026 (0.022 – 0.030)	0.014 (0.008 – 0.026)	0.018 (0.002 – 0.034)
	DENV-2	0.004 (0.003 – 0.006)	0.003 (0.002 – 0.004)	0.045 (0.014 – 0.182)	0.046 (0.038 – 0.060)	0.091 (0.086 – 0.097)	0.106 (0.082 – 0.126)	0.011 (0.007 – 0.024)
	DENV-3	NA	NA	0.115 (0.017 – 0.309)	0.006 (0.004 – 0.014)	NA	0.028 (0.019 – 0.046)	0.021 (0.004 – 0.035)
	DENV-4	NA	NA	0.126 (0.032 – 0.317)	0.029 (0.016 – 0.041)	NA	0.030 (0.018 – 0.049)	0.026 (0.006 – 0.041)
$\sum_i \lambda_i$		0.033 (0.030 – 0.036)	0.016 (0.015 – 0.017)	0.452 (0.358 – 0.579)	0.119 (0.111 – 0.126)	0.117 (0.111 – 0.123)	0.180 (0.165 – 0.196)	0.075 (0.070 – 0.080)
φ	$\varphi_{1.}$	4.188 (2.167 – 6.716)	0.361 (0.018 – 1.414)	1.785 (0.244 – 12.465)	0.596 (0.038 – 1.670)	0.011 (0.000 – 0.053)	0.397 (0.018 – 1.641)	9.434 (0.202 – 19.264)
	$\varphi_{2.}$	0.126 (0.005 – 0.736)	0.143 (0.005 – 0.719)	0.237 (0.013 – 1.065)	0.333 (0.013 – 1.345)	4.904 (3.736 – 6.291)	2.781 (1.492 – 4.612)	0.653 (0.031 – 3.294)
	$\varphi_{3.}$	NA	NA	1.095 (0.150 – 5.693)	0.464 (0.018 – 2.789)	NA	0.473 (0.029 – 1.526)	11.475 (1.227 – 19.503)
	$\varphi_{4.}$	NA	NA	0.510 (0.052 – 2.011)	4.277 (1.804 – 7.217)	NA	0.759 (0.080 – 1.978)	9.644 (1.374 – 19.101)
R_{0i}	**DENV-1**	1.41 (1.17 – 1.72)	1.47 (1.35 – 1.47)	5.08 (1.13 – 12.07)	3.71 (2.30 – 5.12)	5.02 (4.78 – 5.26)	5.03 (2.77 – 6.63)	1.46 (1.06 – 5.20)
	DENV-2	2.02 (1.61 – 2.19)	1.45 (1.23 – 1.54)	11.94 (7.10 – 17.58)	4.43 (2.88 – 5.25)	1.43 (1.20 – 1.72)	2.48 (1.49 – 3.79)	5.03 (3.74 – 5.62)
	DENV-3	NA	NA	7.17 (2.47 – 13.78)	3.59 (1.34 – 5.17)	NA	4.99 (3.13 – 6.59)	1.24 (1.04 – 4.02)
	DENV-4	NA	NA	10.52 (5.90 – 16.49)	1.55 (1.00 – 2.08)	NA	4.25 (2.57 – 6.29)	1.45 (1.08 – 4.05)
	LnL	-1625.4	1091.8	-136.7	-2629.1	-2804.8	-1316.3	-1779

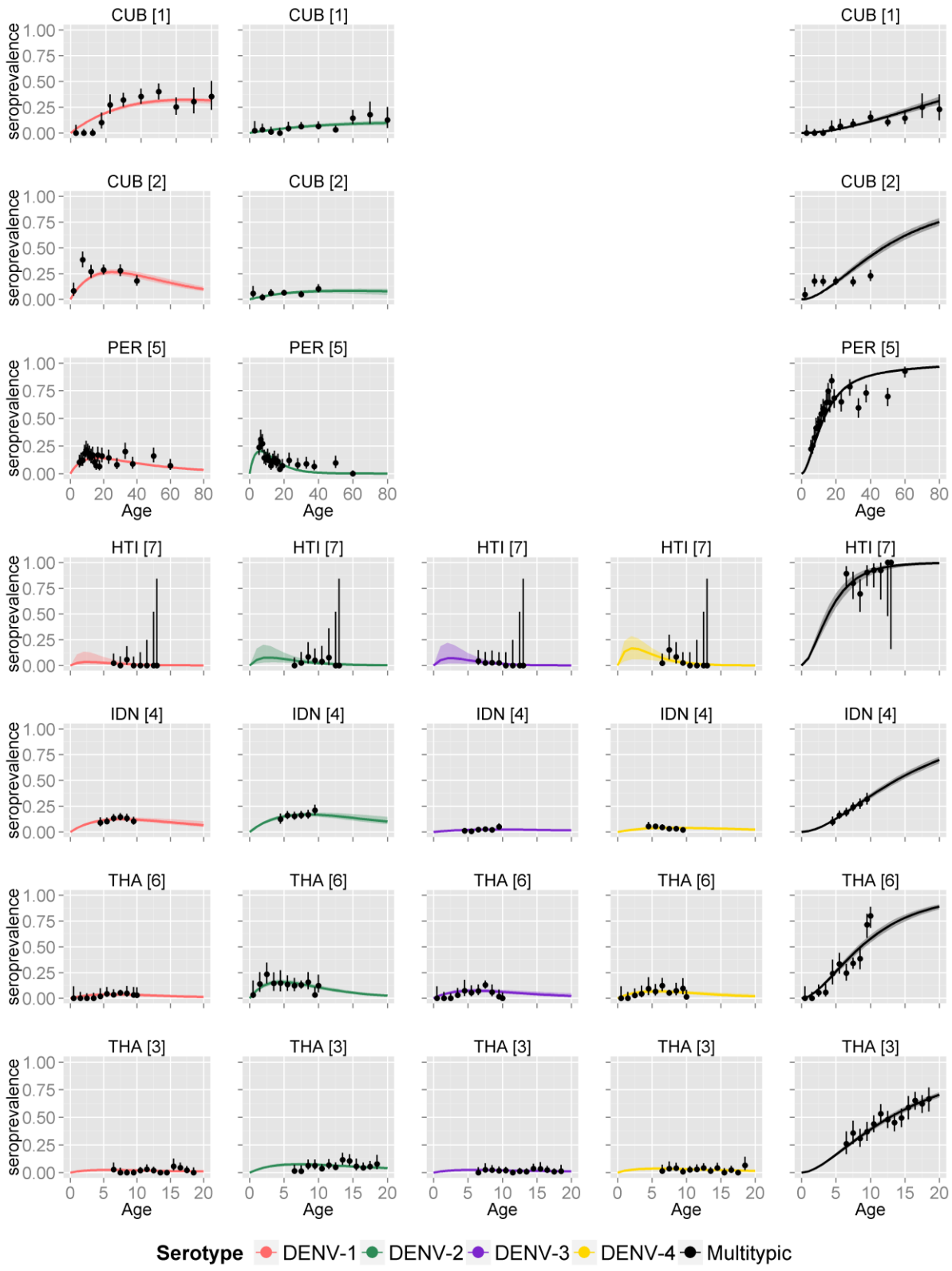

Figure 3.5: Model fits from the multi-serotype secondary interaction model (D4) fit to PRNT data (points). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown. Multitypic (right-most column) defined as multi-typically infected with more than one serotype. PRNT > cut-off point for ≥2 serotypes. [Ref] refers to ISO/reference list at end of chapter.

Table 3.5: Summary estimates of the force of infection (λ) and serotype-specific reproduction number (R_{0i}) assuming inter-serotype interactions are dependent only on the secondary infecting serotype. Model D4 (secondary interaction) fitted to PRNT data.

	Country	**Cuba**		**Haiti**	**Indonesia**	**Peru**	**Thailand**	
	Author	Guzman *et al.*[161]	Guzman *et al.*[162]	Halstead *et al.*[29]	Graham *et al.*[163]	Morrison *et al.*[158]	Sangkawibha *et al.*[164]	Rodriguez-Barraquer *et al.*[165]
λ_i	**DENV-1**	0.028 (0.026 – 0.031)	0.013 (0.012 – 0.015)	0.035 (0.008 – 0.174)	0.044 (0.033 – 0.053)	0.026 (0.022 – 0.030)	0.017 (0.011 – 0.026)	0.013 (0.009 – 0.018)
	DENV-2	0.004 (0.003 – 0.006)	0.003 (0.002 – 0.004)	0.076 (0.023 – 0.267)	0.055 (0.044 – 0.067)	0.092 (0.086 – 0.097)	0.096 (0.078 – 0.113)	0.029 (0.024 – 0.039)
	DENV-3	NA	NA	0.077 (0.016 – 0.313)	0.007 (0.005 – 0.010)	NA	0.035 (0.023 – 0.048)	0.013 (0.009 – 0.019)
	DENV-4	NA	NA	0.208 (0.056 – 0.401)	0.013 (0.010 – 0.017)	NA	0.033 (0.022 – 0.046)	0.019 (0.014 – 0.027)
$\sum_i \lambda_i$		0.033 (0.030 – 0.036)	0.016 (0.015 – 0.017)	0.456 (0.363 – 0.575)	0.119 (0.111 – 0.126)	0.117 (0.111 – 0.124)	0.180 (0.165 – 0.196)	0.075 (0.071 – 0.080)
φ	$\varphi_{\cdot 1}$	0.125 (0.005 – 0.699)	0.142 (0.005 – 0.705)	1.061 (0.026 – 8.135)	0.558 (0.021 – 2.443)	4.909 (3.735 – 6.313)	3.030 (0.138 – 8.914)	5.287 (0.343 – 9.690)
	$\varphi_{\cdot 2}$	4.158 (2.173 – 6.727)	0.359 (0.016 – 1.444)	1.322 (0.056 – 8.146)	1.061 (0.066 – 2.882)	0.011 (0.000 – 0.052)	0.187 (0.008 – 0.965)	7.975 (3.015 – 9.929)
	$\varphi_{\cdot 3}$	NA	NA	0.479 (0.013 – 5.901)	2.774 (0.106 – 9.050)	NA	1.793 (0.100 – 5.862)	4.838 (0.319 – 9.715)
	$\varphi_{\cdot 4}$	NA	NA	0.372 (0.014 – 3.571)	0.912 (0.038 – 4.090)	NA	1.260 (0.054 – 5.463)	4.408 (0.321 – 9.570)
R_{0i}	**DENV-1**	1.41 (1.17 – 1.71)	1.47 (1.35 – 1.54)	7.44 (4.46 – 12.44)	2.82 (2.00 – 4.08)	5.03 (4.80 – 5.27)	3.65 (2.38 – 5.22)	2.27 (1.95 – 2.78)
	DENV-2	2.02 (1.63 – 2.19)	1.45 (1.24 – 1.53)	9.04 (5.42 – 14.24)	3.39 (2.39 – 4.63)	1.43 (1.20 – 1.73)	3.10 (2.32 – 3.95)	3.46 (2.84 – 3.93)
	DENV-3	NA	NA	8.01 (3.86 – 13.77)	1.99 (1.07 – 3.47)	NA	3.27 (2.08 – 5.12)	2.56 (1.98 – 3.41)
	DENV-4	NA	NA	7.86 (4.56 – 13.27)	2.69 (1.98 – 3.50)	NA	3.42 (2.43 – 5.17)	2.33 (1.97 – 2.98)
	LnL	-1625.4	-1091.8	-137.1	-2632.7	-2804.8	-1317.6	-1784.6

Table 3.6: DIC comparison of different model variants (A, D1-D4) for serotype-specific PRNT datasets.

Author/Country/Ref	**Model Variant DIC**			
	D1 **No interaction**	**D2** **Equal interaction**	**D3** **Primary interaction**	**D4** **Secondary interaction**
Guzman/Cuba/[161]	3300	3300	3279	3283
Guzman/Cuba/[162]	2223	2223	2221	2220
Halstead/Haiti/[29]	278	278	277	275
Graham/Indonesia/[163]	5300	5300	5294	5298
Morrison/Peru/[158]	5819	5819	5632	5633
Sangkawibha/Thailand/[164]	2657	2657	2648	2649
Rodriguez-Barraquer/Thailand/[165]	3602	3602	3582	3597

Interestingly, the serotype-specific estimates of the reproduction number did not scale linearly with the estimated values of the force of infection, although the relative order is maintained i.e. if $\lambda_3 < \lambda_4$ then $R_{03} < R_{04}$. If one serotype dominates, as was the case in Haiti, changes in the force of infection of the other non-dominant serotypes marginally affect the estimates of the reproduction number of the non-dominating serotypes.

In order to compare the estimates of dengue force of infection derived from IgG and PRNT assays, we also analysed the PRNT data ignoring strain-specificity (*i.e.* treating PRNT data as if it were IgG data), by categorising individuals as 'seronegative' if their PRNT titers were negative for all serotypes, or seropositive if they tested positive for at least one serotype. We used the same thresholds for seronegativity used by each source study. The resulting force of infection estimates generated using model A were consistent with the sum of the individual serotype-specific λ estimates obtained from the full PRNT datasets (Table 3.7 summarises the parameter estimates and Figure 3.7 show the model fits). This consistency was highest when some level of inter-serotype interaction (cross-protection or enhancement) was allowed for (Figure 3.6).

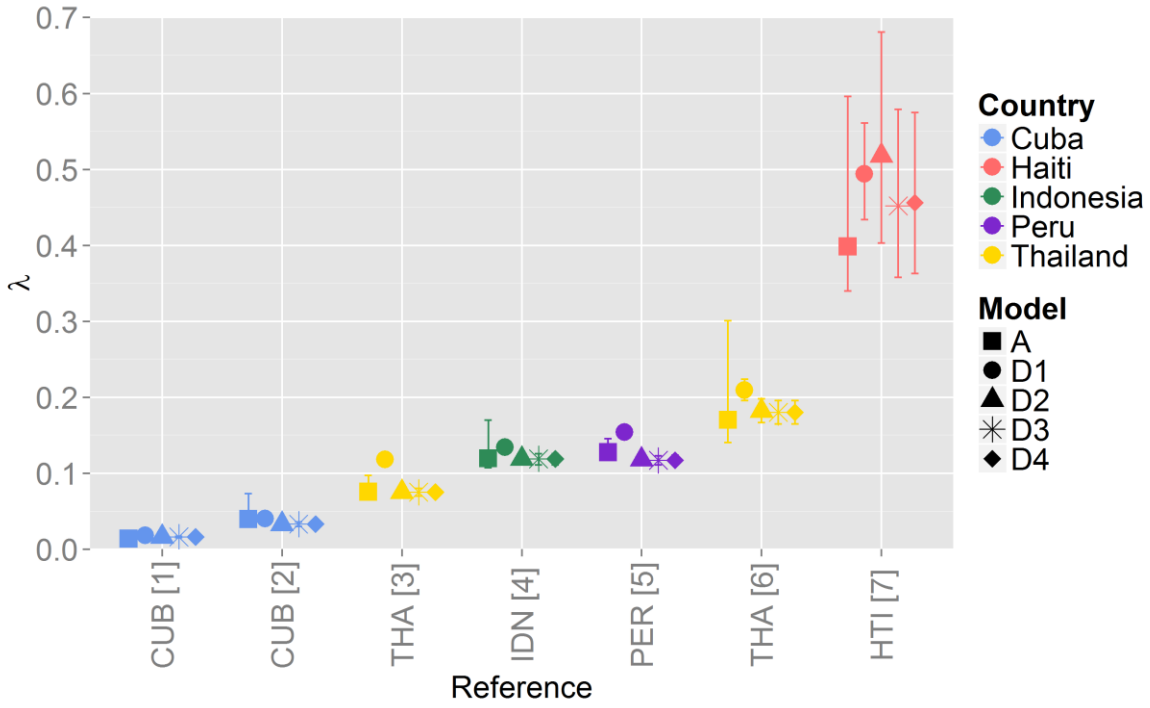

Figure 3.6: Total force of infection (λ) estimates (for all 4 serotypes) derived from models A (constant force of infection), D1-D4 (no interaction, equal interaction, primary interaction, and secondary interaction models) fitted to PRNT datasets (treating PRNT data as IgG data). Models D2 – D4 allow for cross-protection between serotypes. Posterior median and 95% CrI shown.

Table 3.7: Summary estimates where the constant force of infection model (A) was fitted to PRNT data re-categorised into 'seronegative' (PRNT < cut-off for all serotypes) or 'seropositive' (PRNT > cut-off for at least one serotype).

				R_{0i} (95% CrI)		
Country	**Author**	λ **(95% CrI)**	ψ **(95% CrI)**	**Assumption 1**	**Assumption 2**	**LnL**
Cuba	Guzman *et al.*[161]	0.040 (0.032 – 0.073)	0.184 (0.136-0.424)	1.52 (1.40 – 2.14)	1.52 (1.40 – 2.14)	-893
	Guzman *et al.*[162]	0.014 (0.012 – 0.021)	0.176 (0.137-0.337)	1.14 (1.12 – 1.23)	1.14 (1.12 – 1.23)	-652
Haiti	Halstead *et al.*[29]	0.398 (0.340 – 0.596)	0.062 (0.023-0.520)	3.67 (3.26 – 5.08)	6.32 (5.49 – 9.16)	-22
Indonesia	Graham *et al.*[163]	0.120 (0.107 – 0.170)	0.074 (0.047-0.272)	1.89 (1.79 – 2.32)	2.81 (2.59 – 3.77)	-1234
Peru	Morrison *et al.*[158]	0.128 (0.121 – 0.146)	0.037 (0.028-0.087)	2.94 (2.82 – 3.28)	2.94 (2.82 – 3.28)	-10254
Thailand	Sangkawibha *et al.*[164]	0.170 (0.141 – 0.301)	0.334 (0.280-0.529)	2.15 (1.94 – 3.15)	3.33 (2.86 – 5.45)	-581
	Rodriguez-Barraquer *et al.*[165]	0.076 (0.069 – 0.097)	0.097 (0.073-0.216)	1.81 (1.73 – 2.09)	2.77 (2.56 – 3.50)	-1071

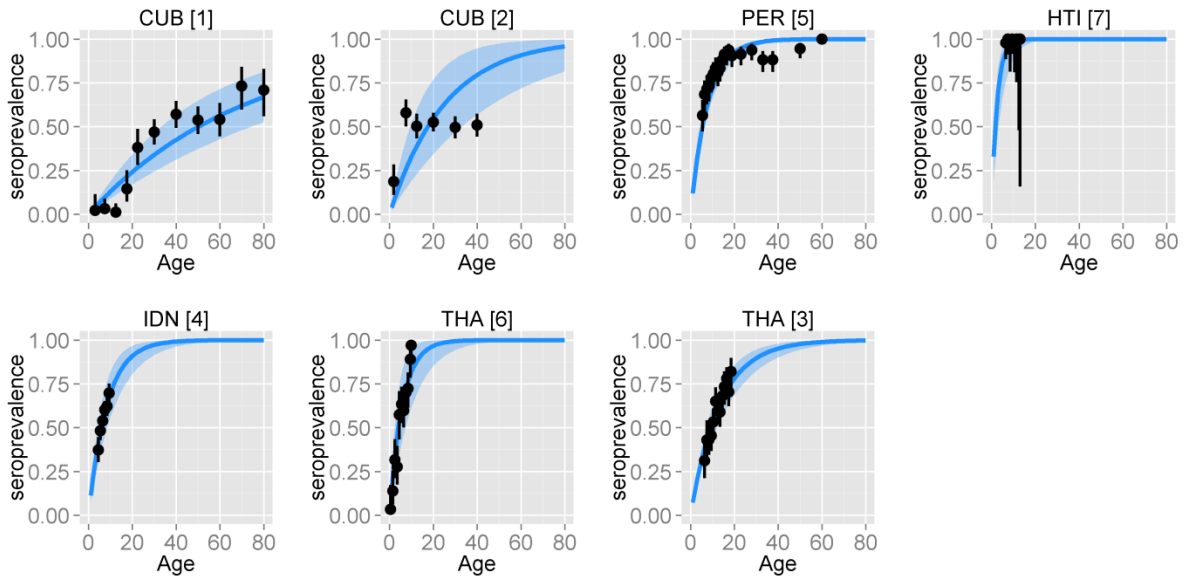

Figure 3.7: Model A (constant force of infection) fit to PRNT data (points), having re-categorised them as 'seropositive' (PRNT > cut-off for at least one serotype) and 'seronegative' (PRNT < cut-off for all serotypes). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown.

3.3.2 Regression Analysis

Multiple regression analysis was conducted to explore the relationship between estimated dengue transmission intensity and the covariates summarised in Figure 3.8. Table 3.8 summarises the analysis results. The multiple regression with all 6 predictors produced R^2=0.37. The only predictor with strong evidence for an association with λ was whether the study was conducted in an urban or rural setting, indicating that urban environments are associated with a higher force of infection. The distance from the equator (absolute latitude) and GDP per capita had weak evidence for a negative association with transmission intensity (Table 3.8).

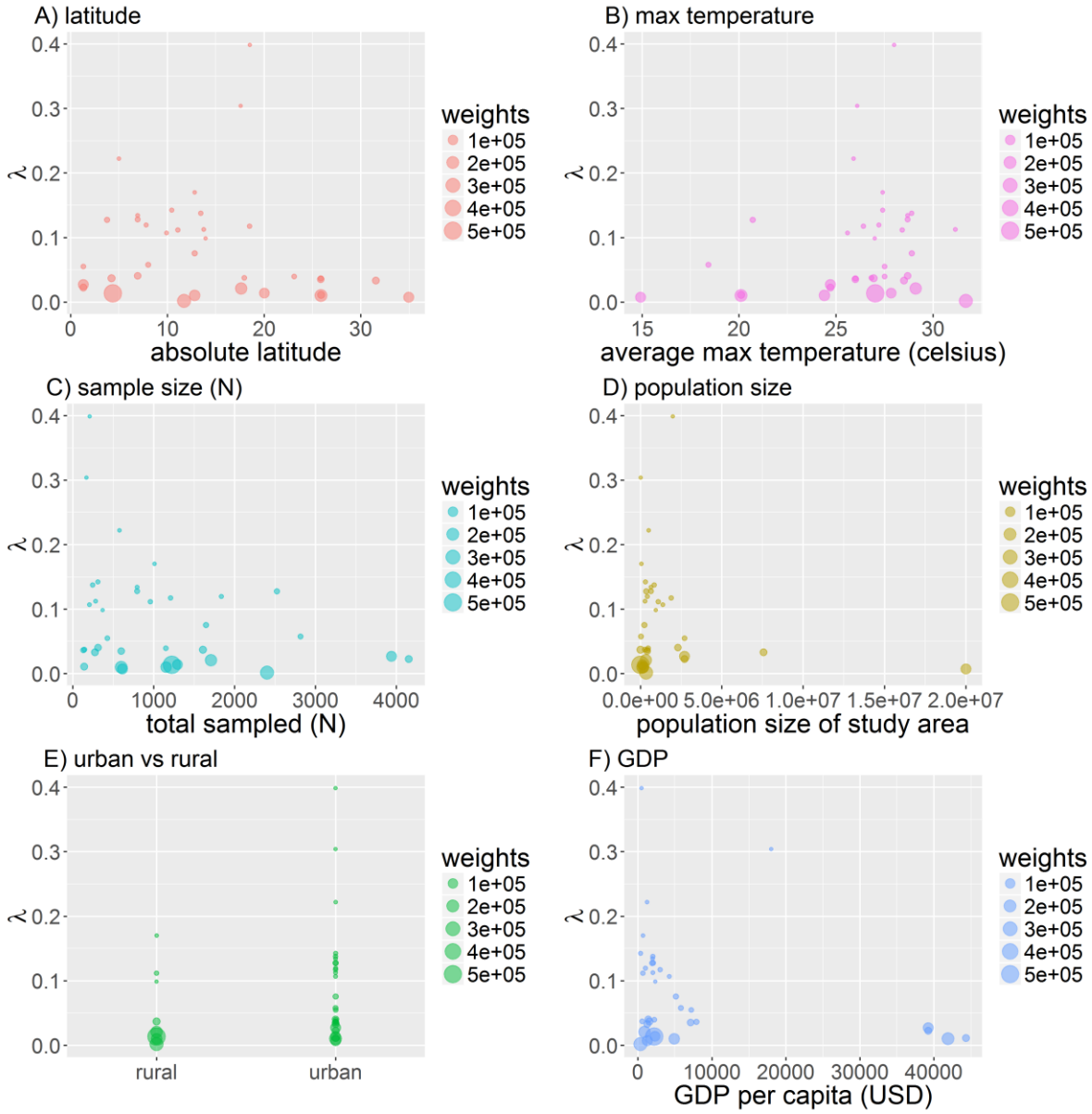

Figure 3.8: Scatterplots showing the relationship between estimated force of infection, and demographic and environmental covariates. A) Absolute latitude, B) average maximum temperature, C) sample size, D) population size of study region, E) whether the study was conducted in an urban or rural setting, and F) GDP per capita (USD). Each point is an estimate for a single year.

Table 3.8: Weighted multiple regression results

Variable	**Correlation with λ**	**Coefficients (95% CI)**	**p-value**
Intercept	-	5.33×10^{-2} ($-3.16 \times 10^{-2} - 1.38 \times 10^{-1}$)	0.21
Absolute latitude	-0.14	-8.98×10^{-4} ($-1.88 \times 10^{-3} - 8.15 \times 10^{-5}$)	0.07
Average maximum temperature	0.20	-1.08×10^{-3} ($-4.44 \times 10^{-3} - 2.28 \times 10^{-3}$)	0.52
Sample size	-0.29	-2.54×10^{-7} ($-1.09 \times 10^{-5} - 1.04 \times 10^{-5}$)	0.96
Population size of study region	-0.16	-1.57×10^{-9} ($-4.31 \times 10^{-9} - 1.17 \times 10^{-9}$)	0.25
Urban/Rural^	0.18	3.66×10^{-2} ($1.71 \times 10^{-2} - 5.60 \times 10^{-2}$)	<0.001
GDP per capita (USD)	-0.23	-8.03×10^{-7} ($-1.64 \times 10^{-6} - 3.56 \times 10^{-8}$)	0.06

^coded as 1=urban, 0=rural.

3.4 Discussion

In the first part of this discussion I will discuss the results of the PRNT data, and in the latter half discuss the results and limitations of serology data in general (chapter 2 and 3).

From a literature review, we selected 7 studies reporting age-structured and serotype-specific seroprevalence data obtained with PRNT assays from 5 countries between 1980 and 2010. As in the previous chapter, from each dataset, we estimated dengue transmission intensity, quantified by the force of infection (λ) and the basic reproduction numbers (R_{0i}). Although we can only calculate a total force of infection across all serotypes from non-serotype specific data (such as surveys using IgG ELISA assays), such data are still sufficient for assessing heterogeneity in overall dengue transmission intensity between different populations. However as demonstrated by the variable serotype specific λ_i estimated from the PRNT data, even within the same population, the dominant serotype in circulation changes over time [23,28,166]. Furthermore, we found that estimates of R_{0i} varied between serotypes, suggesting serotypes (or genotypes) differ in their intrinsic transmissibility [28,104,165]. These findings are in line with recent studies estimating type-specific R_{0i} from 10 endemic countries [167]. Therefore the assumption that all serotypes have identical λ_i required to estimate serotype-specific transmission intensity from IgG data must be regarded as a crude simplification. However, we found that non-serotype specific data do yield an estimate of the total force of infection from all serotypes consistent with the sum of serotype-specific forces of infection able to be derived from PRNT data, particularly when analysis of the latter allowed for inter-serotype interaction (cross-protection or enhancement) [23].

Given the highly heterogeneous nature of dengue transmission, weighted multiple regression was conducted to explore the relationship between the estimated forces of infection and various potential predictors. Whether the study was conducted in an urban or rural environment was the only covariate to have a statistically significant association, with urban areas associated with a higher force of infection. Ideally we would have explored the associations using a meta-regression, allowing for the between trial variance with a random effects model. However since the outcome of interest (force of infection) was in itself calculated from a model, we could not calculate sampling variances from our data.

Our analysis has a number of additional limitations. First, in translating force of infection estimates into estimates of R_{0i} we rely on a model which assumes exposure is due to endemic transmission, meaning all resulting R_{0i} estimates are by definition greater than one. Clearly this is less appropriate for settings with low seroprevalence such as Texas (chapter 2), where some or all of the seropositivity detected is due to imported cases rather than local transmission.

Second, as in chapter 2 it is not possible to disentangle temporal from any age-dependent variation in exposure from single cross-sectional PRNT surveys, requiring broad assumptions to be made about such variation. Hence, for simplicity, we generally assumed constant transmission intensity over time when analysing single cross-sectional surveys. However we know from analysis of Nicaraguan data collected over 7 years (chapter 2) that there is long term variation in transmission intensity. Unfortunately PRNT data from the same site across multiple years were not available. Furthermore the majority of surveys analysed here were conducted in the 1990s hence the estimates may no longer be an accurate reflection of current dengue transmission dynamics.

Third, estimates of transmission intensity (particularly R_{0i}) are sensitive to assumptions about cross-protective immunity between serotypes – and most notably the extent to which tertiary and quaternary infections contribute to transmission. While there is increasing evidence that tertiary and quaternary infections occur [25,28], there is little quantitative data on the infectiousness of such infections relative to primary and secondary infections. Consistent with published theory [166], our estimates of R_{0i} were lower when we assumed tertiary and quaternary infections were as infectious as earlier infections (Assumption 1) than when we assumed complete immunity was acquired after secondary infection (Assumption 2). When one serotype had a very large force of infection relative to the other three serotypes (e.g. Haiti model 2: DENV-1 at 0.046 (95% CI: 0.010 – 0.179) compared to DENV-4 at 0.219 (95% CI: 0.088 – 0.445)), then regardless of the value of λ_i of the remaining serotypes, all R_{0i} estimates were large and similar to each other. Thus it appears that the value of R_{0i} is dominated by very large λ_i and changes in the other three λ_i play a minimal role. This uncertainty has relevance for planning interventions [23,26,105], since R_0

determines the coverage and effectiveness of vaccination or vector control measures required to achieve control of transmission [168]. The results from trials of the Sanofi live-attenuated chimeric vaccine [60,61] make this issue more pressing, since reliable estimates of transmission intensity – and of the health burden due to dengue – will be important in strategic planning and resource allocation for vaccination in different contexts.

Fourth, while PRNT assays are currently the gold standard for routine dengue serotyping, cross-reactivity means care must be taken when interpreting the results of serosurveys in areas where there is co-circulation of different flaviviruses or routine use of yellow fever or Japanese Encephalitis vaccine [20].

Finally, our literature search highlighted that use of serological surveys as a tool to assess transmission remains rare for dengue, with publications of outbreak reports and notified case incidence data being much more common. Generally, published models estimating dengue transmission risk have therefore used notification data, the reliability of which therefore heavily depend on the quality of the surveillance system [169]. Gaining a better global picture of the variation in transmission will improve both estimates of the disease burden caused by dengue and assist in control planning. We would therefore advocate much more widespread and routine use of serological surveys as a surveillance tool which provides invaluable data for an immunising infection such as dengue. While PRNT data provide the maximum information, these chapters (chapters 2 and 3) shows that even the much less expensive ELISA-based assays would provide reasonable baseline estimates of overall transmission intensity.

3.5 References for Figures

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3.6 ISO Abbreviations

ISO 3 letter code	Country
CUB	Cuba
PER	Peru
HTI	Haiti
IDN	Indonesia
THA	Thailand

4 Estimating Dengue Transmission Intensity from Case-notification Data from Multiple Countries

Work in this chapter formed the basis of: Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating Dengue Transmission Intensity from Case-notification Data from Multiple Countries. *PLoS Negl Trop Dis* 2016; **10**: e0004833.

In this chapter, I collate age-stratified case notification data from the literature and develop models to estimate the force of infection. Comparing these estimates to those obtained from seroprevalence data (chapters 2 and 3) shows that incidence data can be equally useful whilst also highlighting the limitations associated with such data.

4.1 Introduction

Dengue is the most widely distributed mosquito-borne viral infection, but assessment of its geographic variation in transmission remains challenging. Analysis based on mapping the probability of occurrence of dengue estimated dengue causes 390 million annual infections worldwide [108]. However, these estimates relied on assuming a direct linear correlation between probability of occurrence and incidence, rather than estimating transmission intensity as quantified by the force of infection or reproduction number. Here we develop methods to estimate transmission intensity from routine, age-stratified surveillance data on suspected dengue case incidence.

All four serotypes of dengue virus (DENV-1, 2, 3, and 4) can cause dengue fever with the risk of severe dengue increasing with subsequent heterologous infections. Once infected, individuals develop long-lived protective homotypic immunity and short-lived heterotypic immunity [23,123]. Once antibody levels wane below the threshold required to provide protection ADE becomes a risk, leading to secondary heterologous infection having an enhanced risk of causing clinically apparent disease [4,20]. Hence while the majority of primary dengue infections are asymptomatic [170], secondary heterologous infection has been identified as a major risk factor for symptomatic and severe dengue [13,171,172]. Therefore the majority of cases seen in hospitals [122] or reported via surveillance systems [173] tend to be secondary infections.

In previous work, we estimated dengue transmission intensity from age-stratified seroprevalence data but highlighted the relative paucity of seroprevalence data compared with routine surveillance data on the incidence of suspected dengue [174]. This reflects dengue fever, DHF, and DSS being notifiable diseases in most countries [90–94]. Indeed, in many countries, incidence reports are the only type of data available. However the clinical diagnostic criteria vary and different countries have their own reporting standards [53]. The WHO collates surveillance data from dengue affected countries via its DengueNet system, but the data are not always updated regularly and there can be inconsistencies with other sources (e.g. WHO regional offices or countries) of national and subnational data [53].

The lack of systematic data on dengue incidence, the lack of standardized reporting procedures or diagnostic criteria, and the lack of integration between private and public sectors makes accurate estimation of the true dengue burden difficult [52]. Previous studies have attempted to estimate the burden of dengue and associated economic costs in South East Asia and South America by calculating expansion factors from systematic literature reviews, collation of existing data, and population-based cohorts [52,54–57]. However, the lack of standardisation also affects the validity of expansion factors (calculated by dividing the cumulative incidence of dengue cohort studies by that from passive data at both national and local levels) as estimates of underreporting. Due to the wide spectrum of clinical manifestations and the lack of routine laboratory testing, dengue is globally underreported and analyses of officially reported dengue numbers need to take this into account [58].

While reported incidence levels cannot be relied upon to directly quantify disease burden, the age distribution of dengue cases provides more reliable information on dengue transmission intensity. Here we propose an approach for estimating average transmission intensity - as quantified by the force of infection or basic reproduction number (R_0) – from age-stratified incidence data. We compare estimates derived from seroprevalence and incidence data and assess the level of under-reporting of dengue disease. In addition, we estimate the relative contribution of primary to quaternary infections to the observed burden of dengue disease incidence.

4.2 Methods

4.2.1 Literature Search

Web of Knowledge and PubMed were searched for age-stratified incidence data since 1980 as we were interested in contemporary dengue transmission and wanted to be consistent with our previous study (chapters 2 and 3) where we collated age-stratified seroprevalence data [174]. Search terms used were: 'dengue' and 'age' and ('incidence' or 'cases' or 'notifications' or 'notified cases') with inclusion criteria mapped to subject headings. Additional web-based searches were performed to augment the primary literature search. Data were extracted from published datasets where authors reported age-stratified incidence data with corresponding population age-structure data.

4.2.2 Estimating the Force of Infection and Reporting Rates

We consider a population stratified into *M* age groups and denote a_j and a_{j+1} the lower and upper age bounds respectively of age group j ($j=0,\ldots, M-1$). Our model assumes perfect homotypic protection following infection with any serotype. Thus, an individual can experience a maximum of four dengue infections in their life (corresponding to the four dengue serotypes). Ideally, we would allow forces of infection to vary by serotype (DENV-1 to DENV-4). However as serotype-specific data were not available, we assumed circulating serotypes were equally transmissible, i.e. had the same force of infection, λ, which does not vary over time. The incidence of primary infections (I_1) for any one serotype for people in an age group j is calculated as the integral of the probability of being seronegative to all four strains at age a multiplied by four times the constant serotype-specific infection hazard, λ, (since primary infection can occur with any of the four serotypes). Age a spans the range $[a_j, a_{j+1}]$, as described by the bounds of integrations. Equations (4.1) - (4.4) give the incidence of primary to quaternary infections respectively when four serotypes are in circulation.

The incidence of primary infections ($I_1(j)$) is given by:

$$\begin{aligned} I_1(j) &= \int_{a_j}^{a_{j+1}} 4\lambda\left(e^{-\lambda a}\right)^4 da \\ &= \int_{a_j}^{a_{j+1}} 4\lambda e^{-4\lambda a} da = \left(e^{-4\lambda a_j} - e^{-4\lambda a_{j+1}}\right) \quad . \end{aligned} \tag{4.1}$$

The incidence of secondary infections ($I_2(j)$) is given by:

$$\begin{aligned} I_2(j) &= 4\int_{a_j}^{a_{j+1}} 3\lambda(1-e^{-\lambda a})\left(e^{-\lambda a}\right)^3 da \\ &= 4\left[e^{-3\lambda a_j} - e^{-3\lambda a_{j+1}}\right] - 3\left[e^{-4\lambda a_j} - e^{-4\lambda a_{j+1}}\right] \quad . \end{aligned} \tag{4.2}$$

The incidence of tertiary infections ($I_3(j)$) is given by:

$$\begin{aligned} I_3(j) &= 4\int_{a_j}^{a_{j+1}} 3\lambda(1-e^{-\lambda a})^2\left(e^{-\lambda a}\right)^2 da \\ &= 4\int_{a_j}^{a_{j+1}} 3\lambda\left(e^{-2\lambda a} - 2e^{-3\lambda a} + e^{-4\lambda a}\right) da \\ &= 12\lambda\left(\left[-\frac{e^{-2\lambda a}}{2\lambda}\right]_{a_j}^{a_{j+1}} - \left[-\frac{2e^{-3\lambda a}}{3\lambda}\right]_{a_j}^{a_{j+1}} + \left[-\frac{e^{-4\lambda a}}{4\lambda}\right]_{a_j}^{a_{j+1}}\right) \\ &= 6\left[e^{-2\lambda a_j} - e^{-2\lambda a_{j+1}}\right] + 8\left[e^{-3\lambda a_{j+1}} - e^{-3\lambda a_j}\right] + 3\left[e^{-4\lambda a_j} - e^{-4\lambda a_{j+1}}\right] \quad . \end{aligned} \tag{4.3}$$

Finally the incidence of quaternary infections ($I_4(j)$) is given by:

$$\begin{aligned} I_4(j) &= 4\int_{a_j}^{a_{j+1}} \lambda\left(1-e^{-\lambda a}\right)^3 e^{-\lambda a} da \\ &= 4\lambda\int_{a_j}^{a_{j+1}} \left(e^{-\lambda a} - 3e^{-2\lambda a} + 3e^{-3\lambda a} - e^{-4\lambda a}\right) da \\ &= 4\lambda\left[\left[\frac{-e^{-\lambda a}}{\lambda}\right]_{a_j}^{a_{j+1}} - \left[-\frac{3e^{-2\lambda a}}{2\lambda}\right]_{a_j}^{a_{j+1}} + \left[-\frac{3e^{-3\lambda a}}{3\lambda}\right]_{a_j}^{a_{j+1}} - \left[-\frac{e^{-4\lambda a}}{4\lambda}\right]_{a_j}^{a_{j+1}}\right] \\ &= 4\left[e^{-\lambda a_j} - e^{-\lambda a_{j+1}} + e^{-3\lambda a_j} - e^{-3\lambda a_{j+1}}\right] + 6\left[e^{-2\lambda a_{j+1}} - e^{-2\lambda a_j}\right] + \left[e^{-4\lambda a_{j+1}} - e^{-4\lambda a_j}\right] \quad . \end{aligned} \tag{4.4}$$

Total dengue infection incidence $(T) = I_1 + I_2 + I_3 + I_4$ is, as expected:

$$\begin{aligned} T(j) &= \int_{a_j}^{a_{j+1}} \left[4\lambda\left(e^{-\lambda a}\right)^4 + 12\lambda(1-e^{-\lambda a})\left(e^{-\lambda a}\right)^3 + 12\lambda\left(1-e^{-\lambda a}\right)^2\left(e^{-\lambda a}\right)^2 + 4\lambda\left(1-e^{-\lambda a}\right)^3\left(e^{-\lambda a}\right) \right] da \\ &= 4\int_{a_j}^{a_{j+1}} \lambda e^{-\lambda a}\left(e^{-\lambda a} + \left[1-e^{-\lambda a}\right]\right)^3 da \\ &= \int_{a_j}^{a_{j+1}} 4\lambda e^{-\lambda a} da \\ &= 4e^{-\lambda a_j} - 4e^{-\lambda a_{j+1}} \end{aligned}$$

The average observed annual disease incidence rate per person in an age group is then given by a weighted sum of the primary to quaternary infection rates:

$$D(j) = \frac{1}{w(j)}\left\{\rho\left[I_2(j) + \gamma_1 I_1(j) + \gamma_3\left(I_3(j) + I_4(j)\right) + B\right]\right\} \quad (4.5)$$

,

where $w(j) = a_{j+1} - a_j$ is the width of the age group j, ρ is the probability that a secondary infection results in a detected dengue case (=reporting rate), γ_1 is the probability that a primary infection is detected relative to a secondary infection, and γ_3 is the probability that a tertiary or quaternary infection is detected relative to a primary infection. Here B is a baseline risk of disease used to represent any non-dengue related illnesses that are misdiagnosed as dengue, and is only estimated when fitting incidence where laboratory confirmation was lacking. Since we assumed that most symptomatic cases were secondary infections, we estimated the probability of detecting all other cases relative to secondary cases. We estimated these parameters using age-structured incidence data taking into account the age-structure of the population. Where fewer than 4 serotypes were in circulation, we changed the weighted sum of infection incidence accordingly as described below.

