

# Reconstructing historical changes in the force of infection of dengue fever in Singapore: implications for surveillance and control

Joseph R Egger,<sup>a</sup> Eng Eong Ooi,<sup>b</sup> David W Kelly,<sup>c</sup> Mark E Woolhouse,<sup>d</sup> Clive R Davies<sup>a</sup> & Paul G Coleman<sup>a</sup>

**Objective** To reconstruct the historical changes in force of dengue infection in Singapore, and to better understand the relationship between control of *Aedes* mosquitoes and incidence of classic dengue fever.

**Methods** Seroprevalence data were abstracted from surveys performed in Singapore from 1982 to 2002. These data were used to develop two mathematical models of age seroprevalence. In the first model, force of infection was allowed to vary independently each year, while in the second it was described by a polynomial function. Model-predicted temporal trends were analysed using linear regression. Time series techniques were employed to investigate periodicity in predicted forces of infection, dengue fever incidence and mosquito breeding.

**Findings** Force of infection estimates showed a significant downward trend from 1966, when vector control was instigated. Force of infection estimates from both models reproduced significant increases in the percentage and average age of the population susceptible to dengue infections. Importantly, the year-on-year model independently predicted a five to six year periodicity that was also displayed by clinical incidence but absent from the *Aedes* household index.

**Conclusion** We propose that the rise in disease incidence was due in part to a vector-control-driven reduction in herd immunity in older age groups that are more susceptible to developing clinical dengue.

Bulletin of the World Health Organization 2008;86:187–196.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

## Introduction

Dengue fever is a viral infection transmitted by *Aedes* mosquitoes that has recently re-emerged globally as the most important arboviral disease.<sup>1</sup> There are four antigenically distinct dengue virus serotypes (DEN 1–4) that induce permanent serotype-specific, IgG antibody-mediated protective immunity following first infection.<sup>2</sup> Dengue fever presents as a spectrum of increasingly severe clinical manifestations ranging from classic dengue fever to dengue haemorrhagic fever to dengue shock syndrome,<sup>2</sup> although the distinction between these conditions is often blurred.<sup>3</sup> In an endemic situation, the majority of dengue infections are subclinical and the risk factors for severity of clinical outcome include age, viral strain, host genetics and time between heterotypic infection.<sup>4–6</sup> Classic dengue fever is most commonly associ-

ated with primary viral infection, and in fully naive individuals the probability of developing clinical disease increases with age.<sup>5</sup> Early studies in the Philippines demonstrated that the risk of classic disease was very high in young adults following primary infection,<sup>7,8</sup> while more recent findings in Indonesia and Thailand indicate that most classic illness in children is the result of secondary infection.<sup>9,10</sup> Due to the complex set of factors that contribute to risk of dengue haemorrhagic fever, as well as the extremely low incidence of dengue haemorrhagic fever in Singapore, this analysis has limited its scope to classic dengue illness.

*Ae. aegypti*, the primary vector for dengue fever, is well adapted to breeding in human-made breeding sites in urban and periurban environments.<sup>11</sup> Dengue is now endemic in over 100 countries, with a dramatic increase in incidence

and geographical range recorded in recent years. Reasons for this increase include growing levels of urbanization, international trade and travel disseminating both the vector and viruses, and the inadequacies of current methods to reduce dengue transmission.<sup>12</sup>

Singapore is one of the few settings that have recorded sustained suppression of the vector population. The dengue control programme combines all WHO-recommended control activities, including public health education and community participation, active breeding site detection, environmental management, reactive insecticide fogging, and geo-referenced entomologic and clinical surveillance systems.<sup>13</sup> Since the first legislation to enforce vector control was introduced in 1966, Singapore has seen the *Aedes* household index (the percentage of all properties with breeding sites of *Aedes* mosquitoes) reduced from

<sup>a</sup> Disease Control and Vector Biology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

<sup>b</sup> Defence Medical and Environmental Research Institute, Singapore, Singapore.

<sup>c</sup> Oxitec Limited, Oxford, England.

<sup>d</sup> Institute of Infection and Immunology Research, School of Biological Sciences, University of Edinburgh, Edinburgh, Scotland.

Correspondence to Joseph R Egger (e-mail: Joe.Egger@lshtm.ac.uk).

doi:10.2471/BLT.07.040170

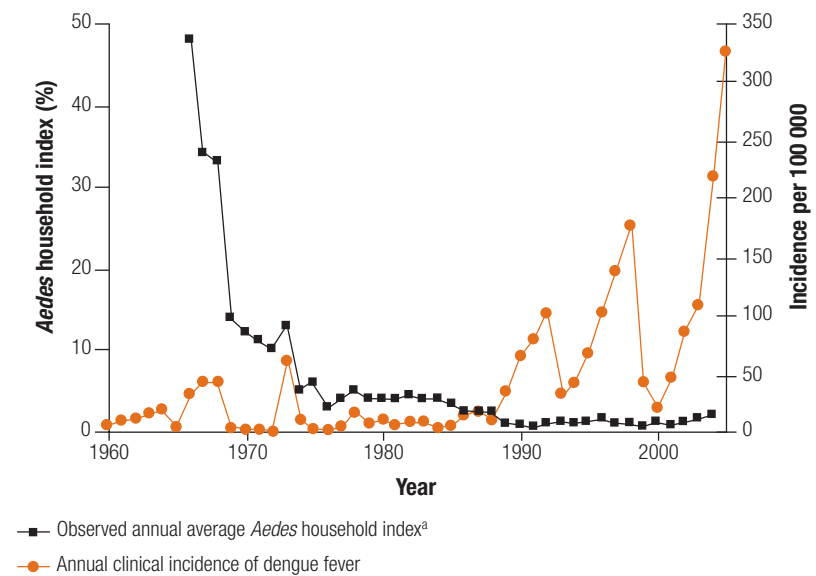
(Submitted: 9 January 2007 – Revised version received: 14 March 2007 – Accepted: 2 April 2007 – Published online: 22 November 2007)

over 50% to less than 1% (Fig. 1).<sup>14</sup> However, a contradictory phenomenon is occurring in Singapore, whereby the incidence of dengue fever has recently increased despite the success of the vector control programme. Notably, the overwhelming majority of cases in recent years have been as classic dengue fever, with dengue haemorrhagic fever representing less than 1% of the 21 000 officially reported cases between 2000 and 2004.<sup>15,16</sup>

