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Dengue Endemicity, Force of Infection, and Variation in Transmission Intensity in 13 Endemic Countries

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Dengue endemicity varies but comparative, multicountry data are extremely limited. An improved understanding is needed to prioritize prevention, including vaccination, which is currently recommended only under specific epidemiological conditions. We used serological study data from 46 geographical sites in 13 countries to estimate dengue force of infection (FOI, the proportion of children seroconverting per year) under assumptions of either age-constant or age-varying FOI, and the age at which 50% and 80% of children had been infected. After exclusions, 13 661 subjects were included. Estimated constant FOI varied widely, from 1.7% (Singapore) to 24.1% (the Philippines). In the site-level analysis 44 sites (96%) reached 50% seroconversion and 35 sites (75%) reached 80% seroconversion by age 18 years, with significant heterogeneity. These findings confirm that children living in dengue-endemic countries receive intense early dengue exposure, increasing risk of secondary infection, and imply serosurveys at fine spatial resolutions are needed to inform vaccination campaigns.

Keywords. dengue; epidemiology; seroprevalence; vaccines; endemicity; infectious disease transmission.

Dengue viruses infect approximately 400 million people annually at frequencies that vary according to environmental, ecological, and behavioral factors [1, 2]. Disease burden estimates have historically been unreliable but more recent studies using more comprehensive data synthesis and systematic methods estimate that dengue viruses likely result in 24–130 million symptomatic episodes, 10 000–50 000 deaths, and costs of US $4–19 billion, annually [2–4]. Dengue represents a significant source of morbidity in affected regions and 50% of the global population is at risk of infection, with local variations caused by geographical, microclimatic, and ecological factors at the subnational and local levels [2, 5, 6].

Following infection, the likelihood of suffering mild or more serious symptoms depends on immunological or other factors that predispose individuals to more severe disease, particularly during chronological and/or immunological windows of enhancement caused by antibody-dependent enhancement or other mechanisms arising from infection with heterologous viral serotypes [7–9]. The risk of suffering a symptomatic episode is therefore a complex function of ecological and immunological factors with time-varying risk windows, determined by the underlying transmission intensity. A result is that the age distribution of symptomatic dengue disease is dependent on the epidemiological setting, with more intense transmission resulting in a younger median age of cases [10]. Infection frequency may be constant or may be shaped by individual events such as outbreaks or changes in human behavior that affect the risk of exposure [11].

Because most dengue infections are asymptomatic, prospective measurements of infection rates require longitudinal studies with blood samples at multiple time points, which are resource intensive and generally conducted in single study sites with limited geographical representativeness [12]. However, dengue seroprevalence at a given age is an alternative measure of endemicity, which can be measured relatively efficiently from age-stratified cross-sectional surveys [13]. Assuming transmission intensity is constant over time, the rate at which seroprevalence increases with age can provide a measure of the force of infection (FOI) or the rate at which susceptible (seronegative) individuals acquire infection [14]. Under assumptions of constant or varying endemicity, FOI can be used to estimate seroprevalence at a given age, an approach which can complement empirical seroprevalence measurements [15, 16].

Reliable estimates of age-stratified dengue seroprevalence are particularly important when considering immunization, because the efficacy of the world's first dengue vaccine (CYD-TDV, Dengvaxia; Sanofi Pasteur) is dependent on an individual's infection history [17]. World Health Organization (WHO) guidelines recommend vaccination only after individual screening for dengue antibodies or, if this is not feasible,

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where seroprevalence in 9 year olds exceeds a threshold of 80% [18]. Dengue seroprevalence is therefore an important determinant of the impact and cost-effectiveness of dengue vaccination.

Here, we used age-stratified dengue seroprevalence data from healthy children in 13 countries involved in dengue vaccine clinical trials and epidemiological studies to describe dengue endemicity across a wide range of geographical regions, using FOI as an indicator. We estimated the age at which seroprevalence reached 50% and 80% in countries overall and at each of 46 geographically distinct sites, to inform the feasibility and optimum age for efficient dengue vaccination strategies, aligned with WHO Strategic Advisory Group of Experts on Immunization recommendations.

METHODS

Ethical Approval

This is a secondary analysis of anonymized data. Ethics approval for analyses and publication of study data were secured from relevant ethical committees prior to the collection of any data (all approval numbers are in Supplementary Table 1).