If there are fewer than four serotypes in circulation

When there are fewer than four serotypes in circulation, the maximum number of infections an individual can acquire also changes accordingly.

1) Only one serotype in circulation

With only one serotype in circulation, individuals will only be infected once in their lifetime. Thus the incidence of primary infection in age group j (with lower age bound a_j and upper age bound a_{j+1}) $I_1(j)$ is given by:

$$\begin{aligned} I_1(j) &= \int_{a_j}^{a_{j+1}} \lambda\left(e^{-\lambda a}\right) da \\ &= e^{-\lambda a_j} - e^{-\lambda a_{j+1}} \end{aligned}$$

The incidence of disease in age group j is then given by:

$$D(j) = \frac{1}{w(j)}\left\{\rho\left[I_1(j) + B\right]\right\}.$$

2) With two serotypes in circulation

With two serotypes in circulation, individuals can have up to two infections in their lifetime.

The incidence of primary infection in age group j (with lower age bound a_j and upper age bound a_{j+1}) $I_1(j)$ is given by:

$$\begin{aligned} I_1(j) &= 2\int_{a_j}^{a_{j+1}} \lambda\left(e^{-\lambda a}\right)^2 da \\ &= \left(e^{-2\lambda a_j} - e^{-2\lambda a_{j+1}}\right) \end{aligned}$$

and the incidence of secondary infection in age group j, $I_2(j)$ is given by:

$$\begin{aligned} I_2(j) &= 2\int_{a_j}^{a_{j+1}} \lambda\left[1 - e^{-\lambda a}\right]\left(e^{-\lambda a}\right) da \\ &= 2\lambda\left[\frac{e^{-\lambda a_j}}{\lambda} - \frac{e^{-\lambda a_{j+1}}}{\lambda} + \frac{e^{-2\lambda a_{j+1}}}{2\lambda} - \frac{e^{-2\lambda a_j}}{2\lambda}\right] \\ &= 2\left[e^{-\lambda a_j} - e^{-\lambda a_{j+1}}\right] - \left[e^{-2\lambda a_j} - e^{-2\lambda a_{j+1}}\right] \end{aligned}$$

The incidence of disease in age group j is then given by:

$$D(j) = \frac{1}{w(j)}\left\{\rho\left[I_2(j) + \gamma_1 I_1(j) + B\right]\right\}.$$

3) With three serotypes in circulation

With three serotypes in circulation, individuals can have a maximum of 3 infections.

The incidence of primary infection in age group j (with lower age bound a_j and upper age bound a_{j+1}) $I_1(j)$ is given by:

$$\begin{aligned} I_1(j) &= 3\int_{a_j}^{a_{j+1}} \lambda\left(e^{-\lambda a}\right)^3 da \\ &= \left(e^{-3\lambda a_j} - e^{-3\lambda a_{j+1}}\right) \end{aligned}$$

The incidence of secondary infection in age group j, $I_2(j)$ is given by:

$$\begin{aligned} I_2(j) &= 3\int_{a_j}^{a_{j+1}} 2\lambda\left[1 - e^{-\lambda a}\right]\left(e^{-\lambda a}\right)^2 da \\ &= 6\lambda\left[\frac{e^{-2\lambda a_j}}{2\lambda} - \frac{e^{-2\lambda a_{j+1}}}{2\lambda} + \frac{e^{-3\lambda a_{j+1}}}{3\lambda} - \frac{e^{-3\lambda a_j}}{3\lambda}\right] \\ &= 3\left[e^{-2\lambda a_j} - e^{-2\lambda a_{j+1}}\right] - 2\left[e^{-3\lambda a_j} - e^{-3\lambda a_{j+1}}\right] \end{aligned}$$

and the incidence of tertiary infection in age group j, $I_3(j)$ is given by:

$$\begin{aligned} I_3(j) &= 3\int_{a_j}^{a_{j+1}} \lambda\left[1 - e^{-\lambda a}\right]^2\left(e^{-\lambda a}\right) da \\ &= 3\lambda\left[\frac{e^{-\lambda a_j}}{\lambda} - \frac{e^{-\lambda a_{j+1}}}{\lambda} + \frac{2e^{-2\lambda a_{j+1}}}{2\lambda} - \frac{2e^{-2\lambda a_j}}{2\lambda} + \frac{e^{-3\lambda a_j}}{3\lambda} - \frac{e^{-3\lambda a_j}}{3\lambda}\right] \\ &= 3\left[e^{-\lambda a_j} - e^{-\lambda a_{j+1}}\right] - 3\left[e^{-2\lambda a_j} - e^{-2\lambda a_{j+1}}\right] + \left[e^{-3\lambda a_j} - e^{-3\lambda a_{j+1}}\right] \end{aligned}$$

The incidence of disease in age group j is then given by:

$$D(j) = \frac{1}{w(j)}\left\{\rho\left[I_2(j) + \gamma_1(I_1(j) + I_3(j)) + B\right]\right\}.$$

Where population numbers were not available, the population age-structure closest to the survey population was used (taken from census data or from United Nations estimates [128]). We defined two model variants.

Model 1A and 1B: assuming a single reporting rate across all ages

For model 1 we assumed a single baseline reporting rate (ρ) across all age groups and estimated 4 (or 5) parameters: λ_i, ρ, γ_1, γ_3 (and B). Where multiple years of incidence data were available from the same survey we fitted each model variant to individual years (model 1A), and to the cumulative incidence (model 1B).

Models 2A and 2B: Assuming age-dependent reporting rates

For model 2 we assumed an age-dependent reporting rate (ρ_y and ρ_o) that changed at a certain age threshold $A_{threshold}$;

$$\begin{aligned}\rho &= \rho_y, \text{if } a < a_{threshold} \\ &= \rho_o, \text{if } a \geq a_{threshold}\end{aligned};$$

that we estimated additionally to λ_i, γ_1, γ_3 (and B) for a total of 6 (or 7) parameters.

A single value of γ_1 and γ_3 were estimated per country. Where incidence data were available for multiple years, we fitted each model variant to individual years (model 2A) and to the cumulative incidence (model 2B).

When fitting to the cumulative incidence e.g. cumulative incidence over 10 years, we multiplied the estimated annual disease incidence by 10 to take into account the survey period.

Estimation Procedure

The expected number of cases per year in age-group j (C_j) is:

$$C_j = n_j D_j \tag{4.6}$$

where n_j is the population size of age group j.

We assumed that the number of cases reported in each age-group were Dirichlet-multinomially (DMN) distributed, as we expected the overall distribution of cases would be more over-dispersed than what we would expect from a multinomial distribution [175]. The log-likelihood is given by:

$$LnL\left(p_j,\psi;y_j\right)=-\left(\ln\Gamma\left(1/\psi+N\right)-\ln\Gamma\left(1/\psi\right)\right)+\sum_{j=1}^{I}\left(\ln\Gamma\left(\frac{1}{\left(\psi/p_j\right)}+y_j\right)-\ln\Gamma\left(\frac{1}{\left(\psi/p_j\right)}\right)\right), \quad (4.7)$$

where ψ is the over-dispersion parameter characterising how different a DMN distribution is from the corresponding multinomial distribution (MN) with the same category probabilities (the larger the ψ, the greater the difference) and y_j is the observed number of cases in age class j. The probabilities (p_j) are then calculated as the expected proportion of cases in one age group relative to the total number of cases across all age groups.

$$p_j=\frac{C_j}{\sum_j C_j}. \quad (4.8)$$

We then assumed that the total number of cases across all ages (N) is Poisson distributed:

$$P(\mu=N)=\frac{\mu^N e^{-\mu}}{N!}, \quad (4.9)$$

where μ is the total expected number of cases across all age groups $\left(\sum_j C_j\right)$.

The full log-likelihood is then:

$$LnL\left(p_j,\psi;y_j\right)=-\left(\ln\Gamma\left(1/\psi+N\right)-\ln\Gamma\left(1/\psi\right)\right)+\sum_{j=1}^{I}\left(\ln\Gamma\left(\frac{1}{\left(\psi/p_j\right)}+y_j\right)-\ln\Gamma\left(\frac{1}{\left(\psi/p_j\right)}\right)\right)+N\ln\left(\mu\right)-\mu-\ln\left(N!\right). \quad (4.10)$$

Finally, the average annual incidence rate per person can be calculated using equation (4.5).

All models were fitted to the data using a MH MCMC algorithm using a Dirichlet-multinomial log-likelihood with uniform priors in version 3.1.0 of the R statistical language [159].

4.2.3 Calculating the Basic Reproduction Number (R_{0i})

We assumed dengue transmission was at endemic equilibrium and that the force of infection (λ) was constant in time. We additionally assumed that all serotypes in circulation were equally transmissible, i.e. had the same force of infection and basic reproduction number. We calculated a strain-specific basic reproduction number (R_{0i}) from the single force of infection (λ_i) estimated under two different assumptions about the number of infections required to acquire complete immunity. Under assumption 1, complete protection is acquired upon quaternary infection. Under assumption 2, complete protection is reached after secondary infection (i.e. only primary and secondary infections are infectious). These assumptions match that of our previous work estimating the force of infection from serological data (chapters 2 and 3) and allowed us to compare the R_{0i} estimates obtained from both types of data [174].

Assumption 1 – individuals can be infected 4 times, there is no cross-immunity between serotypes. The basic reproduction number for serotype i is given by:

$$R_{0i} = \frac{1}{1-\int_0^{\infty} f(a) z_i(a) da} \quad , \tag{4.11}$$

where $f(a)$ is the proportion of the population aged a. $z_i(a)$ is the proportion of population aged a seropositive to serotype i and is calculated by:

$z_i(a) = 1 - e^{-\frac{\lambda}{n}a}$ where n = the number of serotypes in circulation.

$$\begin{aligned} R_{0i} &= \frac{1}{1-\int_{a_j}^{a_{j+1}} f(a)\left[1-e^{-\frac{\lambda}{n}a}\right] da} \\ &= \frac{1}{1-\int_{a_j}^{a_{j+1}} \left[f(a)+f(a)e^{-\frac{\lambda}{n}a}\right] da} \\ &= \frac{1}{1-\int_{a_j}^{a_{j+1}} f(a)da+\int_{a_j}^{a_{j+1}} f(a)e^{-\frac{\lambda}{n}a} da} \end{aligned} \quad . \tag{4.12}$$

$\int_{a_j}^{a_{j+1}} f(a)da$ = 1, so we are left with:

$$
\begin{aligned}
R_{0i} &= \frac{1}{\int_{a_j}^{a_{j+1}} f(a) e^{-\frac{\lambda}{n}a} da} \\
&= \frac{1}{\sum_j \frac{f(a_{j+1} \to a_j)}{a_{j+1} - a_j} \left[-\frac{n \exp[-\lambda a / n]}{\lambda} \right]_{a_j}^{a_{j+1}}} \\
&= \frac{1}{\sum_j \frac{f(a_{j+1} \to a_j)}{a_{j+1} - a_j} \frac{n}{\lambda} \left[\exp[-\lambda a_j / n] - \exp[-\lambda a_{j+1} / n] \right]} \\
&= \frac{\lambda}{\sum_j \frac{f(a_{j+1} \to a_j)}{a_{j+1} - a_j} n \left[\exp[-\lambda a_j / n] - \exp[-\lambda a_{j+1} / n] \right]} .
\end{aligned}
\tag{4.13}
$$

Assumption 2 – Complete immunity after secondary infection.

If only primary and secondary infections can occur, we can relax the assumption of no cross-immunity between serotypes. The basic reproduction number (the same for any serotype) is given by:

$$
R_{0i} = \frac{1}{\int_0^\infty f(a) \left[x(a) + (n-1) z(a) \right] da} , \tag{4.14}
$$

where $f(a)$ is the proportion of the population aged a, n is the number of serotypes in circulation, $x(a)$ is the proportion of the population seronegative at age a calculated by: $x(a) = \exp[-\lambda a]$, and $z_i(a)$ is the proportion of the population seropositive for serotype i at age a calculated by:

$$
\begin{aligned}
z_i(a) &= \left[1 - \exp[-\lambda a / n] \right] \left[\exp\left[-(n-1) \lambda a / n \right] \right] \\
&= \exp\left[-(n-1) \lambda a / n \right] - \exp[-n \lambda a / n] \\
&= \exp\left[-(n-1) \lambda a / n \right] - \exp[-\lambda a] .
\end{aligned}
\tag{4.15}
$$

Integrating between ages a_j and a_{j+1}:

$$
\begin{aligned}
R_{0i} &= \frac{1}{\int_{a_j}^{a_{j+1}} f(a)\left[x(a)+(n-1)z(a)\right]da} \\
&= \frac{1}{\int_{a_j}^{a_{j+1}} f(a)\left[(n-1)\exp\left[-(n-1)\lambda a/n\right]-(n-2)\exp\left[-\lambda a\right]\right]da} \\
&= \frac{1}{\sum_j \frac{f(a_{j+1}\to a_j)}{a_{j+1}-a_j}\left[\begin{array}{l}\frac{n\left(\exp\left[-(n-1)\lambda a_j/n\right]-\exp\left[-(n-1)\lambda a_{j+1}/n\right]\right)}{\lambda} - \\ (n-2)\left(\frac{\left(\exp\left[-\lambda a_j\right]-\exp\left[-\lambda a_{j+1}\right]\right)}{\lambda}\right)\end{array}\right]} \\
&= \frac{\lambda}{\sum_j \frac{p(a_{j+1}\to a_j)}{a_{j+1}-a_j}\left[\begin{array}{l}n\left(\exp\left[-(n-1)\lambda a_j/n\right]-\exp\left[-(n-1)\lambda a_{j+1}/n\right]\right) \\ -(n-2)\left(\exp\left[-\lambda a_j\right]-\exp\left[-\lambda a_{j+1}\right]\right)\end{array}\right]}
\end{aligned}
\qquad (4.16)
$$

4.2.4 Comparing Force of Infection Estimates by Data Type

We used weighted regression to assess how comparable force of infection estimates obtained from incidence data (λ_{inc}) were with those derived from serological data (λ_{sero}). We compared force of infection estimates from seroprevalence data described previously [174] and from 4 additional seroprevalence datasets (summarised in Table 4.3. Estimated as described in chapter 1, model A) with the estimates we derived from incidence data. Location- and time-matched incidence and serology data were not available, so we matched datasets by country, region, and survey year (within 5 years of each other). Since seroprevalence data represent all past infections, we compared force of infection estimates with those obtained from cumulative incidence data (models 1B and 2B) rather than yearly incidence data (Table 4.1). We used the deming regression (a weighted regression) method described by Ripley and Thompson [176] which explicitly accounts for measurement errors in both force of infection estimates from seroprevalence data (y-axis) and incidence data (x-axis) to estimate the maximum likelihood estimation (MLE) line. Confidence intervals for the regression line were estimated using the jackknife estimate of the variance-covariance matrix between the estimated intercept and slope of the regression. The areas of the

symbols on the plots are proportional to the point weights, which correspond to the reciprocal of the variance of the error term in the linear regression. The larger circles indicate greater weight, i.e. smaller error. This was implemented using the *deming* package in R [177].

4.2.5 Multiple Linear Regression

A weighted regression analysis was used to explore the relationship between the λ values (estimated using the single reporting rate model fitted to cumulative incidence data (1B) where possible) and a number of environmental and demographic covariates (equation (4.17)).

$$\lambda = \beta_0 + \beta_1 Lat_{abs} + \beta_2 T_{\max} + \beta_3 P + \beta_4 N + \beta_5 G + \beta_6 U + \beta_7 Lab \quad (4.17)$$

where λ is the force of infection, Lat_{abs} is the absolute latitude, $T_{\max}$ is the average maximum temperature, P is the population size of the study region, N is the total number of individuals sampled, G is the GDP per capita (USD), U is whether the study was conducted in an rural or urban area (0=rural, 1=urban, 3=both), and Lab is whether the cases were laboratory confirmed as dengue (0=no, 1=yes). Data on each covariate was extracted from the source publication, United Nations estimates [128], or World Bank estimates [160]. The model was weighted according to the variance of the λ estimates (weights = 1/variance of the posterior distribution) and fitted in the R Statistical Package (version 3.1.0) [159].

Table 4.1: Incidence datasets matched to closest serology datasets by region, year, or country

	Incidence Datasets					Serology Datasets			
Country	**Author**	**Survey Year**	**Region**	**Diagnosis**	**Ref**	**Author**	**Survey Year**	**Region**	**Ref**
Brazil	Penna	2001/06	Amazon	Clinical	[178]	Silva-Nunez	2004	Ramal do Granada (Acre State Amazon)	[179]
Brazil	Cordeiro	2002/06	Pernambuco (Recife)	Lab confirmed	[180]	Braga	2005/06	Recife (NE)	[129]
Brazil	Cardoso	2000/09	Vitoria (~Rio)	Lab confirmed	[181]	Lima	1998	Sao Paulo	[92]
Brazil	Cordeiro	1995/01	Pernambuco (Recife)	Lab confirmed	[180]	Fernando	1996	Paco do Lumiar, Sao Jose de Ribamar, Estado do Maranho	[182]
Laos	Anker	2000/06	National	Clinical	[183]	Vallee	2006	Vientiane	[135]
Nicaragua	Hammond	1999/01	Leon	Clinical/Lab	[184]	Balmaseda	2001/06	Managua	[30]
Singapore	Anker	1999/05	National	Clinical/Lab	[183]	Yew	2004	National	[147]
Singapore	Ler	2000/07	National	Lab confirmed	[185]	Yap	2007	National	[148]
Taiwan	Lin	2003/09	Kaohsiung City	Lab confirmed	[186]	Shu	1997-1998	Liuchiu Hsiang	[35]
Thailand	Thai MoH*	2000	Bangkok^	Lab confirmed	[187]	Perret	2000	Bangkok	[152]
Thailand	Thai MoH*	2000	Ratchaburi^	Lab confirmed	[187]	Tuntaprasart	2000	Ratchaburi	[153]
Thailand	Thai MoH*	2010	Rayong	Lab confirmed	[187]	Rodriguez-Barraquer	2010	Rayong	[188]
Vietnam	Cuong	1998/09	Hanoi	Lab confirmed	[189]	Bartley	1996-1997	Dong Thap	[154]

*Although not cumulative incidence, these datasets were retained for analysis as they matched the corresponding seroprevalence surveys exactly by year and region. ^The two datasets reported DHF cases only; we therefore assumed all observed cases were due to secondary infections.

4.3 Results

4.3.1 Literature Search

We identified 23 papers reporting incidence data. Figure 4.1 describes the search process and Table 4.2 summarises the studies identified. Seven papers reported age-stratified incidence data from multiple years, one paper reported data where the number of serotypes in circulation had changed over the survey years, 6 papers reported cumulative age-stratified incidence data, 8 papers reported age-stratified incidence data from a single year, and 2 papers reported age-stratified incidence data from multiple countries.

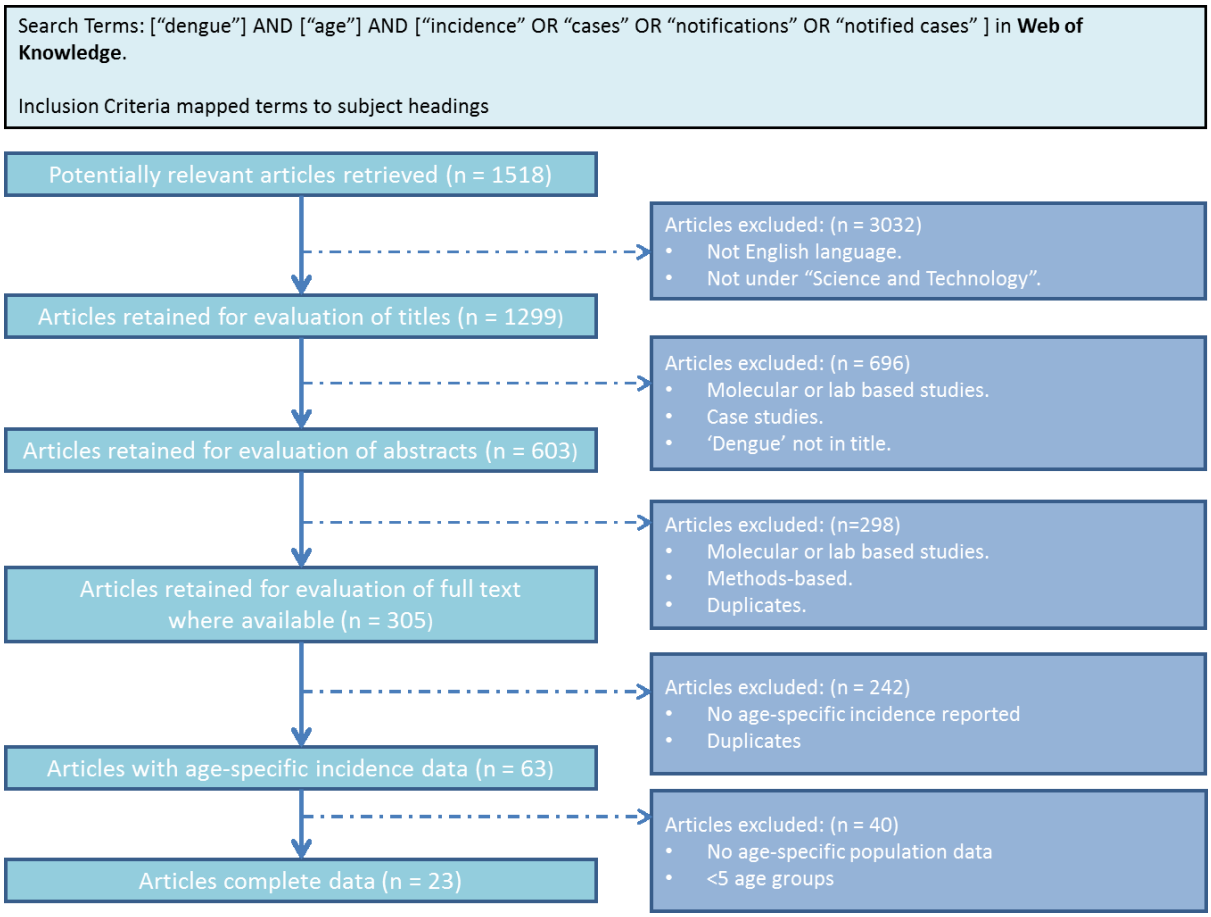

Figure 4.1: Flowchart describing the literature search process for age-stratified incidence data.

When considering each year separately, the identified studies provided a total of 96 datasets from 13 countries. The years included ranged from 1978 – 2011. The dataset reporting incidence data from 1978 was included since data were presented for the 11-year time period of 1978 – 1988 [190]. Of the 23 papers, 10 reported dengue incidence at the

national level and only 2 studies reported cases detected via active as well as passive surveillance. Three additional surveys were obtained from the Ministry of Health in Thailand [187] that reported age-specific incidence from Bangkok (2000), Ratchaburi (2000), and Rayong (2010) giving a total of 99 datasets from 13 countries.

Table 4.2: Summary of cross-sectional incidence datasets identified and associated demographics. *with active surveillance.

Country	Survey Year	Region	Diagnosis	# serotypes in circulation	Age range sampled	Number surveyed	Population size of study region	Urban/Rural	Ref
Brazil	1995-2001	Pernambuco State	Lab confirmed	2	0 - 80+	8355325	8.5M	Urban/Rural	[191]
	2002-2006	Pernambuco State	Lab confirmed	3	0 - 80+	8355325	8.5M	Urban/Rural	[191]
	2000-2009	Vitoria	Lab confirmed	3	0 - 80+	292304	0.28M–0.32M	Urban/Rural	[181]
	2001-2006	Amazon	Clinical	4	0 - 70	3478916	23.6M	Rural/Urban	[178]
Cambodia	2006-2008	Kampong Chan Province	Lab confirmed*	4	0 - 20	804943	90000	Urban/Rural	[192]
	2006-2007	Kampong Chan	Lab confirmed	4	0-14	14493	90000	Urban/Rural	[193]
China	1978-1988	Guangzhou	Clinical	4	0 - 71+	69671492	11.64M	Urban	[190]
	1989-1999	Guangzhou	Clinical	4	0 - 71+	68990737	11.64M	Urban	[190]
	2000-2009	Guangzhou	Clinical	4	0 - 71+	39489838	11.64M	Urban	[190]
	2005-2011	Guangdong	Clinical	4	0 - 80+	88918687	104.3M	Urban	[90]
Laos	2000-2006	National	Clinical/Lab	4	0 - 15+	4980938	5.4M	Urban/Rural	[183]
	2010	Savannakhet Province	Clinical	4	0 - 40+	4879056	0.83M	Urban	[194]
	2010	National	Clinical	4	0 - 40+	6388648	6.5M	Urban/Rural	[195]
Nicaragua	1999-2001	Leon	Lab confirmed	3	0 - 55	359723	0.39M	Urban	[184]
Philippines	1998-2005	National	Clinical/Lab	4	0 - 15+	71661584	77.7M	Urban/Rural	[183]
Puerto Rico	2006	Patillas	Lab confirmed	4	0 - 40+	16741	20200	Urban	[196]
	2007	National	Lab confirmed	4	0 - 70+	3823678	3.8M	Urban/Rural	[197]
	2010	National	Lab confirmed	4	0 - 70+	3717885	3.7M	Urban/Rural	[173]
	1994	National	Lab confirmed	3	0 - 75+	3525248	3.5M	Urban/Rural	[198]
	1995-1997	National	Lab confirmed	3	0 - 75+	3525248	3.5M	Urban/Rural	[198]
Singapore	1999-2005	National	Clinical/Lab	4	0 - 15+	2617012	4M	Urban	[183]
	2005	National	Lab confirmed	4	0 - 80	3447129	4.3M	Urban	[199]
	2005	National	Lab confirmed	4	0 - 55+	4265809	4.3M	Urban	[185]
	2007	National	Lab confirmed	4	1 - 55+	4588466	4.6M	Urban	[185]
Sri Lanka	1997	National	Clinical	4	0 - 65	17337179	17.3M	Urban/Rural	[200]
	1996-2005	National	Clinical	4	0 - 15+	17706365	17.3M	Urban/Rural	[183]

Table 4.2 continued

Country	Survey Year	Region	Diagnosis	# serotypes in circulation	Age range sampled	Number surveyed	Population size of study region	Urban/Rural	Ref
Taiwan	2003-2009	Kaohsiung City	Lab confirmed	4	0 - 74+	10555563	1.5M	Urban	[186]
Thailand	2000-2010	National	Clinical	4	0-65+	796686	66.4M	Urban/Rural	[201]
	2006-2007	Ratchaburi	Lab confirmed	4	0-14	6381	38208	Urban	[193]
	2000	Bangkok	Lab confirmed	4	0-65	5054	6355144	Urban	[187]
	2000	Ratchaburi	Lab confirmed	4	0-65	1371	791217	Urban	[187]
	2010	Rayong	Lab confirmed	4	0-72	1059	616916	Urban	[187]
Vietnam	1998-2009	Hanoi	Lab confirmed	4	0 - 80	6346088	6.5M	Urban	[189]
Yemen	2010	Hadramout	Lab confirmed	3	0 - 55+	797049	0.7M	Urban/Rural	[202]

Table 4.3: Summary parameter estimates from four extra seroprevalence datasets

Country	Author	Region	Urban/Rural	λ force of infection (95% CrI)	ψ over-dispersion (95% CrI)	R_{0i} Assumption 1 (95% CrI)	R_{0i} Assumption 2 (95% CrI)	Ref
Brazil	Fernando	Paco do Lumiar Sao Jose de Ribamar Estado do Maranho	Urban	0.013 (0.011-0.021)	0.070 (0.044-0.270)	1.09 (1.08-1.15)	1.12 (1.10-1.21)	[182]
Brazil	da Silva-Nunes	Amazon	Rural	0.008 (0.007-0.017)	0.026 (0.009-0.319)	1.05 (1.05-1.12)	1.06 (1.05-1.16)	[203]
Brazil	Lima	Campinas	Urban	0.007 (0.006-0.016)	0.111 (0.079-0.319)	1.05 (1.04-1.11)	1.06 (1.05-1.15)	[204]
Taiwan	Shu	Liuchiu Hsiang	Urban	0.026 (0.023-0.037)	0.157 (0.112-0.380)	1.24 (1.21-1.34)	1.38 (1.32-1.60)	[35]

4.3.2 Additional Seroprevalence Surveys

In addition to the seroprevalence surveys identified in chapters 2 and 3, the force of infection was estimated from four more surveys from Brazil and Taiwan to correspond to the incidence datasets identified here. Parameter estimates are given in Table 4.3, and model fits are shown in Figure 4.2.

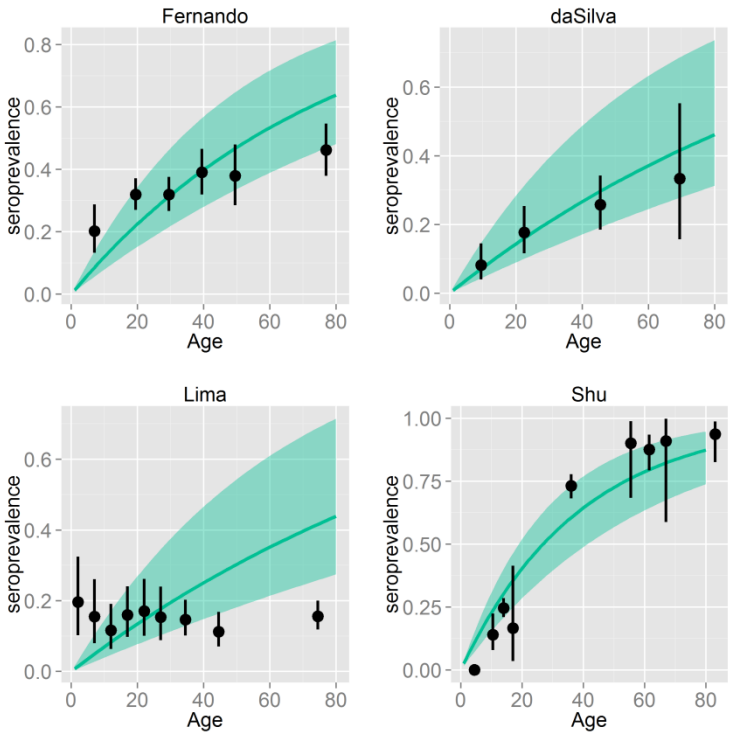

Figure 4.2: Model fits from non-serotype specific constant force of infection model (A) fitted to the extra seroprevalence datasets (as described previously [174] and chapter 2. Datasets described in Table 4.3). 95% exact confidence intervals around data points, posterior median (line) and 95% CrI (shaded area) shown.

4.3.3 Parameter Estimates

As expected, force of infection estimates varied widely between countries, with less variation seen within countries. Figure 4.3 and Figure 4.4 show the distribution of the total force of infection (λ_{total}) grouped by country (calculated by multiplying the serotype-specific force of infection by the number of serotypes in circulation) from models 1A (single reporting rate, ρ, fitted to yearly incidence data) and 2A (age-dependent reporting rate, ρ_y and ρ_o, fitted to yearly incidence data) respectively. Individual estimates are given in Table 4.4 - Table 4.5 and the model fits are shown in Figure 4.5 – Figure 4.29.

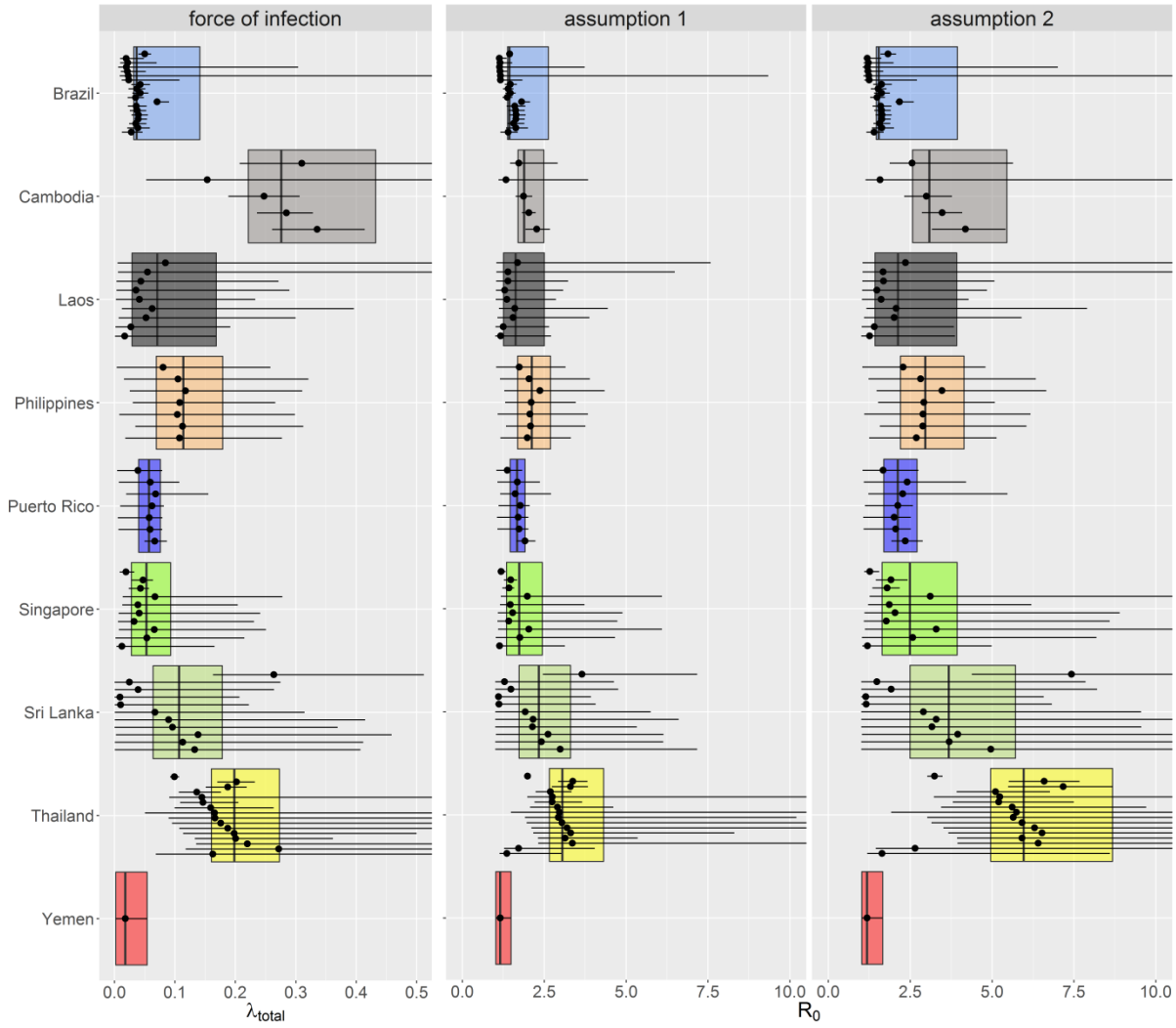

Figure 4.3: Total force of infection and corresponding R_{0i} estimates from models 1A (single reporting rate) fitted to yearly incidence data grouped by country. Each point represents the posterior median estimate and the error bars the 95% CrI. The box represents the country-specific central estimate calculated by taking the mean values of the MCMC output for each country (the line and limits of the box represents the posterior median and 95% CrI respectively).

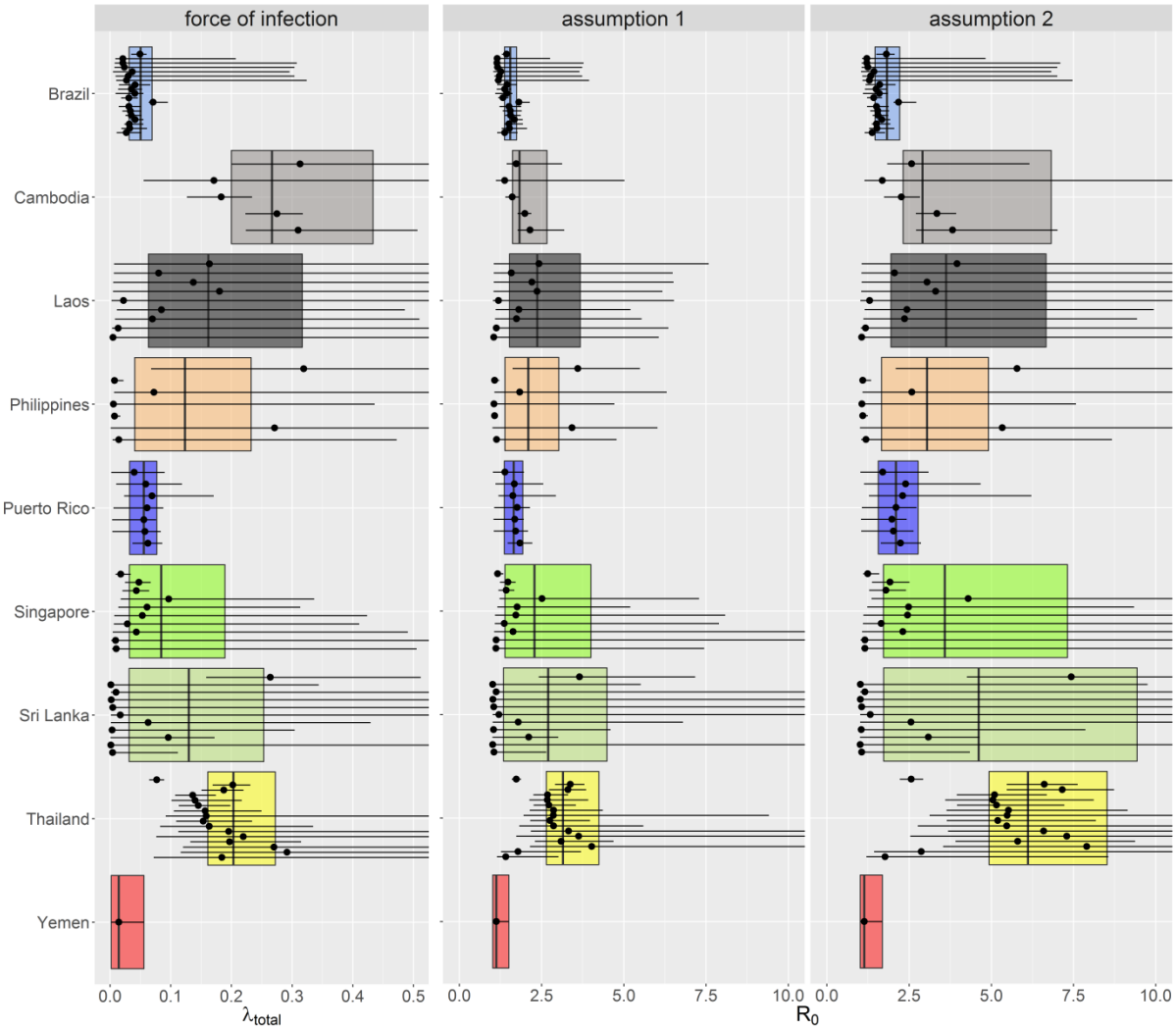

Figure 4.4: Total force of infection and corresponding R_{0i} estimates from models 2A (age-dependent reporting rate) fitted to yearly incidence data grouped by country. Each point represents the posterior median estimate and the error bars the 95% CrI. The box represents the country-specific central estimate calculated by taking the mean values of the MCMC output for each country (the line and limits of the box represents the posterior median and 95% CrI respectively).