Intuitively, it would be expected that a decrease in the mosquito population would lower the force of infection (the per capita rate at which susceptible individuals acquire infection) and consequently decrease disease incidence. While the *Aedes* household index and the observed increases in average age of clinical dengue<sup>17</sup> (Fig. 2) are consistent with a decrease in the force of infection, the disease incidence continues to climb. The number of confirmed dengue cases climbed from a record level of 9292 in 2004 to a new high of over 13 800 in 2005 (Fig. 1).<sup>18</sup> Determining the temporal pattern of force of infection is essential to understanding the extent to which vector control in Singapore has reduced the intensity of dengue transmission, thus helping to clarify the unprecedented rise in disease incidence.

Force of infection has been used widely to understand the intensity of disease transmission within a

Fig. 1. Observed annual average *Aedes* household index and annual clinical incidence of dengue fever



<sup>a</sup> 2005 household index estimate is not yet available.

community.<sup>19–23</sup> In an endemic situation, the force of infection can be approximated by the reciprocal of the average age of infection.<sup>19</sup> However, the force of infection has likely been in a dynamic state in Singapore due to the long-term programme to reduce *Aedes* mosquitoes. While estimates of force of dengue infection have never been published for Singapore, seroprevalence surveys have been performed on an ad hoc basis for several decades. These

data provide a historical record of the percentage of the population that have ever been infected by dengue virus. Here we develop a mathematical model that allows the changes in force of dengue infection in Singapore to be reconstructed from these published, age-stratified seroprevalence data. The modelling procedures and resulting insights have major implications for routine surveillance activities, the long-term monitoring of control activities and the choice of strategies aimed at controlling dengue fever, not only in Singapore but across all endemic settings.

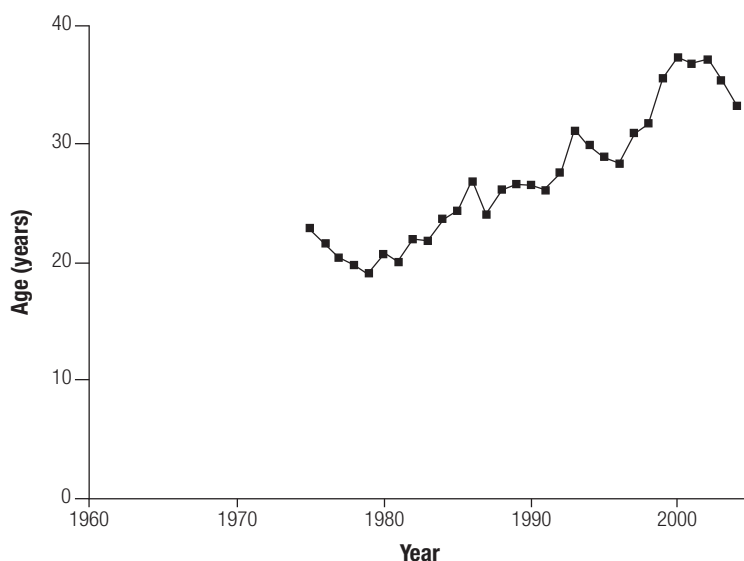
## Materials and methods

### Age-stratified seroprevalence data

Five age-stratified seroprevalence surveys of dengue IgG antibodies conducted in Singapore were identified in the literature. These surveys, conducted in 1982, 1991, 1993, 1999 and 2002, included serosamples from a total of 3954 individuals (Table 1).<sup>17,24,25</sup> The studies reported the number sampled and number seropositive in a variety of different age categories. For model fitting purposes, the midpoint age (to the nearest half year) for each category was used.

The surveys performed in 1982, 1991 and 1993 used the hemagglutination-inhibition procedure.<sup>26</sup> All three

Fig. 2. Observed average age of clinical cases of dengue fever reported in Singapore<sup>a</sup>



<sup>a</sup> National dengue control activities were instigated in 1966.

surveys used dengue serotype 2 virus as the antigen; however, the hemagglutination-inhibition test is broadly cross-reactive and would detect antibodies to all four serotypes of dengue virus.<sup>27</sup> For the 1982 survey, a titre of < 8 was considered negative, while in 1991 and 1993 a titre of < 10 was considered negative. The surveys performed in 1999 and 2002 both used the PanBio (PanBio, Brisbane, Australia) dengue IgG-ELISA test kit. Similar to the hemagglutination-inhibition test, the IgG-ELISA procedure does not distinguish viral serotype, and seroprevalence from these surveys is based on infection with any of the four dengue serotypes. For the purposes of this paper, the relative difference in seroprevalence between age classes, not absolute seroprevalence, is important. Therefore, while the hemagglutination-inhibition and IgG-ELISA tests may have relatively low specificity and have likely underestimated seroprevalence in Singapore, there is no evidence that specificity for either test is age-dependent so this should not significantly affect the proportional increase in seroprevalence between age classes.

### Epidemiological and entomologic data

Official records of annual classic dengue fever incidence from 1960 (when official records began) to 2002 (the latest serosurvey year), and the *Aedes* household index collated between 1966 (when records began) and 2002, were obtained from the appropriate Singapore government departments (Fig. 1). It is worth noting most dengue cases in Singapore acquire the infection locally, rather than through imported cases.<sup>28</sup>

The average age of dengue fever cases was calculated from the number of cases recorded in seven age categories (0–4, 5–14, 15–24, 25–34, 35–44, 45–54 and ≥ 55 years) for each year from 1975, when age-stratified records were first available, to 2002. The best estimate of the average age of clinical disease was calculated using the mid-age of each category, assuming 65 years for the oldest age class.

