

Testing the impact of virus importation rates and future climate change on dengue activity in Malaysia using a mechanistic entomology and disease model

C. R. WILLIAMS¹*, B. S. GILL², G. MINCHAM¹, A. H. MOHD ZAKI²,
N. ABDULLAH³, W. R. W. MAHIYUDDIN³, R. AHMAD⁴, M. K. SHAHAR⁴,
D. HARLEY⁵, E. VIENNET⁵, A. AZIL⁶ AND A. KAMALUDDIN⁷

¹ *Sansom Institute for Health Research, University of South Australia, Adelaide, Australia*

² *Disease Control Division, Ministry of Health Malaysia*

³ *Epidemiology and Biostatistics Unit, Institute for Medical Research, Malaysia*

⁴ *Medical Entomology Unit & WHO Collaborating Centre, Institute for Medical Research, Malaysia*

⁵ *National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia*

⁶ *Department of Parasitology and Medical Entomology, Universiti Kebangsaan Malaysia, Malaysia*

⁷ *Environmental Health Research Centre, Institute for Medical Research, Malaysia*

*Received 12 September 2014; Final revision 19 November 2014; Accepted 12 December 2014;
first published online 16 January 2015*

SUMMARY

We aimed to reparameterize and validate an existing dengue model, comprising an entomological component (CIMSIM) and a disease component (DENSIM) for application in Malaysia. With the model we aimed to measure the effect of importation rate on dengue incidence, and to determine the potential impact of moderate climate change (a 1 °C temperature increase) on dengue activity. Dengue models (comprising CIMSIM and DENSIM) were reparameterized for a simulated Malaysian village of 10 000 people, and validated against monthly dengue case data from the district of Petaling Jaya in the state of Selangor. Simulations were also performed for 2008–2012 for variable virus importation rates (ranging from 1 to 25 per week) and dengue incidence determined. Dengue incidence in the period 2010–2012 was modelled, twice, with observed daily weather and with a 1 °C increase, the latter to simulate moderate climate change. Strong concordance between simulated and observed monthly dengue cases was observed (up to $r = 0.72$). There was a linear relationship between importation and incidence. However, a doubling of dengue importation did not equate to a doubling of dengue activity. The largest individual dengue outbreak was observed with the lowest dengue importation rate. Moderate climate change resulted in an overall decrease in dengue activity over a 3-year period, linked to high human seroprevalence early on in the simulation. Our results suggest that moderate reductions in importation with control programmes may not reduce the frequency of large outbreaks. Moderate increases in temperature do not necessarily lead to greater dengue incidence.

Key words: Arboviruses, dengue fever, epidemiology, estimating, modelling, prevalence of disease.

INTRODUCTION

Dengue, a mosquito-borne viral disease transmitted principally by *Aedes aegypti* and *Aedes albopictus*

mosquito vectors is emerging as one of the world's most rapidly spreading and important infectious diseases [1]. About half of the world's population lives in dengue-endemic countries, with estimations that over 50 million infections occur annually [2]. Most clinical cases are non-fatal illnesses with fever, arthralgia and rash, although fatal haemorrhagic disease

* Author for correspondence: Dr C. R. Williams, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia. (Email: craig.williams@unisa.edu.au)

occurs in a proportion. Dengue incidence, especially in South-East Asian countries including Malaysia, Cambodia, Vietnam and Singapore numbers in the tens of thousands annually with an overall increasing trend in case numbers reported through time [1]. In Malaysia, dengue incidence has been increasing, with a rise in reported cases from 7103 in 2000 to >46000 cases in 2010 [3]. In more recent times a 98% increase in dengue incidence has been reported, from 21900 cases in 2012 to 43346 cases in 2013. Similarly, deaths due to dengue increased 163%, with 92 and 35 deaths in 2013 and 2012, respectively [4].

Uncontrolled urbanization, population increase and movement, the circulation of multiple dengue serotypes, ineffective public health infrastructure, increased international trade and travel have all been implicated in the spread of dengue around the world [5]. Control programmes principally reliant on vector control strategies have had some success in reducing dengue incidence, but have been largely ineffective in controlling the continued global spread of the disease [6–10]. There remains a need to develop new strategies to control the spread of this disease.

In Malaysia the established dengue surveillance programme functions basically as a passive system with little predictive capacity [11]. However, data generated by the surveillance system has an enormous potential for disease prediction [12]. Computer-based mathematical models can potentially be used to increase understanding of local dengue epidemiology, and then inform the development of novel targeted control measures. Mathematical models have been used in the prediction of dengue outbreaks [13].