Study Design

We analyzed data from cross-sectional, age-stratified serological surveys in 13 countries collected over 6 years. Data and blood samples originated from baseline measurements of clinical trials before any vaccine or placebo were administered, or from dedicated cross-sectional seroprevalence surveys.

Study Population

Eligible subjects were participants in Sanofi Pasteur dengue vaccine clinical trials or epidemiological studies, which collected dengue serological data from healthy, asymptomatic, unvaccinated individuals (Table 1). Enrollment methods in these studies varied and included investigators directly recruiting subjects under their care or following informational events at primary health care centers, schools, or community centers, depending on the local health care system and community organization. For phase 2b or phase 3 vaccine efficacy studies, which provided 29% of data, subjects were typically recruited following school-based (in Asia) or community-based (in Latin America) meetings held in proximity to participating hospital study sites, during which parents were informed about upcoming dengue vaccine studies and implications of participating [19, 20]. Recruitment for epidemiological studies, which provided approximately 42% of data, was conducted at multiple sites selected to provide geographical variability across countries. After school/community educational events, families wishing to participate presented to local health care facilities for recruitment [21, 22]. The remaining subjects were enrolled in earlier-phase clinical trials and were typically recruited directly from medical facilities by study investigators.

Data from all studies were combined into a single database and categorized according to the geographical district

Table 1. Site Description and Data (Country-Level Analysis)

Country	Sites	No. of sites	Studies	n	Age Range, y	First Enrollment	Last Enrollment
India	Delhi, Pune, Ludhiana, Bangalore, West Bengal, Wardha, Mumbai, Hyderabad	8	CYD47,[a] DNG10[b]	2562	5–18.7	Jan 11	Oct 12
Indonesia	Bali, West Java, Jakarta, Aceh, North Sumatera, West Sumatera, Jambi, Lampung, Banten, Central Java, East Java, East Kalimantan, South Sulawesi, Southeast Sulawesi	14	CYD14,[c] DNG26[b]	3539	1–18.9	Jun 11	Nov 14
Malaysia	Kuala Lumpur, Penang, Ipoh (Perak), Seremban (Negeri Sembilan), Kuching	5	CYD14,[c] CYD32[a]	547	2–14.8	Dec 10	Sep 11
Philippines	San Pablo (Region IV-A)	1	CYD08,[a] CYD14[a]	820	0.9–14.9	Jan 10	Jul 11
Singapore	Singapore	1	CYD28[a]	384	2–18	Apr 09	Oct 09
Thailand	Ratchaburi, Kamphaeng Phet	2	CYD14,[c] CYD23[c]	637	2–14.8	Feb 09	Nov 11
Vietnam	Long Xuyen (An Giang), My Tho (Tien Giang)	2	CYD14,[c] CYD22[a]	607	2–18.7	Mar 09	Oct 11
Brazil	Nordeste, Espirito Santo, Goias, Mato Grosso Sud	4	CYD15,[c] CYD30[a]	450	8.9–16.9	Aug 10	Nov 11
Colombia	Santander, Quindio, Cundinamarca, Meta, Casanare, Cali	6	CYD13,[a] CYD15,[c] CYD29[a]	1518	0.9–16.9	Oct 09	Mar 12
Honduras	Tegucigalpa	1	CYD13,[a] CYD15[c]	455	9–16.9	Oct 09	Sep 11
Mexico	San Luis, Veracruz, Morelos, Yucatan, Guerrero, Nuevo León	6	CYD13,[a] CYD15,[c] CYD33[a]	1213	0.6–16.9	Nov 09	Jul 12
Peru	Peru	1	CYD24,[a] CYD29[a]	671	0.9–11.9	Sep 08	Mar 12
Puerto Rico	Puerto Rico	1	CYD13,[a] CYD15[c]	258	9–16.9	Nov 09	Oct 11

[a]Clinical trial.

[b]Epidemiological study.

[c]Efficacy trial.

or comparable administrative unit (hereafter, "site") of each participating study center, on the advice of local Sanofi Pasteur staff with expertise on local geography. The analysis was restricted to subjects aged 7 months to < 19 years on the day of blood sampling, as data on older subjects were limited and indicated minimal variation in seroprevalence in older age groups. A sensitivity analysis was conducted on the entire population aged > 7 months for India, Singapore, and Vietnam, the only countries where subjects > 19 years had been enrolled, to assess the impact of excluding older adults from the analysis. Data from areas that are not dengue endemic (Australia, United States, and Mexico City) and from subjects with inconclusive dengue serological results were excluded from analysis (Figure 1). A country-level analysis was followed by a site-level analysis, in which sites with < 10 subjects and those that enrolled only subjects aged < 2 years were removed.