Table 4.4: Summary parameter estimates from model 1 fitted to yearly incidence data (model 1A).

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95% CrI)	B (95% CrI)	ψ (95% CrI)	γ_1 (95% CrI)	γ_3 (95% CrI)	λ_{tot} (95% CrI)	R_{0i} * (95% CrI)		LnL
										1	2	
Cordeiro [191]	1995	Brazil	0.014 (0.011-0.023)	0.261 (0.211-0.804)	NA	0.012(0.008-0.067)	0.023 (0.014-0.060)	0.541 (0.282-0.980)	0.028 (0.023-0.046)	1.40 (1.32-1.69)	1.40 (1.32-1.69)	-17854
	1996		0.019 (0.016-0.030)	0.390 (0.338-0.810)	NA	0.010 (0.007-0.053)			0.039 (0.033-0.059)	1.63 (1.53-2.01)	1.63 (1.53-2.01)	-40383
	1997		0.018 (0.014-0.027)	0.610 (0.530-0.948)	NA	0.009 (0.006-0.047)			0.035 (0.031-0.054)	1.57 (1.48-1.90)	1.57 (1.48-1.90)	-57709
	1998		0.020 (0.018-0.027)	0.883 (0.800-0.994)	NA	0.005 (0.003-0.029)			0.039 (0.037-0.054)	1.63 (1.59-1.90)	1.63 (1.59-1.90)	-93278
	1999		0.020 (0.018-0.028)	0.572 (0.20-0.844)	NA	0.005 (0.003-0.025)			0.040 (0.036-0.055)	1.64 (1.58-1.92)	1.64 (1.58-1.92)	-64112
	2000		0.019 (0.017-0.026)	0.452 (0.407-0.719)	NA	0.006 (0.004-0.033)			0.038 (0.034-0.052)	1.64 (1.56-1.89)	1.64 (1.56-1.89)	-50580
	2001		0.018 (0.016-0.026)	0.289 (0.257-0.515)	NA	0.002 (0.001-0.009)			0.036 (0.032-0.052)	1.60 (1.52-1.90)	1.60 (1.52-1.90)	-31022
	2002		0.024 (0.023-0.031)	0.962 (0.928-0.999)	NA	0.044 (0.029-0.157)			0.071 (0.068-0.094)	1.81 (1.78-2.11)	2.18 (2.13-2.68)	-209223
	2003		0.012 (0.010-0.016)	0.382 (0.339-0.709)	NA	0.008 (0.005-0.035)			0.035 (0.031-0.049)	1.37 (1.32-1.53)	1.48 (1.41-1.73)	-47533
	2004		0.014 (0.013-0.019)	0.075 (0.069-0.128)	NA	0.006 (0.003-0.032)			0.043 (0.038-0.056)	1.46 (1.41-1.63)	1.63 (1.55-1.88)	-11581
	2005		0.012 (0.011-0.017)	0.173 (0.157-0.312)	NA	0.007 (0.004-0.035)			0.037 (0.033-0.051)	1.40 (1.35-1.56)	1.53 (1.46-1.78)	-23548
	2006		0.014 (0.013-0.021)	0.214 (0.192-0.339)	NA	0.009 (0.006-0.048)			0.042 (0.038-0.062)	1.46 (1.41-1.70)	1.62 (1.54-1.99)	-34400
Penna [178]	2001		0.006 (0.005-0.015)	0.457 (0.333-0.947)	0.007 (0.003-0.238)	0.022 (0.010-0.332)			0.023 (0.018-0.059)	1.16 (1.13-1.44)	1.24 (1.18-1.80)	-14639
	2002		0.005 (0.004-0.095)	0.304 (0.192-0.851)	0.006 (0.003-0.713)	0.022 (0.008-0.411)			0.022 (0.017-0.381)	1.15 (1.12-4.55)	1.22 (1.16-8.78)	-9046
	2003		0.006 (0.004-0.179)	0.348 (0.228-0.864)	0.007 (0.003-0.817)	0.024 (0.010-0.451)			0.022 (0.017-0.715)	1.16 (1.12-8.28)	1.23 (1.17-16.66)	-10371
	2004		0.005 (0.003-0.673)	0.214 (0.103-0.857)	0.007 (0.003-0.905)	0.036 (0.014-0.598)			0.019 (0.013-2.691)	1.14 (1.09-31.46)	1.19 (1.12-63.04)	-5540

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.4 continued (2/5).

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95% CrI)	B (95% CrI)	ψ (95% CrI)	γ_1 (95% CrI)	γ_3 (95% CrI)	λ_{tot} (95% CrI)	R_{0i} * (95% CrI)		LnL
										1	2	
Penna [178]	2005	Brazil	0.005 (0.004-0.020)	0.298 (0.196-0.883)	0.007 (0.003-0.408)	0.032 (0.014-0.384)	0.023 (0.014-0.060)	0.541 (0.282-0.980)	0.021 (0.016-0.082)	1.15 (1.11-1.62)	1.22 (1.15-2.21)	-8556
	2006		0.005 (0.004-0.014)	0.325 (0.237-0.854)	0.004 (0.002-0.206)	0.013 (0.005-0.280)			0.019 (0.015-0.058)	1.13 (1.10-1.42)	1.19 (1.14-1.77)	-7823
Vong [192]	2006	Cambodia	0.084 (0.078-0.104)	0.190 (0.183-0.201)	NA	0.014 (0.011-0.030)	0.128 (0.097-0.286)	0.506 (0.506-0.977)	0.335 (0.311-0.414)	2.27 (2.16-2.67)	4.19 (3.85-5.42)	-20854
	2007		0.071 (0.067-0.082)	0.964 (0.928-0.999)	NA	0.006 (0.004-0.012)			0.285 (0.269-0.330)	2.03 (1.97-2.24)	3.48 (3.28-4.11)	-110705
	2008		0.062 (0.057-0.077)	0.303 (0.292-0.327)	NA	0.015 (0.012-0.032)			0.248 (0.228-0.309)	1.87 (1.79-2.14)	3.00 (2.77-3.81)	-34280
Wichmann [193]	2006		0.037 (0.022-0.191)	0.353 (0.251-0.946)	NA	0.209 (0.081-0.937)			0.146 (0.087-0.765)	1.32 (1.18-3.78)	1.54 (1.26-12.89)	-31
	2007		0.078 (0.066-0.176)	0.899 (0.852-0.995)	NA	0.158 (0.047-0.833)			0.313 (0.264-0.705)	1.73 (1.60-2.98)	2.57 (2.23-5.80)	-543
Anker [183]	2000	Laos	0.004 (0.001-0.043)	0.049 (0.023-0.898)	NA	0.179 (0.066-0.909)	0.268 (0.175-0.706)	0.575 (0.328-0.981)	0.015 (0.004-0.172)	1.16 (1.04-2.75)	1.23 (1.04-3.93)	-1051
	2001		0.007 (0.001-0.051)	0.078 (0.047-0.903)	NA	0.165 (0.058-0.906)			0.026 (0.006-0.205)	1.24 (1.05-2.76)	1.39 (1.07-4.04)	-3630
	2002		0.013 (0.006-0.070)	0.135 (0.099-0.855)	NA	0.223 (0.075-0.915)			0.050 (0.026-0.282)	1.53 (1.27-3.74)	1.97 (1.45-5.63)	-8186
	2003		0.015 (0.008-0.098)	0.179 (0.125-0.810)	NA	0.278 (0.135-0.936)			0.059 (0.032-0.392)	1.56 (1.30-4.41)	2.00 (1.51-7.81)	-17292
	2004		0.010 (0.003-0.061)	0.050 (0.035-0.810)	NA	0.153 (0.047-0.869)			0.040 (0.013-0.242)	1.35 (1.12-2.92)	1.59 (1.16-4.43)	-3280
	2005		0.009 (0.002-0.073)	0.092 (0.054-0.922)	NA	0.195 (0.081-0.903)			0.034 (0.010-0.294)	1.28 (1.08-3.11)	1.47 (1.11-4.91)	-5243
	2006		0.009 (0.003-0.067)	0.093 (0.059-0.877)	NA	0.201 (0.052-0.897)			0.036 (0.012-0.267)	1.33 (1.10-3.20)	1.56 (1.14-5.00)	-5948
Khampapongpane [195]	2010		0.013 (0.007-0.401)	0.115 (0.064-0.484)	0.095 (0.033-0.932)	0.075 (0.041-0.460)			0.052 (0.029-1.603)	1.37 (1.21-15.5)	1.64 (1.32-30.5)	-33953
Prasith [194]	2010		0.022 (0.010-0.791)	0.092 (0.057-0.647)	0.336 (0.099-0.970)	0.377 (0.211-0.935)			0.086 (0.039-3.164)	1.70 (1.30-27.8)	2.39 (1.50-55.1)	-22762

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after 2 infections.

Table 4.4 continued (3/5)

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95% CrI)	B (95% CrI)	ψ (95% CrI)	γ_1 (95% CrI)	γ_3 (95% CrI)	λ_{tot} (95% CrI)	R_{0i} * (95% CrI)		LnL
										1	2	
Anker [183]	1998	Philippines	0.019 (0.001-0.065)	0.034 (0.025-0.930)	NA	0.274 (0.106-0.930)	0.178 (0.059-0.831)	0.532 (0.269-0.977)	0.077 (0.003-0.262)	1.71 (1.03-3.20)	2.25 (1.03-4.90)	-33865
	1999		0.028 (0.021-0.088)	0.006 (0.005-0.014)	NA	0.195 (0.066-0.901)			0.113 (0.085-0.351)	2.09 (1.82-4.07)	2.89 (2.46-6.77)	-9156
	2001		0.023 (0.012-0.086)	0.018 (0.013-0.666)	NA	0.278 (0.109-0.937)			0.094 (0.048-0.343)	1.96 (1.48-4.21)	2.71 (1.87-7.02)	-23843
	2002		0.025 (0.016-0.077)	0.015 (0.011-0.184)	NA	0.330 (0.167-0.936)			0.101 (0.062-0.308)	2.03 (1.64-3.78)	2.81 (2.17-5.67)	-16213
	2003		0.019 (0.001-0.067)	0.032 (0.023-0.860)	NA	0.398 (0.223-0.946)			0.077 (0.004-0.267)	1.89 (1.04-3.94)	2.68 (1.05-5.95)	-28567
	2004		0.023 (0.011-0.086)	0.016 (0.015-0.755)	NA	0.275 (0.113-0.942)			0.093 (0.045-0.345)	1.92 (1.45-4.09)	2.63 (1.80-6.79)	-22020
	2005		0.018 (0.002-0.069)	0.030 (0.021-0.842)	NA	0.269 (0.111-0.919)			0.071 (0.008-0.277)	1.65 (1.07-3.29)	2.14 (1.10-5.09)	-32194
Rigau-Perez [198]	1994	Puerto Rico	0.022 (0.020-0.028)	0.355 (0.314-0.490)	NA	0.005 (0.003-0.018)	0.391 (0.272-0.860)	0.634 (0.403-0.986)	0.067 (0.061-0.085)	1.91 (1.83-2.20)	2.35 (2.21-2.82)	-50388
	1995		0.020 (0.017-0.026)	0.033 (0.029-0.355)	NA	0.007 (0.003-0.129)			0.059 (0.051-0.079)	1.73 (1.63-2.02)	2.05 (1.89-2.52)	-3062
	1996		0.019 (0.016-0.026)	0.030 (0.026-0.358)	NA	0.009 (0.004-0.161)			0.058 (0.048-0.079)	1.71 (1.58-2.01)	2.01 (1.82-2.51)	-2697
	1997		0.020 (0.018-0.027)	0.035 (0.031-0.528)	NA	0.006 (0.003-0.149)			0.061 (0.053-0.082)	1.76 (1.65-2.05)	2.10 (1.92-2.58)	-3370
Ramos [196]	2006		0.017 (0.013-0.039)	0.369 (0.307-0.807)	NA	0.043 (0.018-0.444)			0.069 (0.050-0.155)	1.62 (1.44-2.70)	2.29 (1.82-5.44)	-203
Sharp [173]	2010		0.015 (0.011-0.026)	0.165 (0.140-0.746)	NA	0.029 (0.020-0.106)			0.061 (0.044-0.106)	1.70 (1.48-2.34)	2.46 (1.92-4.14)	-24291
Tomashek [197]	2007		0.010 (0.006-0.020)	0.053 (0.043-0.379)	NA	0.025 (0.018-0.080)			0.040 (0.025-0.081)	1.39 (1.23-1.86)	1.71 (1.37-2.83)	-7042
Anker [183]	1999	Singapore	0.004 (0.002-0.041)	0.133 (0.053-0.912)	NA	0.161 (0.050-0.919)	0.052 (0.032-0.141)	0.520 (0.259-0.976)	0.014 (0.006-0.166)	1.16 (1.07-3.13)	1.23 (1.09-4.99)	-521
	2000		0.013 (0.004-0.055)	0.023 (0.020-0.894)	NA	0.217 (0.082-0.942)			0.051 (0.015-0.220)	1.71 (1.19-4.76)	2.46 (1.29-8.36)	-362
	2001		0.016 (0.009-0.064)	0.061 (0.057-0.591)	NA	0.289 (0.098-0.955)			0.064 (0.04-0.255)	2.00 (1.48-6.20)	3.23 (1.93-11.86)	-940

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.4 continued (4/5). *Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95% CrI)	B (95% CrI)	ψ (95% CrI)	γ_1 (95% CrI)	γ_3 (95% CrI)	λ_{tot} (95% CrI)	R_{0i} * (95% CrI)		LnL
										1	2	
Anker [183]	2002	Singapore	0.009 (0.003-0.062)	0.125 (0.090-0.919)	NA	0.229 (0.068-0.945)	0.052 (0.032-0.141)	0.520 (0.259-0.976)	0.034 (0.013-0.248)	1.44 (1.16-5.02)	1.83 (1.24-9.20)	-1506
	2003		0.010 (0.004-0.058)	0.140 (0.106-0.855)	NA	0.246 (0.082-0.953)			0.039 (0.017-0.233)	1.50 (1.21-4.75)	1.96 (1.34-8.60)	-1859
	2004		0.010 (0.006-0.050)	0.345 (0.260-0.915)	NA	0.247 (0.086-0.942)			0.038 (0.023-0.200)	1.46 (1.26-3.67)	1.85 (1.44-6.09)	-4135
	2005		0.016 (0.009-0.072)	0.293 (0.258-0.822)	NA	0.280 (0.090-0.951)			0.065 (0.038-0.288)	1.94 (1.51-6.30)	3.01 (1.99-12.20)	-6857
Koh [199]	2005		0.011 (0.009-0.014)	0.267 (0.250-0.470)	NA	0.007 (0.005-0.034)			0.043 (0.038-0.058)	1.43 (1.37-1.59)	1.80 (1.66-2.20)	-20559
Ler [185]	2005		0.012 (0.011-0.016)	0.265 (0.250-0.369)	NA	0.006 (0.003-0.041)			0.047 (0.043-0.065)	1.47 (1.42-1.68)	1.91 (1.79-2.43)	-25085
	2007		0.005 (0.004-0.008)	0.337 (0.276-0.872)	NA	0.005 (0.003-0.033)			0.019 (0.015-0.033)	1.18 (1.14-1.32)	1.27 (1.19-1.56)	-14719
Anker [183]	1996	Sri Lanka	0.033 (0.020-0.105)	0.004 (0.003-0.500)	NA	0.336 (0.168-0.943)	0.216 (0.155-0.575)	0.617 (0.373-0.979)	0.133 (0.081-0.419)	2.99 (2.15-7.33)	4.98 (3.38-12.70)	-1139
	1997		0.027 (0.015-0.099)	0.002 (0.002-0.443)	NA	0.235 (0.071-0.929)			0.108 (0.060-0.395)	2.35 (1.72-5.94)	3.58 (2.40-10.96)	-810
	1998		0.034 (0.023-0.113)	0.003 (0.002-0.355)	NA	0.197 (0.059-0.920)			0.135 (0.093-0.453)	2.58 (2.07-6.08)	3.89 (3.01-11.53)	-989
	1999		0.024 (0.010-0.098)	0.004 (0.003-0.684)	NA	0.233 (0.082-0.920)			0.097 (0.040-0.392)	2.16 (1.45-5.58)	3.19 (1.83-10.18)	-1174
	2000		0.021 (0.008-0.099)	0.008 (0.006-0.739)	NA	0.225 (0.079-0.924)			0.084 (0.033-0.395)	2.09 (1.39-6.34)	3.16 (1.70-11.82)	-2302
	2001		0.018 (0.004-0.079)	0.012 (0.009-0.801)	NA	0.286 (0.128-0.948)			0.071 (0.017-0.315)	1.98 (1.20-5.75)	3.03 (1.31-9.55)	-2218
	2002		0.002 (0.000-0.057)	0.049 (0.011-0.913)	NA	0.134 (0.043-0.882)			0.008 (0.002-0.226)	1.10 (1.02-4.12)	1.13 (1.02-6.93)	-2262
	2003		0.002 (0.000-0.060)	0.025 (0.006-0.806)	NA	0.137 (0.047-0.929)			0.009 (0.001-0.242)	1.10 (1.01-4.42)	1.14 (1.01-7.54)	-1215
	2004		0.008 (0.001-0.065)	0.019 (0.013-0.905)	NA	0.176 (0.064-0.923)			0.030 (0.002-0.259)	1.37 (1.03-4.69)	1.66 (1.03-8.06)	-2864
	2005		0.007 (0.000-0.067)	0.006 (0.004-0.673)	NA	0.156 (0.056-0.898)			0.028 (0.002-0.269)	1.33 (1.02-4.56)	1.57 (1.02-7.72)	-881

Table 4.4 continued (5/5). ^All cases reported = DHF, we have assumed that all cases were due to secondary cases and fixed γ_1 and γ_3 = 0.

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95% CrI)	B (95% CrI)	ψ (95% CrI)	γ_1 (95% CrI)	γ_3 (95% CrI)	λ_{tot} (95% CrI)	R_{0i} * (95% CrI)		LnL
										1	2	
Kulatilaka [200]	2010	Sri Lanka	0.066 (0.056-0.369)	0.001 (0.001-0.001)	0.083 (0.058-0.539)	0.009 (0.006-0.052)	0.216 (0.155-0.575)	0.617 (0.373-0.979)	0.265 (0.226-1.478)	3.66 (3.18-26.65)	7.46 (6.22-85.19)	-1565
Limkittikul [201]	2000	Thailand	0.055 (0.049-0.199)	0.012 (0.009-0.016)	0.060 (0.032-0.686)	0.033 (0.018-0.213)	0.009 (0.005-0.040)	0.505 (0.263-0.978)	0.221 (0.195-0.795)	3.37 (3.04-11.67)	6.44 (5.67-23.65)	-29875
	2001		0.050 (0.045-0.094)	0.089 (0.071-0.121)	0.062 (0.033-0.213)	0.033 (0.019-0.153)			0.201 (0.178-0.377)	3.14 (2.86-5.58)	5.92 (5.25-11.26)	-225605
	2002		0.052 (0.044-0.246)	0.068 (0.036-0.103)	0.091 (0.042-0.884)	0.051 (0.027-0.244)			0.207 (0.177-0.984)	3.45 (3.01-17.10)	6.87 (5.80-35.60)	-188228
	2003		0.049 (0.041-0.229)	0.032 (0.018-0.058)	0.132 (0.051-0.825)	0.053 (0.027-0.238)			0.196 (0.165-0.915)	3.33 (2.88-16.32)	6.62 (5.50-34.43)	-107289
	2004		0.044 (0.038-0.231)	0.023 (0.011-0.036)	0.094 (0.040-0.918)	0.045 (0.023-0.232)			0.177 (0.151-0.923)	3.05 (2.68-16.59)	5.94 (5.01-34.97)	-66730
	2005		0.042 (0.036-0.179)	0.026 (0.016-0.043)	0.103 (0.045-0.691)	0.038 (0.020-0.204)			0.168 (0.144-0.715)	2.95 (2.62-12.81)	5.70 (4.86-27.29)	-79945
	2006		0.042 (0.035-0.207)	0.026 (0.015-0.045)	0.115 (0.047-0.747)	0.053 (0.028-0.223)			0.166 (0.140-0.829)	2.97 (2.59-15.33)	5.76 (4.79-32.31)	-80484
	2007		0.041 (0.036-0.154)	0.048 (0.034-0.065)	0.056 (0.029-0.569)	0.035 (0.020-0.193)			0.163 (0.144-0.616)	2.96 (2.68-11.34)	5.76 (5.04-23.94)	-112810
	2008		0.037 (0.034-0.059)	0.076 (0.066-0.091)	0.031 (0.018-0.318)	0.016 (0.009-0.106)			0.147 (0.135-0.236)	2.74 (2.57-4.19)	5.21 (4.78-8.74)	-159451
	2009		0.036 (0.033-0.179)	0.042 (0.022-0.058)	0.061 (0.029-0.900)	0.024 (0.012-0.172)			0.146 (0.131-0.715)	2.76 (2.53-13.70)	5.26 (4.68-28.46)	-103220
	2010		0.034 (0.032-0.045)	0.101 (0.092-0.119)	0.027 (0.016-0.086)	0.009 (0.005-0.052)			0.136 (0.127-0.179)	2.67 (2.54-3.38)	5.07 (4.71-6.88)	-215302
Wichmann [193]	2006		0.039 (0.025-0.156)	0.380 (0.284-0.961)	NA	0.164 (0.060-0.904)			0.156 (0.099-0.623)	1.34 (1.20-3.02)	1.60 (1.31-8.59)	-31
	2007		0.070 (0.045-0.186)	0.617 (0.551-0.954)	NA	0.232 (0.108-0.908)			0.282 (0.181-0.743)	1.75 (1.44-3.92)	2.76 (1.85-12.38)	-114
Bangkok^ [187]	2000		0.047 (0.044-0.055)	0.055 (0.054-0.058)	NA	0.013 (0.010-0.030)	0	0	0.188 (0.175-0.219)	3.31 (3.11-3.84)	7.19 (6.59-8.69)	-11467
Ratchaburi^ [187]	2000		0.050 (0.048-0.058)	0.108 (0.106-0.114)	NA	0.012 (0.009-0.034)	0	0	0.202 (0.192-0.232)	3.37 (3.23-3.82)	6.60 (6.25-7.66)	-2810
Rayong [187]	2010		0.025 (0.024-0.027)	0.114 (0.112-0.122)	NA	0.001 (0.001-0.002)	0.009 (0.005-0.040)	0.505 (0.263-0.978)	0.099 (0.097-0.107)	1.99 (1.96-2.09)	3.25 (3.16-3.50)	-4128
Ghouth [202]	2010	Yemen	0.006 (0.003-0.018)	0.159 (0.109-0.902)	NA	0.083 (0.048-0.446)	0.233 (0.088-0.943)	0.501 (0.244-0.977)	0.019 (0.008-0.055)	1.16 (1.07-1.49)	1.19 (1.07-1.67)	-1792

Table 4.5: Summary parameter estimates from model 2 fitted to yearly incidence data (model 2A).

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} * (95%CrI)		LnL
												1	2	
Cordeiro [191]	1995	Brazil	0.013 (0.008-0.026)	0.281 (0.163-0.944)	0.312 (0.183-0.939)	NA	65 (20-80)	0.009 (0.004-0.052)	0.038 (0.027-0.072)	0.553 (0.284-0.983)	0.026 (0.017-0.052)	1.36 (1.23-1.79)	1.36 (1.23-1.79)	-17854
	1996		0.016 (0.013-0.030)	0.478 (0.364-0.947)	0.382 (0.283-0.934)	NA	65 (50-80)	0.010 (0.006-0.058)			0.032 (0.025-0.059)	1.51 (1.39-2.02)	1.51 (1.39-2.02)	-40383
	1997		0.016 (0.014-0.028)	0.667 (0.516-0.979)	0.519 (0.400-0.938)	NA	65 (50-80)	0.008 (0.005-0.046)			0.032 (0.027-0.056)	1.51 (1.43-1.95)	1.51 (1.43-1.95)	-57709
	1998		0.021 (0.019-0.028)	0.718 (0.560-0.988)	0.826 (0.659-0.990)	NA	35 (20-80)	0.006 (0.003-0.040)			0.041 (0.038-0.056)	1.67 (1.61-1.94)	1.67 (1.61-1.94)	-93277
	1999		0.017 (0.015-0.027)	0.661 (0.558-0.972)	0.487 (0.390-0.929)	NA	65 (65-80)	0.003 (0.002-0.022)			0.035 (0.030-0.053)	1.55 (1.47-1.89)	1.55 (1.47-1.89)	-64111
	2000		0.017 (0.014-0.026)	0.494 (0.423-0.953)	0.458 (0.352-0.949)	NA	65 (50-80)	0.004 (0.003-0.028)			0.035 (0.029-0.052)	1.57 (1.47-1.90)	1.57 (1.47-1.90)	-50580
	2001		0.015 (0.011-0.025)	0.362 (0.281-0.951)	0.369 (0.264-0.940)	NA	65 (50-80)	0.005 (0.003-0.029)			0.029 (0.022-0.049)	1.48 (1.34-1.85)	1.48 (1.34-1.85)	-31021
	2002		0.024 (0.023-0.031)	0.952 (0.906-0.999)	0.683 (0.386-0.993)	NA	80 (65-80)	0.044 (0.029-0.177)			0.071 (0.068-0.094)	1.81 (1.77-2.12)	2.18 (2.11-2.69)	-209223
	2003		0.011 (0.009-0.017)	0.450 (0.366-0.962)	0.419 (0.333-0.956)	NA	65 (35-80)	0.008 (0.004-0.045)			0.032 (0.027-0.050)	1.34 (1.28-1.55)	1.44 (1.35-1.76)	-47533
	2004		0.014 (0.013-0.019)	0.076 (0.069-0.366)	0.398 (0.102-0.967)	NA	80 (80-80)	0.005 (0.003-0.039)			0.041 (0.038-0.056)	1.45 (1.40-1.63)	1.60 (1.54-1.89)	-11581

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (2/8).

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} * (95%CI)		LnL
												1	2	
Cordeiro [191]	2005	Brazil	0.012 (0.010-0.018)	0.180 (0.156-0.741)	0.288 (0.168-0.961)	NA	80 (65-80)	0.007 (0.004-0.040)	0.038 (0.027-0.072)	0.553 (0.284-0.983)	0.036 (0.031-0.053)	1.38 (1.32-1.59)	1.50 (1.41-1.82)	-23548
	2006		0.014 (0.012-0.022)	0.215 (0.189-0.806)	0.290 (0.201-0.946)	NA	80 (50-80)	0.009 (0.006-0.054)			0.042 (0.036-0.066)	1.45 (1.39-1.76)	1.61 (1.51-2.09)	-34400
Penna [178]	2001		0.007 (0.0052-0.081)	0.277 (0.093-0.922)	0.473 (0.288-0.971)	0.020 (0.005-0.883)	70 (50-90)	0.047 (0.015-0.671)			0.027 (0.019-0.226)	1.19 (1.13-7.75)	1.30 (1.19-8.57)	-14641
	2002		0.006 (0.004-0.076)	0.239 (0.047-0.879)	0.397 (0.216-0.948)	0.011 (0.003-0.907)	70 (50-90)	0.046 (0.012-0.704)			0.024 (0.016-0.362)	1.17 (1.11-5.81)	1.25 (1.15-7.72)	-9048
	2003		0.006 (0.004-0.074)	0.219 (0.047-0.861)	0.415 (0.246-0.953)	0.020 (0.004-0.939)	70 (50-90)	0.059 (0.016-0.680)			0.026 (0.017-0.295)	1.18 (1.12-5.03)	1.27 (1.16-7.05)	-10374
	2004		0.005 (0.003-0.076)	0.169 (0.049-0.841)	0.340 (0.170-0.954)	0.009 (0.002-0.809)	70 (50-90)	0.048 (0.017-0.675)			0.021 (0.013-0.305)	1.15 (1.09-5.62)	1.21 (1.12-7.33)	-5541
	2005		0.006 (0.004-0.077)	0.204 (0.052-0.851)	0.396 (0.214-0.956)	0.014 (0.004-0.910)	70 (50-90)	0.062 (0.021-0.705)			0.024 (0.016-0.311)	1.17 (1.11-3.68)	1.26 (1.15-7.83)	-8558
	2006		0.005 (0.004-0.016)	0.279 (0.137-0.853)	0.409 (0.237-0.951)	0.006 (0.002-0.538)	70 (50-90)	0.023 (0.007-0.423)			0.020 (0.014-0.063)	1.14 (1.10-7.28)	1.20 (1.13-14.59)	-7825
Vong [192]	2006	Cambodia	0.077 (0.069-0.127)	0.190 (0.177-0.221)	0.097 (0.055-0.798)	NA	16 (15-21)	0.011 (0.008-0.027)	0.141 (0.108-0.369)	0.601 (0.368-0.980)	0.309 (0.276-0.507)	2.15 (2.00-3.20)	3.82 (3.37-7.03)	-20853
	2007		0.068 (0.065-0.080)	0.955 (0.912-0.999)	0.307 (0.159-0.947)	NA	20 (19-21)	0.004 (0.003-0.010)			0.274 (0.259-0.318)	1.98 (1.92-2.19)	3.33 (3.15-3.94)	-110702
	2008		0.046 (0.042-0.058)	0.344 (0.326-0.424)	0.042 (0.030-0.123)	NA	18 (18-18)	0.005 (0.004-0.012)			0.184 (0.167-0.233)	1.61 (1.54-1.81)	2.27 (2.10-2.82)	-34269

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (3/8).

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} * (95%CrI)		LnL
												1	2	
Wichmann [193]	2006	Cambodia	0.041 (0.023-0.254)	0.317 (0.229-0.927)	0.545 (0.303-0.980)	NA	10 (10-15)	0.228 (0.094-0.937)	0.141 (0.108-0.369)	0.601 (0.368-0.980)	0.164 (0.092-0.905)	1.36 (1.19-5.51)	1.65 (1.28-7.28)	-31
	2007		0.078 (0.065-0.187)	0.880 (0.814-0.993)	0.637 (0.351-0.986)	NA	15 (10-15)	0.158 (0.049-0.886)			0.314 (0.261-0.747)	1.73 (1.59-3.12)	2.58 (2.22-6.16)	-543
Anker [183]	2000	Laos	0.001 (0.001-0.156)	0.368 (0.082-0.948)	0.269 (0.1089-0.941)	NA	15 (15-15)	0.206 (0.076-0.909)	0.115 (0.062-0.461)	0.496 (0.261-0.975)	0.006 (0.003-0.623)	1.06 (1.03-6.23)	1.07 (1.03-11.03)	-1052
	2001		0.004 (0.002-0.171)	0.263 (0.016-0.958)	0.243 (0.112-0.938)	NA	15 (15-15)	0.227 (0.086-0.918)			0.017 (0.008-0.685)	1.16 (1.07-6.55)	1.23 (1.09-13.88)	-3631
	2002		0.019 (0.007-0.146)	0.120 (0.046-0.929)	0.243 (0.164-0.917)	NA	15 (15-15)	0.234 (0.089-0.919)			0.076 (0.029-0.584)	1.81 (1.30-6.13)	2.48 (1.52-10.86)	-8186
	2003		0.023 (0.008-0.123)	0.135 (0.072-0.950)	0.379 (0.248-0.965)	NA	15 (15-15)	0.248 (0.108-0.926)			0.092 (0.033-0.492)	1.88 (1.32-5.26)	2.54 (1.54-10.10)	-17292
	2004		0.007 (0.002-0.177)	0.152 (0.014-0.957)	0.229 (0.100-0.922)	NA	15 (15-15)	0.221 (0.080-0.928)			0.028 (0.008-0.706)	1.24 (1.07-6.53)	1.40 (1.09-14.37)	-3281
	2005		0.045 (0.004-0.162)	0.026 (0.019-0.954)	0.303 (0.148-0.956)	NA	15 (15-15)	0.233 (0.091-0.923)			0.179 (0.018-0.648)	2.35 (1.14-5.63)	3.29 (1.22-11.94)	-5243
	2006		0.045 (0.006-0.167)	0.030 (0.020-0.935)	0.292 (0.126-0.944)	NA	15 (15-15)	0.225 (0.088-0.929)			0.180 (0.026-0.669)	2.54 (1.23-6.44)	3.65 (1.37-13.88)	-5948
Khampapongpane [195]	2010		0.019 (0.009-0.161)	0.092 (0.040-0.658)	0.229 (0.140-0.895)	0.110 (0.031-0.869)	40 (30-40)	0.085 (0.040-0.573)			0.075 (0.034-0.605)	1.54 (1.24-9.00)	1.97 (1.39-10.81)	-33953
Prasith [194]	2010		0.043 (0.016-0.281)	0.068 (0.045-0.524)	0.346 (0.171-0.957)	0.358 (0.137-0.962)	80 (15-80)	0.357 (0.189-0.942)			0.172 (0.066-0.713)	2.51 (1.52-5.42)	4.13 (1.98-6.62)	-22762

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (4/8)

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} * (95%CrI)		LnL
												1	2	
Anker [183]	1998	Philippines	0.006 (0.002-0.127)	0.196 (0.017-0.965)	0.097 (0.041-0.870)	NA	15 (15-15)	0.278 (0.102-0.924)	0.082 (0.048-0.225)	0.323 (0.140-0.954)	0.022 (0.010-0.508)	1.20 (1.09-5.05)	1.32 (1.12-9.40)	-33864
	1999		0.060 (0.001-0.147)	0.004 (0.003-0.933)	0.111 (0.036-0.857)	NA	15 (15-15)	0.351 (0.159-0.941)			0.239 (0.005-0.587)	3.17 (1.04-6.01)	4.80 (1.05-11.80)	-9157
	2001		0.002 (0.001-0.066)	0.601 (0.340-0.981)	0.099 (0.055-0.652)	NA	15 (15-15)	0.252 (0.095-0.929)			0.008 (0.005-0.264)	1.07 (1.05-3.54)	1.10 (1.06-5.54)	-23843
	2002		0.002 (0.001-0.124)	0.507 (0.127-0.970)	0.116 (0.043-0.818)	NA	15 (15-15)	0.348 (0.177-0.936)			0.007 (0.004-0.496)	1.07 (1.04-5.15)	1.09 (1.05-8.55)	-16213
	2003		0.011 (0.003-0.135)	0.093 (0.012-0.941)	0.060 (0.030-0.810)	NA	15 (15-15)	0.373 (0.188-0.937)			0.044 (0.012-0.540)	1.49 (1.13-6.34)	1.92 (1.19-10.80)	-28567
	2004		0.002 (0.001-0.125)	0.432 (0.158-0.974)	0.083 (0.036-0.789)	NA	15 (15-15)	0.266 (0.101-0.941)			0.009 (0.005-0.501)	1.08 (1.05-5.39)	1.11 (1.06-10.03)	-22019
	2005		0.057 (0.004-0.141)	0.012 (0.009-0.938)	0.170 (0.070-0.874)	NA	15 (15-15)	0.354 (0.173-0.958)			0.226 (0.016-0.566)	2.92 (1.14-5.48)	4.32 (1.21-10.57)	-32194
Rigau-Perez [198]	1994	Puerto Rico	0.022 (0.018-0.029)	0.438 (0.376-0.894)	0.517 (0.400-0.962)	NA	55 (25-99)	0.003 (0.002-0.016)	0.198 (0.098-0.648)	0.539 (0.299-0.979)	0.066 (0.053-0.087)	1.90 (1.70-2.23)	2.33 (2.00-2.89)	-50387
	1995		0.019 (0.017-0.027)	0.040 (0.034-0.636)	0.403 (0.139-0.972)	NA	85 (85-85)	0.007 (0.003-0.159)			0.058 (0.051-0.080)	1.73 (1.62-2.02)	2.05 (1.87-2.53)	-3062
	1996		0.018 (0.010-0.026)	0.037 (0.032-0.846)	0.397 (0.151-0.960)	NA	85 (75-85)	0.011 (0.005-0.285)			0.055 (0.030-0.077)	1.67 (1.34-1.98)	1.96 (1.44-2.46)	-2697
	1997		0.020 (0.015-0.029)	0.042 (0.036-0.831)	0.359 (0.109-0.973)	NA	85 (75-85)	0.010 (0.004-0.235)			0.061 (0.046-0.087)	1.75 (1.56-2.14)	2.09 (1.78-2.72)	-3371

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (5/8)

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} * (95%CrI)		LnL
												1	2	
Ramos [196]	2006	Puerto Rico	0.017 (0.013-0.042)	0.441 (0.351-0.930)	0.470 (0.327-0.959)	NA	40 (30-61)	0.038 (0.014-0.450)	0.198 (0.098-0.648)	0.539 (0.299-0.979)	0.069 (0.050-0.170)	1.62 (1.43-2.92)	2.29 (1.81-6.17)	-203
Sharp [173]	2010		0.015 (0.009-0.030)	0.195 (0.158-0.943)	0.276 (0.194-0.940)	NA	60 (20-81)	0.020 (0.012-0.076)			0.061 (0.035-0.119)	1.69 (1.38-2.56)	2.45 (1.68-4.69)	-24289
Tomashek [197]	2007		0.010 (0.003-0.022)	0.066 (0.051-0.936)	0.240 (0.096-0.947)	NA	70 (30-85)	0.023 (0.015-0.075)			0.039 (0.011-0.087)	1.37 (1.10-1.93)	1.67 (1.14-3.01)	-7042
Anker [183]	1999	Singapore	0.003 (0.001-0.124)	0.312 (0.025-0.954)	0.307 (0.135-0.936)	NA	15 (15-15)	0.231 (0.065-0.954)	0.042 (0.023-0.131)	0.505 (0.258-0.971)	0.010 (0.006-0.496)	1.11 (1.07-7.32)	1.16 (1.08-14.52)	-521
	2000		0.003 (0.001-0.169)	0.321 (0.012-0.970)	0.171 (0.064-0.928)	NA	15 (15-15)	0.264 (0.107-0.951)			0.010 (0.005-0.675)	1.13 (1.06-12.55)	1.18 (1.07-14.64)	-362
	2001		0.010 (0.003-0.124)	0.146 (0.027-0.955)	0.178 (0.079-0.938)	NA	15 (15-15)	0.320 (0.124-0.958)			0.041 (0.013-0.496)	1.59 (1.16-7.13)	2.20 (1.24-12.77)	-940
	2002		0.008 (0.003-0.104)	0.197 (0.035-0.962)	0.282 (0.145-0.951)	NA	15 (15-15)	0.288 (0.099-0.956)			0.032 (0.013-0.417)	1.42 (1.16-8.00)	1.77 (1.24-14.23)	-1506
	2003		0.014 (0.005-0.105)	0.135 (0.043-0.946)	0.265 (0.150-0.948)	NA	15 (15-15)	0.314 (0.116-0.960)			0.055 (0.018-0.421)	1.75 (1.22-8.03)	2.53 (1.35-16.24)	-1859
	2004		0.016 (0.007-0.078)	0.233 (0.104-0.937)	0.432 (0.318-0.961)	NA	15 (15-15)	0.298 (0.096-0.959)			0.062 (0.029-0.310)	1.77 (1.34-5.15)	2.52 (1.60-9.25)	-4135
	2005		0.023 (0.011-0.082)	0.241 (0.132-0.947)	0.372 (0.288-0.944)	NA	15 (15-15)	0.299 (0.106-0.950)			0.092 (0.044-0.328)	2.42 (1.61-7.12)	4.09 (2.22-14.06)	-6857

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (6/8).