### The basic model

The model population age structure was divided into 0.5 yearly increments. The age-specific seroprevalence,  $i_a$ , in year  $t$  was described by

Table 1. Summary of deviance and percentage deviance explained by models

Survey	Number sampled <sup>a</sup>	Total deviance	Year-on-year model <sup>b</sup>	Polynomial model <sup>b</sup>
1982	425 (8)	181.3	13.3 (92.66%)	18.4 (89.84%)
1991	1409 (11)	531.4	25.8 (95.14%)	29.6 (94.43%)
1993	912 (7)	344.9	17.5 (94.92%)	18.1 (94.74%)
1999	901 (16)	297.2	24.5 (91.74%)	26.4 (91.10%)
2002	298 (3)	48.2	7.2 (85.15%)	7.5 (84.36%)
Overall	3945 (45)	1403.1	88.3 (93.70%)	100.1 (92.86%)

<sup>a</sup> Number of age classes presented in parentheses.

<sup>b</sup> Percentage explained presented in parentheses.

$$i_{0.5,t} = \left(1 - e^{-\lambda_t 0.5t}\right)$$

for individuals aged 0.5 years, assuming there are no remaining maternal antibodies by six months of age, and

$$i_{a,t} = i_{a-1,t-1} + \left(1 - e^{-\lambda_t}\right)\left(1 - i_{a-1,t-1}\right)$$

for all other ages  $\geq 1$  year, in which  $a$  is the age years and  $\lambda_t$  is the age-independent force of infection in year  $t$ . To illustrate this model, consider a serologic survey conducted in the year 2000. The observed difference in mean seroprevalence from this survey between five-year-olds (i.e. born in 1995) and six-year-olds (i.e. born in 1994) is a measure of the force of infection between 1994 and 1995. Our model assumes the seroresponse following first infection is lifelong.<sup>9</sup> The model further assumes an endemic situation in 1960 with the age-specific seroprevalence profile in that year given by

$$1 - e^{-\lambda_{1960} a}$$

### Fitting the year-on-year model

The force of infection in each year from 1960 to 2002 was varied to maximize the likelihood between the observed and model-predicted age seroprevalence.<sup>29</sup> The time period over which the force of infection was allowed to fluctuate was chosen as clinical incidence measures are only available from 1960 and the latest seroprevalence survey was conducted in 2002. The significance of this full year-on-year model (with 43 independent estimates of  $\lambda_t$  from  $t = 1960$  to  $t = 2002$ ) was assessed by comparing the model deviance with total deviance, using the likelihood ratio test.<sup>30</sup> Model deviance was calculated using model-estimated seroprevalence for each age group,

whereas total deviance was calculated by fitting the overall mean seroprevalence across all ages in all surveys.

### Fitting the polynomial model

A simplified model was also fitted in which the temporal profile of the force of infection from 1960 onwards was described by a polynomial of the form

$$\lambda_t = \exp\left[\sum_{j=0}^{k} \alpha_j (1960 - t)^j\right],$$

in which  $j$  is a positive integer from 0 to  $k$ . The likelihood ratio test<sup>30</sup> was used to determine the minimal adequate model with the lowest polynomial order (i.e. the minimum value of  $k$ , whereby moving to a higher order  $k+1$  polynomial did not result in a statistically significant decrease in the amount of deviance).<sup>31</sup> All model fitting was performed using the Solver add-in function in Excel 2000 (Microsoft, Reading, United Kingdom).

### Estimating the proportion and average age of susceptibles

The proportion of each age fully susceptible to any dengue virus infection in year  $t$  was simply taken as  $1 - i_{a,t}$ . The total susceptible proportion of the population was then calculated as

$$S_t = \sum_{a=0.5}^{a=90} (1 - i_{a,t}) p_{a,t}$$

where  $p$  is the proportion of the population aged  $a$  years in year  $t$ , which was estimated from official Singapore government figures, and assuming a maximum age of 90 years in the population. The average age of the susceptible proportion of the population in a given year,  $A_t$ , was calculated as

$$A_t = \frac{\sum_{a=0.5}^{a=90} (1 - i_{a,t}) p_{a,t} a}{S_t}$$

$S_t$  and  $A_t$  were calculated for both the year-on-year and polynomial models.

**Trends in model outputs**

For both models, temporal trends in the predicted outcomes following the instigation of control activities in 1966 were investigated using linear regression conducted in Stata version 8 (StataCorp, College Station, TX, United States of America).

**Periodicity**

Autocorrelation analysis was used to compare the periodicity of clinical incidence, *Aedes* household index and predicted local year-on-year forces of infection.<sup>32</sup> Each of the three time series was first made stationary by taking the natural log, regressing the logged value against time to determine the log-linear trend, and finally subtracting this trend from the logged value. All transformations and autocorrelations were conducted in Stata version 8.

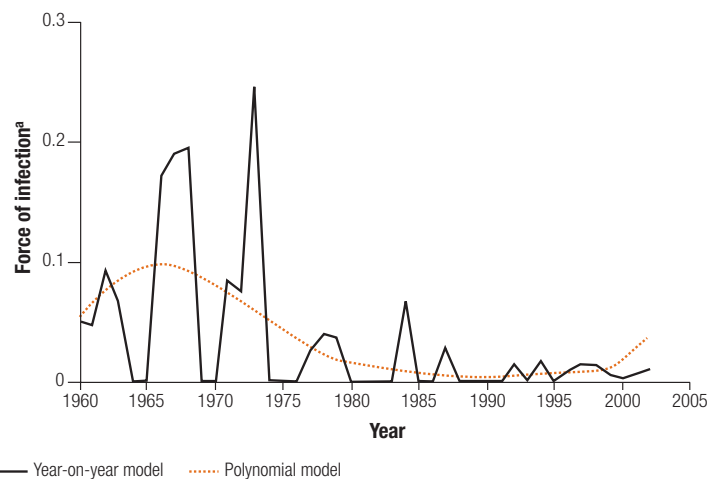
**Results**

The reconstructed year-on-year changes in force of dengue infection are shown in Fig. 3. The observed and predicted age-stratified seroprevalence recorded in each cross-sectional survey are shown in Fig. 4, Fig. 5, Fig. 6, Fig. 7 and Fig. 8. The model produced a highly significant fit to the data ( $\chi^2 = 2630$ , degrees of freedom, d.f. = 42,  $P < 0$ ) explaining almost 94% of the variation in seroprevalence (Table 1).