Data Collection and Laboratory Analyses

Baseline serum samples, drawn before any vaccine was administered from both vaccine and placebo arm subjects of clinical trials, were collected between September 2008 and November 2014 (Table 1). Dengue exposure for each subject was ascertained in clinical trials by 50% plaque reduction neutralization test ($PRNT_{50}$) with a lower limit of quantitation titer of 10 (reciprocal dilution) as described previously [23]. For epidemiological studies DNG10 and DNG26, serostatus was determined by IgG enzyme-linked immunosorbent assay (ELISA; Panbio and Focus Diagnostics); >97% of a positive subset were confirmed by $PRNT_{50}$ providing confidence in the specificity of IgG ELISA assays [21, 24]. As the youngest subject was aged 0.6 years, we assumed declining maternal antibodies had little or no impact on our analyses.

Statistical Methods

FOI was estimated using catalytic models in which seroprevalence is assumed to increase exponentially with age:

$$P_a = 1 - e^{-\lambda a}$$

Here, P_a is the seroprevalence at age a years, and λ represents FOI or the annual risk of seroconversion among initially seronegative individuals. The parameter λ can be estimated through a generalized linear model with complementary log-log link:

$$ln\left(-\ln\left(1 - p_a\right)\right) = \ln\left(\lambda\right) + ln(a)$$

where the logarithm of each subject's age is included as an offset with a coefficient constrained to 1. This model implicitly assumes that FOI is constant throughout the age range and that transmission intensity is stable over time.

FOI estimates were derived for each country and site with uncertainty described through generation of exact binomial 95% confidence intervals (CIs). Intersite variability in countries

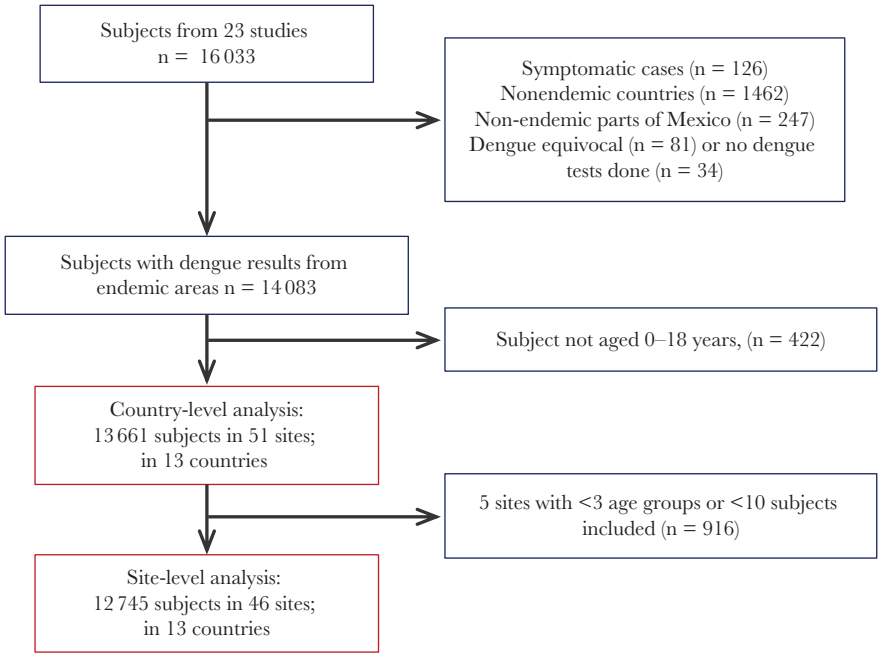

Figure 1. Study flow chart.

with > 1 site was accounted for by generating robust standard errors, assuming sites were independent clusters.

To describe possible changes in FOI within large age strata, we also generated age-varying FOI estimates for specific age groups using linear piecewise models. We fitted log-binomial models with 2 age terms:

$$-\ln(1 - P_a) = \lambda_1 a_1 + \lambda_2 a_2$$

For each study site, we determined the optimal age-varying FOI model by sequentially varying the age breakpoint for each whole year of data with at least 2 adjacent data points (eg, for countries with data starting in 3-year-old children the first possible breakpoint was age 5 years) and identifying the model with the lowest value for Akaike's information criterion. For each country, we determined whether constant or age-varying models fit the data better by 10-fold cross-validation, taking a random 10% of the sample, and selected the model (constant or age varying) with lower root mean squared error. Seroprevalence by age, per country, was estimated from the resulting models. Graphs of estimated constant and age-varying seroprevalence were developed for each country, overlaid with observed seroprevalence and their 95% CIs grouped by year, using robust variance estimates for countries with > 1 site to account for clustering.