The development of computer-based models that can be used to describe dengue activity can improve understanding of dengue epidemiology, and can be used to help inform the development of new control strategies. Dengue models should incorporate weather data to predict incidence in future climates. This has been done previously using both statistical modelling [14] and mechanistic process-based models [15]. Models that include information on population immunity rates can be used to plan future vaccination strategies (should vaccines become available). Models incorporating mosquito ecology allow *in silico* testing of vector control strategies before implementation.

Statistical models, comprising single equations linking dengue incidence with inputs such as meteorological data, have been created to describe dengue activity [14], and mathematical models have also been successfully developed [16]. However, these

incorporate implicit assumptions about dengue ecology. The models typically contain very few input variables, and are therefore heavily limited in their usefulness for exploring dengue ecology and testing new management scenarios, particularly at a fine spatial scale.

Conversely, mechanistic, process-based models explicitly describe disease ecology. For instance, by modelling links between rainfall, breeding habitat, temperature and food input with mosquito larval development rates and using the foregoing independent variables to calculate dengue incidence. Such modelling enables researchers to test a number of hypotheses regarding determinants of dengue incidence, provided that the model can be validated initially against observed incidence. Stochastic mathematical models have been developed to investigate dengue ecology [16–18], which have incorporated greater amounts of environmental inputs and enable sophisticated hypotheses concerning dengue ecology to be tested.

We decided to use an existing two-component system incorporating an entomological model, CIMSIM [19] and a disease model, DENSiM [20]. Both CIMSIM and DENSiM have been validated for mosquito productivity [21] and dengue incidence [15].

We reparameterized the model and tested its validity to provide a practical tool for Malaysian dengue researchers, public health practitioners and policy-makers. Our goal was to develop a reparameterized version of the CIMSIM-DENSiM model for exploring dengue ecology in Malaysia and elsewhere. We sought to demonstrate utility by testing the impact of changes in climate and dengue importation rates on incidence.

METHODS

Mechanistic models for *A. aegypti* and dengue in Malaysia

We used two models, which are linked together in a single software package (Dengue Models v. 3.27, University of California, USA). Within that package reside two sub-models. The entomology model CIMSIM (container inhabiting mosquito simulation) has been previously validated for its ability to simulate mosquito productivity in Australia [21] and has been used to assess *A. aegypti* population dynamics and survival [22] along with population size [23]. The virus model DENSiM (dengue simulation) was used

recently to investigate the impact of inter-annual weather variation on dengue activity in Australia [15]. CIMSIM must be run initially to simulate mosquito population, then DENSiM is run to estimate dengue incidence based on vector population from CIMSIM.

Creation of a location file for Kuala Lumpur

CIMSIM/DENSiM require so-called 'location files' to operate. Such files can be reparameterized with unique information about the weather, human demographics and virus activity at a particular location. No changes to the mathematical relationships linking environmental variables, mosquito productivity and infection were altered during this reparameterization. The district of Petaling was selected in this study, which is an urban district in the state of Selangor with an area of 549.3 km² and a population of 1.88 million in 2012 (population density of 3423/km²).

An initial location file was created as follows:

Human population. A virtual village/community of 10000 people was created. Birth- and death-rate data were obtained from the International database of the United States Census Bureau (<http://www.census.gov/population/international/data/idb/informationGateway.php>) and from published records [24]. While urban populations can be much larger than this, a group of 10000 people is representative of a village or urban enclave of a size typical for a socioeconomically homogeneous Malaysian community.

Meteorological data. Daily weather observations were sourced for the period 2007–2012 (<http://www.tutiempo.net/>) for Subang meteorological station in Petaling district, Malaysia. These were then imported into CIMSIM following calculation of saturation deficit as an atmospheric moisture measure.

Serological data. We modelled a single dengue serotype assuming a starting seroprevalence of 50% (0.5) for all age groups other than those aged <1 year based on published DENV seroprevalence data for Malaysia. In 2008, 91.6% of 1000 subjects were found to have DENV-specific IgG [3, 25]. But the study did not differentiate the four serotypes, all of which circulate in Malaysia. Therefore, we considered 50% seropositivity for a single serotype a reasonable estimate.

Simulations

We conducted a number of simulations of a single dengue serotype into our study population 'village' of 10000 individuals. These were all performed for the period 2007–2012. However, 2007 was used as an equilibration year [19], so only data from 2008 onwards are presented.