A third-order polynomial was the lowest-order model that was not significantly different from the year-on-year model ( $\chi^2 = 23.6$ , d.f. = 39,  $P = 0.976$ ) and could not be significantly improved by moving to a higher, fourth-order polynomial ( $\chi^2 = 1.30$ , d.f. = 1,  $P = 0.254$ ). Estimates and 95% confidence intervals for the parameters describing the polynomial are shown in Table 2 and the predicted temporal changes in force of infection in Fig. 3. The polynomial model fit to the age seroprevalence surveys, which explained almost 93% of the deviance (Table 1), are shown in Fig. 4, Fig. 5, Fig. 6, Fig. 7 and Fig. 8.

Fig. 3 shows that over the period of effective vector control from 1966 onwards, there were highly significant

Fig. 3. Annual forces of infection predicted by models



<sup>a</sup> Per capita rate at which susceptible individuals acquire infection.

Fig. 4. Seroprevalence observed in the 1982 survey and fitted age estimates using models

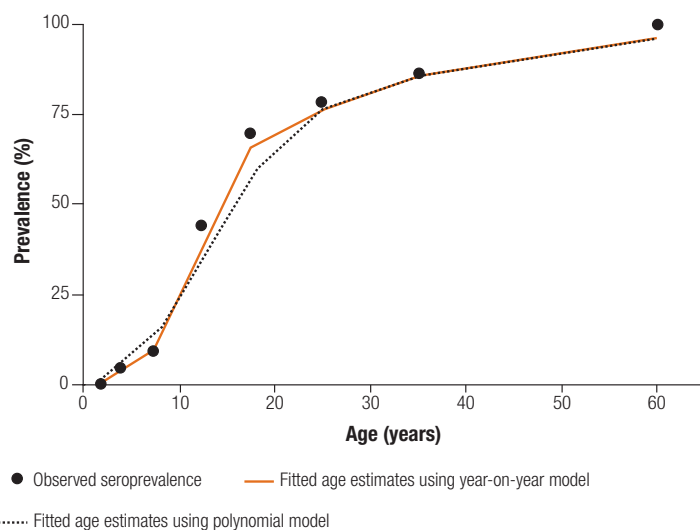
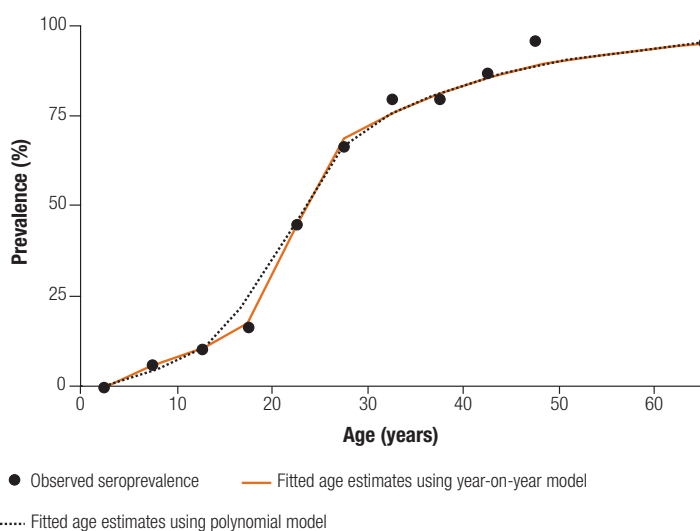


Fig. 5. Seroprevalence observed in the 1991 survey and fitted age estimates using models



negative trends in the forces of infection predicted by both the year-on-year model (correlation coefficient =  $-0.545$ ,  $P = 4.837 \times 10^{-4}$ ) and the simplified polynomial model (correlation coefficient =  $-0.766$ ,  $P = 3.342 \times 10^{-8}$ ).

There were also significant positive trends in the percentage (Fig. 9) and average age (Fig. 10) of the population susceptible to infection by any dengue virus serotype from 1966 onwards. These trends resulted from the force of infection estimates from both the year-on-year and polynomial models (Table 3). The observed average age of clinical dengue cases was consistently higher than the model-estimated average age of the susceptible population (Fig. 10). This is consistent with the probability of infection resulting in clinical disease being greater in older susceptible individuals.<sup>5</sup>

The forces of infection predicted by the year-on-year model show high levels of inter-annual variation, with the major peaks in transmission intensity corresponding well with the recorded peaks in clinical incidence (Fig. 11 and Fig. 12). The autocorrelograms for clinical incidence, *Aedes* household index and predicted year-on-year force of infection from 1966 to 2002 are shown in Fig. 13. There was a strong similarity between the correlogram for the model-predicted forces of infection, with a distinct 5–6 year periodicity, and the profile and periodicity observed in clinical incidence. By contrast, the *Aedes* household index displayed no such periodicity.

## Discussion

Adhering to all WHO recommendations, Singapore has dramatically reduced the percentage of households with *Aedes* mosquitoes since the inception of its vector control programme. The fact that incidence of clinical dengue fever has recently increased despite this sustained reduction in the *Aedes* mosquito population has been difficult to explain.