We estimated the age at which 50% and 80% ($p = 0.5$ or 0.8) of children seroconverted in each country and site from the optimal model for each site, using the following formula in case of constant FOI or if the threshold was reached before the breakpoint:

$$a = \frac{-\ln[p]}{\lambda}$$

or if after the observed breakpoint for age-varying models, by:

$$a_2 = \frac{-\ln[p] - \lambda_1 a_1}{\lambda_2}$$

All analyses were conducted using Stata version 15.0.

RESULTS

Dataset

Our database contained information from 16 033 subjects participating in 23 clinical trials and epidemiological studies. After exclusions, 13 661 subjects from 15 studies were eligible in 13 country-level analyses and 12 745 in 46 site-level analyses, with a mean of 268 subjects per site (Table 1 and Figure 1). Countries with the highest number of sites and subjects were Indonesia, India, Colombia, and Mexico. The range of subject ages was narrowest in Brazil (7.9 years) and widest in Indonesia (17.9 years).

Dengue Force of Infection

Under the assumption of constant FOI, dengue FOI varied between countries from a low of 1.7% (95% CI, 1.4–2.2) in Singapore, increasing to 24.1% (95% CI, 21.8–26.5) in the Philippines (Table 2). FOI was lower than 10% in Singapore, Mexico, Peru, and Puerto Rico. In most countries, constant and age-varying models predicted similar seroprevalence at most ages; constant models fit data better in 8 countries (Table 2 and Figure 2). In all countries except India and Brazil, age-varying FOI was higher in younger children than older children, indicating a decreasing rate of first infection as children aged. The highest FOI estimates occurred in very young Filipino children, with an annual seroconversion risk of 43% up to the age of 2 years. Estimated dengue seroprevalence increased with age in all scenarios, except for the age-varying Singapore model where estimated seroprevalence declined at age 4 years. In a sensitivity analysis, the impact of including adults aged > 19 years from India, Singapore, and Vietnam was minimal (constant FOI changed from 11.9 [95% CI, 8.7–16.2] to 11.5 [95% CI, 8.4–15.6]; 1.7 [95% CI, 1.4–2.2] to 2.0 [95% CI, 1.7–2.3]; and 11.4 [95% CI, 10.2–12.8] to 11.4 [95% CI, 10.3–12.7], respectively). At the site level, the age-constant FOI was > 10% per year at 31 of 46 sites and constant models fit observed data better at 36 of 46 sites. FOI estimates at the site level are provided in Supplementary Table 2.

Age at 50% and 80% Seroconversion Thresholds

According to the best-fitting model, the estimated age at which 50% of children had seroconverted was < 10 years in 12 of 13 countries in our analysis; the youngest was in the Philippines (1.6 years; 95% CI, 1.4–3.1, Table 3). In Singapore, a seroprevalence of 50% was not reached within the range of our observed data, by age 18 years (Table 2). An 80% seroprevalence threshold was reached by the age of 18 years in 10 countries, 3 of which reached this threshold by the age of 9 years (Philippines, Colombia, and Honduras).

Forty-six sites were included in the site level analysis. We estimated 80% of children had been infected by age 18 years (ie, within the range of our observed data) at 35 (76%) sites and by age 9 years at 14 (30%) sites (Figure 3). The youngest estimated age at which 80% of children seroconverted was 5.3 years, observed at Casanare, in Colombia. At least 50% of children were estimated to have seroconverted by the age of 18 years at 44 (96%) sites, and at all 15 sites in Latin America (Supplementary Figure 1). In Kalyani (West Bengal, India), median seroprevalence was not reached. Seroprevalence at age 9 was also high at other sites, notably across Indonesia (Supplementary Table 2). Within countries, there was considerable variation between sites in the age at which 50% and 80% of children seroconverted (Figure 3).