Simulation 1: validation. In order to validate the model for Malaysian conditions, we introduced 10 viraemic people per week into our population for the period 2008–2010 (the time period for which we had available dengue case data). We then used a cross-correlation procedure (Stata v. 11, USA) to compare total monthly simulated dengue prevalence with monthly dengue case data from Petaling district, Malaysia (data provided by Disease Control Division, Ministry of Health).

Simulation 2: testing importance of importation rate. To test the potential importance of importation rate we ran simulations for rates at 1, 5, 10, 15, 20 and 25 people per week, and assessed monthly average dengue infections in our model village.

Simulation 3: testing importance of climate change. To determine the utility of CIMSIM/DENSiM to study future dengue transmission under a climate change scenario, 1 °C was added to the daily 2010, 2011 and 2012 temperature observations. Specifically, each daily temperature value was increased by 1 °C, thereby maintaining the same level of temperature variation. This value was chosen as it represents a likely temperature increase under a range of carbon emission scenarios by 2100 [26].

A simulation was then run to compare monthly dengue activity in 2010–2012 and in a scenario in which each day of that year was 1 °C warmer. Our simulation did not account for the likely spatial heterogeneity of future climate change, nor predictions for greater variation in temperatures. In this way our simulation is very simplistic, but nevertheless demonstrative of possible temperature change effects on dengue epidemiology.

Cross-correlation (Stata v. 12) was then performed to see whether slightly elevated temperatures changed seasonality. Average monthly simulated dengue cases were compared with a Student's *t* test.

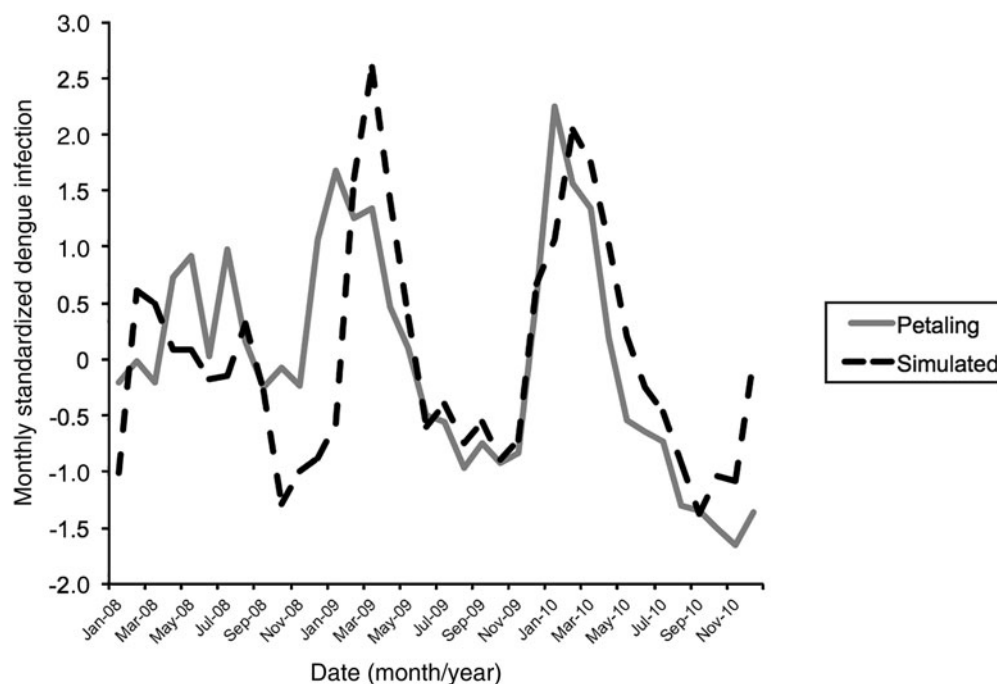


Fig. 1. Results from simulation 1 showing simulated and actual dengue cases in Petaling district, standardized to a mean of zero to demonstrate concordance of seasonality.

RESULTS

CIMSiM/DENSIM validation

Simulation 1 demonstrated very good concordance between predicted and observed case numbers in Petaling district (Fig. 1) with correlations between simulated and observed dengue up to 0.72 (Table 1). Because predicted and observed incidence data were standardized to an overall mean of zero (Fig. 1), we were only seeking to compare seasonality and relative dengue activity, not a direct simulation of the number of expected cases. Inter-annual variation in dengue activity was simulated (and broadly matched that observed in Petaling district). Such variation in the model is related to the unique weather conditions in each year.

