

Short Report: Higher Risk of Infection with Dengue at the Weekend among Male Singaporeans

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Abstract. A growing body of evidence suggests that dengue infection in Singapore predominantly occurs away from the home, but when and where dengue transmission occurs is unclear, confounding control efforts. The authors estimate days of the week in which dengue inpatients in Singapore were infected during the period 2006–2008, based on the day they became febrile and historical data on the incubation period, using Bayesian statistical methods. Among male inpatients, the relative risk of infection is an estimated 57% higher at the weekend, suggesting infections associated with the home or leisure activities. There was no evidence of elevated risk of infection at the weekend for female inpatients. The study motivates further research identifying locales frequented in the week leading up to onset to improve the effective targeting of vector control efforts.

Dengue is endemic to Singapore, a tropical city state in South East Asia, with year-round infection and circulation of all four serotypes.¹ An intensive and well-regarded vector control program was instigated in the 1960s and 70s² and led to a period of low incidence of symptomatic disease; since the 1990s, however, dengue has resurged and was responsible for around 50,000 reported cases and 100 deaths from 2000 to 2009.³ This resurgence accompanied a shift in both infection and clinical disease from children to adults.^{2,4}

It is unclear in what locations infections occur, confounding control efforts. As most people have different activities and frequent different locales on weekdays and on the weekend, being able to identify different risks of infection in these two time periods would suggest locations or behaviors that may be associated with a higher risk of dengue transmission and that could be investigated further to devise enhanced vector control measures. We therefore sought to estimate the proportion of infections occurring in these two time periods, using inpatient records of fever onset to infer the infection day distribution using Bayesian statistical methods.

We reviewed data on all patients admitted to Tan Tock Seng Hospital, the main hospital managing dengue patients in Singapore, during 2006–2008 with 1) dengue infection confirmed by reverse transcription-polymerase chain reaction (RT-PCR) or 2) who tested positive using immunoglobulin M (IgM) and fulfilled the 1997 criteria for dengue fever or the 2009 criteria for probable dengue or both.^{5,6} For each patient we determined a date of onset of fever ($N = 2,126$), excluding those who could not recall the date of onset or duration of fever, or with missing data ($N = 11$). The median time from onset to hospitalization is 5 days; other demographic and clinical data are presented in Table 1. Of particular note, there was a paucity of children (routinely referred instead to nearby KK Women's and Children's Hospital) and twice as many men as women were admitted; in addition, as

in other settings,⁷ women were more likely to present more severe manifestations of dengue. Dates were converted to days of the week for subsequent analysis. Because there are differences in incidence of cases¹ and in dengue seropositivity⁸ between the genders, we consider men and women separately. This study was approved by the Institutional Review Board, National Healthcare Group, Singapore (DSRB E/08/567).

We used early 20th century volunteer challenge study data to quantify uncertainty in the incubation period (i.e., time from infection to symptom onset). These data were originally published by Siler and others⁹ and Simmons and others¹⁰ and recently reanalyzed by Nishiura and Halstead¹¹; the strains used in the two experiments were previously identified to be dengue viruses (DENV-4 and DENV-1), respectively.¹² Nishiura and Halstead¹¹ could find no statistically significant differences between the incubation periods of the two serotypes, and in this analysis we assume that this also holds for DENV-2 and DENV-3, and for primary and subsequent infections. We obtained the challenge data from the authors¹¹ to which we fitted log-normal, Weibull, and gamma distributions. The log-normal fitted substantially better (the difference in posterior mean deviances being 10 and 55) and so all subsequent analyses assumed this form for the incubation period. The log-normal model was parameterized using Bayesian methods,¹³ with uniform priors for the log-mean and log-standard deviation on the real line and positive part of the real line, respectively. The posterior distribution for these two parameters was then sampled using Markov chain Monte Carlo integration with 100,000 iterations after burn-in of 10,000 iterations. Visual inspection confirmed near multivariate normality of the posterior and so the mean and covariance of the Markov chain Monte Carlo sample were used to define a multivariate normal prior distribution for the Tan Tock Seng data; these are tabulated in the Supplementary Information.