Table 2. Constant and Age-Varying FOI Estimates for Each Country

Country	Constant FOI (95% CI)	Age-Varying FOI (95% CI)	Corresponding Age Range, y	Better Fit[a]
India	11.9 (8.7–16.2)	10.7 (6.9–14.4) 20.0 (10.7–29.4)	5–6 7–18	Constant
Indonesia	14.7 (12.8–16.9)	15.1 (13.1–17.1) 4.1 (−3.9 to 12.2)	1–13 14–18	Constant
Malaysia	8.6 (6.7–10.9)	12.2 (11.3–13.1) 4.7 (−0.2 to 9.6)	2–3 4–14	Constant
Philippines	24.1 (21.8–26.5)	42.6 (35.4–49.7) 13.5 (10.1–16.9)	0–1 2–14	Age-varying
Singapore	1.7 (1.4–2.2)	6.6 (4.0–9.2) −0.8 (−2.0 to 0.3)	2–3 4–18	Age-varying
Thailand	14.8 (13.7–16.0)	16.4 (15.0–17.9) 8.7 (6.6–10.9)	2–6 7–14	Age-varying
Vietnam	11.4 (10.2–12.8)	17.3 (16.5–18.1) 5.4 (3.8–7.0)	2–3 4–18	Constant
Brazil	10.7 (7.7–14.8)	9.2 (5.6–12.9) 23.1 (20.3–25.9)	8–10 11–16	Constant
Colombia	18.4 (14.2–23.7)	18.7 (13.1–24.3) 9.9 (−25.9 to −45.8)	0–12 13–16	Constant
Honduras	17.5 (15.6–19.7)	17.8 (14.8–20.8) 15.1 (1.8–32.1)	9–10 11–16	Constant
Mexico	7.1 (5.1–9.8)	7.7 (4.8–10.5) −0.2 (−8.6 to 8.1)	0–11 12–16	Age-varying
Peru	9.2 (8.0–10.7)	13.2 (10.2–16.2) 4.5 (1.7–7.2)	0–2 3–11	Constant
Puerto Rico	8.4 (7.2–9.9)	8.8 (7.1–10.5) 2.8 (−13.3 to 18.8)	9–13 14–16	Age-varying

Abbreviations: CI, confidence interval; FOI, force of infection; RMSE, lower root mean squared error.

[a]For each country the better model fit was assigned based on the lower RMSE.

DISCUSSION

We analyzed data from over 13 000 children to describe dengue transmission intensity at 46 geographically distinct, endemic sites in 13 countries in Asia and Latin America. Study subjects were in age groups likely to seroconvert, providing the necessary variation in seroprevalence to estimate FOI. Dengue serological status was confirmed with gold-standard diagnostics and consistent analyses were used to make comparisons across countries and sites.

Across the age ranges sampled, children at most sites were at high risk of dengue infection, with FOI exceeding 7% in all countries except Singapore. Countries with higher levels of transmission included the Philippines, Colombia, Honduras, Indonesia, and Thailand, in which ≥ 14% of seronegative children were infected each year. In these countries, intense dengue exposure results in a steep reduction in dengue-naive individuals early in life, providing a large pool of individuals at risk of secondary infection. While these data describe the force of primary (ie, first) dengue infections, these transmission intensities would translate, at the population level, to a significant burden of secondary infections, which are more likely to be symptomatic and severe. Malaysia and Singapore had lower transmission than other Asian countries, which could be an indication of improvements in dengue control measures.

Age-varying models were developed to assess whether clear variation in infection risk was observed as children aged. Strong evidence for this variation was lacking; seroprevalence estimates from constant and age-varying models were broadly similar and differences in cross-validation errors from different models were small (Supplementary Table 3). However, in age-varying models transmission intensity was more frequently (11 out of 13 countries) higher in younger children, perhaps indicating their increased exposure to infectious mosquito bites. In Singapore, FOI declined for a significant proportion of the study sample (children aged > 3 years), a finding which is biologically counter intuitive. This is possibly a consequence of intensive and effective vector control activities and behavior that minimizes exposure to infectious bites (eg, use of air conditioning) resulting in low seroprevalence throughout childhood. Singapore also tends to experience severe, cyclical epidemics and a recent large outbreak could result in higher seroprevalence in younger than older children. For example, there was a large outbreak in late 2005, approximately 4 years before study subjects were bled, and if young children were disproportionately infected this could give the impression of declining FOI [25].