Effect of importation rate

Dengue transmission was sensitive to importation rate, with higher rates of importation each week leading to increased monthly incidence (Fig. 2); seasonality was little changed.

Repeated simulations with importation rates varying from 1 to 25 per week demonstrated a positive linear relationship of importations and incidence (Fig. 3). However, halving and doubling importation rates did not equate with a halving and doubling of

Table 1. Cross-correlation result for monthly standardized simulated vs. actual dengue case prevalence in Petaling district (2008–2010), for matched and lagged months

Lag (months)	Correlation
-3	-0.2055
-2	0.1011*
-1	0.4423
0	0.6656
1	0.7206
2	0.5658
3	0.2350

* Not significant at $P < 0.05$.

dengue activity in simulations. Furthermore, higher simulated importation rates did not necessarily lead to the largest individual outbreaks. For instance, the largest outbreak observed in simulation was in 2010 at the lowest importation rate (one viraemic person per week).

Modelling the potential impact of climatic change

Overall dengue activity in a slightly warmer climate [monthly average (\pm S.E.) in our simulated population: 638.7 ± 57.7] was less than that in the current climate

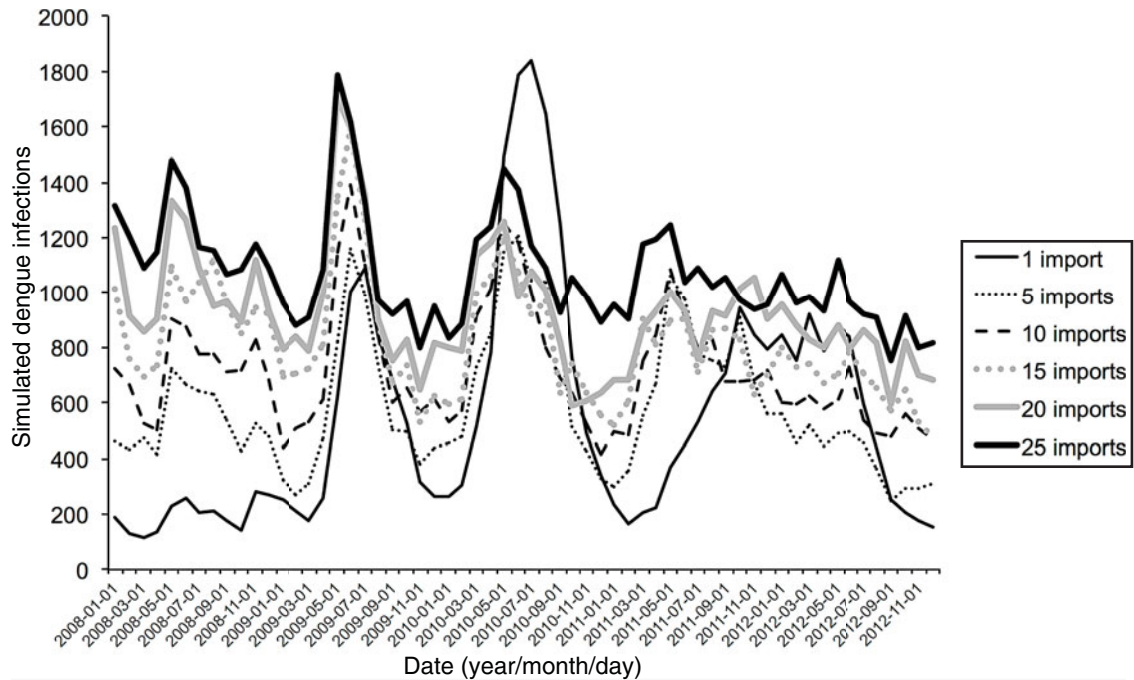


Fig. 2. Results from simulation 2 showing simulated dengue activity in Petaling district for variable rates per week of viraemic human importation.

