

Letter to the editor: Diagnosis of a single imported dengue case who had travelled to Japan – how serious is it for travellers?

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To the editor: We enjoyed reading the meticulous clinical report of an imported dengue case in a German traveller returning from Japan [1]. It is, however, unclear what level of risk the ‘autochthonous’ infection of a single case in Japan represents. By investigating the epidemiological aspects of one imported dengue case, we would like to discuss how serious the implications of autochthonous transmission are for future travellers.

The diagnosed case travelled to Japan in August 2013, during which time the dengue virus infection is believed to have occurred. We would like to estimate how many primary cases there were and how transmissible the dengue virus was.

Let I_t and R_t represent the number of primary cases and the effective reproduction number, respectively, at a generation t (i.e. the mean number of secondary cases generated by a single primary case at generation t). Supposing there were S_t susceptible individuals who can be infected with dengue virus, the probability of producing $I_{t+1}=k$ secondary cases through a single generation interval of dengue (i.e. the time from infection in a primary human case to infection in a secondary human case caused by the primary case through the mosquito vector) is given by [2,3]: (1)

If the diagnosed German patient represents all infected cases, $k=1$. However, dengue was not at the forefront of Japanese physicians’ attention before the case report. If there were other undiagnosed cases in the same generation, $k \geq 2$. As can be seen from Equation 1, the reproduction of k cases in generation $t+1$ depends on three

unknown epidemiological parameters, i.e. I_t , R_t and S_t . The negative loglikelihood of observing k secondary cases reads as follows: (2)

By allocating plausible values for a part of three unknown parameters, we can examine hypothetical situations in which a transmission event in a German traveller could have occurred. The relationship between the effective reproduction number and the number of primary cases with three possible values of k ($k=1, 3$ and 5) and $S_t=50$ is shown (panel A of the Figure). Maximum likelihood estimates of R_t were obtained for each I_t . R_t would have to be above 1 for $I_t < k$, but transmission of dengue virus has not been continuously observed in Japan and R_t is unlikely to be above 1 over several generations. More importantly, for $I_t \geq k$, the large I_t is consistent with R_t sufficiently below 1. Namely, it is likely that the observed event was caused by a certain small number of primary cases I_t presumably with a small $R_t < 1$. S_t had little impact on both R_t and I_t (data not shown) as well as the likelihood value, and thus, we fixed it at 50 for the rest of our analysis. The negative loglikelihood value as a function of I_t and R_t (without involving statistical estimation) is simulated (panel B of the Figure). This represents the situation for $k=1$, but $k > 1$ also yielded qualitatively indistinguishable patterns. As R_t becomes larger (and comes close to 1), the most plausible value of I_t is calculated to be 1. Provided that R_t is as small as 0.2, the minimum negative loglikelihood will be observed at $I_t=5$.

Two limitations of our analysis must be noted. First, an important technical flaw of our exercise is that our

$$(1) \quad \Pr(I_{t+1} = k; I_t, S_t, R_t) = \binom{S_t}{k} \left[1 - \exp\left(-\frac{R_t I_t}{S_t}\right) \right]^k \exp\left(-\frac{R_t I_t}{S_t}\right)^{S_t - k}$$

$$(2) \quad L(I_t, S_t, R_t; I_{t+1} = k) = \sum_{j=1}^k \ln j - \sum_{i=S_t - k + 1}^{S_t} \ln i - k \ln \left[1 - \exp\left(-\frac{R_t I_t}{S_t}\right) \right] + (S_t - k) \frac{R_t I_t}{S_t}$$

arguments start with a rare event (i.e. diagnosis of a single imported case) and thus our results could have over-interpreted the actual risk of dengue in Japan. The actual risk could be even smaller than what has been calculated here, but we decided to use the biased sample, because the over-interpreted risk would still appear to be far smaller than that in dengue-endemic settings (and this notion should be shared with non-experts). Second, due to data limitation, our exercise only extends to the diagnosed dataset of the reported German case. It is hard to take into account unrecognised transmission events at another time and another geographical location.

Despite these limitations, our crude analysis of this diagnostic event indicates the following: (i) the number of primary cases was probably small; and (ii) even with a certain number of primary cases, a large I_t leads to a small R_t , which is substantially below 1. These would not permit dengue virus transmission to continue in the suspected transmission settings in Japan. Of course, demonstrating an autochthonous transmission event is of the utmost importance, because it reflects establishment of a transmission cycle through *Aedes* spp. within Japan. Nevertheless, it should be noted that the diagnosis of an imported case does not directly indicate that the actual risk of infection in

Japan is high or that dengue is endemic in that country. Rather, based on the very limited biased data, our exercise indicates that it is very unlikely that dengue is endemic in Japan. Our results and travel history of the diagnosed case are consistent with an exposure near Narita International Airport, where there could be mosquito vectors that have bitten infected travellers from endemic countries. Indeed, there has been a report of ‘airport dengue’ in Australia [4]. A future seroepidemiological survey could help validate the findings from this short note [5].