Four main suggestions have been proposed to reconcile this contradictory phenomenon: (1) A shift in dengue virus transmission from the household to other sites, such as schools and workplaces.<sup>17</sup> (2) Increased dengue virus transmission by other *Aedes* mosquito species, most notably *Ae. albopictus*, which is not targeted by current control activities. However, evidence suggests

Fig. 6. Seroprevalence observed in the 1993 survey and fitted age estimates using models

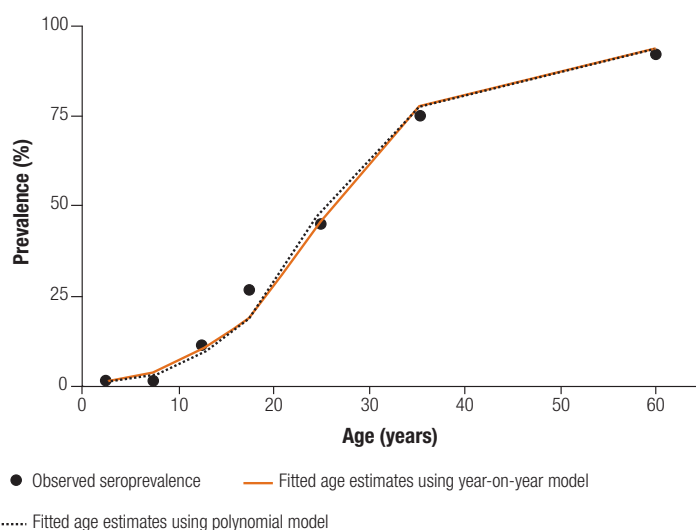


Fig. 7. Seroprevalence observed in the 1999 survey and fitted age estimates using models

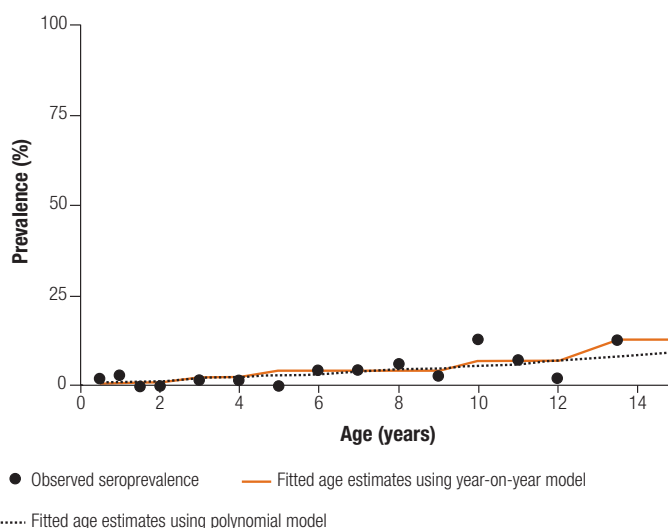
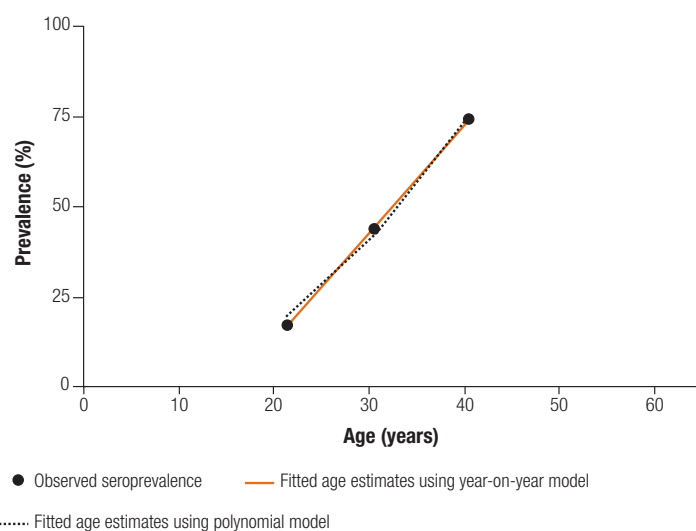


Fig. 8. Seroprevalence observed in the 2002 survey and fitted age estimates using models





that the pattern of dengue incidence in Singapore is strongly spatially associated with that of *Ae. aegypti* populations and not *Ae. albopictus*.<sup>33</sup> (3) Increased reporting probability of clinical cases. Though this is likely correct for the more distant past, it does not reconcile the year-on-year increases in incidence seen in Singapore recently. (4) The decrease in *Aedes* mosquitoes in Singapore caused a reduction in herd immunity and this process, coupled with the increased importation of dengue viruses into Singapore, led to an increase in transmission and a subsequent increase in disease incidence.<sup>34</sup>

While these theories may help to explain the increased clinical incidence, none addresses the central issue of whether vector control has reduced force of infection. In fact, they all invoke a shift or increase in dengue transmission not captured by the *Aedes* household index. However, the patterns from the age-seroprevalence surveys, as elucidated by the simple mathematical models, are robustly consistent with there being a general trend of decreasing force of dengue infection since the introduction of vector control measures in 1966. Confidence in the temporal trends in force of infection is strengthened by the correspondence in peaks of predicted transmission with observed disease incidence (Fig. 11 and Fig. 12), and the predicted periodicity of force of infection with observed periodicity of incidence of clinical disease over the same time period (Fig. 13). It should be stressed that these predictions were made completely independent of clinical incidence data and reveal latent properties of the age seroprevalence data uncovered by the model. It is also noteworthy that the *Aedes* household index failed to display any periodicity in line with disease incidence, supporting the argument that the main driver of the interepidemic interval is herd immunity rather than vector population dynamics.<sup>35</sup>

Therefore, if there has been a decrease in force of infection, how can the increase in disease incidence be explained? Endemic stability is an epidemiological state in which host, disease agent, vector and environment coexist with little or no clinical disease.<sup>36</sup> The concept of endemic stability has recently been proposed as a general hypothesis for the contradictory phenomenon of decreasing force of

Table 2. Parameter value estimates for third order polynomial model describing the forces of dengue virus infection in Singapore, 1960–2002

Parameter	Fitted value	Lower 95% CI <sup>a</sup>	Upper 95% CI <sup>a</sup>
$\alpha_0$	-2.954	-3.039	-2.869
$\alpha_1$	0.217	0.210	0.223
$\alpha_2$	$-2.115 \times 10^{-2}$	$-2.141 \times 10^{-2}$	$-2.092 \times 10^{-2}$
$\alpha_3$	$3.771 \times 10^{-4}$	$3.687 \times 10^{-4}$	$3.842 \times 10^{-4}$

CI, confidence interval.