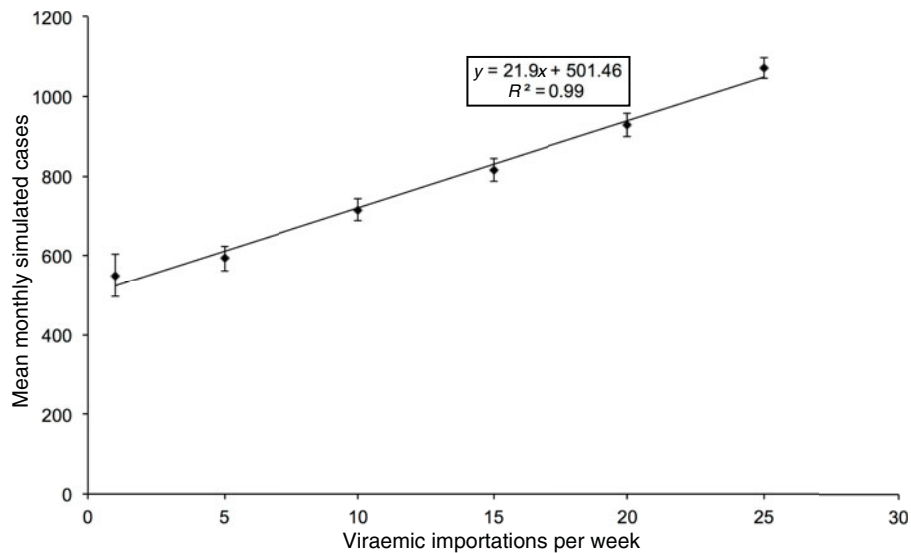


Fig. 3. The relationship between simulated dengue activity and variable rates of viraemic human importation for Petaling district.

(774.3 ± 43.4), a result that was statistically significant ($t = 4.0$, $P = 0.0003$, D.F. = 35).

There was no discernible alteration in simulated dengue seasonality as a result of increased temperature (Fig. 4). Cross-correlation showed the strongest correlation was at 0 months lag (Table 2).

In order to explain the slightly decreased dengue activity simulated when temperatures increased by 1 °C,

human seroprevalence (a marker of immunity in the simulated population) and the abundance of infective mosquitoes were also plotted for the same period (Fig. 4). In a warmer climate, the infective mosquito abundance increases to a higher peak earlier in the simulation compared to the current climate. This is reflected in a concurrent higher level of human seroprevalence earlier in the simulation. These simulations

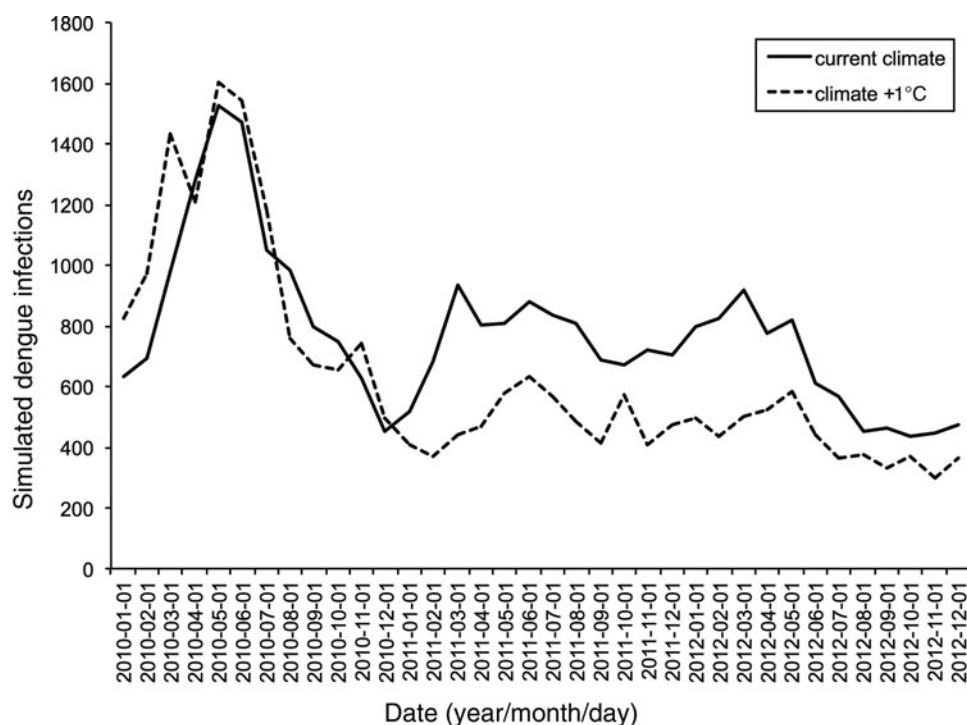


Fig. 4. Results from simulation 3 showing simulated dengue activity in Petaling district for 2010–2012 and with a 1 °C daily temperature increase to demonstrate the potential for the impact of climate change.