According to WHO guidelines, an overall population benefit of dengue vaccination with CYD-TDV dengue vaccine can be expected in very high transmission settings, as defined by

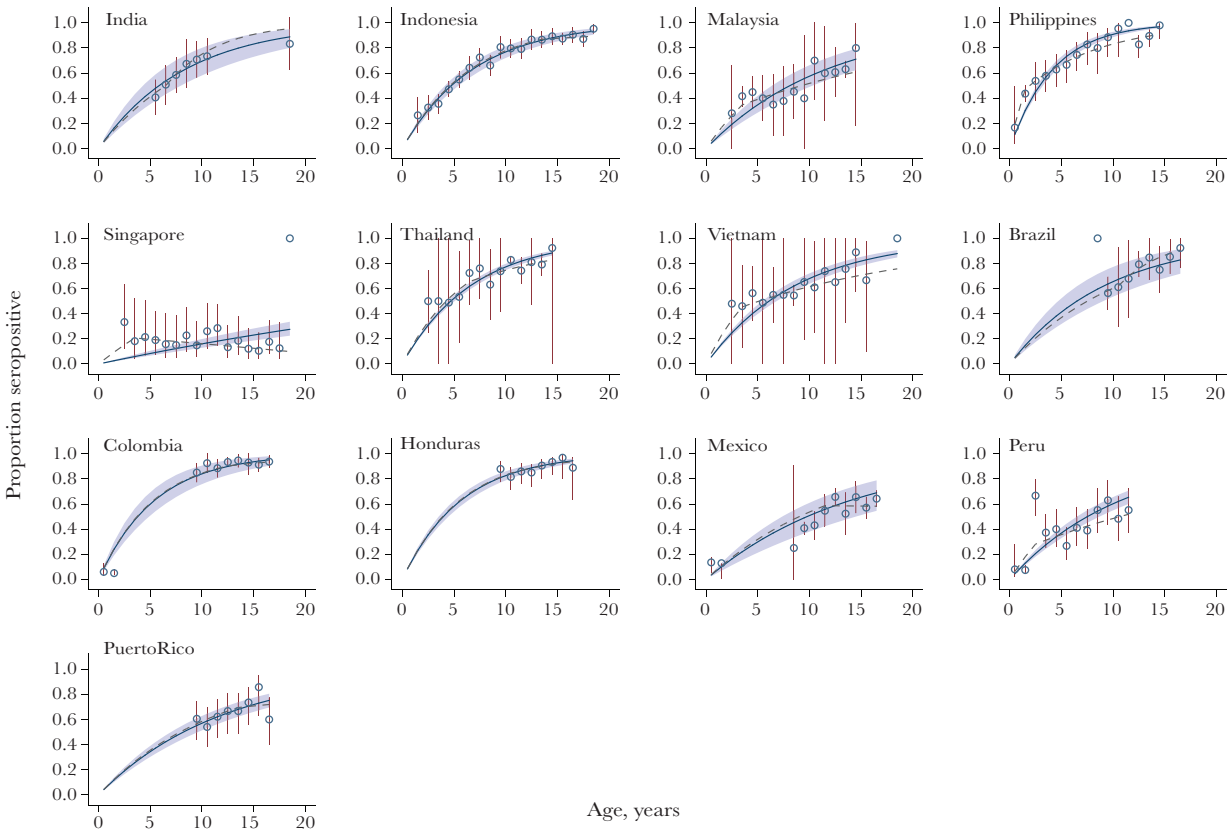

Figure 2. Observed seroprevalence by age (circles) and 95% confidence interval (CI), adjusted for clustering (spikes) and estimate seroprevalence assuming constant force of infection (FOI) (solid line) and 95% CIs (shaded area). Dotted lines correspond to estimated seroprevalence under an assumption of age-varying FOI.

seroprevalence of ≥ 80% in subjects aged 9 years of age or older, noting that such areas are rare [18]. Here, we estimated that 14 of 46 (30%) sites met this criterion: 1 in Brazil, 1 in Honduras, 4 in Colombia, 1 in India, 6 in Indonesia, and at the only site included from the Philippines. These data represent transmission levels when blood samples were drawn, several years ago, but indicate several sites may benefit from dengue vaccination at the population level.