<sup>a</sup> Limits determined using likelihood ratio test.

Fig. 9. Estimated changes in the percentage of the population susceptible to infection by all dengue virus serotypes

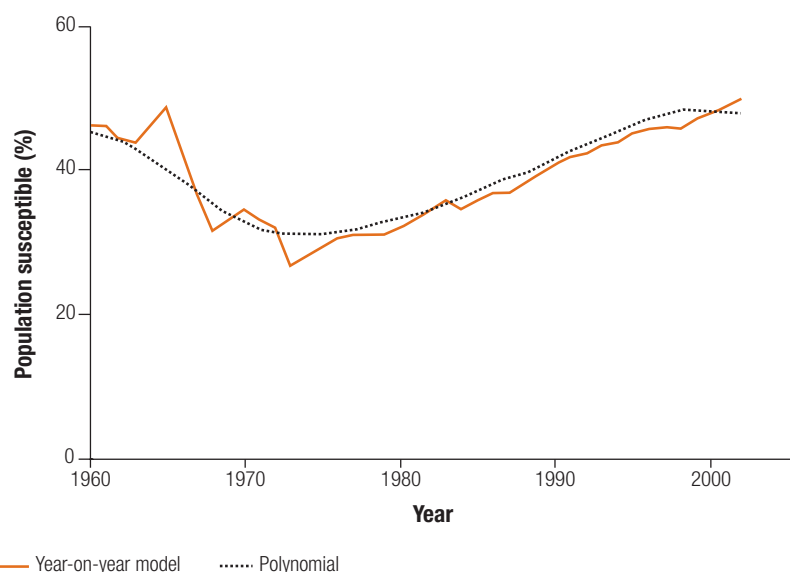


Fig. 10. Estimated changes in the average age of the population susceptible to infection by all dengue virus serotypes

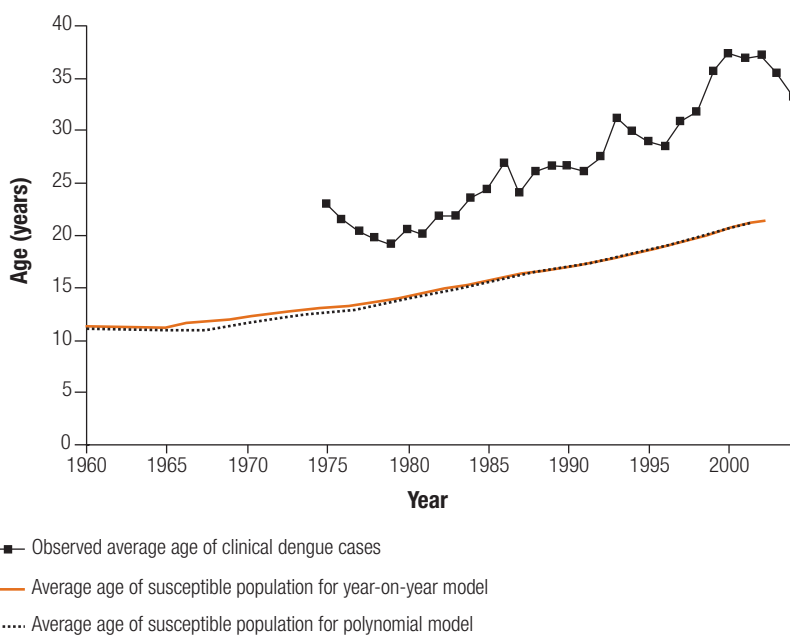


Table 3. Correlation coefficients describing trends since instigation of control in 1966 to 2002

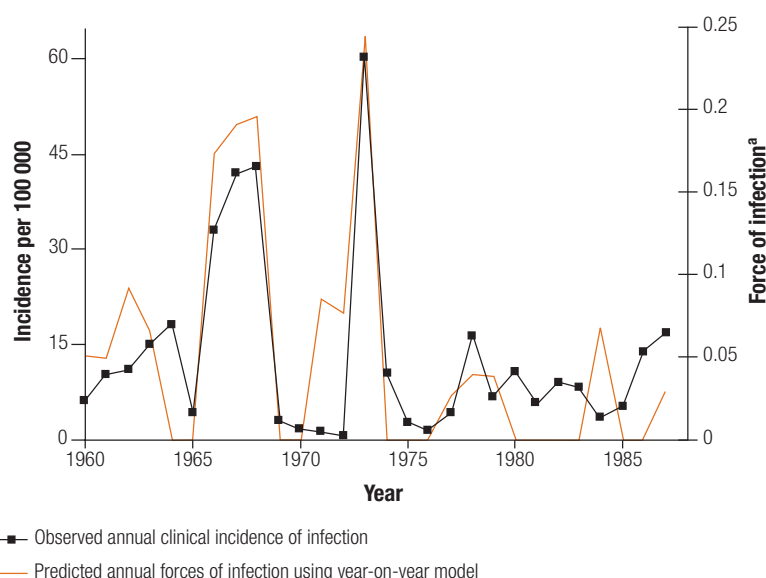
Model outcome	Correlation coefficient	
	year-on-year model	polynomial model
Force of infection <sup>a</sup>	-0.545 ( $P = 4.837 \times 10^{-4}$ )	-0.766 ( $P = 3.342 \times 10^{-8}$ )
Proportion of population susceptible	0.825 ( $P = 3.332 \times 10^{-10}$ )	0.879 ( $P = 8.031 \times 10^{-18}$ )
Average age of susceptible population	0.991 ( $P = 3.692 \times 10^{-32}$ )	0.994 ( $P = 1.096 \times 10^{-35}$ )