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Conflict of interest

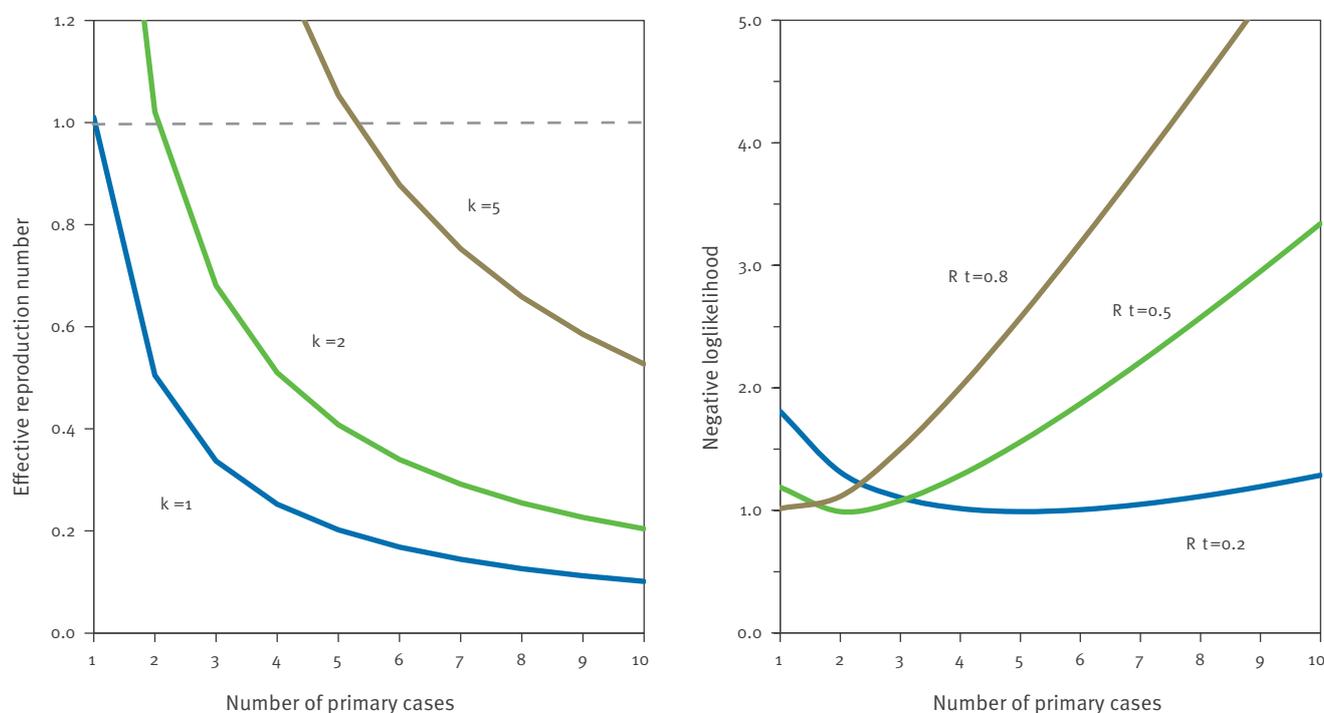
None declared.

Authors’ contributions

Ryo Ueno and Hiroshi Nishiura conceived modelling ideas, interpreted the results and revised the manuscript. Hiroshi Nishiura implemented computational analyses and drafted the manuscript.

FIGURE

Analysis of transmission event data using a chain binomial stochastic model



Panel A. The relationship between the maximum likelihood estimate of the effective reproduction number and the number of primary cases. The number of secondary cases, k , has been varied from 1 to 5. The number of susceptible persons has little impact on the results and was fixed at 50. The horizontal dashed line represents the threshold value of the reproduction number, below which the transmission event does not continue through this generation.

Panel B. The simulated negative loglikelihood values as a function of the effective reproduction number and the number of primary cases. The optimal value of the number of primary cases is seen where the negative loglikelihood takes the minimum value. The effective reproduction number, R_t , is varied from 0.2 to 0.8. The number of secondary cases, k has been fixed at 1, but $k > 1$ does not yield qualitatively different patterns.

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