Another objective of this analysis was to understand variability in endemicity within countries because few multisite

Table 3. Ages at Which 50% and 80% of Children Become Dengue Seropositive, Per Country, Using Constant or Age-Varying Models

	Median Age at Seroconversion, y (95% CI)		80th Percentile Age at Seroconversion, y (95% CI)	
Country	Constant Model	Age-Varying Model	Constant Model	Age-Varying Model
India	**5.8 (5.5–6.1)**	6.5 (6.0–6.9)	**13.5 (12.8–14.3)**	11.1 (8.8–17.4)
Indonesia	**4.7 (4.5–4.9)**	4.6 (4.4–4.8)	**11.0 (10.5–11.5)**	10.6 (10.1–11.2)
Malaysia	**8.1 (7.1–9.2)**	9.2 (5.9–>18)	**18.8 (16.6–21.3)**	>18
Philippines	2.9 (2.6–3.2)	**1.6 (1.4–3.1)**	6.7 (6.1–7.4)	**8.7 (6.6–12.2)**
Singapore	>18	**>18**	>18	**>18**
Thailand	4.7 (4.2–5.2)	**4.2 (3.7–4.9)**	10.9 (9.8–12.0)	**12.7 (0.0–40.2)**
Vietnam	**6.1 (5.5–6.8)**	5.1 (4.3–6.5)	**14.1 (12.7–15.7)**	>18
Brazil	**6.5 (5.8–7.3)**	7.5 (6.4–9.1)	**15.1 (13.4–17.0)**	13.3 (11.9–17.4)
Colombia	**3.8 (3.5–4.1)**	3.7 (3.4–4.1)	**8.8 (8.1–9.5)**	8.6 (7.9–9.4)
Honduras	**4.0 (3.5–4.5)**	3.9 (3.3–4.7)	**9.2 (8.2–10.3)**	9.0 (7.7–10.9)
Mexico	9.8 (8.8–10.9)	**9.0 (8.0–10.4)**	>18	**>18**
Peru	**7.5 (6.5–8.7)**	10.6 (6.5–28.8)	**17.4 (15.1–20.2)**	>18
Puerto Rico	8.2 (7.0–9.6)	**7.9 (6.6–9.8)**	>18	**>18**

Best-fitting models are highlighted in bold.

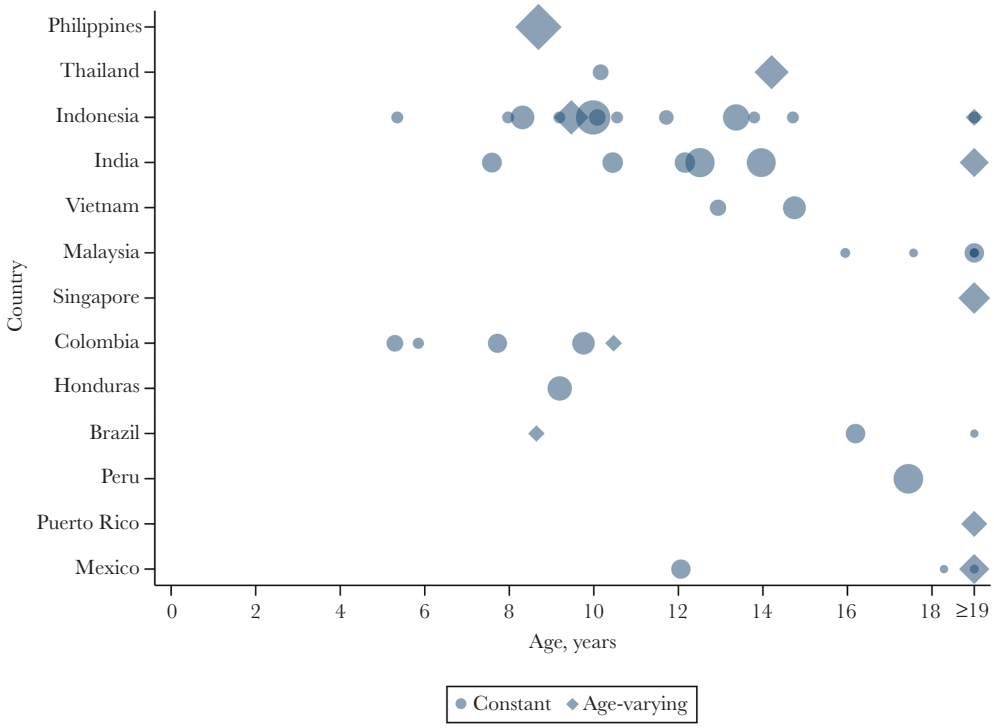

Figure 3. Age of 80% seroconversion by site, estimated from best-fitting constant (circles) or age-varying (diamonds) models. Symbol size corresponds to frequency weights. ≥19 signifies estimates were outside the range of our data.

dengue seroprevalence studies have been conducted. We identified significant variability within the same country: for example, in Indonesia, the median age of first infection varied between sites from 2.3 to 10.1 years, and in Brazil this varied from 3.7 to 11.4 years. We did not have data from multiple sites in all countries but this implies site-specific seroprevalence assessments would be needed prior to dengue vaccine introduction without prior serotesting, and such data would be useful to prioritize areas where vaccination would be most efficient [18]. However, few observed seroprevalence data points fell outside the confidence intervals of our estimated seroprevalence and statistical approaches such as this, accounting for uncertainty, could be considered complementary to empirical seroprevalence studies in endemic countries [13].