<sup>a</sup> Per capita rate at which susceptible individuals acquire infection.

infection and increasing clinical incidence for diseases that meet two criteria: (1) the probability of infection resulting in clinical disease is more likely in older than in younger individuals, and (2) initial infection decreases the probability of subsequent infection.<sup>37</sup> Classic dengue fever fits both of the necessary criteria for endemic stability to occur. Infection with dengue virus confers life-long immunity to the infecting viral serotype. Furthermore, there is substantial evidence that older individuals are more likely to contract classic dengue fever than younger individuals.<sup>5</sup>

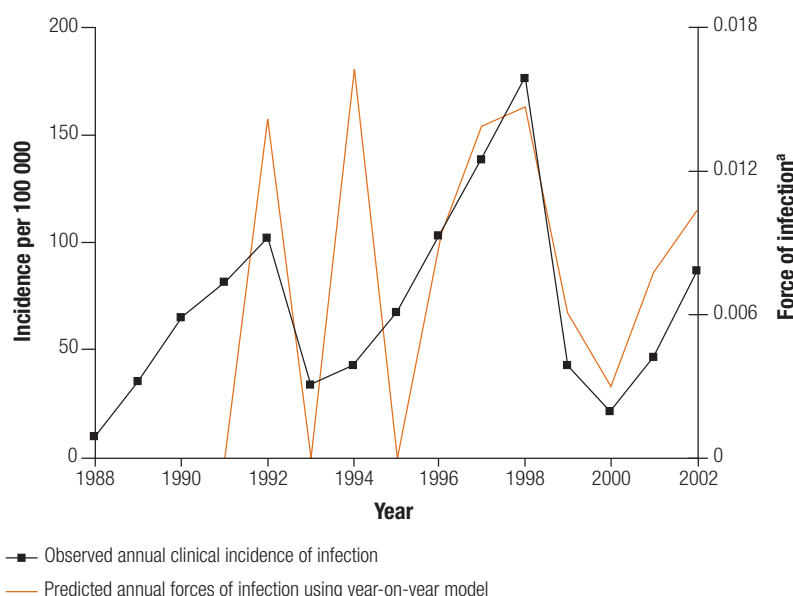
We propose that the marked reduction in force of dengue infection in Singapore, due to mosquito control, resulted not only in an overall reduction in herd immunity but an increase in the average age of first infection, which led to an increase in the incidence of clinical disease by exposing a higher proportion of older age groups to infection. From a surveillance perspective, the performance of the model highlights the potential importance of regular cross-sectional, age-stratified serologic surveys as a surveillance tool for monitoring the impact of dengue prevention activities and helping to plan for potential epidemics. Most endemic communities throughout the world have poor surveillance capabilities for both *Aedes* mosquitoes and dengue.<sup>38</sup> This lack of surveillance means that an emergency response to epidemic dengue has become common practice. But by the time a response is carried out, transmission is usually at or near its peak, at which time vector control has little impact. Due to their relative ease and low cost, age-stratified seroprevalence surveys have proven to be a useful tool in surveillance of several directly transmitted diseases, most notably chickenpox and measles.<sup>31</sup> More recently, researchers have investigated the applicability of age seroprevalence survey data to help monitor the transmission of vector-borne

Fig. 11. Observed annual clinical incidence and predicted annual forces of infection, 1960–1987



<sup>a</sup> Per capita rate at which susceptible individuals acquire infection.

Fig. 12. Observed annual clinical incidence and predicted annual forces of infection, 1988–2002



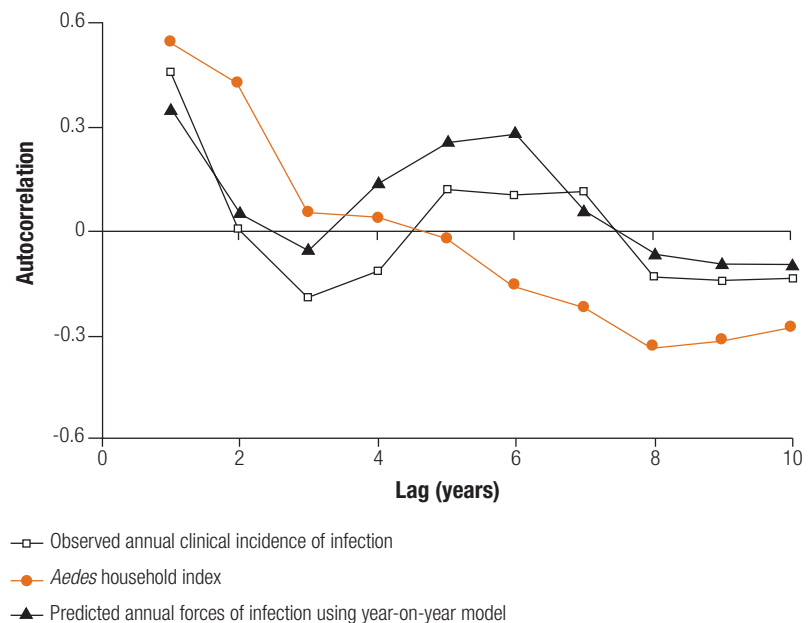
<sup>a</sup> Per capita rate at which susceptible individuals acquire infection.

diseases such as malaria, trypanosomiasis and cutaneous leishmaniasis.<sup>20,21,39</sup>

Our findings have significant implications for dengue prevention and control. Due to the absence of any prophylaxis for dengue, prevention of the disease has focused almost exclusively on controlling the primary vector, *Aedes aegypti*. Singapore has been a world leader in *Aedes* control for decades, yet if Singapore is unable to interrupt dengue transmission, it will likely be difficult for other endemic communities to do so. These findings suggest that a step-change in the effectiveness of current vector control measures is essential to fight dengue and avoid the unwanted effects of piecemeal control activities. ■

**Competing interests:** PG Coleman and DW Kelly are shareholders in Oxitec Limited, a private company developing novel genetic technologies for the control of insect populations.