We then “back fitted” the infection day distribution by combining the information from the onset data with that from the volunteer challenge studies. The model used to do so assumed a probability that a randomly selected dengue patient was infected on a Saturday or Sunday of p_{WE} (the same for both days) with the probability it happened on a

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TABLE 1

Demographic and clinical data on dengue inpatients, Tan Tock Seng Hospital, Singapore, 2006–8*

Characteristic	Proportion (N = 2115)
Female	33% (51%)
Aged < 20	6% (24%)
Aged 20–39	59% (30%)
Aged 40–59	30% (31%)
Aged 60+	6% (14%)
Chinese ethnicity	69% (74%)
Indian ethnicity	12% (9%)
Malay ethnicity	5% (13%)
Other ethnicity	14% (3%)
Singapore citizens	47% (64%) [†]
Satisfying criteria for	
Dengue fever 1997	91%
DHF 1997	22%
DSS 1997	1%
Severe dengue 2009	12%

*Eleven other patients who did not have data on onset of fever were excluded from analysis. Except where otherwise noted, in parenthesis, demographic data for the resident population (i.e., Singapore citizens and permanent residents) are presented for comparison; these are derived from the 2010 census of population published by the Singapore Department of Statistics. Detailed data on *non-residents*, that is, foreigners' resident in Singapore, but without permanent residence status, are not published by the Department of Statistics.

[†]Proportion of citizens to the entire population, which consists of citizens, permanent residents, and *non-residents*.

weekday being $p_{WD} = (1 - 2p_{WE})/5$. We estimated p_{WE} as before using Markov chain Monte Carlo within a Bayesian analysis, combining a uniform prior distribution on $(0, 0.5)$ for p_{WE} with the aforementioned multivariate normal prior for the incubation parameters, and 100,000 iterations following 10,000 as burn-in. We derive an approximate two-sided P value, denoted \tilde{P} , for the hypothesis of equal risk of infection in the two time periods (i.e., of $p_{WD} = p_{WE}$) using credible intervals in lieu of confidence intervals and appealing to the relationship between the coverage of and endpoints of the latter and the null hypothesis tested. All analysis was performed in the R statistical environment.¹⁴

The estimated incubation period is presented in Figure 1 (top) and is consistent with the oft mentioned typical incubation period of 4 to 7 days and a range of 3–14 days¹⁵; the distribution of onset by day of the week is presented in Figure 1 (middle). Among males, a rise toward the end of the week is discernible and consistent with a higher risk of infection at the weekend displaced by the incubation period; for females, onset is almost uniform across the week. The Bayesian analysis (Figure 1, bottom) yields estimates of the proportion infected on a weekend day of 19.2% for males (95% credible interval [CI]: 16.3%, 22.3%) versus on a weekday of 12.3% (95% CI: 11.1%, 13.5%), i.e., a relative risk of 1.57 (95% CI: 1.21, 2.01); for female inpatients, the weekend estimate (15.2%, 95% CI: 11.2%, 19.3%) is similar to that during the week (13.9%, 95% CI: 12.3%, 15.5%), and the relative risk is 1.11 (95% CI: 0.72, 1.58). Approximate two-sided P values suggest strong evidence ($\tilde{P} = 0.0007$) that the male infection rate is not constant over the week; for females $\tilde{P} > 0.05$.