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} * (95%CrI)		LnL
												1	2	
Koh [199]	2005	Singapore	0.011 (0.009-0.016)	0.266 (0.238-0.768)	0.361 (0.278-0.945)	NA	65 (55-85)	0.007 (0.004-0.036)	0.042 (0.023-0.131)	0.505 (0.258-0.971)	0.043 (0.035-0.064)	1.43 (1.34-1.66)	1.80 (1.60-2.37)	-20559
Ler [185]	2005		0.012 (0.010-0.017)	0.268 (0.250-0.734)	0.342 (0.256-0.961)	NA	81 (55-81)	0.006 (0.003-0.056)			0.047 (0.041-0.068)	1.47 (1.41-1.72)	1.91 (1.76-2.54)	-25085
	2007		0.004 (0.003-0.009)	0.390 (0.280-0.952)	0.463 (0.294-0.959)	NA	81 (45-81)	0.005 (0.002-0.034)			0.017 (0.013-0.036)	1.16 (1.12-1.36)	1.24 (1.16-1.64)	-14719
Anker [183]	1996	Sri Lanka	0.001 (0.001-0.028)	0.424 (0.015-0.969)	0.087 (0.032-0.854)	NA	15 (15-15)	0.338 (0.163-0.947)	0.091 (0.066-0.216)	0.529 (0.286-0.975)	0.004 (0.002-0.140)	1.05 (1.02-2.81)	1.05 (1.03-5.12)	-1139
	1997		0.001 (0.000-0.093)	0.535 (0.221-0.978)	0.125 (0.054-0.789)	NA	15 (15-15)	0.229 (0.072-0.918)			0.002 (0.001-0.174)	1.02 (1.01-4.17)	1.02 (1.01-7.27)	-810
	1998		0.001 (0.000-0.024)	0.381 (0.002-0.971)	0.113 (0.047-0.846)	NA	15 (15-15)	0.287 (0.105-0.947			0.003 (0.002-0.125)	1.03 (1.02-3.73)	1.03 (1.02-5.56)	-990
	1999		0.001 (0.000-0.026)	0.260 (0.002-0.962)	0.170 (0.067-0.922)	NA	15 (15-15)	0.308 (0.115-0.956)			0.005 (0.002-0.103)	1.05 (1.02-2.54)	1.06 (1.02-5.02)	-1175
	2000		0.084 (0.001-0.103)	0.005 (0.003-0.951)	0.198 (0.063-0.933)	NA	15 (15-15)	0.330 (0.133-0.943)			0.334 (0.004-0.151)	5.53 (1.05-2.74)	9.91 (1.06-5.53)	-2302
	2001		0.002 (0.001-0.031)	0.288 (0.005-0.968)	0.150 (0.045-0.918)	NA	15 (15-15)	0.321 (0.147-0.936)			0.009 (0.004-0.150)	1.10 (1.04-2.40)	1.14 (1.05-5.98)	-2218
	2002		0.002 (0.001-0.075)	0.160 (0.004-0.964)	0.284 (0.121-0.948)	NA	15 (15-15)	0.256 (0.092-0.942)			0.010 (0.003-0.270)	1.11 (1.03-6.22)	1.15 (1.04-12.97)	-2263

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (7/8).

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} *(95%CrI)		LnL
												1	2	
Anker [183]	2003	Sri Lanka	0.001 (0.000-0.055)	0.463 (0.152-0.970)	0.269 (0.116-0.908)	NA	15 (15-15)	0.205 (0.069-0.909)	0.091 (0.066-0.216)	0.529 (0.286-0.975)	0.002 (0.001-0.218)	1.03 (1.01-6.45)	1.03 (1.02-13.2)	-1215
	2004		0.003 (0.001-0.059)	0.162 (0.005-0.957)	0.228 (0.083-0.948)	NA	15 (15-15)	0.301 (0.105-0.957)			0.011 (0.004-0.240)	1.13 (1.04-6.74)	1.18 (1.05-14.23)	-2865
	2005		0.001 (0.000-0.086)	0.428 (0.098-0.962)	0.246 (0.107-0.899)	NA	15 (15-15)	0.188 (0.057-0.936)			0.002 (0.001-0.324)	1.02 (1.01-7.22)	1.02 (1.01-15.06)	-882
Kulatilaka [200]	2010		0.066 (0.058-0.128)	0.001 (0.001-0.002)	0.459 (0.216-0.979)	0.079 (0.058-0.507)	65 (65-65)	0.010 (0.006-0.057)			0.266 (0.230-0.467)	3.67 (3.23-7.54)	7.48 (6.36-14.43)	-1566
Limkittikul [201]	2000	Thailand	0.060 (0.051-0.439)	0.009 (0.004-0.016)	0.457 (0.173-0.974)	0.127 (0.040-0.901)	80 (80-80)	0.056 (0.025-0.280)	0.008 (0.004-0.036)	0.466 (0.235-0.972)	0.240 (0.204-0.758)	3.61 (3.16-8.14)	6.99 (5.95-16.47)	-29877
	2001		0.049 (0.043-0.080)	0.099 (0.087-0.127)	0.322 (0.122-0.960)	0.043 (0.025-0.148)	80 (65-80)	0.027 (0.016-0.133)			0.194 (0.173-0.319)	3.06 (2.79-4.75)	5.73 (5.10-9.50)	-225604
	2002		0.051 (0.044-0.275)	0.070 (0.050-0.104)	0.354 (0.124-0.963)	0.084 (0.039-0.447)	80 (65-80)	0.049 (0.027-0.231)			0.203 (0.174-0.901)	3.38 (2.97-19.26)	6.71 (5.70-39.95)	-188228
	2003		0.063 (0.044-0.458)	0.015 (0.010-0.058)	0.451 (0.189-0.970)	0.429 (0.098-0.965)	80 (80-80)	0.088 (0.048-0.294)			0.253 (0.175-0.831)	4.21 (3.01-14.14)	8.72 (5.83-27.66)	-107291
	2004		0.041 (0.037-0.073)	0.030 (0.026-0.039)	0.385 (0.133-0.962)	0.036 (0.019-0.281)	80 (80-80)	0.025 (0.016-0.134)			0.163 (0.146-0.291)	2.86 (2.62-4.86)	5.45 (4.85-10.22)	-66728
	2005		0.040 (0.036-0.271)	0.032 (0.021-0.044)	0.391 (0.132-0.970)	0.059 (0.029-0.910)	80 (80-80)	0.029 (0.016-0.202)			0.161 (0.143-0.308)	2.86 (2.60-4.53)	5.46 (4.81-10.86)	-79944

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.5 continued (8/8).

Author [Ref]	Year	Country	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} (95%CrI)*		LnL
												1	2	
Limkittikul [201]	2006	Thailand	0.041 (0.035-0.267)	0.028 (0.019-0.046)	0.409 (0.158-0.970)	0.094 (0.034-0.670)	80 (80-80)	0.046 (0.026-0.207)	0.008 (0.004-0.036)	0.466 (0.235-0.972)	0.164 (0.141-0.680)	2.94 (2.61-10.1)	5.68 (4.84-19.90)	-80483
	2007		0.039 (0.035-0.062)	0.054 (0.046-0.067)	0.323 (0.114-0.956)	0.034 (0.018-0.133)	80 (65-80)	0.025 (0.016-0.120)			0.157 (0.140-0.247)	2.86 (2.62-4.32)	5.51 (4.88-9.04)	-112810
	2008		0.036 (0.034-0.050)	0.077 (0.071-0.092)	0.367 (0.136-0.973)	0.028 (0.015-0.097)	80 (65-80)	0.014 (0.009-0.071)			0.145 (0.134-0.198)	2.72 (2.56-3.54)	5.16 (4.74-7.22)	-159451
	2009		0.036 (0.032-0.071)	0.043 (0.033-0.059)	0.347 (0.105-0.966)	0.053 (0.027-0.227)	80 (80-80)	0.021 (0.012-0.117)			0.144 (0.130-0.284)	2.73 (2.53-5.13)	5.19 (4.66-10.87)	-103220
	2010		0.033 (0.031-0.044)	0.103 (0.093-0.124)	0.284 (0.109-0.961)	0.028 (0.016-0.145)	80 (65-80)	0.009 (0.005-0.053)			0.134 (0.125-0.176)	2.65 (2.51-3.33)	5.01 (4.64-6.75)	-215303
Wichmann [193]	2006		0.045 (0.026-0.164)	0.340 (0.259-0.933)	0.573 (0.344-0.981)	NA	10 (10-15)	0.184 (0.067-0.897)			0.179 (0.105-0.654)	1.40 (1.22-3.17)	1.74 (1.34-9.44)	-31
	2007		0.073 (0.049-0.177)	0.603 (0.529-0.956)	0.600 (0.376-0.984)	NA	15 (10-15)	0.241 (0.100-0.919)			0.292 (0.196-0.707)	1.79 (1.49-3.70)	2.87 (1.97-11.33)	-114
Bangkok^ [186]	2000		0.047 (0.044-0.055)	0.055 (0.054-0.058)	0.508 (0.248-0.974)	NA	98 (98-98)	0.013 (0.010-0.032)	0	0	0.188 (0.175-0.219)	3.30 (3.10-3.83)	7.17 (6.57-8.68)	-11467
Ratchaburi^ [186]	2000		0.050 (0.048-0.058)	0.109 (0.106-0.114)	0.502 (0.247-0.974)	NA	98 (98-98)	0.012 (0.009-0.031)	0	0	0.202 (0.191-0.232)	3.37 (3.22-3.82)	6.59 (6.23-7.66)	-2810
Rayong [186]	2010		0.019 (0.018-0.022)	0.156 (0.147-0.187)	0.074 (0.069-0.088)	NA	28 (28-31)	0.000 (0.000-0.001)	0.008 (0.004-0.036)	0.466 (0.235-0.972)	0.077 (0.072-0.089)	1.73 (1.68-1.87)	2.56 (2.44-2.93)	-4115
Ghouth [202]	2010	Yemen	0.005 (0.002-0.021)	0.201 (0.112-0.947)	0.384 (0.172-0.973)	NA	80 (55-80)	0.090 (0.049-0.463)	0.222 (0.090-0.931)	0.491 (0.248-0.980)	0.015 (0.007-0.063)	1.13 (1.06-1.57)	1.15 (1.06-1.78)	-1792

*Assumption1 = 4 infection, assumption 2 = 2 infections. ^All cases reported = DHF, we have assumed that all cases were due to secondary cases and fixed γ_1 and $\gamma_3 = 0$.

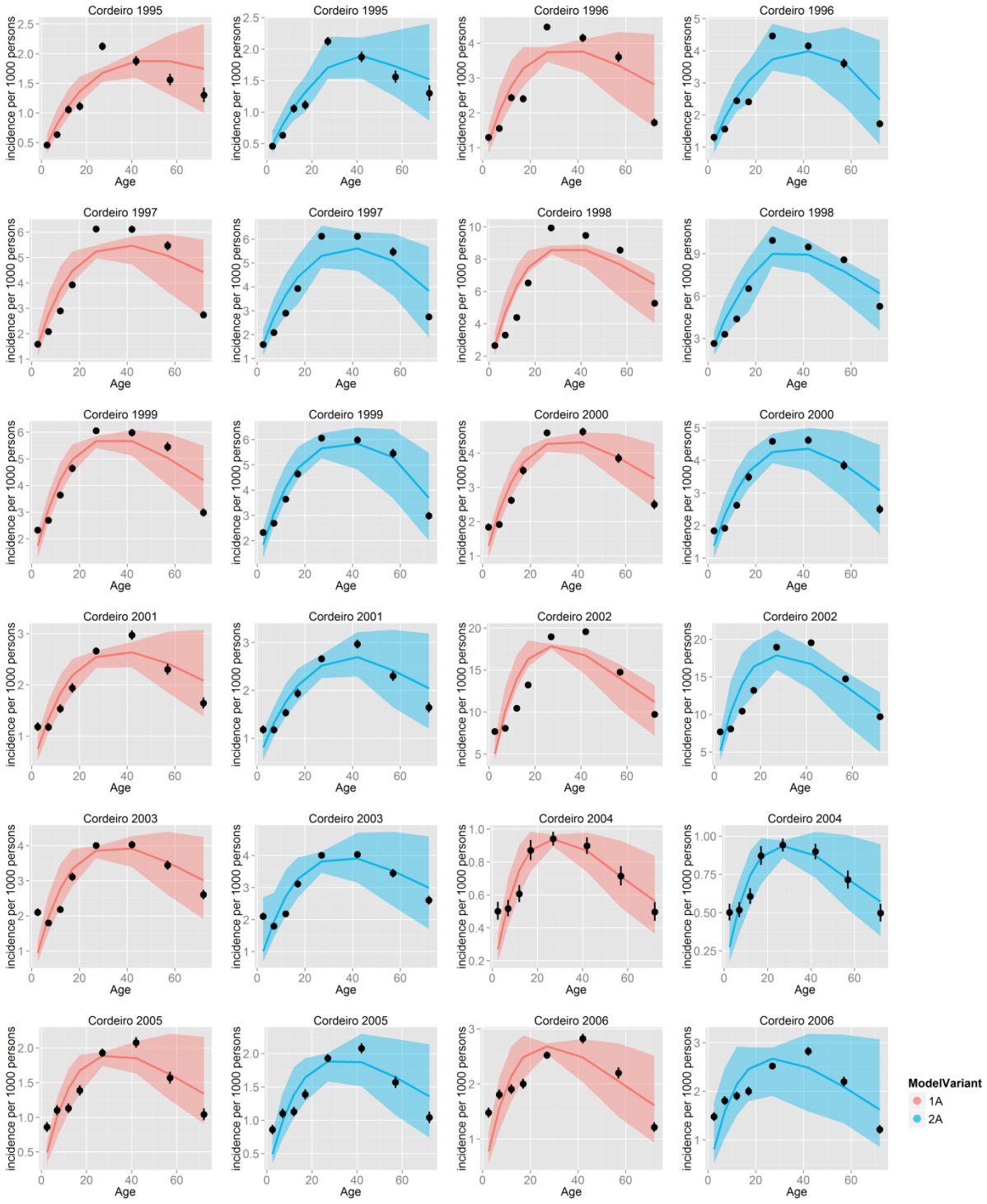

Figure 4.5: Model fits of models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Brazil (Cordeiro *et al*. [191]). 95% exact confidence intervals shown around data points, posterior median (line) and 95% credible interval (shaded area) shown.

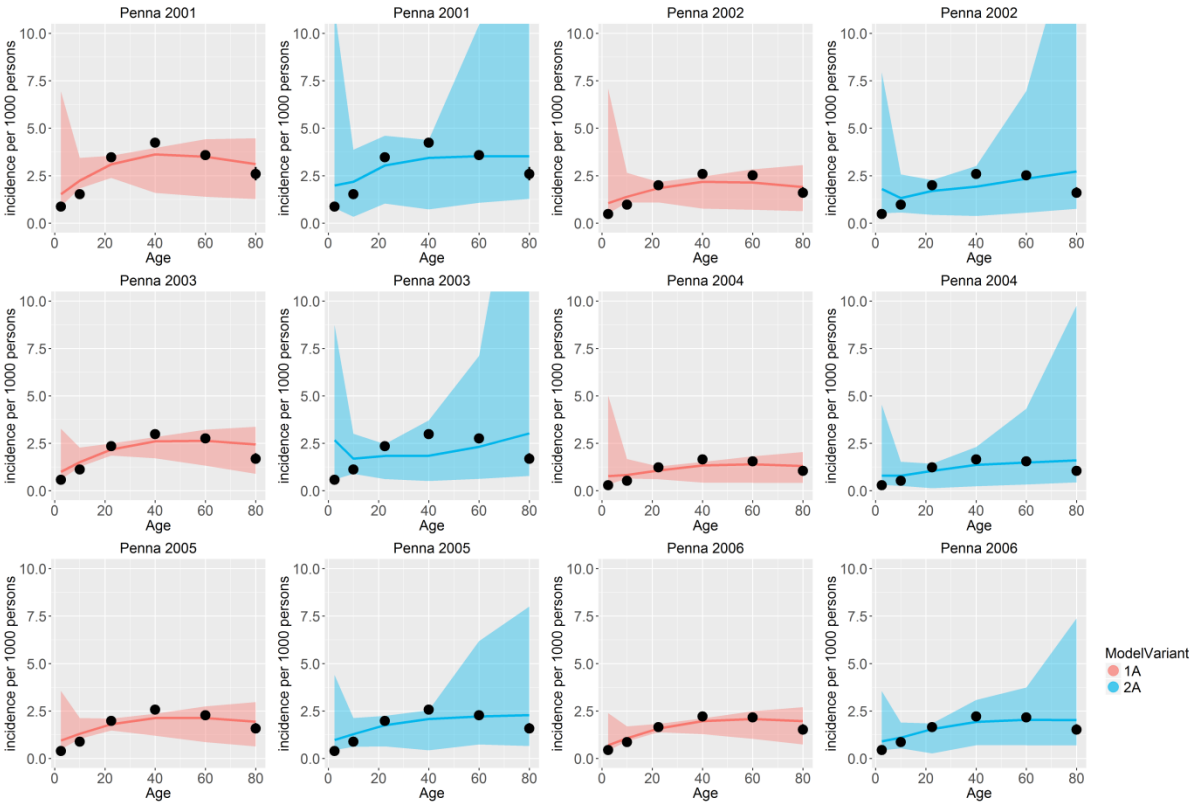

Figure 4.6: Model fits of models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Brazil (Penna *et al*. [178]). 95% exact confidence intervals shown around data points, posterior median (line) and 95% credible interval (shaded area) shown.

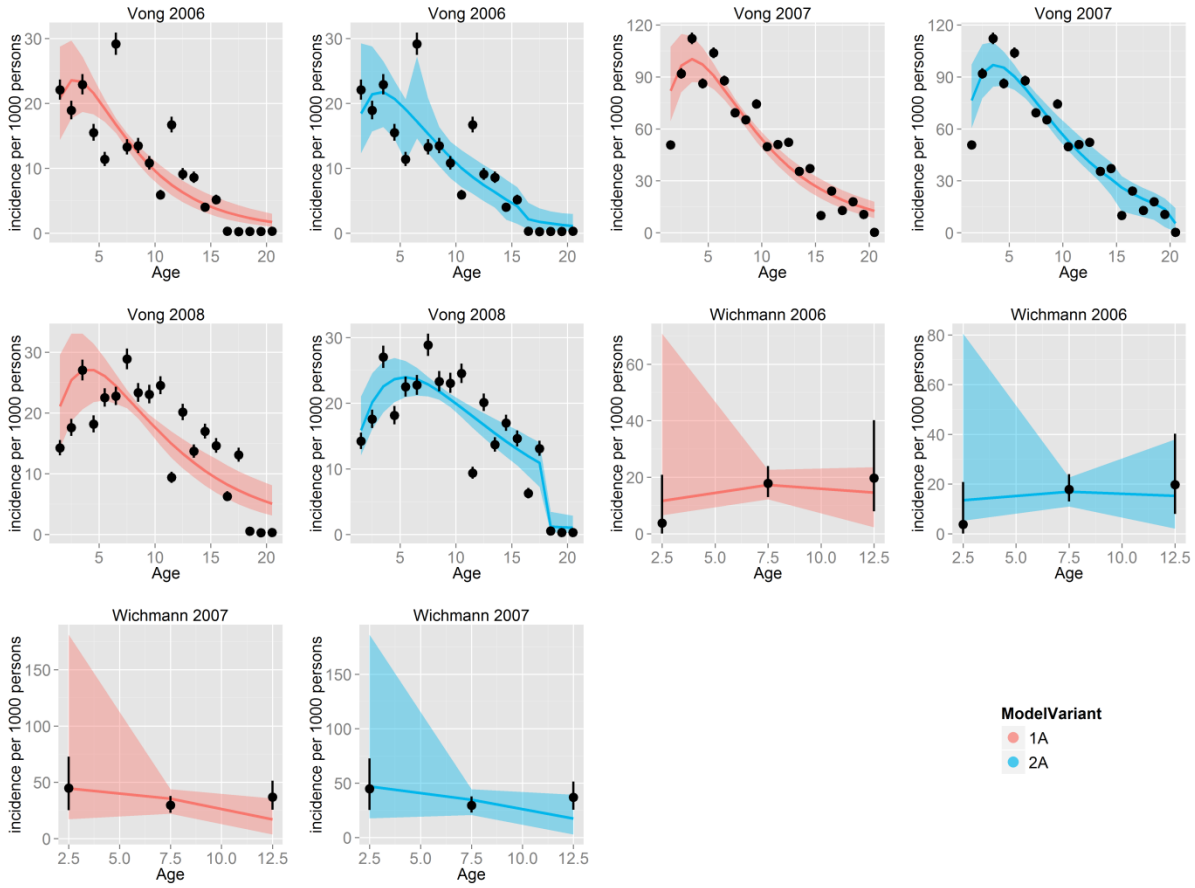

Figure 4.7: Model fits of models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Cambodia (Vong *et al*. [192] and Wichmann *et al*. [193]).
95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

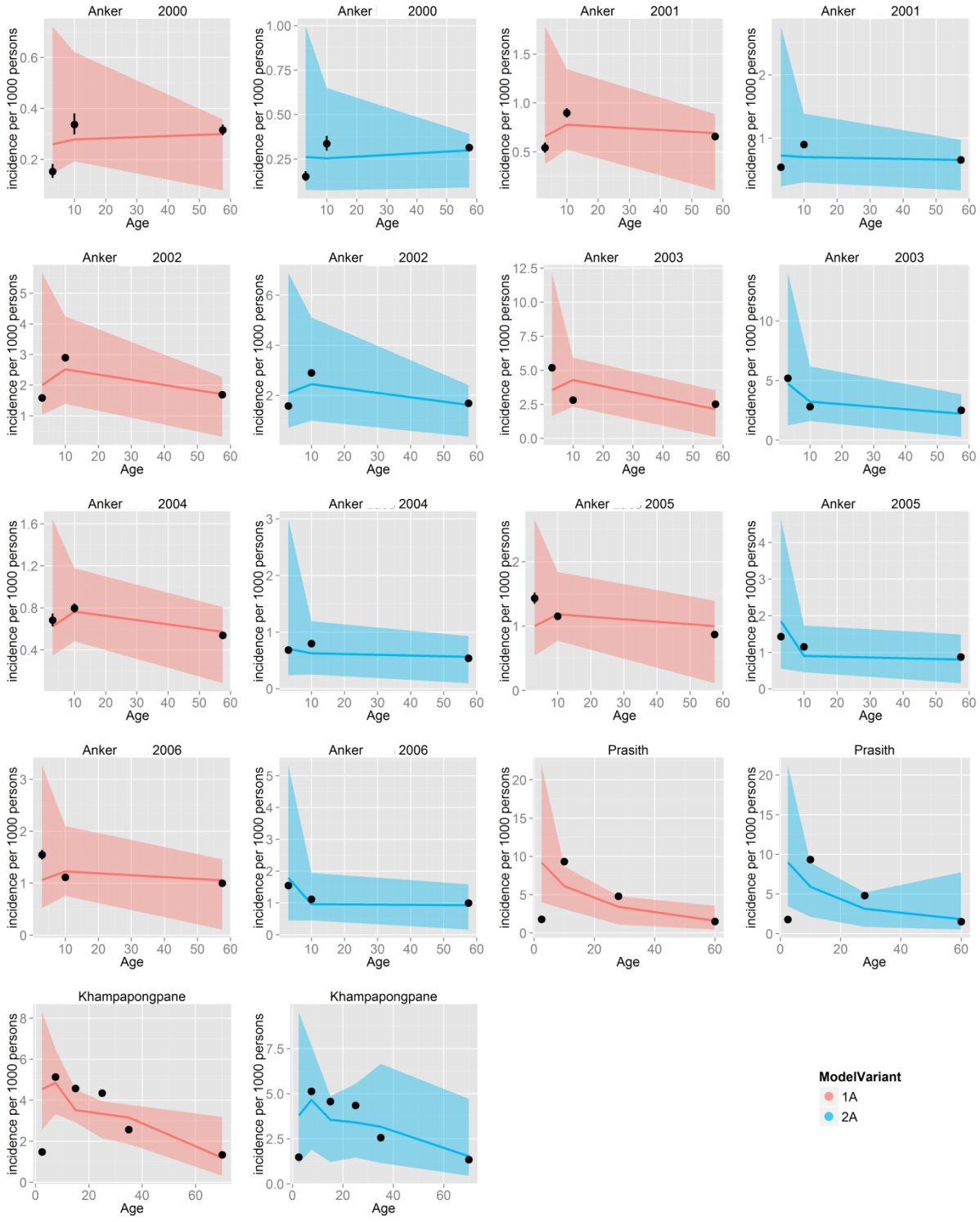

Figure 4.8: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Laos (Anker *et al.,* [183] Prasith *et al.,* [194] and Khampapongpane *et al.* [195]). 95% exact confidence interval around data points, posterior median (line), and 95% credible interval (shaded area) shown.

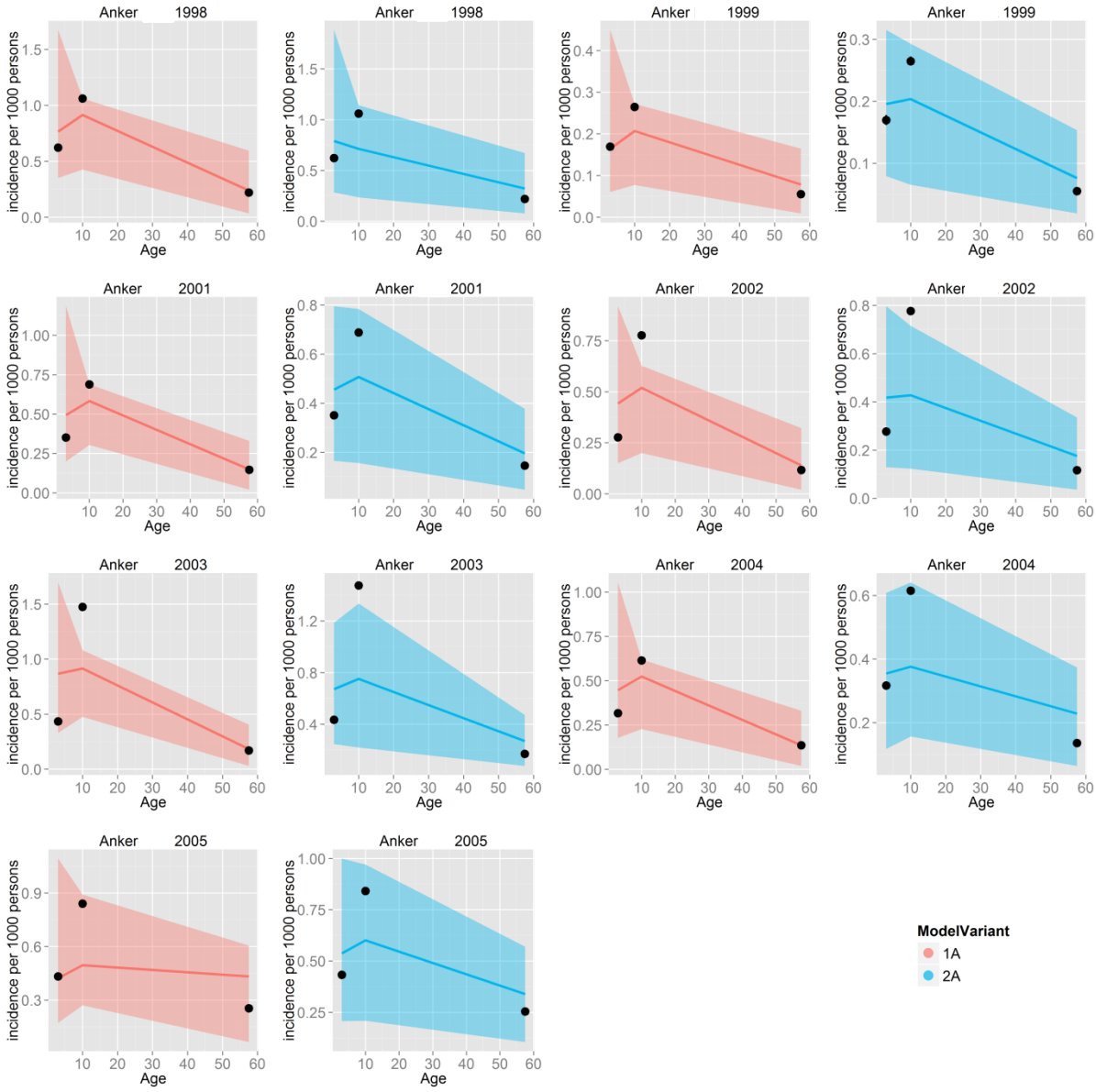

Figure 4.9: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from the Philippines (Anker *et al.* [183]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible intervals (shaded area) shown.

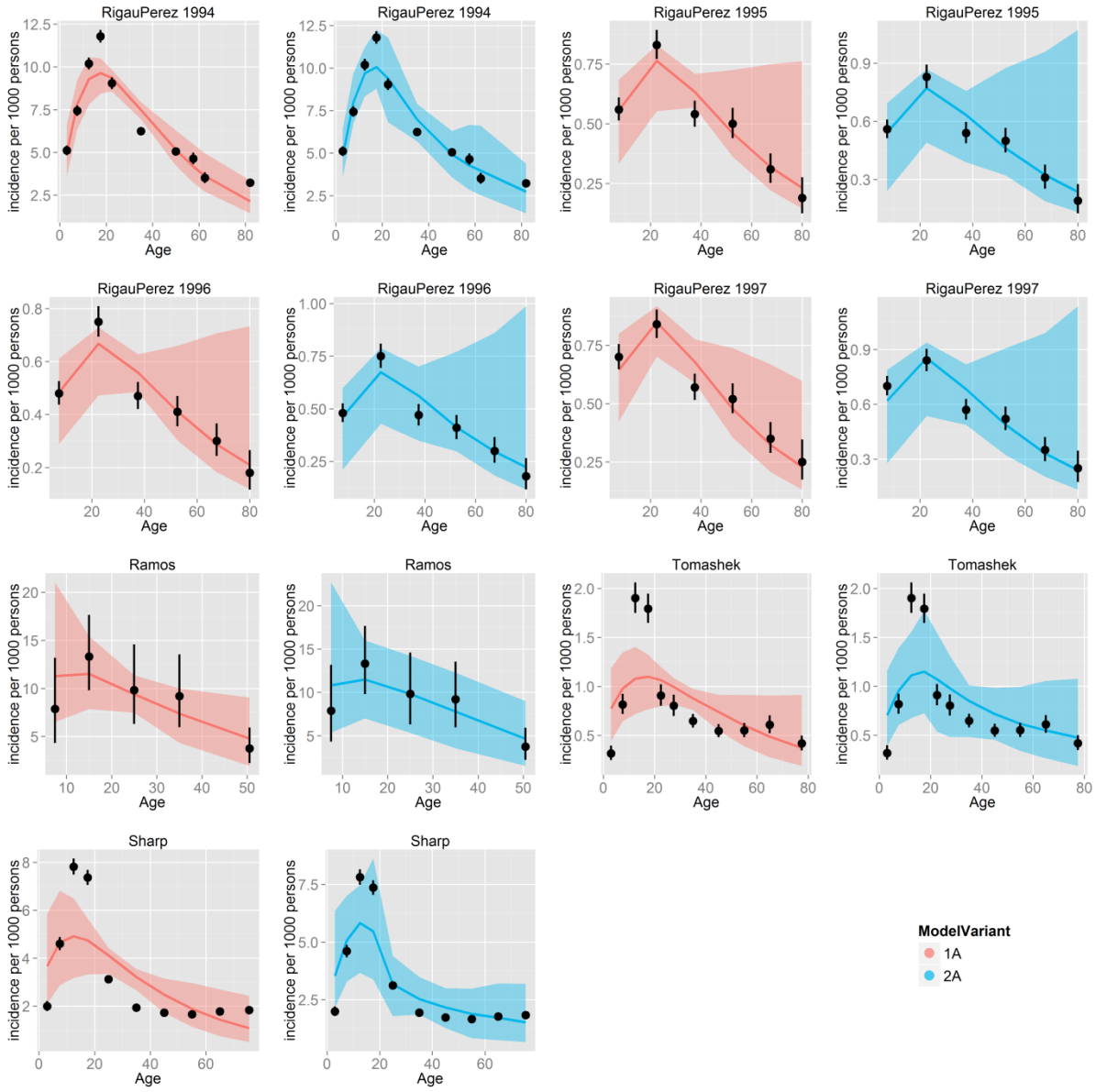

Figure 4.10: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Puerto Rico (Rigau-Perez *et al.*, [198] Ramos *et al.*, [196] Tomashek *et al.*, [197] and Sharp *et al.* [173]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible interval (shaded area) shown.

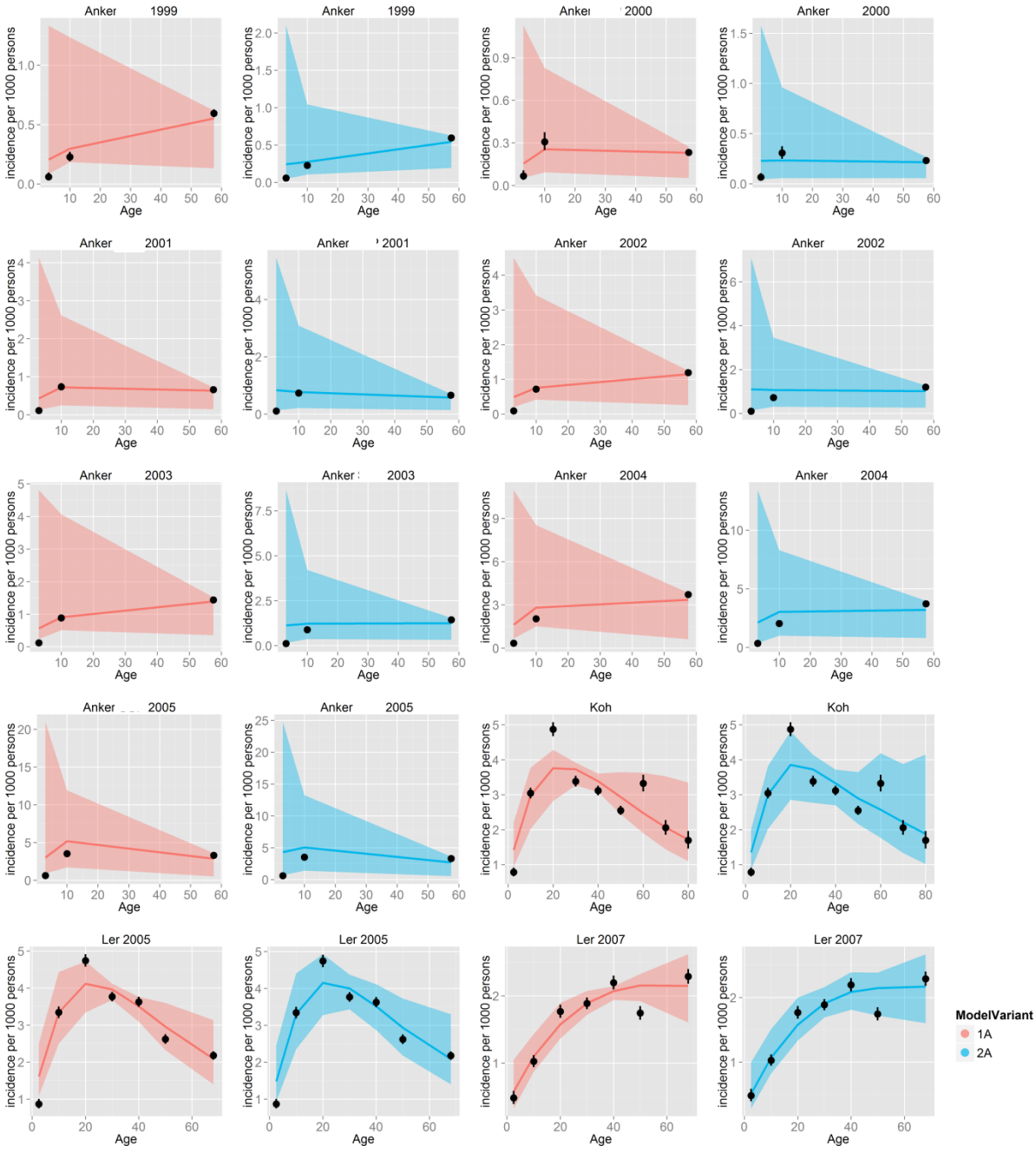

Figure 4.11: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Singapore (Anker *et al.*, [183] Koh *et al.*, [199] and Ler *et al.* [185]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible interval (shaded area) shown.

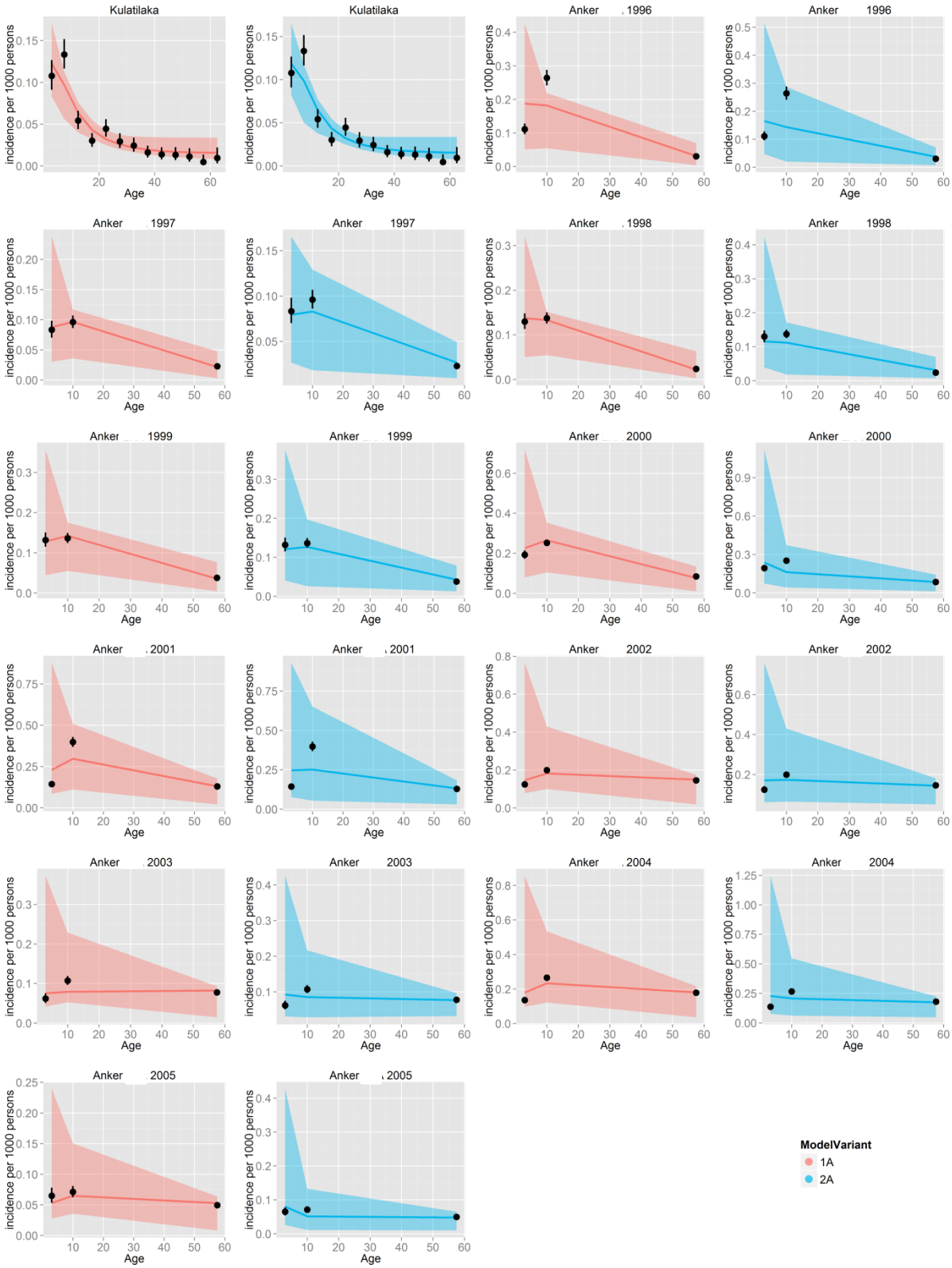

Figure 4.12: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Sri Lanka (Anker *et al.* [183]). 95% exact confidence interval around data points, posterior median (line), and 95% credible interval (shaded area) shown.