Table 2. Cross-correlation result for simulated dengue case prevalence in Petaling district (2010–2012) compared to 2010–2012 (+1 °C)

Lag (months)	Correlation
–3	0.4870
–2	0.6402
–1	0.7620
0	0.8113
1	0.7006
2	0.4954
3	0.2691

indicate large outbreaks with consequently increased seroprevalence. Because of high seroprevalence, incidence is lower due to a smaller population at risk later in the simulation.

DISCUSSION

Seasonal variation is evidence for the association between local weather and dengue incidence. Inter-annual variation in weather creates changes in dengue incidence consistent with observed incidence in the district of Petaling, Malaysia. Our results show that the seasonality and relative magnitude of

dengue in Malaysia can be modelled using DENSiM. The results also validate our reparameterization.

Despite the success of the model's reparameterization (evidenced by the strong cross-correlation result), DENSiM is not capable of accurately predicting future dengue case numbers. Rather, the model should be used to project seasonality and transmission intensity, and can aid in predictions of future trends in dengue cases (rather than actual case numbers). This limitation is due in part to the fact that DENSiM models dengue infection, not clinical cases, which may or may not develop as a result of infection. Furthermore, great discrepancies typically exist between the number of clinical cases and those recorded by health authorities, owing to the highly variable nature of patients attending healthcare facilities when infected, and of the performance of serological diagnostics [27]. Nonetheless, a number of scenarios can be explored for their potential impact on dengue ecology and management using DENSiM. For example, importation rates and changes to climate (as described here) can be assessed for their relative impact on dengue dynamics. Utilizing functions in the entomological component in this model (CIMSiM), the effect of various mosquito control scenarios on dengue transmission can be specifically

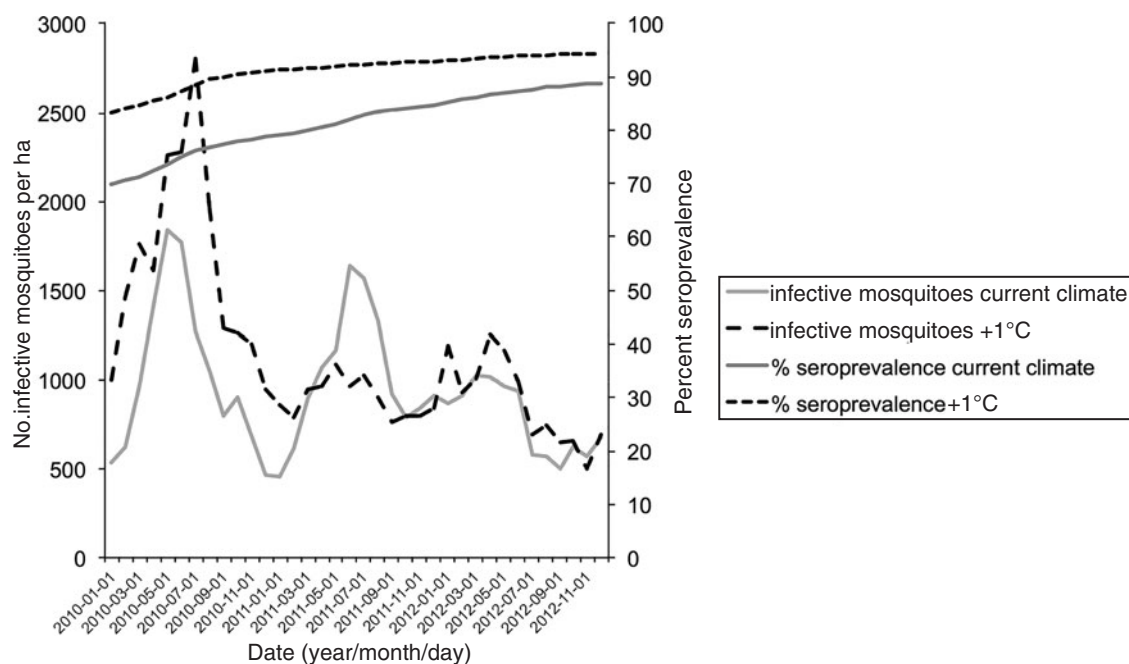


Fig. 5. Simulated dengue infective mosquitoes and human seroprevalence for dengue in Petaling district for 2010–2012 and with a 1 °C daily temperature increase (from simulation 3) to demonstrate the potential for the impact of climate change.

tested. Such tests can be used to design optimal mosquito control strategies and plan expenditure.