The resurgence of dengue in Singapore over the last 20 years is enigmatic and has been variously ascribed to declining herd immunity, climate change, virus changes, less effective vector control, and changes in patterns of infection.^{2,16,17} A key unanswered question is where and when infection is acquired. Answering this question would allow high-risk areas to be identified and targeted for responsive and structured control measures. In finding a significantly higher infection rate for

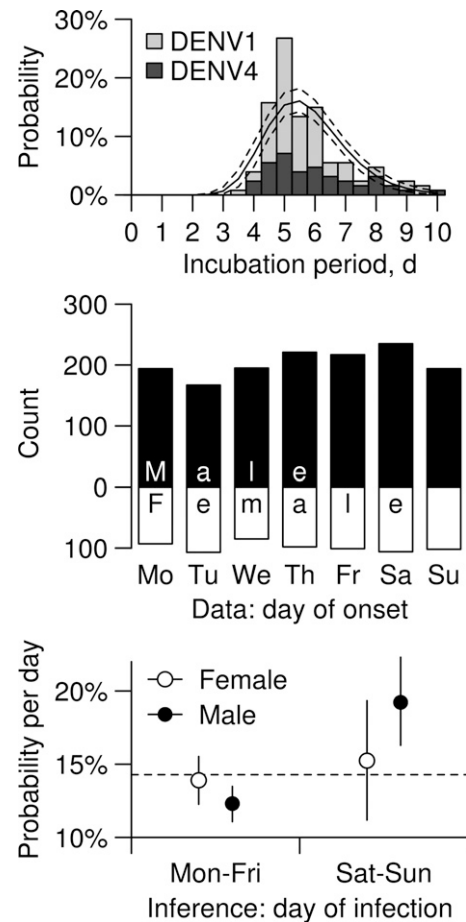


FIGURE 1. Estimated incubation period from early 20th century volunteer challenge studies, empirical distribution of onset days among dengue inpatients, Tan Tock Seng Hospital, Singapore, 2006–8, and inferred distribution of infection days for these inpatients. Top: incubation period data of dengue viruses 1 (DENV-1) and 4 (DENV-4) extracted from Nishiura and Halstead¹¹ (bars); the inferred distribution is overlaid (solid line, posterior mean, dashed line 95% credible interval [CI]). Middle: distribution of day of onset of fever in dengue patients at Tan Tock Seng Hospital by sex. Bottom: posterior mean (dot) and 95% CI (lines) for the per day probability of infection, for weekdays and weekends, by sex; the dashed line corresponds to what would be expected were infection rates homogeneous across the week.

men at weekends than weekdays, this study suggests some hypotheses for subsequent investigation. The working pattern in Singapore is similar to that in other developed countries, with most non-service workers working Monday to Friday, suggesting that the increase in infections at weekends is associated with either the home, or with leisure and other weekend activities. In Singapore, a small proportion (~30%) of cases can be linked to a cluster around the household,² and there are few infections among children,⁴ which have led to speculation of a switch toward infection away from the home, around which the current emphasis on vector control focuses. Research in Taiwan also suggests infection not be associated with time spent at home or the workplace.¹⁸ Combining the current study's findings, that infection among Singaporean men is higher on the weekend, with the implication of previous studies, that infection increasingly occurs away from the home, suggests weekend leisure activities may be a risk factor.

There are several limitations to the study: 1) in the absence of data to the contrary, we assume the same distribution for all four serotypes and for primary and subsequent infections. Although this may not be correct, we do not have data to inform alternative incubation period distributions for different combinations of serotypes and clinical phenotypes, or to quantify differences between these combinations. 2) It is likely that a small proportion of patients testing positive on IgM but negative on RT-PCR are not currently infected with dengue. 3) Almost everyone in our cohort is an adult, so we are unable to assess the timing of pediatric infections, which in Singapore constitute about 15% of notified cases,² lower than in many neighboring countries. 4) To generalize from the day of the week of infection of adult inpatients to that of all adults requires making the assumption that the probability of eventually requiring hospitalization is the same regardless of the day the infection occurred. Most importantly, 5) the study design is unable to answer the question of *where* transmission occurs—we think that a similar approach, combining elicited information on locales frequented in the week leading up to onset with the onset distribution, would allow enhanced targeting of vector control to areas in which transmission is more likely to have occurred.

Anecdotally, Singaporeans, especially males, engage more in leisure activities outside the house on the weekend and thus, in light of our findings, future investigation of weekend leisure activities, such as visits to parks, shopping and food centers, and other recreation areas, as a source of putative dengue infection would be warranted and may prove fruitful.

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