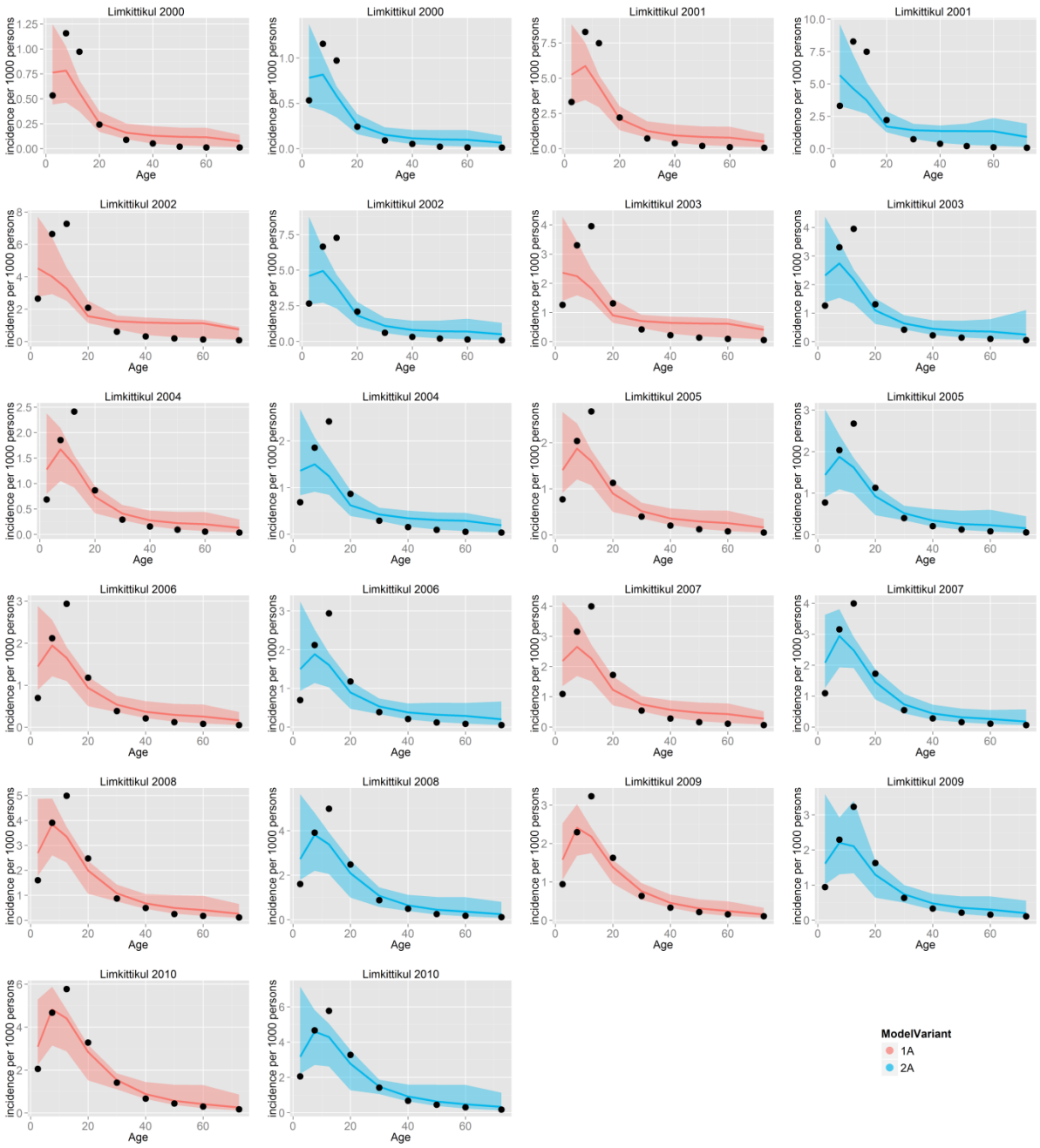

Figure 4.13: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Thailand (Limkittikul *et al.* [201]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible interval (shaded area) shown.

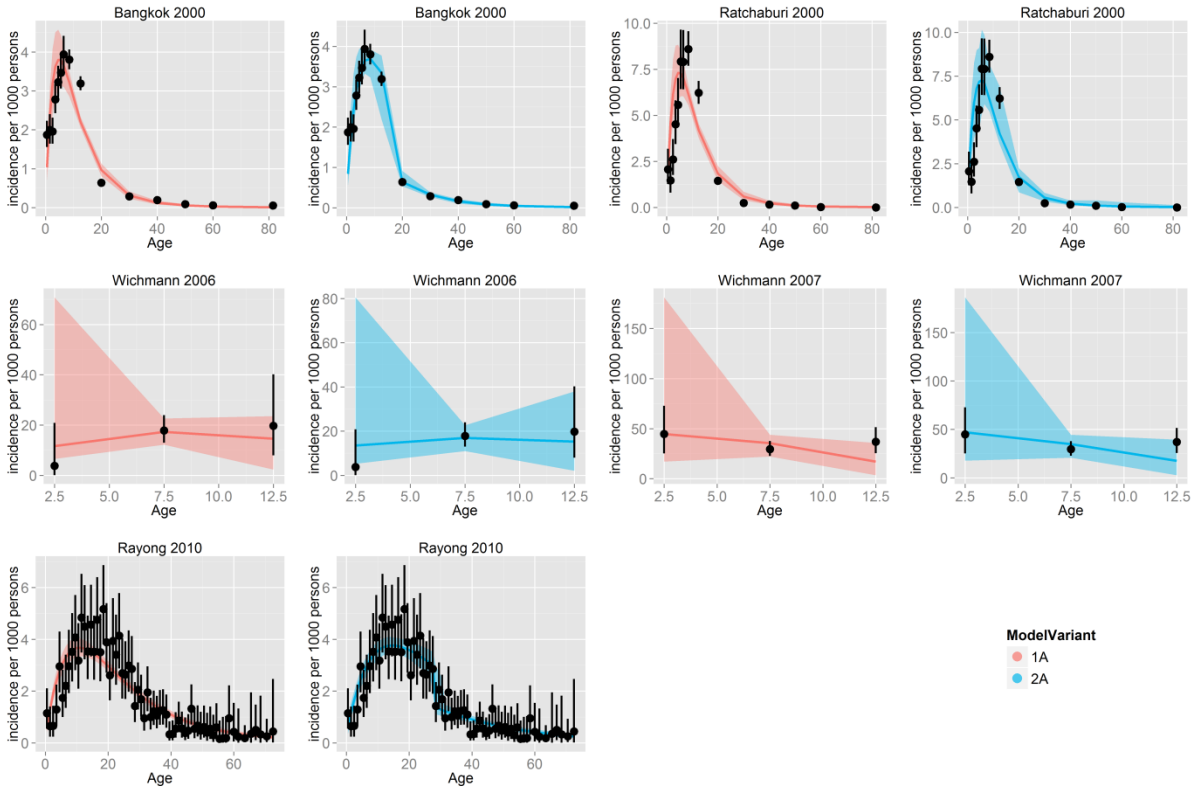

Figure 4.14: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Thailand (Wichmann *et al.*, [193] and data from Bangkok, Ratchaburi, and Rayong [187]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible interval (shaded area) shown.

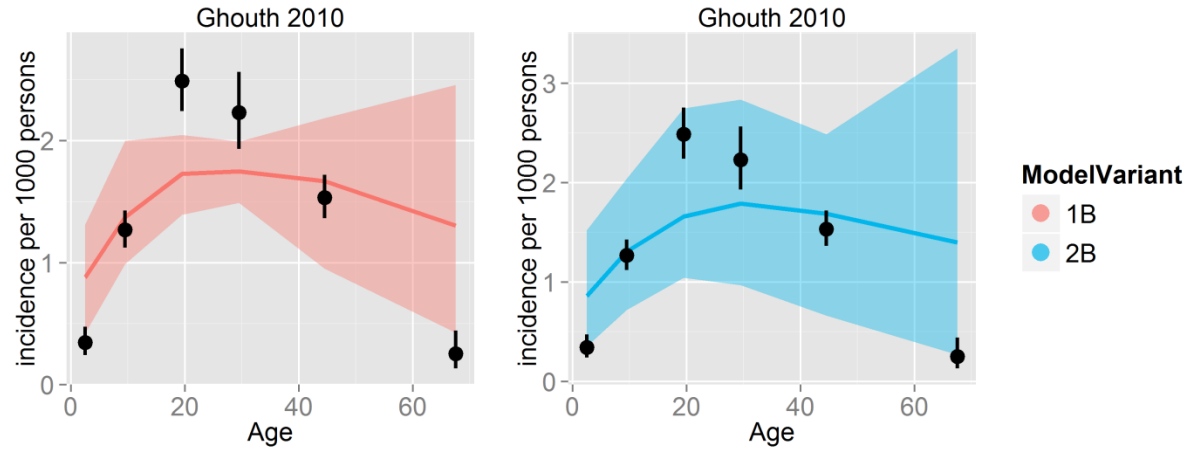

Figure 4.15: Model fits from model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data from Yemen (Ghouth *et al.* [202]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible intervals (shaded area) shown.

Figure 4.16 and Figure 4.17 show the distribution of the total force of infection (λ_{total}) grouped by country (calculated by multiplying the serotype-specific force of infection by the number of serotypes in circulation) from models 1B (single reporting rate, ρ , fitted to cumulative incidence data) and 2B (age-dependent reporting rate, ρ_y and ρ_o , fitted to cumulative incidence data) respectively. Individual estimates are given in Table 4.6 and Table 4.7 and the model fits are shown in Figure 4.18 – Figure 4.29.

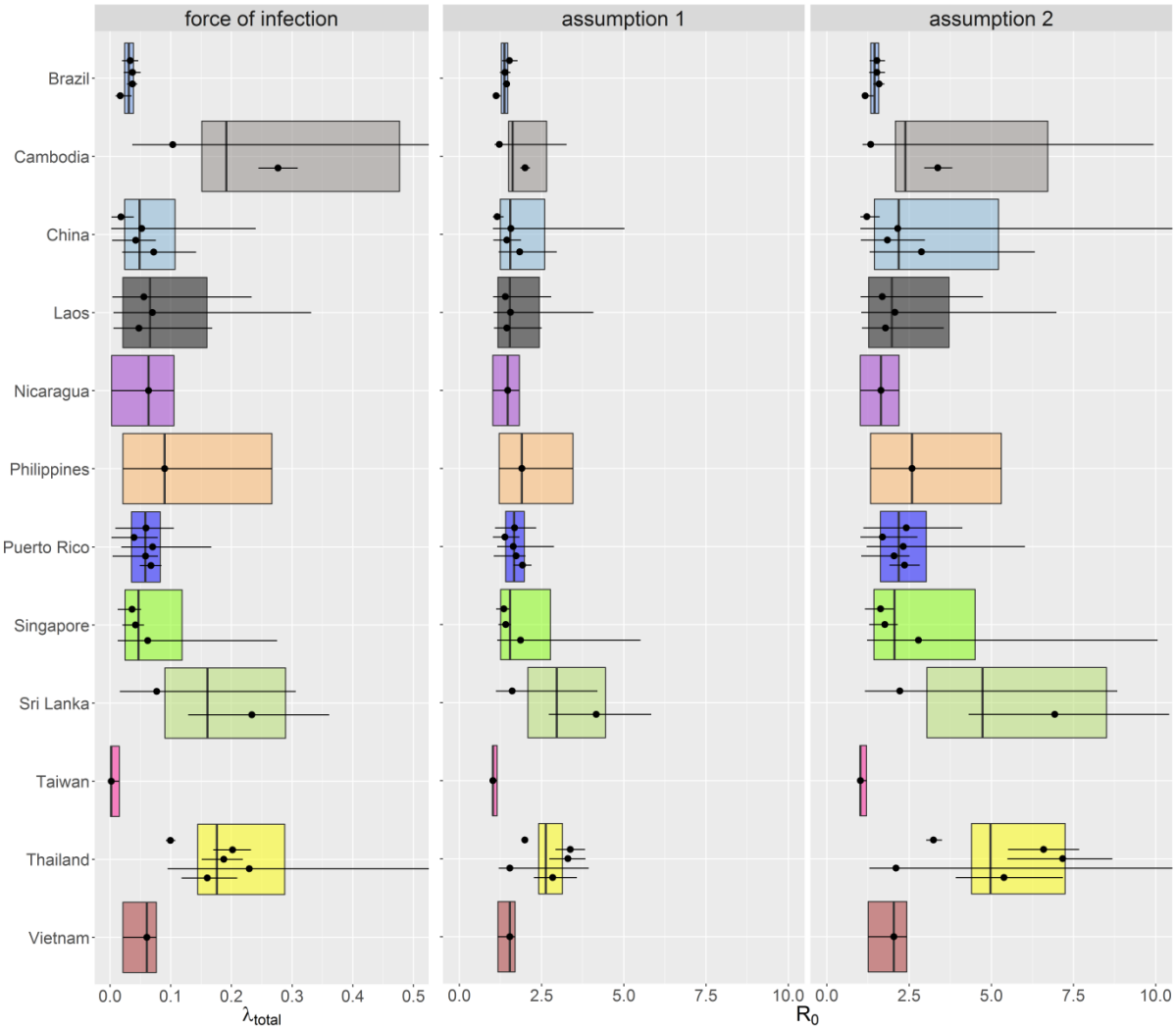

Figure 4.16: Total force of infection and corresponding R_{0i} estimates from model 1B (single reporting rate) fitted to cumulative incidence data grouped by country. Each dot represents the posterior median estimate and the error bars the 95% CrI. The box represents the country-specific central estimate calculated by taking the mean values of the MCMC output for each country (the line and limits of the box represent the posterior median and 95% CrI respectively).

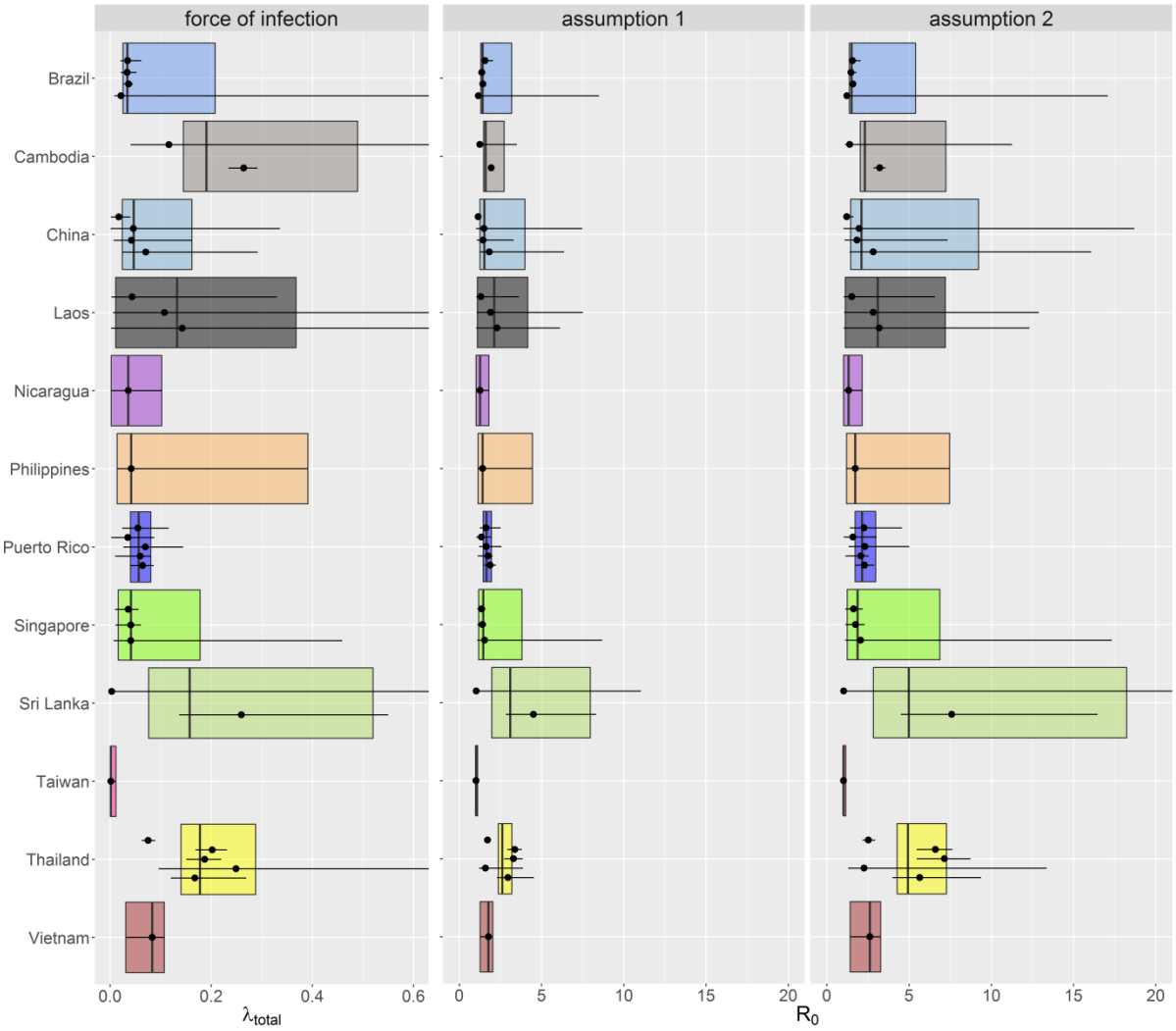

Figure 4.17: Total force of infection and corresponding R_{0i} estimates from model 2B (age-dependent reporting rate) fitted to cumulative incidence data grouped by country. Each dot represents the posterior median estimate and the error bars the 95% CrI. The box represents the country-specific central estimate calculated by taking the mean values of the MCMC output for each country (the line and limits of the box represent the posterior median and 95% CrI respectively)

Table 4.6: Summary parameter estimates from model 1 fitted to cumulative incidence data where available by country (single reporting rate, model 1B).

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95%CrI)	B (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} (95%CrI)*		LnL
										1	2	
Cordeiro [191]	1995/01	Brazil	0.016 (0.013-0.024)	0.546 (0.468-0.956)	NA	0.008 (0.005-0.041)	0.034 (0.018-0.144)	0.496 (0.268-0.976)	0.033 (0.026-0.047)	1.52 (1.40-1.77)	1.52 (1.40-1.77)	-355182
	2002/06		0.012 (0.011-0.018)	0.479 (0.432-0.791)	NA	0.006 (0.004-0.036)			0.037 (0.033-0.053)	1.40 (1.35-1.58)	1.53 (1.46-1.81)	-326485
Cardoso [181]	2000/09		0.012 (0.012-0.015)	0.078 (0.073-0.103)	NA	0.002 (0.001-0.008)			0.037 (0.035-0.045)	1.44 (1.40-1.54)	1.59 (1.53-1.75)	-4333
Penna [178]	2001/06		0.005 (0.003-0.011)	0.373 (0.251-0.901)	0.005 (0.003-0.076)	0.025 (0.011-0.244)			0.019 (0.014-0.043)	1.13 (1.10-1.31)	1.18 (1.13-1.53)	-55909
Vong [192]	2006/08	Cambodia	0.069 (0.067-0.077)	0.180 (0.173-0.189)	NA	0.003 (0.002-0.007)	0.037 (0.015-0.229)	0.383 (0.170-0.961)	0.277 (0.266-0.308)	2.00 (1.95-2.14)	3.37 (3.24-3.80)	-55933
Wichmann [193]	2006/07		0.027 (0.016-0.163)	0.263 (0.150-0.946)	NA	0.159 (0.058-0.896)			0.107 (0.062-0.652)	1.22 (1.13-3.16)	1.34 (1.17-9.37)	-30
Luo [190]	1978/88	China	0.018 (0.014-0.235)	0.000 (0.000-0.001)	0.399 (0.237-0.741)	0.002 (0.001-0.023)	0.046 (0.020-0.366)	0.514 (0.255-0.970)	0.071 (0.056-0.941)	1.82 (1.62-2.72)	2.83 (2.28-5.76)	-12911
	1989/99		0.011 (0.009-0.019)	0.000 (0.000-0.001)	0.062 (0.021-0.645)	0.003 (0.001-0.028)			0.042 (0.037-0.077)	1.44 (1.38-1.90)	1.84 (1.69-3.05)	-12430
	2000/09		0.012 (0.005-0.081)	0.000 (0.000-0.006)	0.243 (0.084-0.560)	0.055 (0.034-0.269)			0.049 (0.022-0.352)	1.53 (1.22-5.72)	2.05 (1.34-11.45)	-4413
Guo [90]	2005/11		0.004 (0.003-0.010)	0.000 (0.000-0.005)	0.006 (0.002-0.099)	0.028 (0.018-0.104)			0.018 (0.011-0.040)	1.15 (1.09-1.36)	1.22 (1.12-1.63)	-3459
Anker [183]	2000/06	Laos	0.011 (0.006-0.042)	0.102 (0.074-0.372)	NA	0.177 (0.062-0.909)	0.201 (0.073-0.917)	0.530 (0.259-0.978)	0.043 (0.024-0.168)	1.40 (1.22-2.50)	1.71 (1.36-3.55)	-45133
Khampapongpane [195]	2010		0.013 (0.006-0.049)	0.150 (0.076-0.744)	0.060 (0.022-0.860)	0.065 (0.034-0.382)			0.053 (0.026-0.197)	1.38 (1.18-2.49)	1.64 (1.28-4.07)	-33953
Prasith [194]	2010		0.018 (0.009-0.082)	0.139 (0.082-0.469)	0.164 (0.059-0.934)	0.297 (0.162-0.937)			0.072 (0.038-0.328)	1.57 (1.29-4.04)	2.10 (1.49-6.92)	-22762
Hammond [184]	1999/01	Nicaragua	0.021 (0.005-0.035)	0.026 (0.021-0.858)	NA	0.014 (0.009-0.058)	0.489 (0.258-0.969)	0.506 (0.239-0.979)	0.062 (0.016-0.104)	1.46 (1.11-1.81)	1.62 (1.13-2.18)	-1182
Anker [183]	1998-2005	Philippines	0.022 (0.011-0.059)	0.116 (0.089-0.860)	NA	0.265 (0.119-0.938)	0.316 (0.137-0.932)	0.460 (0.225-0.967)	0.086 (0.043-0.237)	1.86 (1.43-3.21)	2.53 (1.76-4.82)	-166118

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.6 continued (2/2)

Author [Ref]	Year	Country	λ_i (95% CrI)	ρ (95%CrI)	B (95%CrI)	ψ (95%CI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} (95%CrI)*		LnL
										1	2	
Rigau-Perez [198]	1994	Puerto Rico	0.022 (0.021-0.028)	0.350 (0.304-0.496)	NA	0.005 (0.003-0.019)	0.408 (0.282-0.904)	0.656 (0.416-0.987)	0.067 (0.062-0.085)	1.92 (1.83-2.20)	2.36 (2.22-2.83)	-50388
	1995/97		0.020 (0.017-0.026)	0.032 (0.028-0.389)	NA	0.006 (0.003-0.143)			0.060 (0.052-0.079)	1.74 (1.64-2.01)	2.07 (1.91-2.51)	-9112
Ramos [196]	2006		0.017 (0.013-0.043)	0.364 (0.300-0.804)	NA	0.043 (0.018-0.422)			0.070 (0.051-0.170)	1.64 (1.44-2.93)	2.32 (1.83-5.20)	-203
Sharp [173]	2010		0.015 (0.011-0.028)	0.160 (0.134-0.504)	NA	0.028 (0.020-0.094)			0.062 (0.046-0.111)	1.71 (1.50-2.43)	2.48 (1.97-4.37)	-24291
Tomashek [173]	2007		0.010 (0.005-0.020)	0.053 (0.044-0.699)	NA	0.025 (0.018-0.075)			0.040 (0.021-0.079)	1.38 (1.20-1.83)	1.69 (1.30-2.75)	-7042
Anker [183]	1999/05	Singapore	0.016 (0.009-0.069)	0.136 (0.114-0.631)	NA	0.328 (0.112-0.956)	0.047 (0.020-0.444)	0.488 (0.229-0.974)	0.062 (0.035-0.275)	1.86 (1.45-5.50)	2.78 (1.86-10.03)	-16182
Koh [199]	2005		0.011 (0.009-0.014)	0.268 (0.251-0.527)	NA	0.008 (0.005-0.039)			0.043 (0.037-0.057)	1.42 (1.35-1.58)	1.79 (1.63-2.18)	-20559
Ler [185]	2005/07		0.009 (0.008-0.013)	0.243 (0.223-0.779)	NA	0.006 (0.003-0.050)			0.037 (0.031-0.052)	1.36 (1.30-1.53)	1.64 (1.51-2.06)	-40149
Anker [183]	1996/05	Sri Lanka	0.019 (0.013-0.079)	0.070 (0.057-0.356)	NA	0.197 (0.060-0.928)	0.179 (0.093-0.645)	0.458 (0.228-0.970)	0.075 (0.053-0.315)	1.95 (1.65-5.24)	2.89 (2.28-9.10)	-16555
Kulatilaka [200]	2010		0.059 (0.050-0.090)	0.001 (0.001-0.001)	0.059 (0.044-0.105)	0.008 (0.005-0.029)			0.236 (0.201-0.361)	3.31 (2.89-4.94)	6.55 (5.49-10.74)	-1565
Lin [186]	2003/09	Taiwan	0.001 (0.000-0.004)	0.123 (0.033-0.889)	NA	0.010 (0.007-0.053)	0.034 (0.019-0.399)	0.508 (0.253-0.980)	0.002 (0.001-0.015)	1.02 (1.01-1.15)	1.02 (1.01-1.21)	-4241
Limkittikul [201]	200./10	Thailand	0.041 (0.037-0.058)	0.057 (0.052-0.069)	0.034 (0.021-0.142)	0.017 (0.011-0.083)	0.018 (0.008-0.073)	0.514 (0.254-0.973)	0.163 (0.149-0.231)	2.88 (2.68-3.91)	5.48 (4.99-7.97)	-1387845
Wichmann [193]	2006/07		0.058 (0.037-0.198)	0.470 (0.411-0.945)	NA	0.191 (0.075-0.909)			0.231 (0.147-0.493)	1.56 (1.33-4.10)	2.19 (1.58-9.13)	-146
Cuong [189]	1998/09	Vietnam	0.015 (0.014-0.019)	0.024 (0.022-0.044)	NA	0.010 (0.007-0.031)	0.039 (0.016-0.682)	0.496 (0.253-0.971)	0.061 (0.055-0.076)	1.54 (1.48-1.69)	2.06 (1.92-2.42)	-58901

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.7: Summary parameter estimates from model 2 fitted to cumulative incidence data by country (age-dependent reporting rate, model 2B).

Author [Ref]	Country	Year	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	Ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} (95%CrI)*		LnL
												1	2	
Cordeiro [191]	Brazil	1995/01	0.018 (0.014-0.030)	0.481 (0.341-0.943)	0.460 (0.369-0.942)	NA	65 (20-79)	0.007 (0.004-0.044)	0.047 (0.024-0.193)	0.491 (0.258-0.970)	0.036 (0.029-0.059)	1.57 (1.45-2.00)	1.57 (1.45-2.00)	-355181
		2002/06	0.012 (0.010-0.018)	0.514 (0.449-0.966)	0.494 (0.368-0.946)	NA	65 (50-79)	0.006 (0.004-0.035)			0.035 (0.029-0.053)	1.37 (1.30-1.58)	1.48 (1.38-1.81)	-326485
Cardoso [181]		2000/09	0.012 (0.011-0.015)	0.078 (0.072-0.134)	0.342 (0.093-0.973)	NA	90 (90-90)	0.002 (0.001-0.008)			0.037 (0.034-0.045)	1.43 (1.40-1.54)	1.58 (1.53-1.76)	-4333
Penna [178]		2001/06	0.006 (0.004-0.177)	0.225 (0.033-0.910)	0.403 (0.222-0.968)	0.014 (0.003-0.820)	70 (30-90)	0.045 (0.017-0.536)			0.024 (0.016-0.708)	1.17 (1.11-8.19)	1.25 (1.15-16.48)	-55911
Vong [192]	Cambodia	2006/08	0.066 (0.064-0.073)	0.183 (0.177-0.193)	0.049 (0.029-0.216)	NA	19 (19-21)	0.002 (0.001-0.005)	0.033 (0.015-0.197)	0.425 (0.197-0.966)	0.265 (0.256-0.292)	1.94 (1.91-2.07)	3.22 (3.10-3.58)	-55927
Wichmann [193]		2006/07	0.030 (0.016-0.185)	0.235 (0.136-0.931)	0.495 (0.272-0.969)	NA	15 (10-15)	0.183 (0.068-0.889)			0.119 (0.064-0.739)	1.25 (1.13-3.63)	1.40 (1.18-7.02)	-31
Luo [190]	China	1978/88	0.017 (0.014-0.073)	0.001 (0.000-0.001)	0.491 (0.245-0.976)	0.378 (0.217-0.748)	90 (90-90)	0.002 (0.001-0.024)	0.049 (0.021-0.394)	0.522 (0.262-0.979)	0.070 (0.054-0.191)	1.80 (1.60-3.17)	2.79 (2.22-6.83)	-12911
		1989/99	0.011 (0.009-0.024)	0.001 (0.000-0.001)	0.511 (0.254-0.979)	0.071 (0.023-0.701)	90 (90-90)	0.003 (0.001-0.031)			0.042 (0.037-0.097)	1.44 (1.38-2.19)	1.84 (1.69-3.91)	-12430
		2000/09	0.012 (0.005-0.084)	0.001 (0.00-0.008)	0.498 (0.242-0.978)	0.199 (0.060-0.552)	90 (90-90)	0.052 (0.033-0.256)			0.047 (0.020-0.357)	1.50 (1.20-10.71)	1.98 (1.30-12.43)	-4413
Guo [90]		2005/11	0.004 (0.003-0.010)	0.001 (0.00-0.007)	0.471 (0.219-0.973)	0.007 (0.002-0.117)	90 (90-90)	0.029 (0.019-0.104)			0.018 (0.011-0.039)	1.15 (1.09-1.35)	1.22 (1.12-1.61)	-3459

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.7 continued (2/3).

Author [Ref]	Country	Year	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CrI)	γ_3 (95%CrI)	λ_{tot} (95%CrI)	R_{0i} (95%CrI)*		LnL
												1	2	
Anker [183]	Laos	2000/06	0.016 (0.003-0.150)	0.079 (0.024-0.949)	0.331 (0.176-0.955)	NA	15 (15-15)	0.204 (0.074-0.908)	0.171 (0.070-0.828)	0.476 (0.248-0.972)	0.063 (0.010-0.601)	1.59 (1.09-5.86)	2.05 (1.13-11.58)	-45134
Khampapongpane [195]		2010	0.014 (0.006-0.095)	0.117 (0.060)	0.234 (0.137-0.885)	0.059 (0.023-0.582)	40 (20-40)	0.070 (0.034-0.432)			0.057 (0.024-0.380)	1.41 (1.17-4.06)	1.70 (1.26-7.51)	-33953
Prasith [194]		2010	0.025 (0.012-0.173)	0.097 (0.061-0.435)	0.451 (0.236-0.969)	0.260 (0.097-0.937)	80 (40-80)	0.340 (0.188-0.929)			0.098 (0.047-0.692)	1.81 (1.36-7.41)	2.63 (1.64-12.71)	-22762
Hammond [184]	Nicaragua	1999/01	0.014 (0.002-0.034)	0.038 (0.023-0.937)	0.398 (0.131-0.959)	NA	55 (39-55)	0.016 (0.010-0.059)	0.451 (0.227-0.971)	0.502 (0.264-0.975)	0.043 (0.005-0.103)	1.31 (1.04-1.80)	1.40 (1.04-2.16)	-1183
Anker [183]	Philippines	1998-2005	0.010 (0.006-0.096)	0.253 (0.094-0.943)	0.170 (0.117-0.788)	NA	15 (15-15)	0.301 (0.132-0.930)	0.186 (0.105-0.829)	0.443 (0.207-0.968)	0.042 (0.024-0.385)	1.41 (1.23-4.40)	1.73 (1.38-7.35)	-166118
Rigau-Perez [198]	Puerto Rico	1994	0.022 (0.017-0.029)	0.456 (0.377-0.920)	0.514 (0.413-0.967)	NA	55 (25-99)	0.003 (0.002-0.015)	0.165 (0.080-0.658)	0.565 (0.313-0.977)	0.065 (0.052-0.087)	1.89 (1.68-2.24)	2.31 (1.97-2.90)	-50387
		1995/97	0.020 (0.016-0.027)	0.040 (0.035-0.841)	0.368 (0.127-0.969)	NA	85 (75-85)	0.008 (0.003-0.212)			0.059 (0.047-0.080)	1.73 (1.56-2.03)	2.05 (1.78-2.54)	-9113
Ramos [196]		2006	0.017 (0.013-0.039)	0.454 (0.364-0.917)	0.470 (0.317-0.957)	NA	40 (30-61)	0.038 (0.014-0.395)			0.069 (0.051-0.156)	1.63 (1.44-2.71)	2.31 (1.84-5.49)	-203
Sharp [173]		2010	0.016 (0.009-0.030)	0.193 (0.158-0.942)	0.274 (0.194-0.939)	NA	60 (20-81)	0.019 (0.011-0.078)			0.062 (0.038-0.120)	1.71 (1.41-2.57)	2.50 (1.75-4.73)	-24289
Tomashek [197]		2007	0.010 (0.003-0.022)	0.070 (0.052-0.916)	0.217 (0.091-0.935)	NA	60 (30-85)	0.022 (0.015-0.080)			0.039 (0.010-0.087)	1.38 (1.09-1.93)	1.68 (1.12-3.01)	-7041

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

Table 4.7 continued (3/3).

Author [Ref]	Country	Year	λ_i (95%CrI)	ρ_y (95%CrI)	ρ_o (95%CrI)	B (95%CrI)	$A_{threshold}$ (95%CrI)	ψ (95%CrI)	γ_1 (95%CI)	γ_3 (95%CI)	λ_{tot} (95%CI)	R_{0i} (95%CI)*		LnL
												1	2	
Anker [183]	Singapore	1999/05	0.011 (0.005-0.108)	0.201 (0.053-0.942)	0.249 (0.151-0.942)	NA	15 (15-15)	0.300 (0.117-0.952)	0.052 (0.022-0.398)	0.535 (0.275-0.970)	0.044 (0.020-0.431)	1.58 (1.24-8.19)	2.14 (1.40-16.10)	-16182
Koh [199]		2005	0.010 (0.008-0.016)	0.267 (0.238-0.869)	0.375 (0.279-0.919)	NA	65 (55-85)	0.008 (0.005-0.047)			0.042 (0.031-0.063)	1.41 (1.30-1.65)	1.75 (1.51-2.35)	-20560
Ler [185]		2005/07	0.009 (0.007-0.014)	0.242 (0.214-0.814)	0.350 (0.252-0.945)	NA	80 (55-80)	0.006 (0.003-0.062)			0.036 (0.027-0.057)	1.36 (1.26-1.59)	1.63 (1.43-2.20)	-40150
Anker [183]	Sri Lanka	1996/05	0.001 (0.000-0.188)	0.165 (0.003-0.953)	0.115 (0.036-0.738)	NA	15 (15-15)	0.238 (0.098-0.910)	0.250 (0.112-0.899)	0.507 (0.262-0.975)	0.004 (0.001-0.521)	1.05 (1.02-11.17)	1.05 (1.02-24.38)	-16555
Kulatilaka [200]		2010	0.065 (0.055-0.128)	0.001 (0.001-0.001)	0.491 (0.215-0.974)	0.083 (0.058-0.374)	65 (65-65)	0.009 (0.006-0.035)			0.260 (0.221-0.514)	3.61 (3.12-7.20)	7.31 (6.07-16.67)	-1566
Lin [200]	Taiwan	2003/09	0.001 (0.000-0.003)	0.221 (0.069-0.933)	0.429 (0.211-0.963)	NA	75 (55-85)	0.010 (0.006-0.051)	0.033 (0.017-0.334)	0.527 (0.270-0.973)	0.002 (0.001-0.011)	1.01 (1.01-1.11)	1.01 (1.01-1.14)	-4241
Limkittikul [201]	Thailand	200./10	0.044 (0.038-0.375)	0.047 (0.033-0.067)	0.393 (0.131-0.974)	0.069 (0.038-0.790)	80 (80-80)	0.030 (0.016-0.196)	0.022 (0.011-0.070)	0.512 (0.252-0.978)	0.174 (0.154-0.500)	3.04 (2.75-7.40)	5.88 (5.15-15.79)	-1387846
Wichmann [193]		2006/07	0.062 (0.039-0.196)	0.461 (0.387-0.944)	0.591 (0.364-0.985)	NA	10 (10-15)	0.183 (0.067-0.916)			0.248 (0.155-0.786)	1.61 (1.35-4.05)	2.34 (1.63-13.65)	-146
Cuong [189]	Vietnam	1998/09	0.018 (0.014-0.026)	0.021 (0.010-0.106)	0.025 (0.023-0.894)	NA	30 (15-79)	0.005 (0.002-0.024)	0.044 (0.020-0.270)	0.523 (0.284-0.982)	0.072 (0.055-0.103)	1.64 (1.48-1.98)	2.31 (1.91-3.15)	-58897

*Assumption 1: individuals can be infected up to four times. Assumption 2: individuals are immune after two infections.

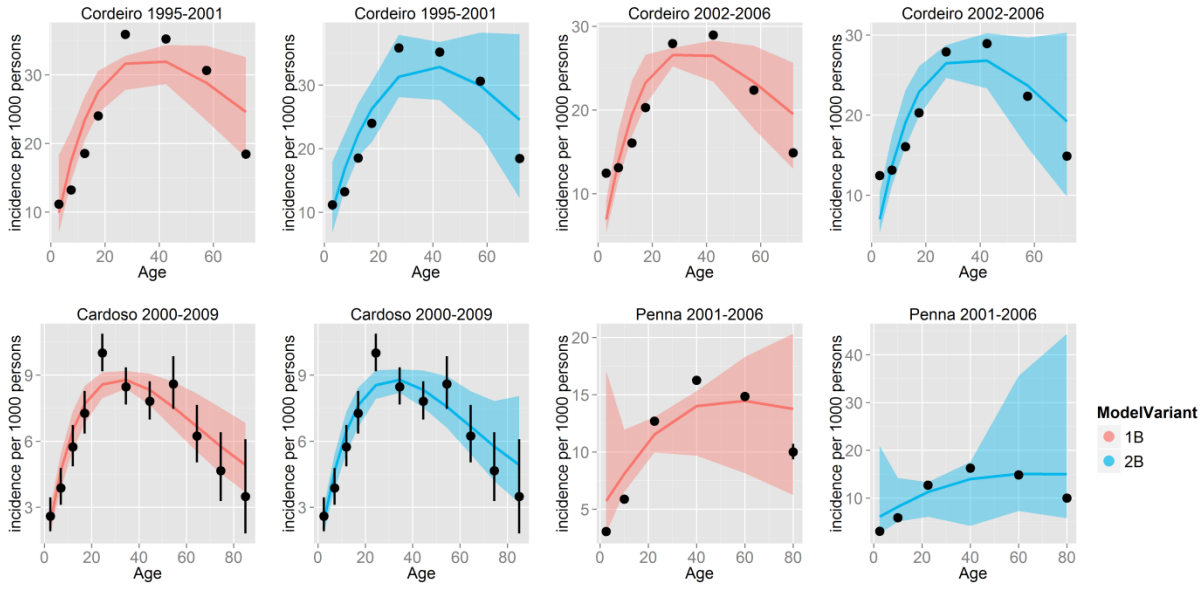

Figure 4.18: Model fits of model 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to cumulative incidence data from Brazil (Cordeiro *et al.*, [191] Cardoso *et al.*, [181] and Penna *et al.* [178]). 95% exact confidence intervals around data points, posterior median (line), and 95% credible interval (shaded area) shown.