Influence of importation rate on dengue activity

The impact of importation rate on dengue activity can be estimated (Fig. 3). If viraemic importations to a district were halved, this would not necessarily halve dengue activity. A reduction from 20 importations per week to 10 would only lead to a 23% reduction in dengue (from 927 to 715 cases per month on average; Fig. 3). Changes to industry and economic conditions may alter migration patterns and our DENSiM simulations have utility for predicting consequent changes in dengue epidemiology, permitting appropriate public health responses.

Extreme reductions in viraemic traveller importation rate (to as low as one person per week here) do not lead to reduced risk of large outbreaks (Fig. 3). Indeed, the largest outbreak observed in simulations occurred at the lowest importation rate. This is probably related to low simulated seroprevalence with the initial low importation rate.

These results challenge the presumed effectiveness of control programmes with moderate impacts on dengue transmission. Reduced immunity in a population as a result of reduced transmission can create

later explosive outbreaks. It has been demonstrated that reductions in dengue activity associated with vector control in Thailand potentially exacerbate the frequency of dengue haemorrhagic disease [28]. The importance of seroprevalence in modulating dengue epidemiology (as in Fig. 5), and the relative ineffectiveness that halving the importation rate has on the size of dengue outbreaks (as in Fig. 2), again highlights the importance of vaccine development for dengue. The results presented here indicate that widespread use of a dengue vaccine to raise seroprevalence is likely to be the most effective way to control dengue transmission.

Climate change

DENSiM could be used to examine changes to transmission under climate change. Increases in temperature (for instance) could be programmed into weather files and the simulations re-run. Our 3-year simulation with a 1 °C rise in daily temperature altered simulated transmission. However, dengue activity was reduced, most likely due to a higher initial intensity of transmission. Transmission intensity was increased because of higher abundance of infective mosquitoes, leading to a more precipitous increase in human seroprevalence, and hence immunity to dengue, with reduced

incidence later in the simulation. Future work that incorporates a range of climate change projections and captures predictions for changes in weather variability could be conducted using the DENSiM model as long as future climate predictions downscaled to daily increments were available.

This work demonstrates that temperature elevations have the capacity to change dengue transmission dynamics in South East Asia, albeit using only a single serotype for simulation. It is simplistic to assume that increased temperature will increase dengue incidence. Our results suggest temperature increase is likely to cause changes to the intensity of outbreaks, perhaps with reduced dengue transmission in some circumstances.

The reparameterization of dengue models (CIMSIM and DENSiM) for Malaysian conditions provides users with a sophisticated tool to enable a number of hypotheses concerning dengue management to be addressed. This allows anticipation of changes in transmission and consequently targeting of control measures. These models are a useful tool for predicting future dengue trends. Augmenting the existing passive dengue surveillance programme in Malaysia with a weather-based predictive capacity using these models can establish an effective early warning system for the disease.

Climate change is likely to impact transmission intensity and consequently human immunity. Human importation rate is likely to be an important factor for dengue transmission management in the future. In low- and middle-income countries in South East Asia the efficient allocation of scarce health resources is crucial. The modelling approach presented here, which we have demonstrated to be feasible, has great potential to increase cost-efficiency of resource allocation to dengue surveillance and control.

ACKNOWLEDGEMENTS

The authors thank the Director General of Health Malaysia for permission to publish. We acknowledge the financial assistance of the Regional World Health Organization Representative Office to Malaysia, Brunei Darussalam and Singapore. Professor Tom Scott and Andy Garcia from the University of California Davis are thanked for their collaboration and provision of the latest updated dengue models, and for permission to extend the use of these to the Malaysian context. Dana Focks and Tessa Knox provided guidance on the initial use of

CIMSIM and DENSiM. This project was partially funded through the Australian National Health and Medical Research Council (project 1003371).

DECLARATION OF INTEREST

None.