Fig. 13. Correlogram of the observed annual clinical incidence, *Aedes* household index and predicted annual forces of infection, 1966–2002



## Résumé

### Reconstitution des variations historiques à Singapour de la virulence de la dengue : implications pour la surveillance et la lutte contre cette maladie

**Objectif** Reconstituer les variations historiques à Singapour de la virulence de l'infection par la dengue et mieux comprendre la relation entre la lutte contre les moustiques *Aedes* et l'incidence de la dengue classique.

**Méthodes** Des données de séroprévalence ont été extraites des enquêtes réalisées à Singapour entre 1982 et 2002. Ces données ont servi à développer deux modèles mathématiques de la séroprévalence en fonction de l'âge. Dans le premier modèle, on a laissé la virulence de l'infection varier chaque année de manière indépendante, tandis que, dans le second, cette virulence était décrite par une fonction polynomiale. On a analysé par régression linéaire les tendances temporelles prédites par les modèles. On a étudié la périodicité des prévisions de la virulence de l'infection, de l'incidence de la dengue et de la reproduction des moustiques par des techniques utilisant des séries temporelles.

**Résultats** La virulence estimée de l'infection présente une tendance à la baisse significative depuis 1966, année de lancement de la lutte antivectorielle. Les estimations de cette virulence fournies par les deux modèles reflètent des augmentations importantes du pourcentage et de l'âge moyen de la population susceptible de contracter la dengue. Point important : la modélisation d'année en année a prédit de manière indépendante une périodicité de cinq à six ans, que présente également l'incidence clinique, mais pas l'indice « maison » du moustique *Aedes*.

**Conclusion** Notre interprétation est que l'augmentation de l'incidence de la maladie est en partie due à une baisse de l'immunité collective induite par la lutte antivectorielle dans les tranches d'âges supérieures, plus sensibles au développement de la dengue clinique.

## Resumen

### Reconstrucción de la evolución de la virulencia del dengue en Singapur: implicaciones para la vigilancia y el control

**Objetivo** Determinar la evolución de la virulencia del dengue en Singapur, y profundizar en la relación entre el control del mosquito *Aedes* y la incidencia de la fiebre del dengue clásica.

**Métodos** A partir de estudios realizados en Singapur entre 1982 y 2002, se reunieron datos de seroprevalencia que se utilizaron para desarrollar dos modelos matemáticos de seroprevalencia por edades. En el primer modelo se permitió que la virulencia de la infección variara de forma independiente cada año, mientras que en el segundo se describió mediante una función polinómica. Las tendencias temporales previstas por el modelo se analizaron

mediante métodos de regresión lineal. Se emplearon técnicas de series temporales para investigar la periodicidad de la virulencia prevista de la infección, la incidencia de fiebre del dengue y la reproducción de los mosquitos.

**Resultados** Las estimaciones de la virulencia de la infección mostraron una tendencia descendente considerable desde 1966, año en que se empezó a fomentar la lucha antivectorial. Las estimaciones de la virulencia de la infección obtenidas con los dos modelos reprodujeron aumentos importantes del porcentaje y la edad promedio de la población vulnerable al dengue. Un hallazgo



importante es que el modelo de año en año predijo de forma independiente una periodicidad de cinco a seis años observable también en la incidencia clínica, pero no así en el índice de *Aedes* en los hogares.

**Conclusión** El aumento de la incidencia de la enfermedad

puede deberse en parte a una reducción, propiciada por la lucha antivectorial, de la inmunidad colectiva en los grupos de personas de edad avanzada que tienen mayor tendencia a desarrollar dengue clínico.

## ملخص

### إعادة بناء تغيّرات تاريخية في قوى العدوى بحمي الضنك في سنغافورة: التأثيرات على أنشطة الترصد والمكافحة

**الموجودات:** أظهرت تقديرات الاتجاه لقوى العدوى انحداراً يعتد به إحصائياً بدءاً من عام 1966، عندما بدت مكافحة نواقل المرض. وقد أعادت تقديرات قوى العدوى المستمدة من كلا النموذجين إحداث زيادات يعتد بها إحصائياً في النسبة المئوية وفي الأعمار الوسطية للسكان الذين لديهم الاستعداد للعدوى بحمي الضنك. والأمر الهام والجدير بالذكر أن النموذج المتركز على الانتقال من سنة لأخرى توقع بشكل مستقل عن غيره دورية تستغرق 5 - 6 سنوات، وقد أضح ذلك بالمعدلات السريرية للانتشار مع غياب مؤشّر الزواج لدى السكان.

**الاستنتاج:** نفترض أن الازدياد في معدلات حدوث المرض نجم جزئياً عن جهود مكافحة النواقل التي أدت إلى نقص في مناعة القطيع لدى مجموعات الأعمار الأعلى والتي تعد أكثر استعداداً للإصابة بحمي الضنك السريرية.

**الغرض:** إعادة بناء التغيّرات التاريخية في قوى العدوى بحمي الضنك في سنغافورة، والوصول إلى فهم أفضل للعلاقة بين مكافحة بعوض الزواجر ومعدل حدوث حمى الضنك المعهودة.

**الطريقة:** استخلصت المعطيات حول الانتشار المصلي من المسوحات التي أجريت في سنغافورة في الفترة بين 1982 و2002، واستخدمت هذه المعطيات لإعداد نموذجين رياضيين للانتشار المصلي والعمرى. وقد سمح لقوى العدوى في النموذج الأول بأن تخضع لاختلافات مستقلة كل عام، فيما وصفت في النموذج الثاني بأنها وظيفة متعدّدة الحدود. ثم حللت الاتجاهات الزمنية وفق التوقعات الخاصة للنموذج باستخدام التحوُّف الخطي، كما استخدم أسلوب السلاسل الزمنية لتقضي الدورية في القوى المتوقعة للعدوى، وفي معدل حدوث حمى الضنك وفي تقيس البعوض.

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