Figure 4.19: Model fits of models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to cumulative incidence data from Cambodia (Vong *et al.* [192] and Wichmann *et al.* [193]). 95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

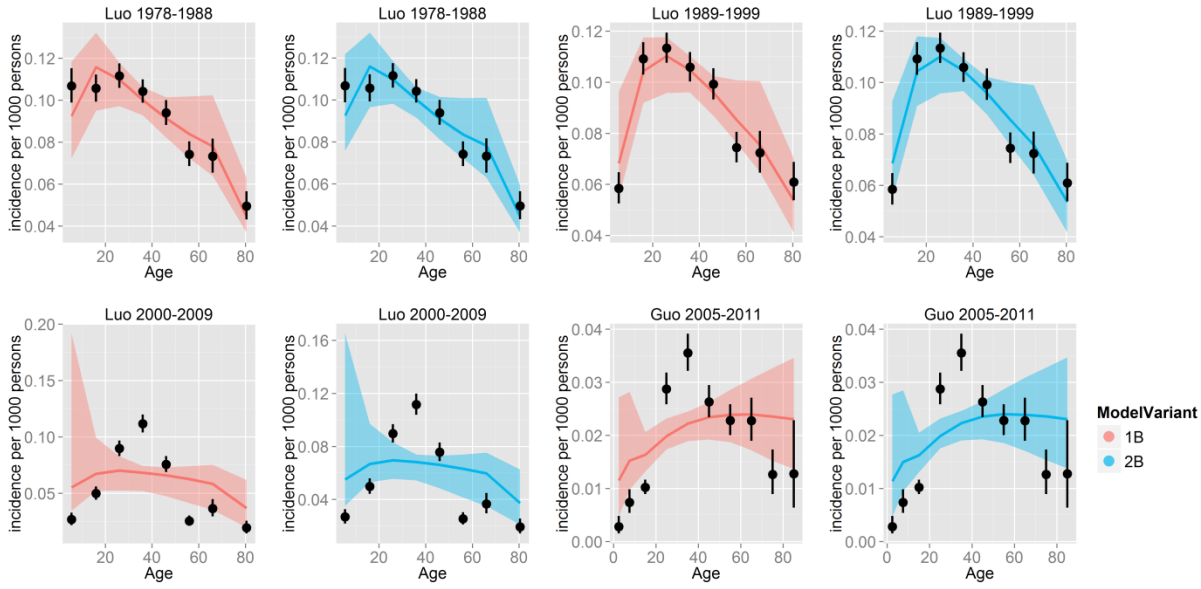

Figure 4.20: Model fits of models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to cumulative incidence data from China (Luo *et al.* [190] and Guo *et al.* [90]). 95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

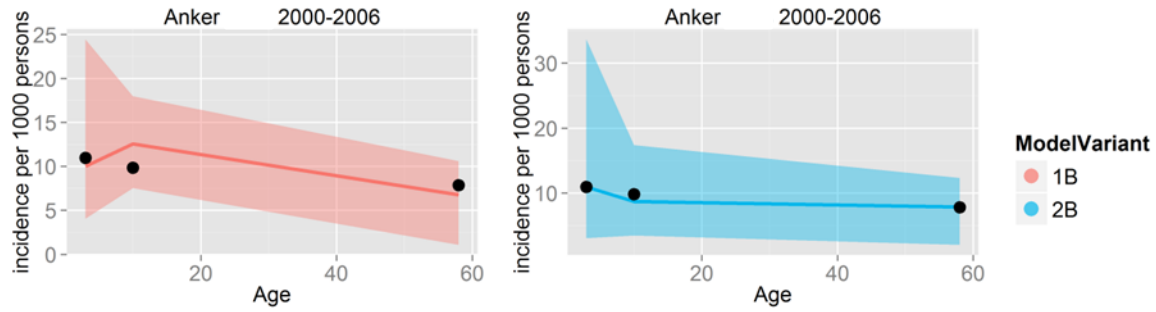

Figure 4.21: Model fits of model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Laos (Anker *et al.* [183]). 95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

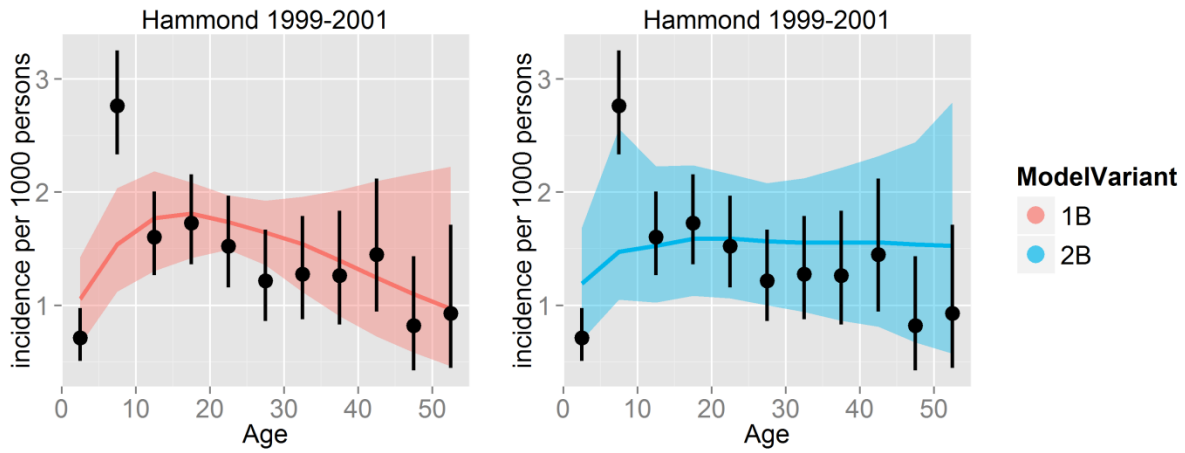

Figure 4.22: Model fits of model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Nicaragua (Hammond *et al.* [184]). 95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

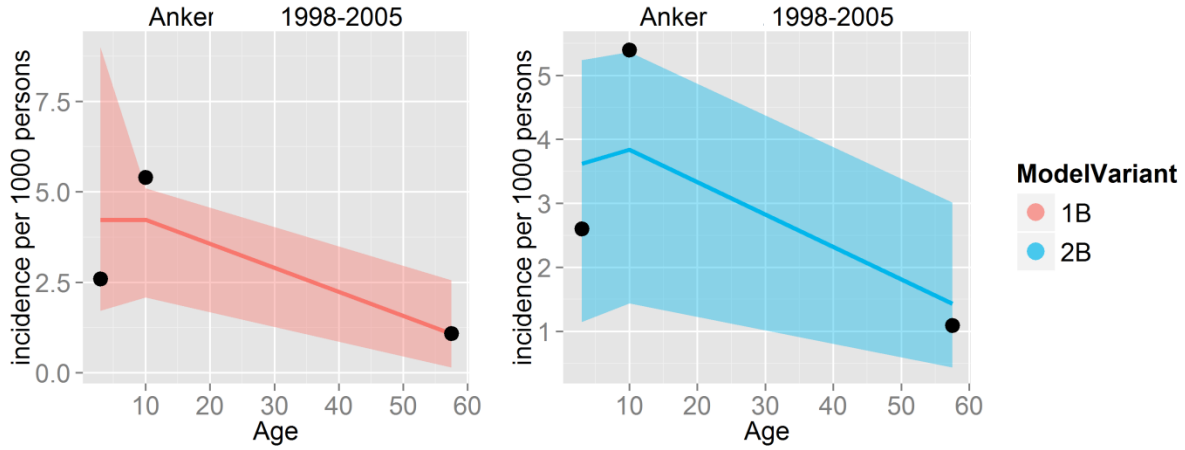

Figure 4.23: Model fits of model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from the Philippines (Anker *et al.* [183]). 95% exact confidence intervals around data points, posterior median (line) and 95% credible interval (shaded area) shown.

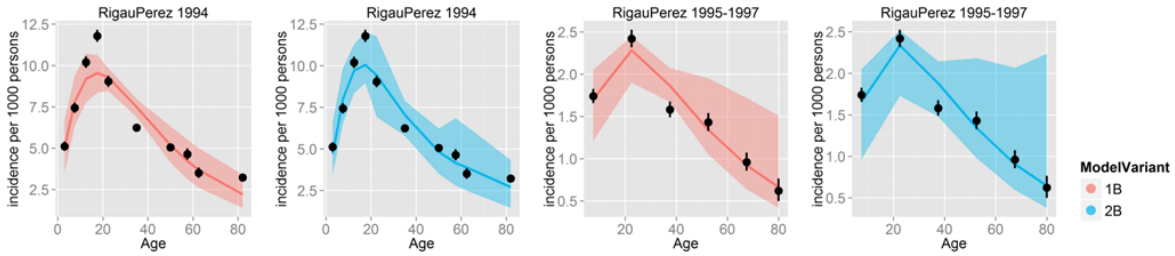

Figure 4.24: Model fits of model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to yearly incidence data from Puerto Rico (Rigau-Perez *et al.* [198]). 95% exact confidence intervals around data points, posterior median (line) and 95% credible intervals (shaded area) shown.

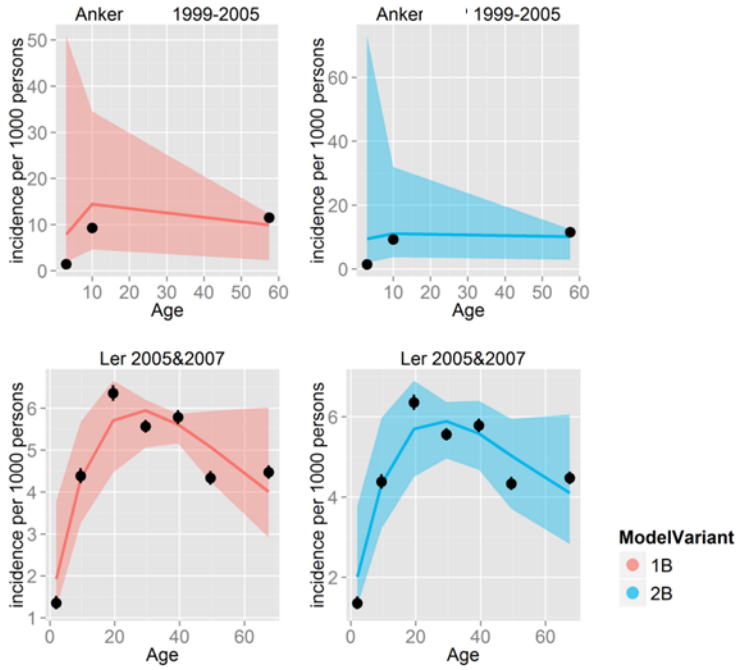

Figure 4.25: Model fits of model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Singapore (Anker *et al.* [183] and Ler *et al.* [185]). 95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

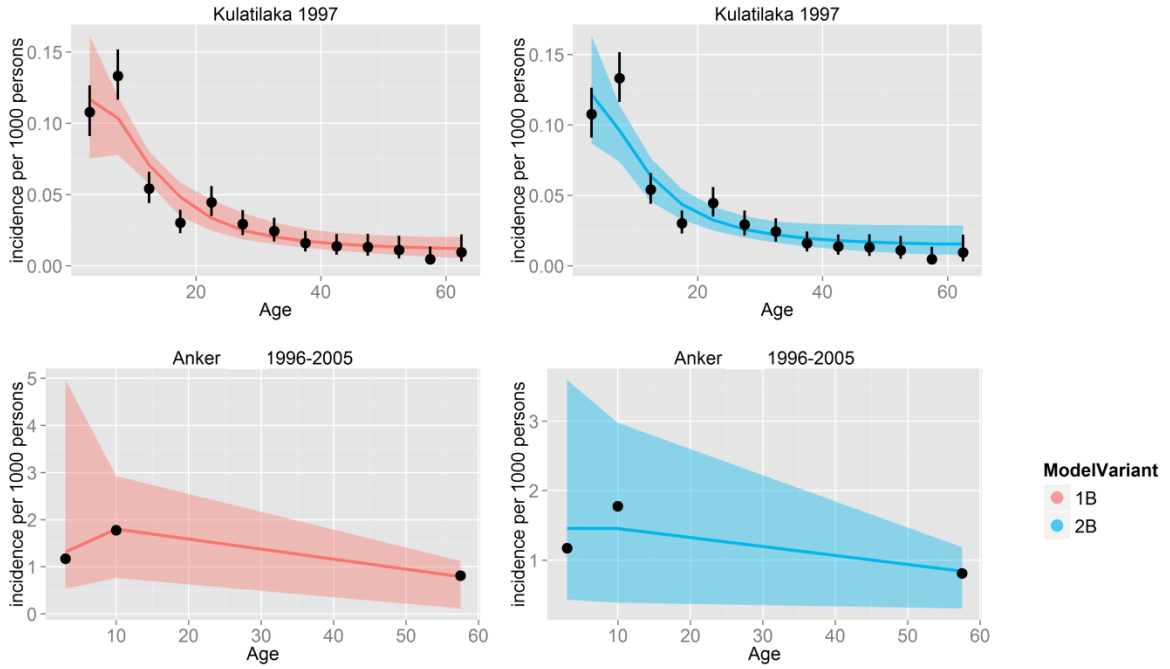

Figure 4.26: Model fits from model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Sri Lanka (Kulatilaka *et al.* [200] and Anker *et al.* [183]). 95% exact confidence interval around data points, posterior median (line) and 95% credible interval (shaded area) shown.

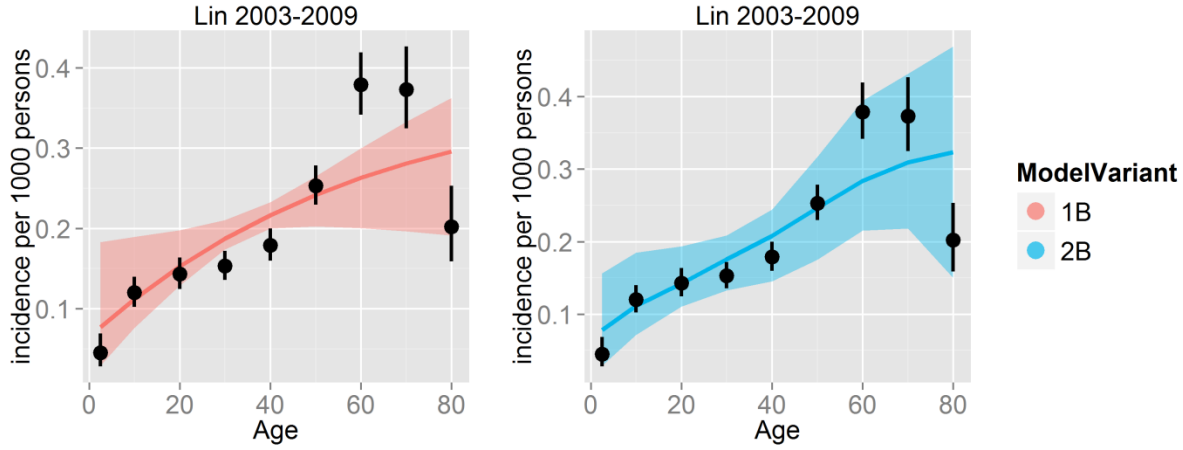

Figure 4.27: Model fits from model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Taiwan (Lin *et al.* [186]). 95% exact confidence intervals around data points, posterior median (line) and 95% credible intervals (shaded area) shown.

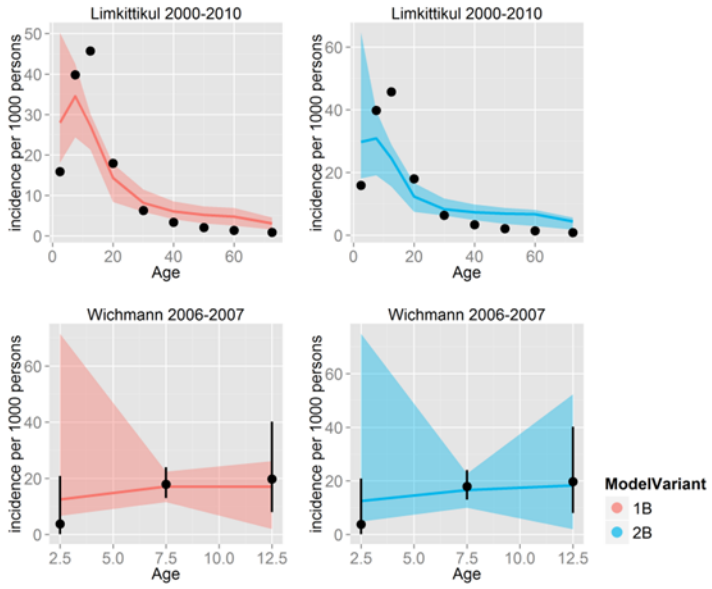

Figure 4.28: Model fits from model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Thailand (Limkittikul *et al.* [201] and Wichmann *et al.* [193]). 95% exact confidence intervals around data points, posterior median (line) and 95% credible interval (shaded area) shown.

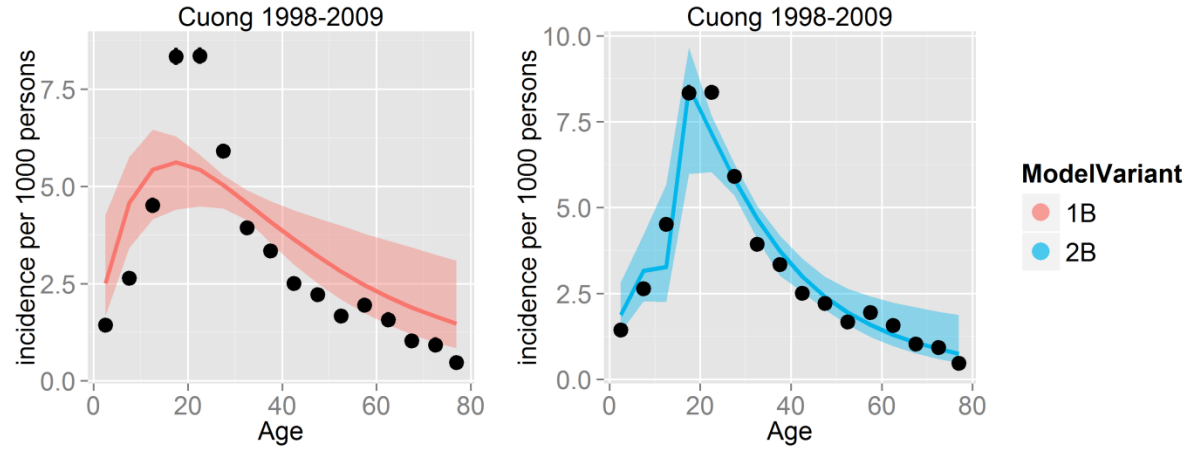

Figure 4.29: Model fits from model 1 (single reporting rate) and model 2 (age-dependent reporting rate) fitted to cumulative incidence data from Vietnam (Cuong *et al.* [189]). 95% exact confidence intervals around data points, posterior median (line) and 95% credible interval (shaded area) shown.

Estimates of R_{0i} varied according to the assumptions made regarding host immunity. Assuming only primary and secondary infections are infectious (assumption 2) gave up to two-fold higher estimates than assuming tertiary and quaternary infections are also infectious (Figure 4.3 and Figure 4.16). This is consistent with our previous results analysing seroprevalence data ([174] and chapters 2 and 3). Some force of infection estimates in Cambodia were very high, perhaps a result of the active surveillance undertaken as part of the study by Vong *et al.* [192]. There was greatest variation in dengue transmission intensity in Asia (Table 4.4 - Table 4.7). The baseline reporting rate (ρ), which is defined as the probability of detecting a secondary infection, was 10% (range: 1% - 79%) and 16% (range: 1%-55%) when fitted to yearly and cumulative incidence data respectively assuming a single reporting rate for all ages. When we allowed for age-dependent reporting rates, estimates of ρ increased to between 26% - 33% and 13% - 37% when fitted to yearly and cumulative incidence data respectively. Figure 4.30 shows the dataset-specific estimates of the baseline reporting rate (ρ, ρ_y, and ρ_o) and the probability of detecting a primary (γ_1) case relative to the baseline reporting rate, and the probability of detecting a tertiary/quaternary (γ_3) case relative to a primary case by model type. The median probability of detecting a primary case relative to a secondary case was consistently low at less than 25% for the majority of data sets and models. However, the credible intervals for some γ_1 estimates were wide. The data proved uninformative about the contribution of post-secondary infections to disease incidence, as our estimates of γ_3 reflected the prior distribution assumed for that parameter (uniform from 0 to 1).

When we allowed for reporting rates to vary by age, we found that the median probability that a secondary infection was detected was higher in older compared with younger individuals (Figure 4.30). However, stratifying parameter estimates by country, when ρ_o was higher than ρ_y the corresponding estimate of the age threshold at which reporting rates changed ($A_{threshold}$) were high (Figure 4.31, Table 4.5 and Table 4.7). In such cases the reporting rate ρ_y applied to the majority of age groups and the estimated values were comparable to the corresponding baseline reporting rates estimated from the model variants which did not incorporate age-dependent reporting.

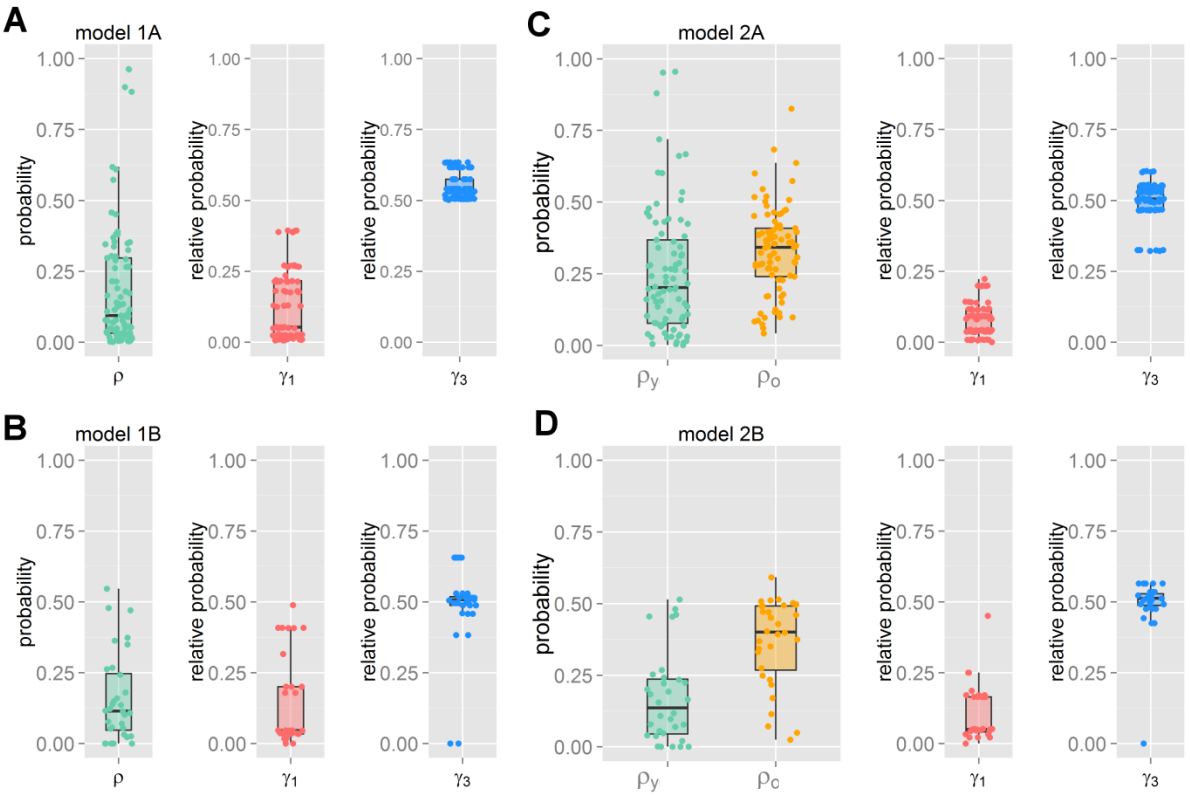

Figure 4.30: Boxplots of estimated reporting rates by model type : A) model 1A, B) model 1B, C) model 2A and D) model 2B. Each point represents the posterior median estimate for one dataset. ρ, ρ_Y, ρ_O = baseline reporting rate or probability of detecting a secondary infection for all ages, individuals younger than threshold age, and individuals older than the threshold age respectively. γ_1 = probability of detecting a primary infection relative to a secondary infection, and γ_3 = probability of detecting a tertiary/quaternary infection relative to a primary infection. Model 1a and 1b were fitted to yearly and cumulative incidence data respectively assuming a non-age dependent reporting rate, while model 2a and 2b were fitted to yearly and cumulative incidence data respectively assuming an age-dependent reporting rate.

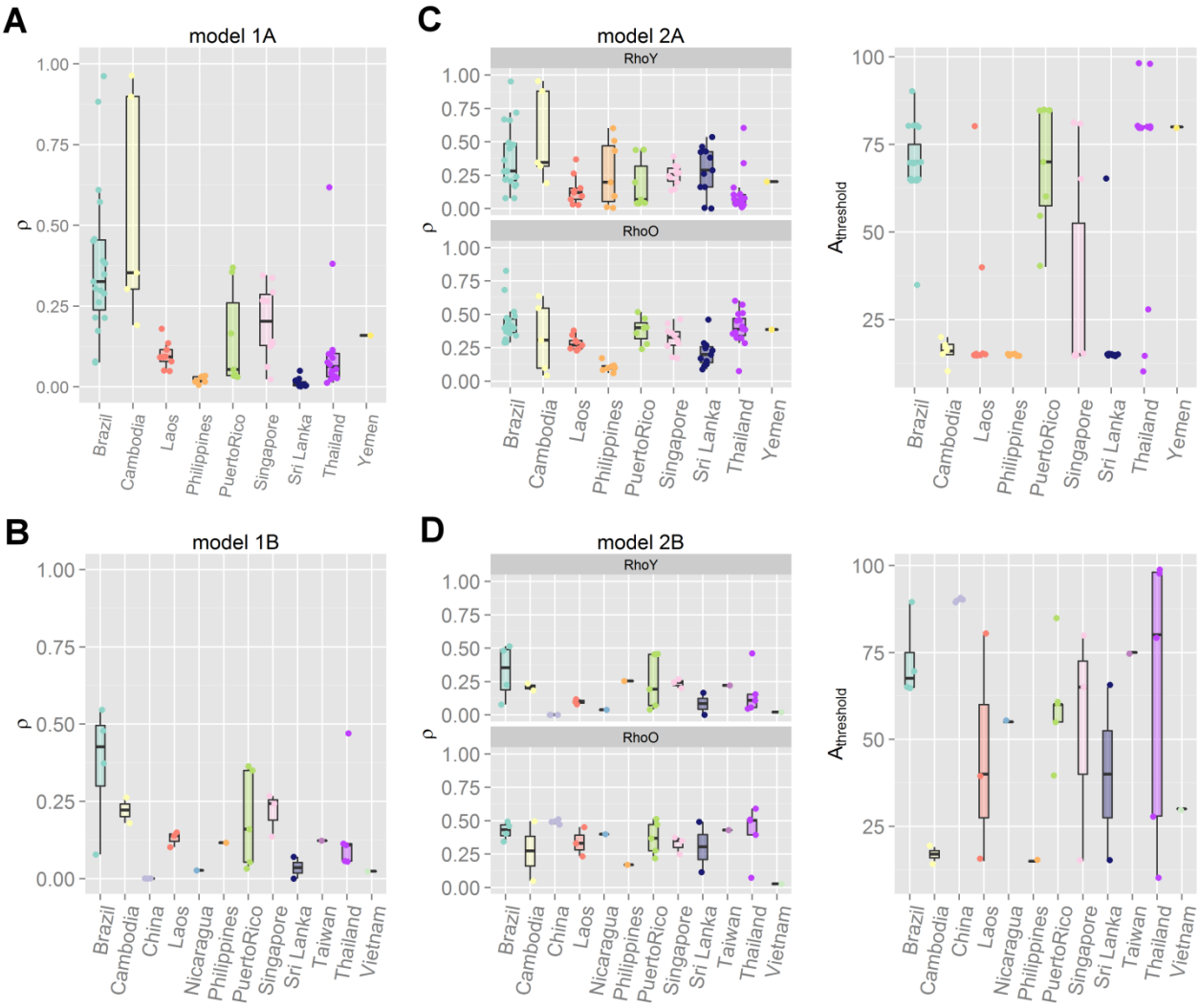

Figure 4.31: Comparison of baseline reporting rates (ρ, ρ_Y, ρ_O) and estimated age (years) at which reporting rates change ($A_{threshold}$) by model. A) model with single reporting rate fitted to yearly incidence data, B) model with single reporting rate fitted to cumulative incidence data, C) model with age-dependent reporting rate fitted to yearly incidence data, and D) model with age-dependent reporting rate fitted to cumulative incidence data. Each point represents the posterior median estimate for one dataset.

The baseline reporting rates (ρ) varied substantially by country (Figure 4.31), likely reflecting differences in healthcare seeking behaviour and surveillance. Generally, estimated reporting rates in the Americas were higher than in South East Asia, with Singapore having the highest rate within SE Asia. Reporting rates also varied within each country depending on survey year or survey region, which may reflect differences in local healthcare systems or changes in public awareness after epidemics. Estimates from Cambodia were high due to the active surveillance employed during that study (Vong *et al.* 2006-2008 [192]). The

estimated age at which reporting rates changed was consistently lower in South East Asia (Cambodia, Laos, Sri Lanka, and the Philippines – except Singapore) than in the Americas (Brazil and Puerto Rico). Comparing models fitted to yearly incidence and cumulative incidence data, model 2 provided a better fit to the data 62% and 59% of the time respectively as assessed by the DIC (Table 4.8 and Table 4.9).

Table 4.8: Summary DIC comparison of model fits to yearly incidence data. Models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to yearly incidence data. Smaller DIC for each dataset is highlighted in bold where the difference is greater than 5.

Author [Ref]	**Year**	**# serotypes**	**Country**	**DIC**	
				Model 1	**Model 2**
Cordeiro [191]	1995	2	Brazil	35710	**35703**
	1996	2		80771	80769
	1997	2		115423	**115414**
	1998	2		186560	**186511**
	1999	2		128229	128227
	2000	3		101163	101163
	2001	3		62048	**62035**
	2002	3		418449	418448
	2003	3		95070	**94633**
	2004	3		23166	23163
	2005	3		47099	47095
	2006	3		68804	**68797**
Penna [178]	2001	4		**27771**	28830
	2002	4		**13788**	17822
	2003	4		**20633**	20681
	2004	4		**3032**	10996
	2005	4		**16643**	16998
	2006	4		**15566**	15592
Vong [192]	2006	4	Cambodia	41711	41710
	2007	4		221410	**221390**
	2008	4		68562	**68544**
Wichmann [193]	2006	4		65	65
	2007	4		1088	1087
Anker [183]	2000	4	Laos	2104	**2055**
	2001	4		7257	**6585**
	2002	4		16365	**15530**
	2003	4		34578	**32495**
	2004	4		6557	**4009**
	2005	4		10482	**9734**
	2006	4		11876	**10165**
Khampapongpane [195]	2010	4		**64888**	67566
Prasith [194]	2010	4		45456	**44129**
Anker [194]	1998	4	Philippines	67732	**65607**
	1999	4		18300	**11191**
	2001	4		**47633**	47674

Table 4.8 continued (2/2).

Author	Year	# serotypes	Country	DIC	
				Model 1	Model 2
Anker [194]	2002	4	Philippines	32395	**32374**
	2003	4		57113	**53741**
	2004	4		**44004**	44018
	2005	3		64390	**64353**
Rigau-Perez [198]	1994	3	Puerto Rico	100776	**100727**
	1995	3		6127	6128
	1996	3		5393	5396
	1997	4		**6742**	6747
Ramos [196]	2006	4		409	409
Sharp [173]	2007	4		**48497**	48514
Tomashek [197]	2010	4		14076	**14014**
Anker [194]	1999	4	Singapore	1041	**785**
	2000	4		725	**474**
	2001	4		1879	**690**
	2002	4		3013	**917**
	2003	4		3719	**1133**
	2004	4		8270	**7606**
	2005	4		13714	**13514**
Koh [199]	2005	4		41122	41121
Ler [185]	2005	4		50174	50175
	2007	4		29440	29440
Anker [183]	1996	4	Sri Lanka	2279	**1967**
	1997	4		1621	1621
	1998	4		**1980**	2210
	1999	4		2350	**1800**
	2000	4		4605	**3594**
	2001	4		**4422**	4672
	2002	4		4509	**3736**
	2003	4		2426	2425
	2004	4		5722	**1706**
	2005	4		1763	**1738**
Kulatilaka [200]	1997	4		**3124**	3138
Limkittikul [201]	2000	4	Thailand	**58282**	59755
	2001	4		**450738**	451213
	2002	4		**371748**	376250
	2003	4		**206304**	214588
	2004	4		**124400**	133462
	2005	4		**157060**	159895
	2006	4		**156750**	160942
	2007	4		**225396**	225623
	2008	4		**318403**	318907
	2009	4		**190752**	206441
	2010	4		**430542**	430608
Wichmann [193]	2006	4		64	64
	2007	4		227	228
Bangkok [186]	2000	4		22938	22939
Ratchaburi [186]	2000	4		5624	5624
Rayong [186]	2010	4		8259	**8236**
Ghouth [202]	2010	3	Yemen	3582	**3576**

Table 4.9: Summary DIC comparison of model fits to cumulative incidence data. Models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to cumulative incidence data. Smaller DIC for each dataset is highlighted in bold where the difference is greater than 5.

Author	Year	Country	Model 1	Model 2
Cordeiro [191]	1995/01	Brazil	710366	**710318**
	2002/06		652964	652966
Cardoso [181]	2000/09		8670	8671
Penna [178]	2001/06		111819	**111696**
Vong [192]	2006/08	Cambodia	111870	**111861**
Wichmann [193]	2006/07		64	64
Luo [190]	1978/88	China	25826	25826
	1989/99		**23810**	24861
	2000/09		8823	8818
Guo [90]	2005/11		6914	**6895**
Anker [183]	2000/06	Laos	90188	**58722**
Hammond [184]	1995/97	Nicaragua	2358	**2335**
Anker [183]	1998/05	Philippines	**332153**	331296
Rigau-Perez [198]	1994	Puerto Rico	100773	**100697**
	1995/97		**18219**	18231
Anker [183]	1999/05	Singapore	32360	**26429**
Ler [185]	2005/07		80303	80304
Anker [183]	1996/05	Sri Lanka	33110	**29570**
Lin [186]	2003/09	Taiwan	8458	**8434**
Limkittikul [201]	2000/10	Thailand	**2775619**	2775687
Wichmann [193]	2006/07		292	289
Cuong [189]	1998/09	Vietnam	117807	**117801**

4.3.4 Comparison of Estimates Obtained from Seroprevalence and Incidence data.

We used weighted regression to compare the force of infection estimates obtained from age-stratified seroprevalence data to cumulative incidence data. Estimates obtained from the model fitted to the cumulative incidence data assuming a single reporting rate (Model 1B) were comparable to force of infection estimates from seroprevalence data. The majority of the total force of infection (λ_{total}) estimates from incidence data (calculated by multiplying the serotype-specific force of infection by the number of serotypes in circulation) were comparable for both models to those obtained from seroprevalence data when λ_{total} was smaller than ~0.1 with greater uncertainty as force of infection increases (Figure 4.32).

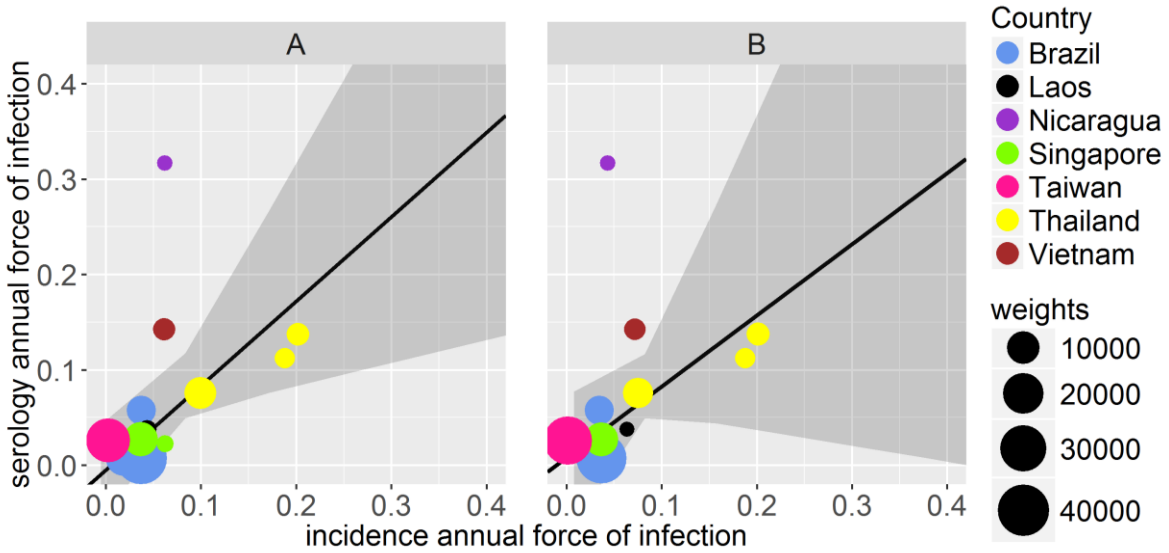

Figure 4.32: Comparison of weighted deming regression of force of infection estimates by country from cumulative incidence data and seroprevalence data for A) model 1B (non-age dependent reporting) and B) model 2B (age-dependent reporting rate). Each point is weighted depending on the error in both serology and incidence estimates, represented by the size of circles (larger circles indicating greater weight). See Table 4.1 for summary of matched datasets.

In two of the three locations in Thailand where region and time matching seroprevalence and incidence data were available [187], the force of infection estimates obtained from the models fitted to incidence data and serology data had overlapping 95% credible intervals. In

Ratchaburi the estimate obtained from seroprevalence data was smaller than that from incidence data (Figure 4.33).

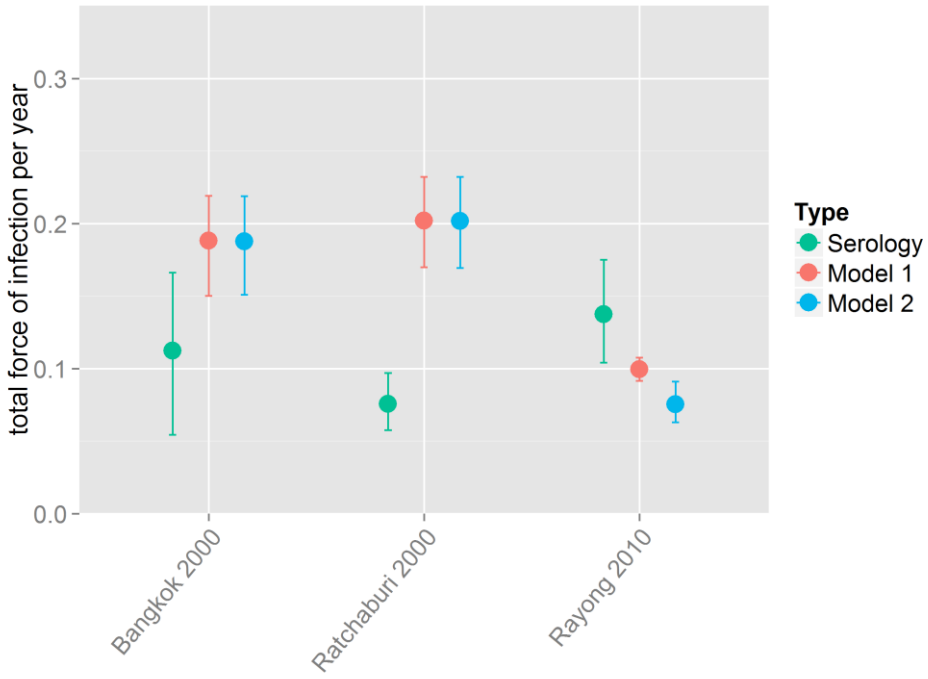

Figure 4.33: Comparison of force of infection estimates derived from incidence data and seroprevalence data. Comparison of posterior median estimates and 95% CrI of the total force of infection from Models 1 (single reporting rate) and 2 (age-dependent reporting rate) fitted to incidence data and model A (as described in [174]) to age-stratified seroprevalence data from Thailand where incidence and serology data were available from the same year and location .

4.3.5 Regression Analysis

Multiple regression analysis was conducted to explore the relationship between estimated dengue transmission intensity and the covariates summarised in Table 4.10. Figure 4.34 summarises the analysis results. The multiple regression with all 7 predictors produced R^2=0.40. Absolute latitude (distance from the equator) and GDP per capita (USD) were both negatively associated with the force of infection (p=0.03 and p=0.01 respectively). The remaining predictors were not associated with the outcome variable.