Our analysis was confined to exploring FOI and seroprevalence as a function of age but, because dengue is a cyclical, epidemic disease, calendar time is another, and perhaps more plausible, explanation for observed variation in FOI, as observed elsewhere [26]. Our study precluded detailed analysis of the effect of time on FOI; although data were available for more than 1 time point in some countries, samples for most countries were collected within a 2-year timeframe. While higher FOI in younger age groups is a finding compatible with higher transmission intensity in more recent years, we could not explore specific and granular cohort effects. Future studies would be needed to shed further light on the contributions of age, time, and geography to variations in dengue endemicity. Another limitation of our analysis is that many of our datasets were collected for the purposes of clinical research rather than as part of geographically representative surveys. These clinical trials, from which 58% of our data were collected, often targeted areas of high dengue endemicity, cannot be considered nationally representative, and, in countries where endemicity is heterogeneous, likely represent populations with higher-than-average exposure. This is especially relevant for Latin American countries where dengue is not endemic nationwide; for example, in Columbia and Mexico significant proportions of the population live in areas where the disease does not circulate [27].

The models used for FOI estimation impose certain constraints; notably, the power of age-varying models to detect a meaningful breakpoint is partly dependent on the age range of the data, which varies between countries. We confined the analysis to single breakpoints corresponding to whole years of age and to years with > 2 years of adjacent data, which is a simplistic design, prohibiting additional flexibility. Comparisons between countries on this point should therefore be made with caution. Akaike's information criterion was used to identify optimal (constant vs age varying) models for each country but in many cases both models fit the data well and we identified only weak evidence for age-varying effects.

All 4 dengue serotypes circulate in most of these countries [28] and we calculated only total (or average) dengue FOI,

assuming this is relatively stable over time, without more granular or serotype specific variation. In fact, dengue epidemiology is characterized by cyclical introductions of different serotypes giving rise to outbreaks, as elegantly demonstrated in an extremely thorough longitudinal serological analysis from the city of Iquitos in Peru [26, 29]. The authors demonstrated high attack rates following the introduction of new serotypes into naive populations of up to 89 infections/100 person-years and accompanying high, time-varying, serotype-specific FOI fluctuating across time and serotypes. From our samples, over 90% tested by $PRNT_{50}$ showed evidence of infection with > 1 serotype (possibly due to cross-reaction rather than true infection) and calculation of meaningful serotype-specific FOI estimates was therefore not possible without making unreliable assumptions from PRNT titers. Because total FOI has been shown to approximate the sum of serotype-specific FOI [10], we considered the approach was reasonable, and more complex modeling activities would be needed to further understand serotype-specific transmission dynamics. Our data should be considered representative of long-term average dengue exposure rates.

The infection history of around 40% of samples was determined by IgG ELISA. In concordance experiments, we found 97% of IgG-positive samples were $PRNT_{50}$ positive, providing a high level of confidence in the specificity of these tests but it was not possible from our dataset to assess sensitivity of the IgG vs PRNT.

We also did not consider the impact of other flavivirus infections but in dengue-endemic areas we considered positive dengue diagnostic results, confirmed by PRNT, to be definitive. Approximately 45% of samples came from India and Indonesia, countries in which large dengue seroprevalence studies had been conducted and the proportions of children in Asian studies were higher than in Latin America, which could affect statistical power.

Nonetheless, these data provide one of the largest dengue seroprevalence analyses performed, provide epidemiological information across endemic countries, can be used to guide public health decision-making, including the benefits/risks of vaccination, and inform health economic analyses.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Data availability. Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

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Potential conflicts of interest. J. N., A. B., M. C., C. F., L. C., and D. M. are or have been employees of Sanofi Pasteur, a company which makes a dengue vaccine. J. N., C. F., and D. M. own Sanofi shares. Sanofi Pasteur staff were involved in all aspects of data collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. C. C. T. has no conflicts of interest to declare. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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