REFERENCES

1. **World Health Organization.** Dengue and severe dengue, Fact Sheet No. 117, 2014 (<http://www.who.int/media-centre/factsheets/fs117/en/>).
2. **Gubler DJ.** The economic burden of dengue. *American Journal of Tropical Medicine and Hygiene* 2012; **86**: 743.
3. **Mohd-Zaki AH, et al.** Epidemiology of dengue disease in Malaysia (2000–2012): a systematic literature review. *PLoS Neglected Tropical Diseases* 2014; **8**: e3159.
4. **Ministry of Health.** Statement by the Minister of Health Malaysia on new initiatives in fighting dengue for 2014 (Press release), 2014 (http://www.moh.gov.my/index.php/database_stores/store_view_page/22/459).
5. **Gubler DJ, Clark GG.** Dengue/dengue hemorrhagic fever: the emergence of a global health problem. *Emerging Infectious Diseases* 1995; **1**: 55–57.
6. **Nam VS, et al.** Elimination of dengue by community programs using *Mesocyclops* (Copepoda) against *Aedes aegypti* in central Vietnam. *American Journal of Tropical Medicine and Hygiene* 2005; **72**: 67–73.
7. **Kay BH, Marten GG, Reid JW.** Eradication of *Aedes aegypti* from a village in Vietnam, using copepods and community participation. *American Journal of Tropical Medicine and Hygiene* 1998; **59**: 657–660.
8. **Ritchie SA, et al.** Dengue control in north Queensland, Australia: case recognition and selective indoor residual spraying. *Dengue Bulletin* 2002; **26**: 7–13.
9. **Egger JR, et al.** Reconstructing historical changes in the force of infection of dengue fever in Singapore: implications for surveillance and control. *Bulletin of the World Health Organisation* 2008; **86**: 187–196.
10. **Eisen L, et al.** Proactive vector control strategies and improved monitoring and evaluation practices for dengue prevention. *Journal of Medical Entomology* 2009; **46**: 1245–1255.
11. **Azil AH, Li M, Williams CR.** Dengue vector surveillance programs: a review of methodological diversity in some endemic and epidemic countries. *Asia-Pacific Journal of Public Health* 2011; **23**: 827–842.
12. **Gubler DJ.** How effectively is epidemiological surveillance used for dengue programme planning and epidemic response? *Dengue Bulletin* 2002; **26**: 96–106.
13. **Helfenstein U.** Box-Jenkins modelling of some viral infectious diseases. *Statistics in Medicine* 2006; **5**: 37–47.
14. **Hales S, et al.** Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. *Lancet* 2002; **360**: 830–834.
15. **Bannister-Tyrrell M, et al.** Weather-driven variation in dengue activity in Australia examined using a

- process-based modeling approach. *American Journal of Tropical Medicine and Hygiene* 2013; **88**: 65–72.
16. **Pongsumpun P, et al.** Dynamics of dengue epidemics in urban contexts. *Tropical Medicine and International Health* 2008; **13**: 1180–1187.
 17. **Barbazan P, et al.** Modelling the effect of temperature on transmission of dengue. *Medical and Veterinary Entomology* 2010; **24**: 66–73.
 18. **de Castro Medeiros LC, et al.** Modeling the dynamic transmission of dengue fever: investigating disease persistence. *PLoS Neglected Tropical Diseases* 2011; **5**: 942.
 19. **Focks DA, et al.** Dynamic life table model for *Aedes aegypti* (Diptera: Culicidae): analysis of the literature and model development. *Journal of Medical Entomology* 1993; **30**: 1003–1017.
 20. **Focks DA, et al.** A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. *American Journal of Tropical Medicine and Hygiene* 1995; **53**: 489–506.
 21. **Williams CR, et al.** Rapid estimation of *Aedes aegypti* population size using simulation modeling, with a novel approach to calibration and field validation. *Journal of Medical Entomology* 2008; **45**: 1173–1179.
 22. **Williams CR, et al.** 2010 The extinction of dengue through natural vulnerability of its vectors. *PLoS Neglected Tropical Diseases* 2010; **4**: 922.
 23. **Williams CR, et al.** 2013. Productivity and population density estimates of the dengue vector mosquito *Aedes aegypti* in Australia. *Medical and Veterinary Entomology* 2013; **27**: 313–322.
 24. **Bujang MA, et al.** Mortality rates by specific age group and gender in Malaysia: Trend of 16 years, 1995–2010. *Journal of Health Informatics in Developing Countries* 2012; **6**: 2.
 25. **Azami NAM, et al.** Dengue epidemic in Malaysia: not a predominantly urban disease anymore. *BMC Research Notes* 2011; **4**: 216.
 26. **IPCC.** Summary for policymakers. In: *Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change* (Field CB, Barros VR, Dokken DJ, Mach KJ, Mastrandrea MD, et al., eds). Cambridge University Press, Cambridge, UK and New York, NY, USA, 2014, pp. 1–32.
 27. **Horstick O, Morrison AC.** Dengue disease surveillance: improving data for dengue control. *PLoS Neglected Tropical Diseases* 2014; **8**: e3311.
 28. **Nagao Y, Koelle K.** Decreases in dengue transmission may act to increase the incidence of dengue hemorrhagic fever. *Proceedings of the National Academy of Sciences USA* 2008; **105**: 2238–2243.