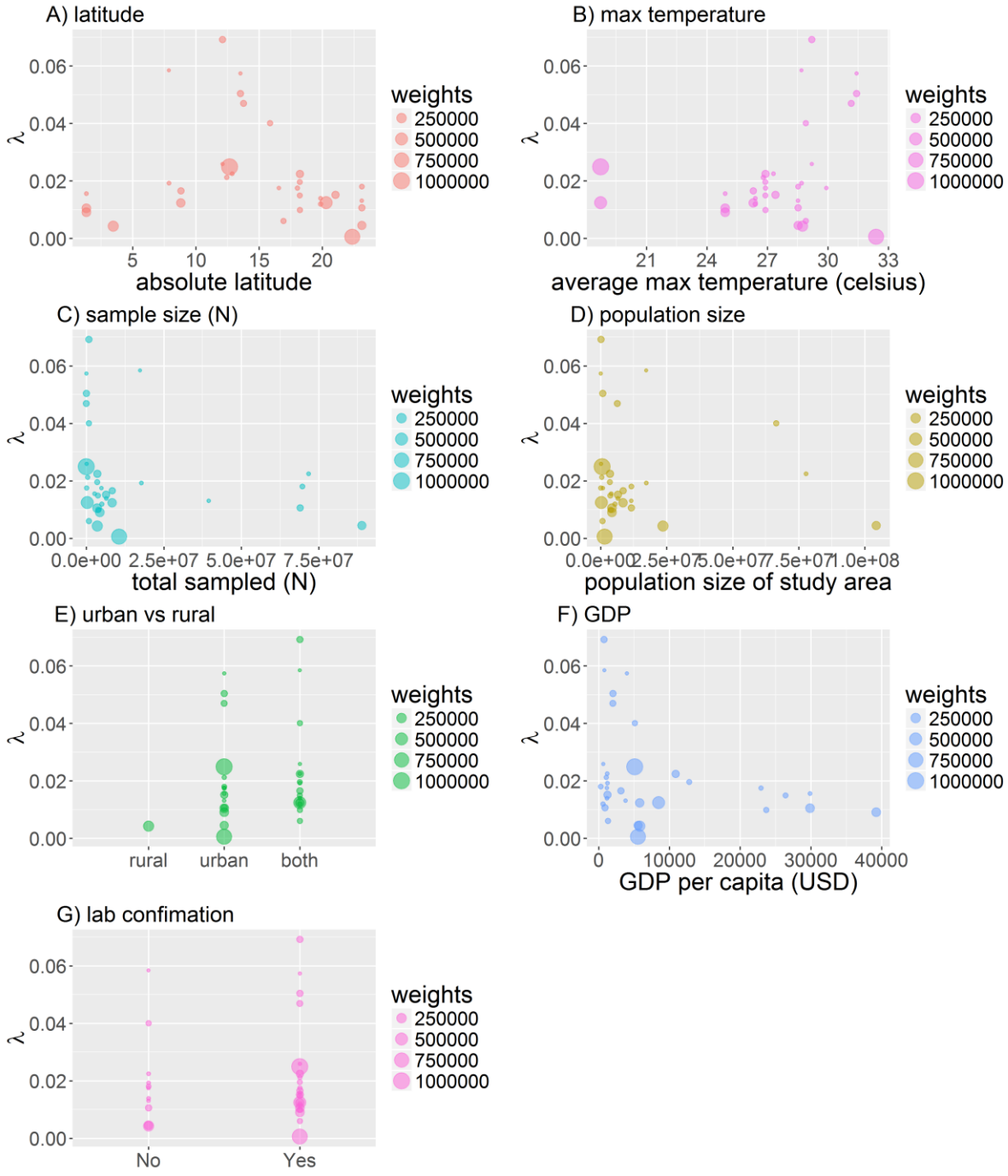

Figure 4.34: Scatterplots showing the relationship between estimated force of infection, and demographic and environmental covariates. A) absolute latitude, B) average maximum temperature, C) sample size, D) population size of study region, E) whether the study was conducted in an urban or rural setting, F) GDP per capita (USD), and G) lab confirmation. Each point represents an estimate for a single year.

Table 4.10: Weighted multiple regression results

Variable	**Correlation with λ**	**Coefficients (95% CI)**	**p-value**
Intercept	-	$3.19x10^{-2}$ ($3.01x10^{-3}$ – $6.08x10^{-2}$)	0.03
Absolute latitude	-0.16	$-1.07x10^{-3}$ ($-2.05x10^{-3}$ – $8.38x10^{-5}$)	0.03
Average maximum temperature	0.31	$-5.23x10^{-4}$ ($-1.36x10^{-3}$ – $3.51x10^{-4}$)	0.23
Sample size	-0.22	$4.80x10^{-11}$ ($-4.09x10^{-10}$ – $5.05x10^{-10}$)	0.83
Population size of study region	-0.07	$9.94x10^{-11}$ ($-3.13x10^{-10}$ – $5.12x10^{-10}$)	0.62
Urban/Rural^	0.13	$2.29x10^{-3}$ ($-2.72x10^{-3}$ – $7.29x10^{-3}$)	0.36
GDP per capita (USD)	-0.29	$-7.89x10^{-7}$ ($-1.40x10^{-6}$ – $-1.75x10^{-7}$)	0.01
Laboratory confirmation*	0.06	$1.59x10^{-2}$ ($-5.07x10^{-3}$ – $3.69x10^{-2}$)	0.13

^coded as 1=urban, 0=rural, 3=both. *coded as 0=no, 1=yes.

4.4 Discussion

From a literature search we selected 23 papers reporting age-stratified case notification data in 13 countries from 1978-2010. When reported incidence data were split into yearly notifications, this gave a total of 96 survey years. For each dataset we estimated dengue transmission intensity as quantified by the force of infection (λ_i) and the basic reproduction number (R_{0i}). The total force of infection (λ_{total}) estimated from cumulative incidence data were compared with previous λ estimates from seroprevalence data.

The incidence models presented in this chapter provide a method for estimating dengue transmission intensity in areas where seroprevalence data are not available. Force of infection estimates and corresponding basic reproduction numbers varied widely across and within countries as expected, highlighting the heterogeneous nature of dengue transmission spatially and temporally. The majority of our R_{0i} estimates ranged from 1 to 5, similar to our estimates obtained from seroprevalence data [174]. As for our serology-based estimates, force of infection estimates were generally higher in South East Asia than for Latin America.

Since we had no serotype-specific notification data, we assumed that all serotypes were equally transmissible. If serotype-specific notification data were available, a serotype-specific force of infection might be estimated.

Generally model 2 provided a better fit to yearly incidence (62% of the time) and cumulative incidence data (59% of the time) as assessed by the DIC. However if the data were age-stratified more finely we predict that model 2 would perform better consistently since it allows for age-dependent reporting rates.

Due to the lack of incidence and serology data collected in the same year and region, we matched incidence and serology datasets according to the year or study region (Table 4.1). While overall estimates from incidence data were comparable with those derived from seroprevalence data, it would nonetheless be beneficial to validate this model with multiple incidence and serology datasets collected simultaneously in the same geographical location. Similarly to the force of infection estimates obtained from seroprevalence data (chapters 2 and 3), weighted multiple regression was conducted to explore the relationship between the estimated forces of infection and various potential predictors. We fitted the single

reporting rate model to cumulative incidence data where possible. Distance from the equator and GDP per capita (USD) were negatively associated with the force of infection (p=0.03 and p=0.01 respectively). This is somewhat consistent with the results from the multiple regression in the previous chapter where these two covariates were weakly associated with the force of infection. However, whether the study was conducted in an urban or rural environment was not associated with transmission intensity unlike the estimates obtained from seroprevalence studies. This is likely due to many of the studies reporting dengue cases at the national level. Ideally we would have explored the associations using a meta-regression, allowing for the between trial variance. However again, we could not calculate sampling variances from our data since our variable of interest – the force of infection is in itself a model output.

Generally, estimated reporting rates (ρ) in the Americas were higher than those in South East Asia with Singapore having the highest rate within South East Asia, consistent with their well-established dengue surveillance program [205]. Reporting rate estimates for Cambodia were very high compared with the rest of South East Asia, presumably due to the active surveillance employed during the study which collected the data [192]. Reporting rate estimates also varied within each country depending on survey year or survey region reflecting variation in healthcare and surveillance systems [53]. Reporting rates are also likely to change in response to recent or current epidemics which affect public awareness of dengue thus affecting healthcare seeking behaviour [206]. Additionally, in an epidemic year clinicians may preferentially diagnose a febrile illness as dengue without laboratory testing [50].

For models 2A and 2B we hypothesised that severity or disease reporting differed by age group and estimated age-dependent reporting rates (ρ_y and ρ_o) and the age at which reporting rates changed ($A_{threshold}$). Allowing reporting rates to vary with age in this manner generally provided a better fit to the data broken down by survey year (model 2A) and cumulative data (model 2B), as assessed by the DIC. In the Americas the threshold age at which reporting rates changed was high (over 50 years of age) and so the majority of age groups had the same reporting rate (ρ_y) – effectively equivalent to assuming the same reporting rate for all ages (i.e. model 1). In contrast, the estimated age at which reporting

rates changed was generally much younger in South East Asia, with the reporting rate in younger individuals (ρ_y) estimated as slightly higher than that of older individuals (ρ_o). This is consistent with dengue tending to be viewed as a paediatric infection in South East Asia (and thus perhaps less likely to be diagnosed in adults), but being widely accepted as a disease affecting all ages in the Americas [6]. Yet with the rapidly changing demographics in Thailand (lower birth and death rates) increasing the average age of DHF, reporting rates in adult age groups may increasing in coming years in such contexts. In contrast to our finding of higher estimated reporting rates in children, there is some evidence that the risk that a dengue infection is symptomatic increases with age [95,205]. However, the higher reporting rates we estimate for children in South East Asia may reflect parents being more likely to seek healthcare for a child than for an adult, or clinicians being more likely to diagnose dengue in children. Importantly estimating the age at which reporting rates changed ($A_{threshold}$) was limited by the age aggregation used in each study, therefore for surveys with few age groups this estimated threshold should be treated with caution.

Since the majority of notified dengue cases are diagnosed as secondary dengue infections [3,4,20,122,173], we assumed that the probability of detecting a primary case would be smaller than the probability of detecting a secondary case, and that the probability of detecting a tertiary/quaternary case would be smaller than the probability of detecting a primary case ($\gamma_3 < \gamma_1 < \rho$). The probability of detecting a primary case was consistently low relative to a secondary case (Figure 4.30) at less than 50%, the majority being under 25%. However, we were not able to estimate the probability of detecting a tertiary/quaternary case (relative to a primary case) from the available data. A prospective cohort study in Nicaragua found that the proportion of inapparent to symptomatic infection did not differ according to whether an individual had a primary, secondary, or tertiary infection [207].

Overall, the impact of cross-immunity and the contribution of tertiary and quaternary infections to onward transmission are still not well quantified. While there is evidence that tertiary and quaternary infections occur [25,28], there is little quantitative data on the infectiousness or severity of such infections relative to primary and secondary infections. Additionally, clinically apparent tertiary or quaternary infections are not routinely reported, nor can they be tested for retrospectively [25]. Wikramaratna *et al*. showed that tertiary

and quaternary infections allows for the high seroprevalence at very young ages observed in Haiti [29] and Nicaragua [30] better than when assuming complete protection after two heterologous infections [25].

Since the majority of dengue infections are mild or asymptomatic, even sensitive healthcare systems can substantially underestimate true rates of infection even for the supposedly more severe secondary infections, as shown by the low baseline reporting rates [122,123]. Furthermore, dengue has a wide spectrum of clinical manifestations making it difficult to accurately diagnose in the first instance [52]. Although incidence data are the most abundant form of data available on dengue transmission, surveillance systems and reporting procedures are not standardised within or across countries making it very difficult to reliably compare estimates [52]. Laboratory capacity and general public health infrastructure and surveillance systems vary widely and there is often no integration between private and public health sectors. With such variable data it is very difficult to estimate dengue burden (or transmission intensity) consistently. Since non-serotype specific serological (IgG) surveys are relatively inexpensive to collect, it would be beneficial for such seroprevalence data to be collected routinely. Such data would provide better baseline estimates of overall transmission intensity against which incidence based-estimates could be calibrated to assess changes in transmission and identify weaknesses in surveillance systems.

4.5 Acknowledgements

I would like to thank Dr. Isabel Rodriguez-Barraquer from Johns Hopkins Bloomberg School of Public Health and Prof. Derek Cummings from The University of Florida for sharing the incidence data from Bangkok, Ratchaburi, and Rayong which allowed for a direct comparison of seroprevalence and incidence data estimates.

5 Estimating the global burden of dengue and the impact of control measures

In this chapter I present methods to estimate the global burden of dengue. Data on the probability of dengue occurrence is used in conjunction with the force of infection estimates I estimated in chapters 2, 3, and 4. The incidence model developed in chapter 4 is then used to estimate the global burden of dengue. The potential impact of novel control measures such as the release of *Wolbachia* infected mosquitoes was explored. The work in this chapter was conducted in collaboration with Dr. Oliver Brady and Prof. Simon Hay (University of Oxford) who shared the probability of dengue occurrence data, and Dr. Wes Hinsley (Imperial College London) who coded the model in Java.

5.1 Introduction

Recent estimates of the global distribution of dengue have refined our understanding of the burden of dengue disease, but remain ambiguous. In particular, Bhatt *et al.*'s estimate of 390 million dengue infections per year (and 96 million apparent infections) is three times higher than previous official World Health Organisation (WHO) estimates, with India accounting for 34% of that total [108]. Motivated by previous work on malaria, the Bhatt *et al.* analysis relied on correlating their geographic niche-modelling based estimates of dengue presence with burden estimates derived from serological surveys. They built a boosted regression tree (BRT) statistical model of dengue transmission risk using an extensive database of geo-located dengue occurrence records, a global evidence-based consensus map of dengue in 2010 [208], and incorporated covariates known to affect dengue transmission such as rainfall and temperature. They then mapped the probability of occurrence (PO) or risk of dengue infection globally for each 5km x 5km pixel. This was further combined with serological cohort studies looking at dengue sero-incidence to build a non-parametric Bayesian hierarchical model to predict the number of inapparent and clinically apparent dengue infections [108]. One weakness of this analysis is that infection incidence was not bounded by population birth rates. Furthermore, unlike malaria, the number of dengue infections an individual can acquire in their lifetime is finite (up to four), yet in the Bhatt *et al.* analysis individuals were allowed to have an infinite number of dengue infections in their lifetime.

Obtaining robust estimates of the geographic variation in average dengue transmission intensity – as quantified by the basic reproduction number, R_0, of each serotype – is key to improving the reliability of burden estimates. In addition, a quantitative understanding of variation in transmission intensity is essential in assessing the likely impact of interventions such as a vaccine [60,61] or novel vector control measures such as *Wolbachia* infected mosquitoes [70,74,110]. Given the highly heterogeneous nature of dengue transmission, age-stratified seroprevalence surveys (preferably serotyped) with high spatial resolution provides the best estimates of dengue transmission intensity ([174] and chapters 2 and 3). I have also shown previously that force of infection (λ) estimates from age-stratified notification data can provide estimates comparable to λ estimates from serological data (chapter 4). However, in areas where dengue is not reported, or areas where dengue is not thought to be endemic, such data are harder to collect. Hence if the presence-absence data can be reliably translated into quantitative measures of dengue burden - such as λ and R_0, then more robust estimates can be made.

Here I develop a model to estimate λ and R_0 from presence-absence data by regressing the force of infection estimates derived from seroprevalence and incidence data from previous work (chapters 2-4) on probability of occurrence estimates from the Bhatt *et al*. model [108]. I then use this regression relationship to generate global force of infection and R_0 estimates at 5 km resolution. This allows me to generate corresponding disease burden estimates that constrain the number of lifelong infections an individual can experience. Furthermore, I look at the potential impact that control measures, specifically *Wolbachia*-infected *Aedes aegypti* can have on the burden of dengue.

5.2 Methods

5.2.1 Regression of Presence-absence Against Force of Infection

Global positioning system (GPS) coordinates of age-stratified seroprevalence and incidence surveys previously identified were used to extract the probability of dengue occurrence (PO, also referred to here as 'presence-absence data') from the corresponding latitude and

longitude at the same spatial scale as the survey in question [108]. The force of infection for each survey was estimated previously ([174] and chapters 2-4).

A simple linear model (5.1), exponential model (5.2), and power model (5.3) were fitted to the force of infection and corresponding presence-absence values using linear least squares (linear model) and non-linear least squares (exponential and power model).

Linear Model:

Since the force of infection should be 0 when the probability of dengue occurrence is also 0, we assume that the intercept is (0, 0) and regress through the origin.

$$\lambda = \beta p \tag{5.1}$$

where λ is the total force of infection, β is the slope, and p is the probability of dengue occurrence.

Exponential Model:

$$\lambda = a\left[\exp\left(kp\right)\right] \tag{5.2}$$

where λ is the total force of infection, a is the scaling factor, p is the probability of dengue occurrence, and k is the exponent.

Power Model:

$$\lambda = ap^k \tag{5.3}$$

where λ is the total force of infection, a is the scaling factor, p is the probability of dengue occurrence, and k is the exponent.

We chose to use an unweighted regression given the lack of seroprevalence surveys available and the inconsistencies in terms of survey design, survey year, and diagnostic test ([174] and chapters 2-3).

Since λ estimates were available from both seroprevalence surveys (one estimate from the IgG model (chapters 2 and 3) and incidence data (two estimates from two model variants 1b

and 2b as described in chapter 4)), the λ estimates used in equation (5.1)-(5.3) were either from; (i) seroprevalence surveys only, (ii) or were a combined estimate from seroprevalence surveys and incidence data model 1b, (iii) or seroprevalence surveys and incidence data model 1b. The strength of association between λ and PO (combinations i – iii) was assessed by a pseudo R-squared (R^2) statistic and the non-linear regression correlation coefficient. The best model was then selected to estimate the force of infection across the globe. All models were fitted in the R Statistical Package [159].

Comparing goodness of fit

The R^2 statistic was calculated by;

$$R^2 = 1 - \frac{\sum_i \left(y_i - \hat{y}_i \right)^2}{\sum_i \left(y_i - \bar{y} \right)^2},$$

where y_i are the data, $\hat{y}_i$ are the associated predicted values, and $\bar{y}$ is the mean y-value.

For non-linear least square fittings, the correlation coefficient is calculated by:

$$r = \sqrt{1 - \frac{SSE}{SST}},$$

where $SSE = \sum_i \left(y_i - \hat{y}_i \right)^2$ and $SST = \sum_i \left(y_i - \bar{y}_i \right)^2$, where y_i are the data, $\hat{y}_i$ are the associated predicted values, and $\bar{y}$ is the mean y-value.

The 95% confidence region was calculated for the two parameters a and k according to Beale's criterion using the R package *nlstools* [209,210]. 5000 parameter sets were randomly sampled from this region and used to calculate the burden of dengue. The maximum and minimum burden from the 5000 sets represents the uncertainty around the estimated dengue burden.

5.2.2 Mapping the Estimated Burden of Dengue

The best fitting model was then used to map the predicted λ, serotype-specific basic reproduction number (R_{0i}), and the burden of dengue (number of dengue infections) across the globe. The global presence-absence data for each 5x5km pixel were generated as described in Bhatt *et al.* [108]. The force of infection at any 5km by 5km area was estimated by transforming the presence-absence data of each pixel into a force of infection estimate using equation (5.1), (5.2), or (5.3). From this, R_{0i} and the expected number of dengue cases could be estimated as described in sections 5.2.3 and 5.2.4. All mapping and burden estimates were done in Java.

5.2.3 Estimating the Basic Reproduction Number

Using λ values estimated from the power model, R_{0i} were calculated under two different assumptions in keeping with previous chapters. Under assumption 1, we assumed that there was no cross-protection between different serotypes, and that individuals can be infected up to four times. Under assumption 2, we assumed that individuals acquired protective immunity after the second heterologous infection. The population age-structure of each country were taken from the 2010 United Nations (UN) world population estimates [128].

A) R_{0i} **calculation assumption 1 –** individuals can be infected 4 times.

The basic reproduction number for a single serotype is given by:

$$R_{0i} = \frac{1}{1-\int_0^\infty f(a)z_i(a)da}, \tag{5.4}$$

where $f(a)$ is the proportion of the population aged a, and $z_i(a)$ is the proportion of the population seropositive calculated by:

$$z_i(a) = 1 - e^{-\frac{\lambda}{n}a}, \tag{5.5}$$

where n is the number of serotypes in circulation.

Substituting (5.5) into (5.4):

$$R_{0i} = \frac{1}{1-\int_{a_1}^{a_2} f(a)\left[1-e^{-\frac{\lambda}{n}a}\right]da}$$
$$= \frac{1}{1-\int_{a_1}^{a_2}\left[f(a)+f(a)e^{-\frac{\lambda}{n}a}\right]da} \quad , \qquad (5.6)$$
$$= \frac{1}{1-\int_{a_1}^{a_2} f(a')da' + \int_{a_1}^{a_2} f(a)e^{-\frac{\lambda}{n}a}da}$$

$\int_{a_1}^{a_2} f(a')da'$ integrates to 1, therefore we are left with:

$$R_{0i} = \frac{1}{\int_{a_1}^{a_2} f(a)e^{-\frac{\lambda}{n}a}da}$$
$$= \frac{1}{\sum_j f\left(a_{j+1}\to a_j\right)\left[-\frac{n\exp\left[-\lambda a/n\right]}{\lambda}\right]_{a_j}^{a_{j+1}}} \quad . \qquad (5.7)$$
$$= \frac{1}{\sum_j f\left(a_{j+1}\to a_j\right)\frac{n}{\lambda}\left[\exp\left[-\lambda a_j/n\right]-\exp\left[-\lambda a_{j+1}/n\right]\right]}$$
$$= \frac{\lambda}{\sum_j f\left(a_{j+1}\to a_j\right)n\left[\exp\left[-\lambda a_j/n\right]-\exp\left[-\lambda a_{j+1}/n\right]\right]}$$

B) R_{0i} **calculation assumption 2 –** individuals become immune after two infections:

The basic reproduction number for a single serotype is given by:

$$R_{0i} = \frac{1}{\int_0^\infty f(a)\left[x(a)+(n-1)z_i(a)\right]da}, \qquad (5.8)$$

where $f(a)$ is the proportion of the population in age group a, n is the number of serotypes in circulation, $x(a)$ is the proportion of the population seronegative at age a given by:

$$x(a) = \exp[-\lambda a] \tag{5.9}$$

and $z(a)$ is the proportion of the population seropositive for a single serotype at age a given by:

$$\begin{aligned} z_i(a) &= [1-\exp[-\lambda a/n]][\exp[-(n-1)\lambda a/n]] \\ &= \exp[-(n-1)\lambda a/n] - \exp[-n\lambda a/n] \\ &= \exp[-(n-1)\lambda a/n] - \exp[-\lambda a] \end{aligned} \quad . \tag{5.10}$$

Integrating between ages a_1 and a_2 gives:

$$\begin{aligned} R_{0i} &= \frac{1}{\int_{a_1}^{a_2} f(a)[x(a)+(n-1)z(a)]da} \\ &= \frac{1}{\int_{a_1}^{a_2} f(a)[(n-1)\exp[-(n-1)\lambda a/n] - (n-2)\exp[-\lambda a]]da} \\ &= \frac{1}{\sum_j \frac{p(a_j)}{a_{j+1}-a_j}\left[\frac{n\left(\exp[-(n-1)\lambda a_j/n] - \exp[-(n-1)\lambda a_{j+1}/n]\right)}{\lambda} - (n-2)\left(\frac{\left(\exp[-\lambda a_j] - \exp[-\lambda a_{j+1}]\right)}{\lambda}\right)\right]} \\ &= \frac{\lambda}{\sum_j \frac{p(a_j)}{a_{j+1}-a_j}\left[n\left(\exp[-(n-1)\lambda a_j/n] - \exp[-(n-1)\lambda a_{j+1}/n]\right) - (n-2)\left(\exp[-\lambda a_j] - \exp[-\lambda a_{j+1}]\right)\right]} \end{aligned} \quad . \tag{5.11}$$

5.2.4 Calculating the Expected Number of Cases

The expected number of cases in each age group can be calculated from the estimated force of infection (equation (5.1)-(5.3)), the population density of a country, and the weighted sum of primary to quaternary infections (chapter 4, equations (4.1) – (4.5)). The population density for each pixel was taken from the Global Rural-Urban Mapping Project [211] and age-structure from the UN Population Estimates [128].

The expected number of cases is given by:

$$C_i = \frac{n_i}{width_i}\left\{w_1 I_1(a) + w_2 I_2(a) + w_3 I_3(a) + w_4 I_4(a)\right\} \quad (5.12)$$

where n_i is the number of individuals in age group i, $width_i$ is the width of that age-group, and $w_1 - w_4$ are the relative weights, or the probability of detecting a primary to quaternary infections respectively. The total number of expected cases over the entire population is simply:

$$Total = \sum_i C_i \,. \quad (5.13)$$

5.2.5 Incorporating Temporary Cross-immunity

For R_{0i} calculated above (equations (5.7) and (5.11)), we assumed dengue transmission was at endemic equilibrium. However, to investigate the effect that temporary cross-immunity may have on dengue burden (as quantified by R_{0i}), we allowed for short-term cross-immunity against the remaining serotypes following infection with one serotype.

The proportion of the population who are infectious at age a, $Y(a)$ is given by:

$$Y(a) = \int_0^a S(a) e^{-\gamma(a-a')} I(a')\, da', \quad (5.14)$$

where $S(a)$ is the survival function – the probability of surviving until age a. We assumed an exponential survival function $e^{-\mu a}$ where μ is the mortality rate. γ is the recovery rate or the rate at which individuals leave the infectious compartment – note that the movement out of the infectious compartment occurs relative to when an individual was infected. $I(a)$ is the weighted sum of primary to quaternary infection incidences which are identical to those equations in chapter 4 for calculating dengue incidence. However the limits of integration have been adjusted to take into account the period of temporary cross immunity (in years) given by d. The lower limit was reset to 0 if $a - d$ was negative. To look at the impact of the duration of temporary cross-immunity after infection with one serotype, the duration of immunity was varied between 6 months to 2 years [21–24] under the three scenarios described in Table 5.1.

The serotype-specific basic reproduction number can then be calculated by

$$R_{0i} = \frac{\lambda / n}{\sum f(a) I(a)} \tag{5.15}$$

where λ is the force of infection, $f(a)$ is the proportion of the population aged a, n is the number of serotypes in circulation, and $I(a)$ is the weighted sum of primary to quaternary infection incidence (chapter 4 equation (4.5)). If there are fewer than 4 serotypes in circulation, the equations change as described in chapter 4.

5.2.6 Estimating the Global Burden of Dengue Under Different Reporting Scenarios

Changing the probability of detecting dengue infection

The expected burden of dengue was calculated under several different scenarios. The weights $w_1 - w_4$ (equation (5.12)) were varied to reflect the probability of detecting a primary – quaternary infection (Table 5.1). In scenario 1 we assumed that all infections are reported which is the equivalent to the total number of infections. In contrast, in scenario 3 the best estimates of the probability of detecting a primary – quaternary infection were used [60,61]. This reflects the number of apparent infections.

Table 5.1: Different scenarios under which the burden of dengue was calculated.

Scenario		**Assumption***	w_1	w_2	w_3	w_4
1	Perfect reporting, maximum burden	1	1	1	1	1
		2	1	1	0	0
2	Only secondary cases are observed	1	0	1	0	0
		2	0	1	0	0
3	Best estimates of proportion of cases observed	1	0.25	0.5	0.1	0.1
		2	0.25	0.5	0	0

*Under assumption 1, individuals can be infected up to four times. Under assumption 2 individuals develop protective immunity after their second infection.

5.3 Results

5.3.1 Linear and Non-linear Regression

Although the simple linear regression had similar correlation coefficients to the non-linear models (Table 5.2-Table 5.4), the R^2 values were much smaller, and the model failed to capture the high force of infection at higher values of the probability of occurrence (Figure 5.1).

Table 5.2: Parameter estimates of the simple linear model and corresponding R^2 values.

Combinations	β **(95% CI)**	**Correlation Coefficient**	R^2	**Fig**
Serology	0.108 (0.078-0.139)	0.59	0.35	Figure 5.1a
Serology + Incidence Model 1b^	0.105 (0.082-0.128)	0.52	0.27	Figure 5.1b
Serology + Incidence Model 2b^	0.102 (0.076-0.128)	0.52	0.27	Figure 5.1c

^Model 1b: incidence model with single reporting rate fitted to cumulative incidence data. Model 2b: incidence model with age-dependent reporting rate fitted to cumulative incidence data as described in chapter 4.

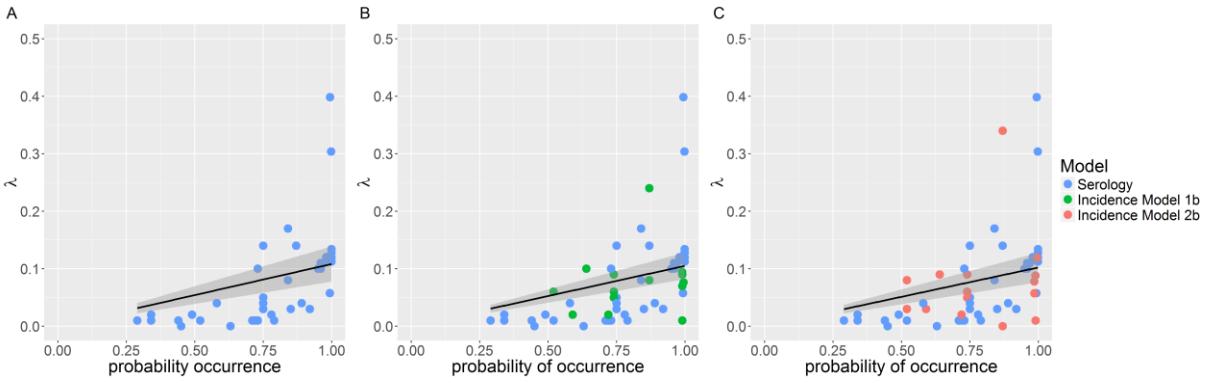

Figure 5.1: Linear regression of probability of occurrence on force of infection. Points show the data, the solid line shows the line of best fit, and the shaded area shows the 95% CI. A) Seroprevalence surveys results only, B) seroprevalence survey and incidence model 1b results, and C) seroprevalence and incidence model 2b results.

The non-linear regression correlation coefficient and R^2 of the exponential and power model were similar for all three combinations (Table 5.3 and Table 5.4). Since the force of infection could not be 0 when the probability of dengue occurrence was 0 with the exponential model, the power model was chosen for subsequent analysis. The best fitting

power model as assessed by R^2 and the non-linear regression correlation coefficient was when only the force of infection estimates from seroprevalence surveys were used with corresponding presence-absence values (Table 5.4 and Figure 5.3). Therefore all subsequent calculations were based on Figure 5.3a. The parameter sets randomly sampled from the 95% confidence region of the two parameters (a and k) from which the 95% CI were calculated are shown in Figure 5.4.

Table 5.3: Parameter estimates of the exponential model and corresponding R^2 values.

Combinations	**Parameter values (95% CI)**		R^2	**Correlation Coefficient***	**Fig.**
	a	k			
Serology	0.001 (0.00002-0.009)	5.47 (2.68-9.55)	0.44	0.67	Figure 5.2a
Serology + Incidence Model 1b^	0.005 (0.001-0.022)	3.36 (1.63-5.55)	0.30	0.55	Figure 5.2b
Serology + Incidence Model 2b^	0.004 (0.0003-0.027)	3.61 (1.48-6.15)	0.25	0.50	Figure 5.2c

*Non-linear least squares correlation coefficient. ^Model 1b: incidence model with single reporting rate fitted to cumulative incidence data. Model 2b: incidence model with age-dependent reporting rate fitted to cumulative incidence data as described in chapter 4.

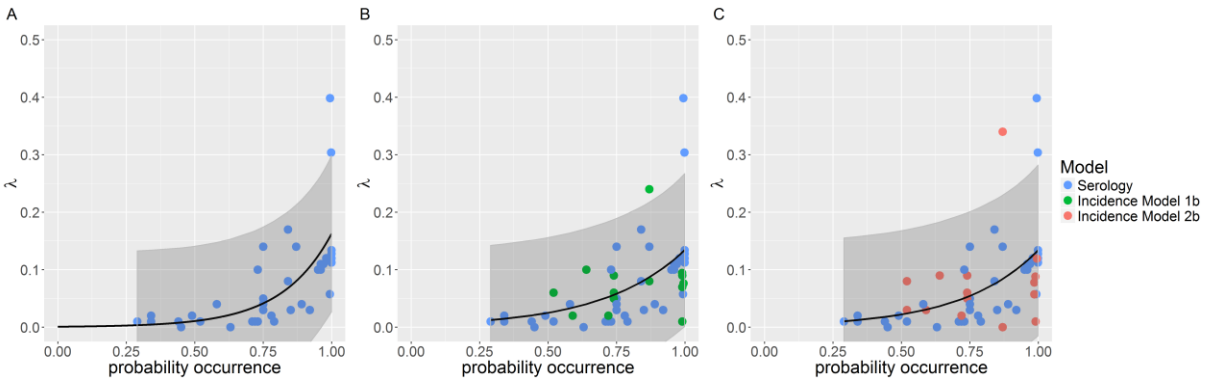

Figure 5.2: Non-linear exponential model regression of probability of occurrence on force of infection. Points show the data, the solid line shows the line of best fit, and the shaded area shows the 95% CI. A) Seroprevalence surveys results only, B) seroprevalence survey and incidence model 1b results, and C) seroprevalence and incidence model 2b results.

Table 5.4: Parameter estimates of the power model and corresponding R^2 values.

Combinations	**Parameter values (95% CI)**		R^2	**Correlation Coefficient***	**Fig.**
	a	k			
Serology	0.161 (0.125-0.211)	4.852 (2.408-8.410)	0.44	0.66	Figure 5.3a
Serology + Incidence Model 1b^	0.132 (0.107-0.166)	2.834 (1.370-4.599)	0.30	0.54	Figure 5.3b
Serology + Incidence Model 2b^	0.131 (0.101-0.171)	3.014 (1.154-5.140)	0.25	0.50	Figure 5.3c

*Non-linear least squares correlation coefficient. ^Model 1b: incidence model with single reporting rate fitted to cumulative incidence data. Model 2b: incidence model with age-dependent reporting rate fitted to cumulative incidence data as described in chapter 4.

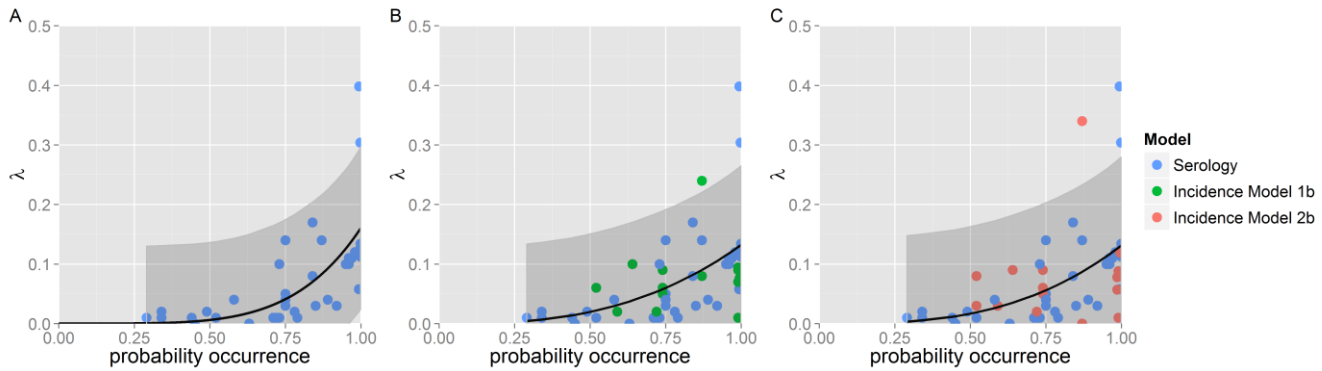

Figure 5.3: Non-linear power model regression of probability of occurrence on force of infection. Points show the data, the solid line shows the line of best fit, and the shaded area shows the 95% CI. A) Seroprevalence surveys results only, B) seroprevalence survey and incidence model 1b results, and C) seroprevalence and incidence model 2b results.

For all combinations shown above (Figure 5.3), the power model captured the gradual increase in λ with increasing PO up to a PO of ~0.7. However the model was unable to capture the wide variation in λ for PO values above 0.7.

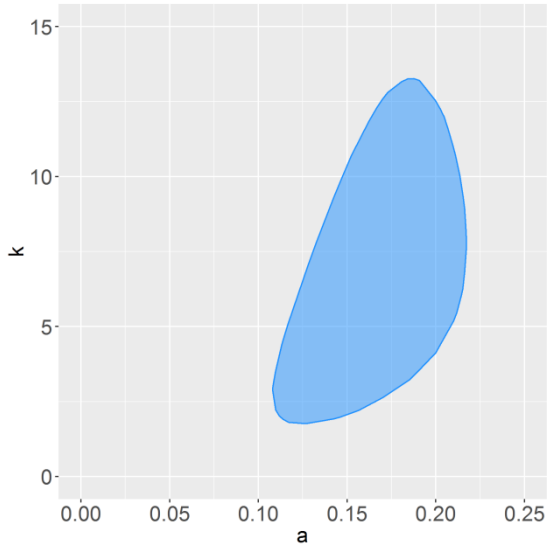

Figure 5.4: Minimum convex polygon of 5000 parameter sets randomly sampled from the 95% confidence region of the two parameters of the power function fitted to seroprevalence survey results only (Fig. 5.1a).

5.3.2 The estimated annual global burden of dengue

The maximum estimated annual global burden (scenario 1 - perfect reporting, maximum burden) based on the 2010 population was 109 million (95% CI: 80 M – 147 M) under the assumption that all countries had four serotypes in circulation and that individuals could be infected up to four times. When we assumed that individuals were immune after two infections the burden decreased to 75 million (95% CI: 56 M – 104 M). Under our most realistic assumptions about the relative contribution of primary – quaternary infections to observed cases (scenario 3) and using the reported number of serotypes for each country where available, the estimated observed case burden was 28 million (95% CI: 21 M – 39 M), decreasing to 25 million (95% CI: 19 M – 35 M) when assuming immunity after two infections. Table 5.5 lists the burden estimates under the three scenarios tested.

Table 5.5: Global burden estimates and 95% CI under different assumptions.

Scenario*	Assumption^	Serotypes¯	Burden**	95% CI
1	1	Fixed (4)	108,000,000	79,700,000 – 147,000,000
	1	Free	102,000,000	75,100,000 – 139,000,000
	2	Fixed (4)	74,800,000	56,000,000 – 104,000,000
	2	Free	71,600,000	53,600,000 – 99,100,000
2	1	Fixed (4)	31,900,000	23,800,000 – 44,300,000
	1	Free	28,900,000	21,600,000 – 40,200,000
	2	Fixed (4)	31,900,000	23,800,000 – 44,300,000
	2	Free	28,900,000	21,600,000 – 40,200,000
3	1	Fixed (4)	30,100,000	22,300,000 – 41,300,000
	1	Free	28,200,000	20,900,000 – 38,800,000
	2	Fixed (4)	26,700,000	19,900,000 – 37,000,000
	2	Free	25,100,000	18,800,000 – 34,800,000

*See Table 5.1. ^Assumption 1: individuals can be infected up to four times, assumption 2: individuals are immune after their second infection. ¯Fixed: the number of serotypes in circulation in each country is fixed to 4. Free: reported number of serotypes used. **Shown to three significant figures.

The estimated burden, probability of dengue occurrence, force of infection, and basic reproduction number were mapped for every 5x5km pixel globally. Figure 5.5 shows these estimates for scenario 3 using the reported number of serotypes for each country under the assumption that individuals can be infected up to four times. As expected the burden was highest in South East Asia with heterogeneity within countries. Country-specific estimates of dengue burden (scenario 3 and using the reported number of serotypes) were then compared to the inapparent and apparent dengue infection estimates by Bhatt *et al.* and the WHO estimates where available [108]. Figure 5.6 to Figure 5.9 show that our estimates are consistently lower than the apparent dengue infection estimates made by Bhatt *et al.* and are generally more consistent with the reported WHO cases. Table 5.6 compares average R_0 values by country estimated here with previously estimated values of R_0 (chapters 2-4), and published values.

Table 5.6: Comparison of R_0 estimates to previously published estimates by country.

