COMMENTARY

How season and serotype determine dengue transmissibility

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Over half of the world's population is at risk for infection by dengue (1), the most ubiquitous human arbovirus. The four distinct dengue virus serotypes, DENV1 to -4, now cocirculate in much of the tropical and subtropical world, causing periodic acute epidemics with substantial associated morbidity. The last 20 y has seen much progress in understanding viral transmission (2, 3), evolution (4), and disease burden (1, 5). However, many uncertainties remain. Addressing these uncertainties is vital to assessing how the first dengue vaccines (6, 7) and novel vector control measures (8, 9) might best be used to reduce the burden of disease caused by dengue or to control transmission. Key issues include: How is disease severity affected by age, host factors or prior exposure? How do different viral genotypes vary in virulence? How does the immunity a person gains to one dengue virus affect the risk of infection or serious illness when she or he is exposed to a second? And how does cross-immunity shape the transmission dynamics of dengue viruses at the population level? Finally, what environmental, human, and seasonal factors determine viral transmissibility?

Quantifying Variability in Transmission

The research published by Reiner et al. in PNAS (10) starts to address the last of these uncertainties by giving us a unique picture of how rates of transmission of the four dengue viruses varied in Iquitos, a small city in Peru, over a 12-y period. Using sera painstakingly collected from a sequence of longitudinal population cohorts, the authors used modern statistical methods to reconstruct the history of infection of each individual participant and thus of the entire community. From these infection incidence trends, Reiner et al. then estimated how the transmissibility of dengue (as quantified by the basic reproduction number, R_0) varied from week to week over more than

a decade. This novel analysis demonstrates how variable dengue transmissibility is, both seasonally within a year but also year to year. Reiner et al.'s results shed light on how the first arrival of DENV3 in 2001 and DENV4 in 2008 perturbed the infection dynamics of dengue in Iquitos. It is notable that in 4 of the 12 y monitored, the risk of infection in individuals still susceptible to one or other of these two viruses exceeded 20%, much higher than typically seen.

Perhaps most intriguing, Reiner et al. find significant transmissibility differences

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between the serotypes, particularly in their apparent overwintering abilities (10). Although DENV1 and DENV2 are able to maintain R_0 above the critical threshold of 1 required for sustained transmission to be possible, R_0 for DENV3 and DENV4 dips below 1 most winters. Moreover, DENV4 appears substantially less transmissible overall than the other three serotypes. These results add to a growing body of evidence suggesting the four dengue serotypes vary substantially in epidemiological characteristics, such as transmissibility (11, 12), temporal dynamics of infection (13–15), and probability of clinical disease (16–18). Given that DENV3 and DENV4 only recently invaded much of South and Central America, it is possible that their lower transmissibility reflects suboptimal adaptation to local *Aedes aegypti* species, and that viral fitness will increase in the coming years. However, if evolutionary trade-offs make such adaptation unlikely then control and potential elimination of those serotypes

might be substantially easier than for DENV1 and DENV2.

Implications for Dengue Control

The magnitude of seasonal variation in transmissibility estimated by Reiner et al. (10) also raises interesting questions about the feasibility and requirements for effective control of dengue. To stop transmission of an infectious disease, interventions need to reduce R_0 to below 1. Most past work quantifying dengue transmissibility has analyzed the age distribution of seropositivity or clinical dengue cases aggregated by year (11, 19, 20) to create estimates of R_0 averaged over entire seasons. If annual peaks in transmissibility are substantially higher than the annual average, control may be more challenging than previously thought. Conversely, winter troughs in transmissibility make it more difficult for dengue to persist year round (at least in small populations), and may therefore make control easier. A priori it is not possible to judge whether it is necessary to target peak transmission rates, even if sustained for only short periods, or whether measures that could control mean transmission levels would be sufficient to achieve elimination. Evaluating the complex interactions between intervention impact, seasonal variation in transmission, local persistence of transmission, and the dynamics of dengue epidemics will thus be critical for assessing the effort required for effective control.

Although unique in developing methods to estimate temporal trends in transmissibility from serological data collected from longitudinal cohorts (10), this new study builds on a number of recent studies analyzing dengue case-report time-series data collected via routine surveillance (21–23). These reports have highlighted the seasonality of transmissibility, importance of off-season transmission rates to annual peaks, and how cross-immunity shapes incidence patterns.

The Value of Long-Term Epidemiological Studies

As always, there are limitations to the Reiner et al. study, most notably the limited extent to which cross-immunity between serotypes was able to be incorporated into analysis of the serological data (10). Developing more refined algorithms for inferring infection events from repeated serological samples (24, 25) is therefore clearly a priority. Repeating this type of analysis for other well-characterized dengue cohorts will also aid the development of robust inferential algorithms, in addition to giving insight into seasonal trends in dengue transmission in a wider variety of settings. However, in an age where the trend is for novel electronic capture of disease trends (26–29), Reiner et al. (10) have demonstrated the value still to be obtained from traditional long-term "shoe leather" epidemiological studies. In particular, this work—together with recent cohort studies of other infections (30)—highlights how serological data remain the most powerful tool to characterize transmission trends for acute immunizing viral infections such as dengue, where the short-lived and often asymptomatic nature of infection makes tracking the prevalence of active infection difficult.

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