Country	**Estimated average R_0 in 2010***	**Range of previously estimated point estimates of R_0 from Serology and Incidence Models (ch. 2- 5)**	**Published R_0 estimates**	**Ref**
Brazil	1.97 – 2.11	1.09 – 2.48	1.6 – 2.5	[119,174]
			3.6 – 12.9	[212]
			2 – 103	[118]
			2.3 - 11	[114]
			0.28 – 5.04	[213]
			2 – 3.3	[167]
Cambodia	1.56 – 1.62	2.01 – 3.40		
Costa Rica	1.85 – 1.92	1.87 – 2.77		[174]
China	0 – 0.32	1.19 – 3.53		
Cuba	3.09 – 3.50	1.14 – 1.52		[174]
Dominican Republic	2.88 – 3.03	1.84 – 2.67		[174]
El Salvador	2.26 – 2.41	1.82 – 2.67		[174]
French Polynesia	3.50 – 3.95	3.73 – 6.90		[174]
Haiti	1.64 – 1.71	3.67 – 6.32		
India	1.73 – 1.82	1.01		[174]
Indonesia	2.45 – 2.65	1.89 – 2.81		[174]
Laos	1.25 – 1.27	1.13 – 2.56		[174]
Mayotte	1.21 – 1.24	1.06 – 1.07		[174]
Mexico	1.19 – 1.25	1.23 – 1.40	1.3 – 2.4	[174,214]
			1.1 – 1.3	[115]
			1.9	[215]
			1.9 – 2.4	[167]
Nicaragua	1.86 – 1.96	1.06 – 6.42		[174]
Pakistan	1.07 – 1.11	1.05 – 1.34		[174]
Papua New Guinea	0.80 – 0.82	2.55 – 4.11		[174]
Peru	0.98 – 1.02	1.11 – 2.94	1.76 (0.83-4.46)	[117,174]
Philippines	2.18 – 2.32	1.04 – 1.05	2.1 – 3.9	[167]
Puerto Rico	3.87 – 4.42	1.57 – 2.86	1.2 – 2.7	[167]
Singapore	4.33 – 5.11	1.21 – 2.05	3.9 – 4.7	[174,216]
Sri Lanka	2.64 – 2.89	1.03 – 9.86		[174]
Thailand	2.21 – 2.42	2.16 – 4.26	4 – 6 or 8	[104,174]
		1.81 – 3.33	5.2 – 6.7	[121,174]
			3.3 (3.1-3.4)	[165]
			3.2 (2.7-3.3)	[165]
			1.9 – 2.3	[217]
			2.2 – 5.2	[167]
USA	0.05 – 0.05	1.08 – 1.12		[174]
Vietnam	1.98 – 2.11	2.02 – 3.62	1.25 – 1.75	[155]
			5 – 7	[218]
			3	[219]
			2 – 3	[167]

*Range given for assumption 1: individuals can be infected 4 times, and assumption 2: immune after 2 infections.

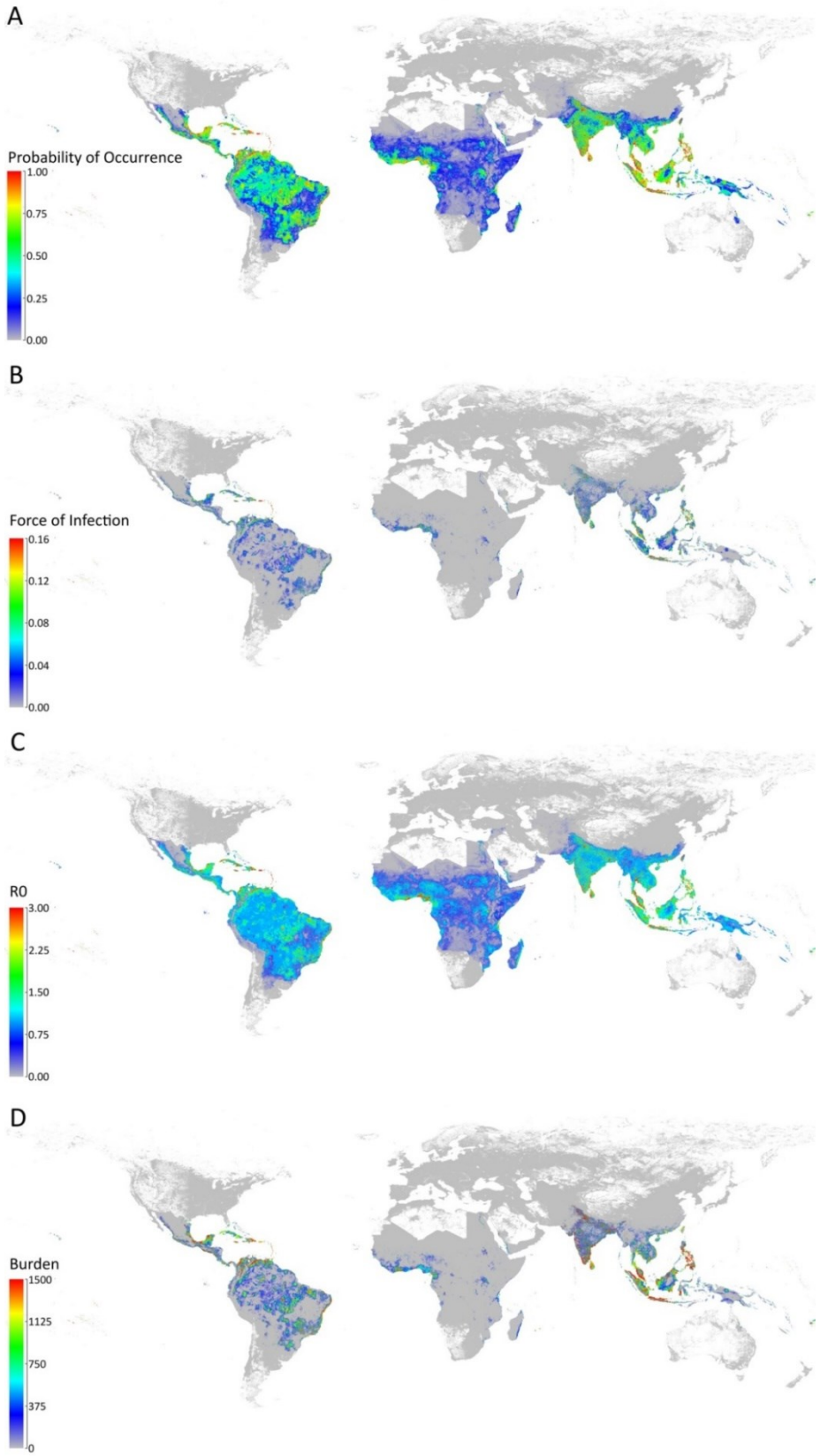

Figure 5.5: Global A) probability of dengue occurrence, B) force of infection, C) R_0, and D) observed dengue cases in 2010 at 5x5km spatial resolution. Results are mapped for scenario 3 assuming individuals can be infected up to 4 times and using the reported number of serotypes for each country. The upper limit shown in panels C and D are fixed at 3 and 1500 respectively.

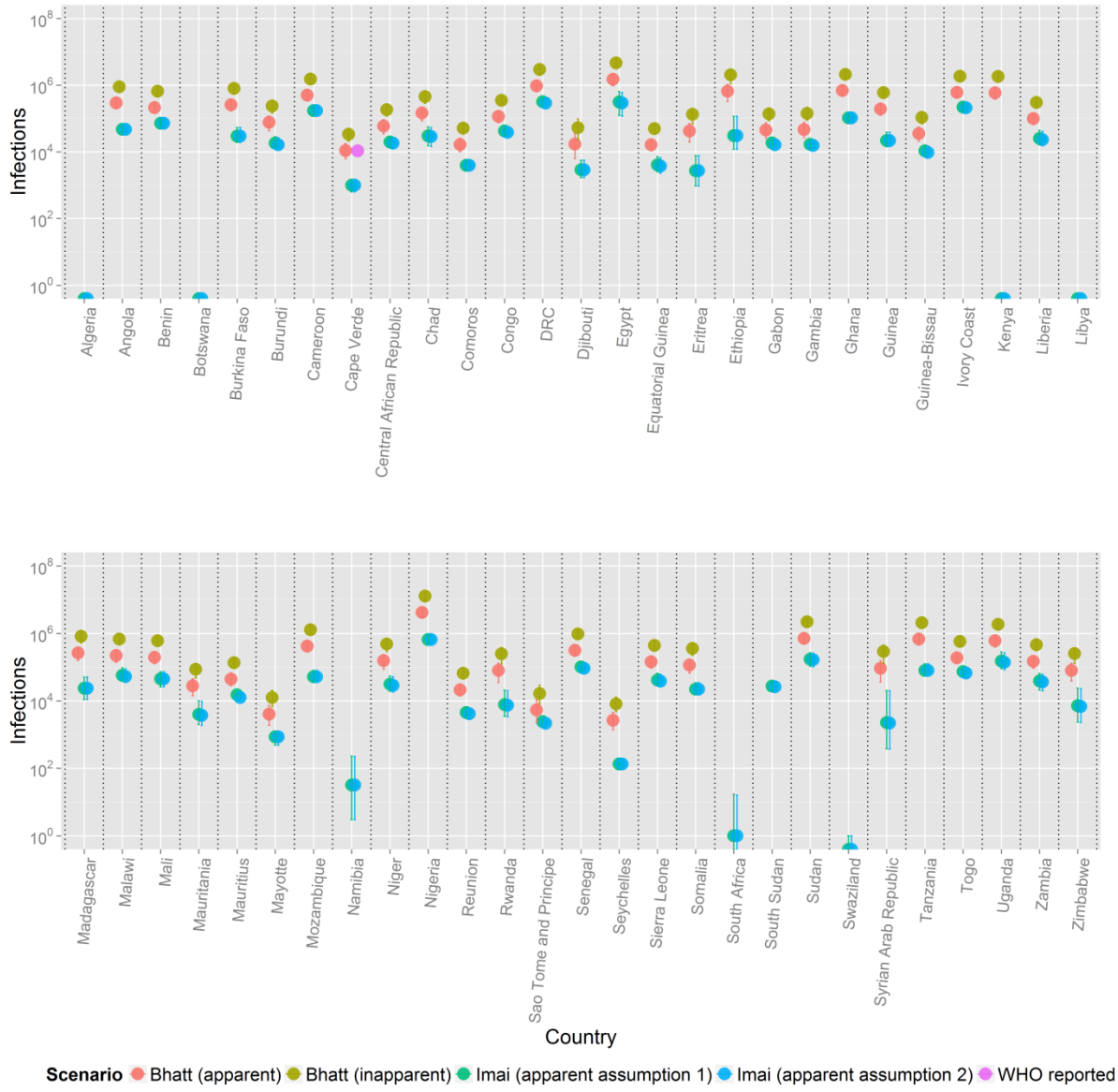

Figure 5.6: Comparisons of the estimated burden of dengue in Africa to estimates from Bhatt *et al*. [108] and where reported, the WHO. Here only estimates from scenario 3 are presented under assumption 1 (individuals can have up to 4 infections) using the reported number of serotypes for each country. Points represent the posterior median estimate, and the lines the 95% CrI.

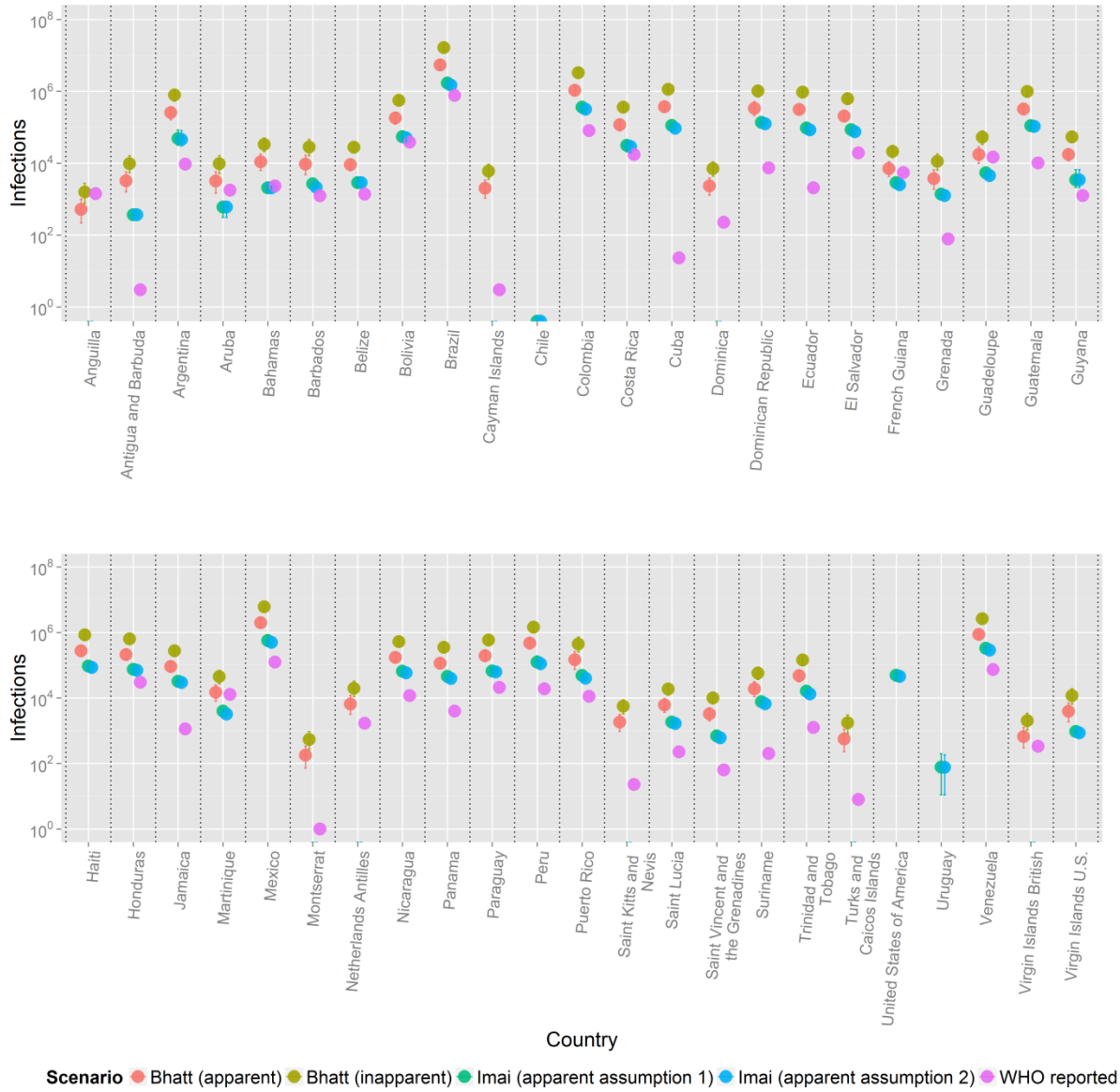

Figure 5.7: Comparisons of the estimated burden of dengue in the Americas to estimates from Bhatt *et al*. [108] and where reported, the WHO. Here only estimates from scenario 3 are presented under assumption 1 (individuals can have up to 4 infections) using the reported number of serotypes for each country. Points represent the posterior median estimate, and the lines the 95% CrI.

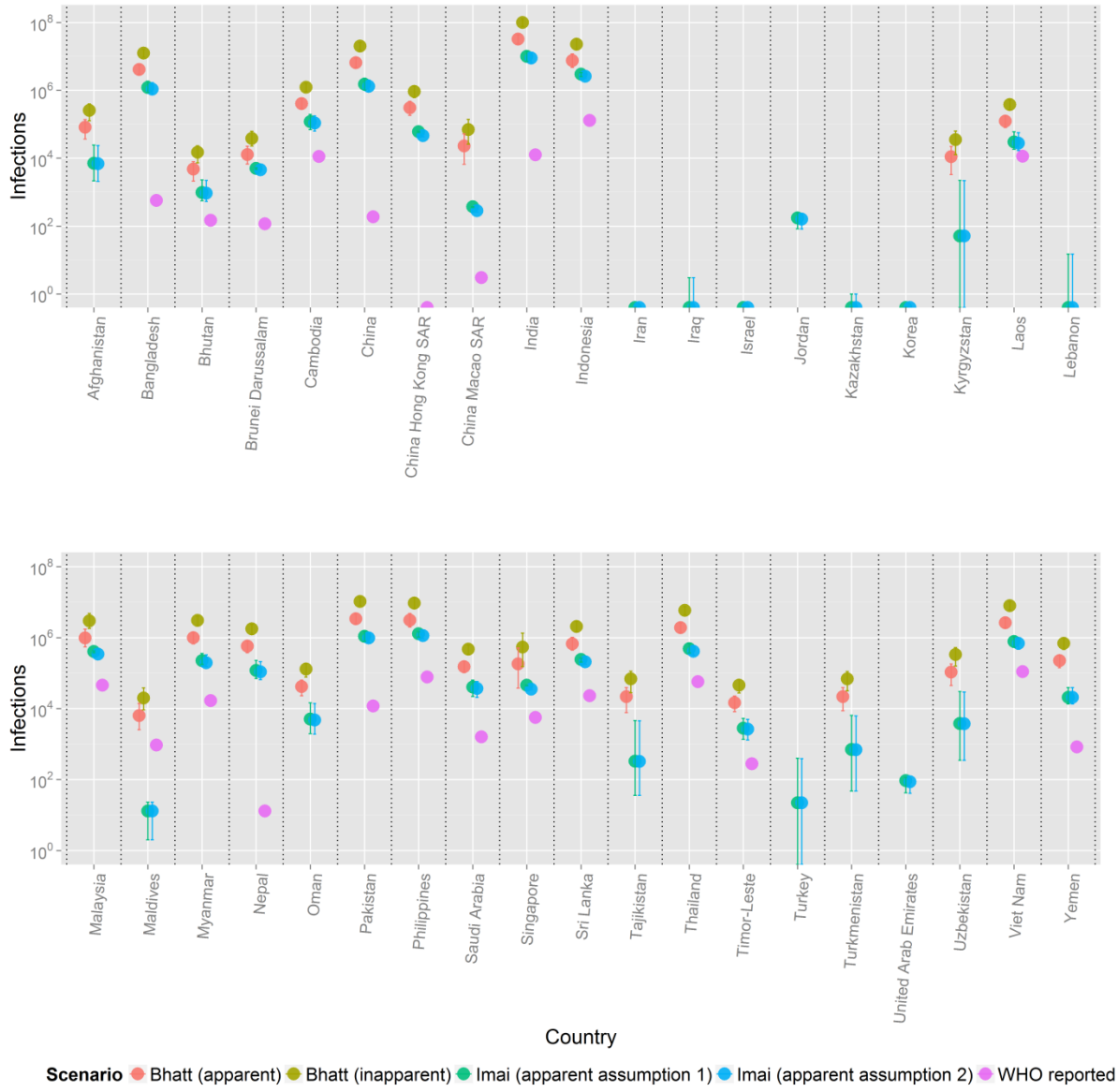

Figure 5.8: Comparisons of the estimated burden of dengue in Asia to estimates from Bhatt *et al*. [108] and where reported, the WHO. Here only estimates from scenario 3 are presented under assumption 1 (individuals can have up to 4 infections) using the reported number of serotypes for each country. Points represent the posterior median estimate, and the lines the 95% CrI.

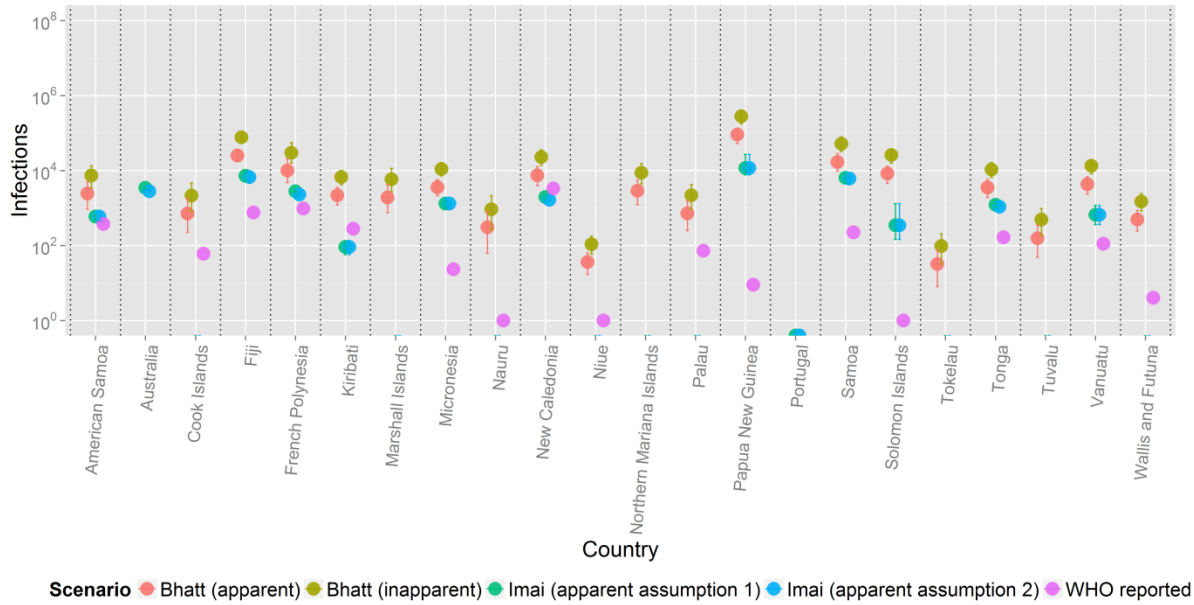

Figure 5.9: Comparisons of the estimated burden of dengue in Europe and Oceania to estimates from Bhatt *et al*. [108] and where reported, the WHO. Here only estimates from scenario 3 are presented under assumption 1 (individuals can have up to 4 infections) using the reported number of serotypes for each country. Points represent the posterior median estimate, and the lines the 95% CrI.

To look at the impact of the duration of temporary cross-immunity after infection with one serotype, the duration of immunity was varied from 6 months to 2 years [21–24] . As expected the reduction in the number of cases was greater when the duration of immunity was longer under all scenarios. Although the percentage reduction in cases was minimal when allowing for temporary cross-immunity compared to no cross-immunity post-infection, reduction in terms of absolute number of cases was still substantial (Table 5.7).

Table 5.7: Estimated global burden of disease (and 95% CI) with and without temporary cross immunity using reported number of serotypes

Scenario*	**Assumption^**	**Burden with No Temporary Cross-Immunity** (95% CI)**	**Burden with Temporary Cross Immunity** (95% CI)**	
			6 months	**2 years**
1	1	102,000,000 (75,100,000 – 139,000,000)	101,000,000 (74,400,000-137,000,000)	98,700,000 (72,400,000-134,000,000)
	2	71,600,000 (53,600,000 – 99,100,000)	71,500,000 (53,500,000-98,800,000)	71,000,000 (53,100,000-98,100,000)
3	1	28,200,000 (20,900,000 – 38,800,000)	28,100,000 (20,800,000-38,500,000)	27,600,000 (20,500,000-37,900,000)
	2	25,100,000 (18,800,000 – 34,800,000)	25,100,000 (18,700,000-34,700,000)	24,800,000 (18,500,000-34,300,000)

*See Table 5.1. ^Assumption 1: individuals can be infected up to four times, assumption 2: individuals are immune after their second infection **Shown to three significant figures.

5.4 Discussion

Using the global evidence consensus of dengue occurrence and subsequent dengue infection risk map [108] we estimated the force of infection, basic reproduction number, and apparent dengue cases at high spatial resolution. Dengue transmission was spatially highly heterogeneous both between and within countries. Force of infection estimates from seroprevalence surveys (chapters 2 and 3) rather than incidence data (chapter 4) resulted in the best fitting power model when regressed on the probability of dengue occurrence as assessed by R^2 and the non-linear regression correlation coefficient. Seroprevalence datasets where the estimated force of infection corresponded to a PO below 25% were not available. At a PO of 25% the power model was able to capture the low force of infection gradually increasing up to a PO of 70%. However above 70% it is very difficult to capture the wide variation in the force of infection (Figure 5.3) due to dengue endemicity at this probability. Consequently in the resulting burden maps, the same λ is mapped for the same PO values. Therefore PO are unable to differentiate between different areas of high transmission – for example Singapore and Malaysia. However this regression produced more realistic estimates of dengue burden compared to the Bhatt *et al.* model where they regressed dengue incidence data on the PO (Figure 5.10). Their model predicted close to 10% infection rate per year at a high PO, and the infection rate declined slowly with decreasing PO. The lack of demographic constraints (such as birth rates) and allowing individuals to have an unlimited number of infections during their lifetime led to unrealistically high estimates of 390 million dengue infections and 96 million symptomatic cases per year [108].

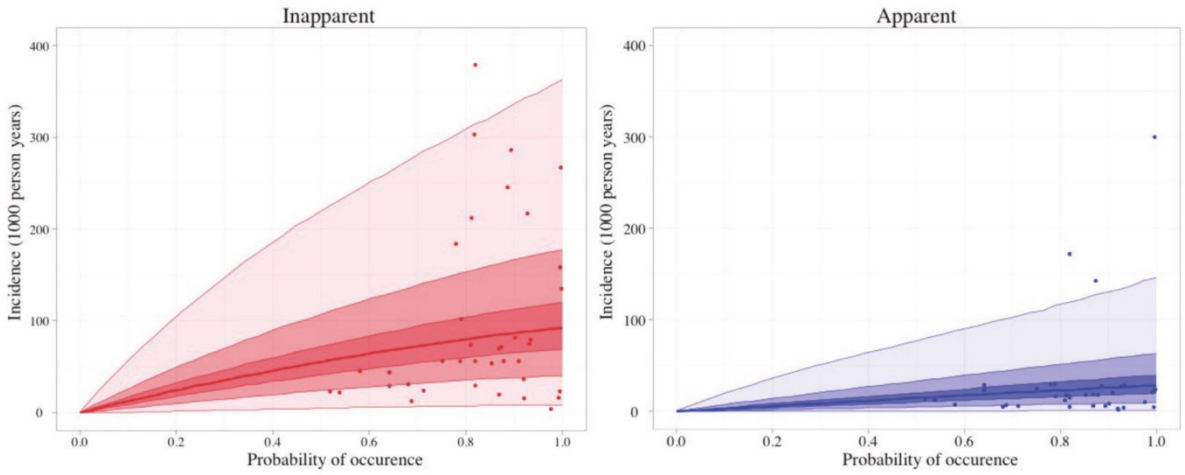

Figure 5.10: Bayesian modelled relationship between the probability of occurrence and incidence for inapparent and apparent number of infections. Reproduced from Bhatt *et al.* [108]. The data are the points, the bold lines are the medians and the envelopes are the 0.25, 0.5 and 0.95 credible intervals centred on the median displayed with progressively lighter shades.

In endemic countries the actual force of infection can fluctuate widely year on year and this dynamic cannot be captured by either the power model nor the probability of dengue occurrence [28,189]. Thus PO data are generally only useful in marginal settings. Additionally, the calculation of the PO itself relies heavily on notification data, however the lack of reported cases does not equate to the lack of dengue transmission. Therefore in ongoing work, we are now directly regressing independent force of infection estimates on environmental covariates, such as temperature, humidity, and rainfall, in endemic settings.

The maximum annual burden estimated was 102 million infections (95% CI: 75.1 M – 139 M) assuming individuals can be infected four times, or 72 million infections (95% CI: 54 M – 99 M) assuming individuals develop protective immunity after two heterologous infections. The apparent infection burden estimated was 28 million cases (95% CI: 21 M – 39 M) and 25 million cases (95% CI: 19 M – 35 M) under the same two assumptions (Table 5.7). The maximum burden estimates are three times smaller than those estimated by Bhatt *et al.*: a total of 390 million infections (95% CrI 284 M – 528 M) and 96 million apparent infections (95% CrI 67 M – 136 M) using the same data on probability of dengue occurrence [108].

Figure 5.6 - Figure 5.9 also show consistently lower estimates for every country with our estimates being closer (where reported) to the WHO estimates. Analogous to malaria modelling, Bhatt *et al.* have allowed individuals to have an infinite number of dengue

infections during their lifetime [108]. This is indeed a valid assumption for non-immunising infections such as malaria [220]. However as an acute immunising infection, the number of dengue infections an individual can acquire is finite (maximum of 4 infections, one for each serotype) [4,221]. This has therefore resulted in a significant discrepancy in the two dengue burden estimates. However a recent study analysing serotype-specific seroprevalence data collected from longitudinal cohort studies in Peru have suggested that protection from homologous re-infection may be incomplete in some circumstances for DENV-2 [19]. However it is not known whether an individual with a homologous re-infection is also then infectious and can contribute to onwards transmission. Comparing the average estimated R_0 by country, my estimates are generally consistent with R_0 values previously estimated or published (Table 5.6). The slight discrepancy arises as our estimates are a weighted average of the R_0 values in each country, whereas published basic reproduction numbers or R_0 estimated from incidence or seroprevalence data are often site-specific, highlighting the heterogeneity in dengue transmission at small spatial scales.

Spatial information on the distribution of dengue burden is essential for the allocation of correct resources, and the planning and evaluation of targeted control programmes. Thus these maps can help identify areas where dengue transmission is high and therefore may benefit the most from interventions.

The estimated duration of short-term cross-protection varies widely from 4 months to 9 years [21], 5–12 months [22], 2 years [23], and 1–3 years [24]. However whether this protects against infection or just against clinically apparent disease, *i.e.* the individual may still be infectious is unknown. Therefore individuals may still contribute to onward transmission [23,25,26] and it is now known that asymptomatic humans can be infectious to mosquitoes despite their lower average viremia [27]. Inclusion of temporary cross-immunity decreased the burden of dengue as expected (Table 5.7). This is consistent with previous studies where a short interval between primary and secondary infection was associated with protection against clinical disease i.e. infection occurred during the period of cross-protection. Predictably when the duration of cross-immunity was increased, there was a corresponding decrease in the overall burden of dengue. Additionally under assumption 2 where we assumed that individuals develop protective immunity after two heterologous

infections, the impact of temporary cross-immunity was unsurprisingly smaller than when assuming individuals could be infected up to four times. However our model is unable to capture the more detailed temporal aspects of cross-protection since it does not take into account the actual time between infection events which will determine whether a second infection results in immunity, asymptomatic infection, or severe apparent infection.

There are a number of additional limitations to these results, primarily in the initial estimation of the force of infection from the probability of dengue occurrence (Figure 5.3). Only 37 datasets were used in the regression with surveys being conducted between 1980 and 2010 with few contemporary surveys, which is not a true representation of dengue transmission in 2010 which I was trying to estimate. The corresponding R^2 values were also fairly low. Additionally the surveys were inconsistent in terms of survey design and diagnostic test (chapters 2 and 3, [174]). As highlighted in chapters 2 and 3, it would be beneficial if countries were to conduct more affordable IgG serosurveys yearly which could be matched to local notification data for validation.

Nevertheless this method utilises the majority of the currently available data on dengue transmission from the evidence-based consensus and environmental covariates informing the probability of dengue occurrence statistics, to seroprevalence surveys conducted at a more local level. The high spatial resolution at which dengue burden can be quantified in multiple ways – the force of infection, basic reproduction number, and the number of apparent and inapparent cases will be highly beneficial in identifying and targeting control measures to key areas of high dengue transmission.

5.5 Acknowledgements

I would like to thank Dr. Oliver Brady and Prof. Simon Hay from the Spatial Ecology and Epidemiology Group at the University of Oxford for generously sharing their global probability of occurrence data used as the basis of this chapter. I would also like to thank Dr. Wes Hinsley from Imperial College London for coding the model in Java, and for help with the mapping.

6 Discussion

The main motivation behind this thesis has been to refine the baseline estimates of dengue transmissibility, quantified by the force of infection (λ) or the basic reproduction number (R_0), given the currently available data. I additionally assessed how comparable force of infection estimates obtained from incidence data (λ_{inc}) were with those derived from serological data (λ_{sero}). Finally using the force of infection estimated from these data, I mapped the estimated burden of dengue disease globally and considered the impact that novel control measures may have.

6.1 Summary of Findings

In chapter 2 and previously published work [174], I estimated the λ and R_0 from age-stratified non-serotype specific seroprevalence data identified from a literature search. I fitted simple catalytic models to these mostly IgG data and found that the estimates of the serotype specific R_{0i} varied according to the assumptions made regarding host immunity. When I assumed that two heterologous infections were sufficient for complete immunity (assumption 2), the estimates of R_{0i} were up to two-fold higher compared to when I assumed that quaternary infections were required for complete immunity (assumption 1). I additionally fitted a catalytic model to 7 years' worth of cross-sectional data from Managua, Nicaragua [30,140] which allowed for the force of infection to vary sinusoidally over time and to change at a (fitted) age threshold. I also identified a general paucity of seroprevalence surveys, particularly of serotype-specific data and cohort data.

In chapter 3 and previously published work [174], I estimated serotype-specific dengue force of infection (λ_i) from serotype-specific PRNT seroprevalence data. For comparison purposes, I fitted a simple catalytic model that tracked individuals from a seronegative to seropositive state (model A described in chapter 2) to the same PRNT data. I defined individuals with PRNT titres below the detection limit for all four dengue serotypes as seronegative and individuals with at least one PRNT titre over the detection limit as seropositive. The resulting force of infection estimates generated using model A were consistent with the sum of the individual serotype-specific λ estimates obtained from the

full PRNT datasets. This showed that while PRNT data provided more information, the less expensive ELISA-based assays could still provide reasonable baseline estimates of overall transmission intensity.

In chapter 4, I collated age-stratified incidence data from the literature and fitted catalytic models to estimate the force of infection and basic reproduction number. To assess the level of under-reporting of dengue disease, I then compared λ estimates derived from seroprevalence data (chapters 2 and 3) to estimates derived from incidence data. In addition, I estimated the relative contribution of primary to quaternary infections to the observed burden of dengue disease incidence. For the three locations in Thailand where region and time matching seroprevalence and incidence data were available, the λ estimates obtained from the models fitted to incidence data were generally comparable to those estimated from seroprevalence data. I showed that the contribution of primary infections to the observed burden of dengue was consistently low (<25% relative to secondary infections), while the contribution of tertiary infections was inconclusive.

Finally in chapter 5, I used the results from chapters 2, 3, and 4 to estimate the force of infection from the probability of dengue occurrence (presence-absence statistic) across the globe at a 5km x 5km spatial resolution [108]. The incidence model developed in chapter 4 was then used to calculate the global burden of dengue. We estimated the maximum annual burden based on the 2010 world population to be 109 million infections (95% CI: 79 M – 147 M) under the assumption that all countries had four serotypes in circulation and that individuals could be infected up to four times.

6.2 Future Work and Limitations

The major limitation of this work has been the quantity and quality of available age-stratified data. In particular, serotype-specific seroprevalence data (PRNT data) have been sparse, and more importantly the data were outdated with most identified studies conducted in the 1980s and 1990s. Although we have shown that IgG data can provide robust estimates, with the imminent release of the dengue vaccine (Mexico and the Philippines having already approved the use of Dengvaxia® developed by Sanofi Pasteur [59]) it is crucial to have detailed baseline data of dengue transmission in all age groups in

order to accurately assess the impact the introduction of the vaccine may have on disease burden at the population level. However, given the cost of large-scale PRNT surveys, estimates of dengue force of infection and basic reproduction number could still be greatly improved by conducting the less expensive IgG surveys more frequently.

Although incidence data are abundant, surveillance systems and reporting procedures are not standardised within or across countries making it very difficult to reliably compare estimates [52]. Laboratory capacity and general public health infrastructure and surveillance systems vary widely and there is often no integration between private and public health sectors. The WHO collates surveillance data from dengue affected countries via its DengueNet system, but the data are not always updated regularly and there can be inconsistencies with other sources of national and subnational data such as those from WHO regional offices [53]. With such variable data, accurate estimation of the true dengue burden is difficult [52].

The aggregation of age-groups in datasets affected the accuracy of the resulting estimates. Datasets with wide age bands (e.g. 0-5 years, 5-15 years, and 15+ years) were less informative than datasets where seroprevalence or cases were presented for every age. Estimates could therefore be improved if age-stratified data were reported at a higher resolution, or at least in equal age widths (e.g. 5 year age bands). In this thesis I have not explicitly looked at the impact of maternal antibodies on estimates of dengue transmissibility or disease burden. Recent studies have shown that infant cases (<1 year old) can yield information about type-specific disease severity given the presence of maternal antibodies, as well as information about transmission within the whole population [222]. Throughout my analysis I have either excluded cases in infants to avoid skewed estimates, or have been unable to explicitly take them into account due to the aggregation of data in the younger age groups. If the same models could be fitted to data from infants, it would be interesting to explore whether there are significant differences in dengue transmission in infants compared to the general population. However, such data can be difficult to obtain since parents can be reluctant to have very young children bled.

Improvement could also be made to the way R_{0i} was calculated in chapters 2, 3, and 4. In translating λ estimates into estimates of R_{0i}, I relied on a model which assumed exposure

was due to endemic transmission. This meant that all resulting R_{0i} estimates were by definition greater than one. Clearly this is less appropriate for settings with low seroprevalence and incidence such as Texas (USA), where some or all of the seropositivity detected is due to imported cases rather than local transmission. The R_{0i} calculation could therefore be adapted in such situations.

In chapter 4, I found that the relative contribution of tertiary and quaternary cases could not be estimated from incidence data. Although there is evidence that tertiary and quaternary infections occur [25,28], there is little quantitative data on the infectiousness or severity of such infections relative to primary and secondary infections. Additionally, clinically apparent tertiary or quaternary infections are not routinely reported, nor can they be tested for retrospectively [25]. Therefore this model could be simplified by assuming all reported cases are due to primary and secondary infections only. Furthermore, a recent study analysing serotype-specific seroprevalence data collected from longitudinal cohort studies in Peru have suggested that protection from homologous re-infection may be incomplete in some circumstances for DENV-2 [19]. Therefore some infection events classed as secondary or tertiary may actually be due to re-infection with the same serotype. Although the relative contribution of such infections to the observed burden of dengue is unknown, they could invalidate the assumption that infection with one serotype provides lifelong protection against re-infection with the same serotype. This may well impact future dengue vaccine formulations.

Finally in chapter 5, in the initial estimation of the force of infection from the probability of dengue occurrence only 37 datasets were used in the regression with surveys being conducted between 1980 and 2010 with few contemporary surveys, which cannot be a true representation of dengue transmission in 2010 which I was trying to estimate. Additionally the surveys were inconsistent in terms of survey design and diagnostic test (chapters 2 and 3, [174]). As highlighted in chapters 2 and 3, it would be beneficial if countries were to conduct more affordable IgG serosurveys yearly which could be matched to local notification data for validation. Furthermore, seroprevalence datasets where the estimated force of infection corresponded to a probability of dengue occurrence (PO) below 25% were not available. Therefore this regression could be improved if more data were available from

low-transmission settings. Alternatively a model with a threshold could be fitted where the force of infection could vary over a wider ranger above a certain PO (e.g. >75% in endemic settings). However the probability of occurrence is a poor predictor of the force of infection in high transmission settings. Therefore it cannot distinguish differences in the force of infection between different SE Asian countries – e.g. Singapore from Malaysia. Global estimates of dengue burden could be best improved by switching from probability of occurrence data to more reliable spatially stratified estimates of the force of infection from geo-located age-stratified data. Therefore in ongoing work, we are now directly regressing independent geo-located force of infection estimates on environmental covariates, such as temperature, humidity, and rainfall, in endemic settings.

6.3 Implications of Research

The research presented here has focused on refining the baseline estimates of dengue transmissibility given the currently published data. With the dengue vaccine due to be rolled out, and other novel control methods such as *Wolbachia* in development, reliable estimates of transmission intensity – and of the health burden due to dengue – will be important in strategic planning and resource allocation in different contexts.

This thesis has collated a comprehensive body of age-stratified seroprevalence and incidence data since 1980 from across the globe. By fitting the same models to these data I have demonstrated the spatio-temporal heterogeneity in dengue transmission. Additionally I have evaluated these data under the same assumptions about immunity when estimating the basic reproduction number for both seroprevalence and incidence data. This allows a more direct comparison of dengue transmission intensity between different regions.

Reporting standards are highly variable with different diagnostic criteria across regions or countries. Consequently the quality, quantity, and the type of data that are collated globally cannot be easily standardised. Therefore the work presented in this thesis where I have compared λ estimates from non-serotype specific (IgG) to serotype-specific (PRNT) seroprevalence data and case-notification data to seroprevalence data will provide a basis for comparing estimates when the data source and data type might differ.

Since dengue and other vector-borne infections are spatially highly heterogeneous, methods (such as those presented in chapter 5) to resolve heterogeneity in dengue

transmission intensity (and thus burden) at a fine spatial resolution will be beneficial for identifying and targeting control measures to key areas of high transmission. These tools can be used to estimate the effectiveness of intervention strategies in dengue control. Since trials and field studies are expensive and difficult to conduct, mathematical modelling is a powerful tool to obtain reliable estimates of baseline transmission and estimate the reduction in transmission and disease burden to quantify the success of a control program.

The methods presented in this thesis to estimate the force of infection and basic reproduction number from seroprevalence and notification data will also be applicable to other acute immunising pathogens – most notably chikungunya and Zika viruses.

6.4 Conclusions

With its re-emergence and spread across the globe, dengue now affects more than 100 countries, causing an estimated 109 million (95% CI: 79 M – 147 M) infections annually. However it is only now, in 2015, that a dengue vaccine is being licensed and new control methods such as *Wolbachia*-infected and genetically modified mosquitoes are being actively developed and tested [67,73,223]. Robust estimates of baseline dengue transmissibility are essential for the assessment and ongoing evaluation of any control measures that may be implemented and the work presented here is a significant contribution to such efforts.

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