REVIEW

Dengue seroprevalence: data from the clinical development of a tetravalent dengue vaccine in 14 countries (2005–2014)

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Dengue seroprevalence data in the literature is limited and the available information is difficult to compare between studies because of the varying survey designs and methods used. We assessed dengue seropositivity across 14 countries using data from 15 trials conducted during the development of a tetravalent dengue vaccine between October 2005 and February 2014. Participants' dengue seropositivity (n=8592) was determined from baseline (before vaccination) serum samples at two centralized laboratories with the plaque reduction neutralization test (PRNT$_{50}$). Seropositivity rates generally increased with age in endemic settings. Although seropositivity rates varied across geographical areas, between countries, and within countries by region, no major differences were observed for given age groups between the two endemic regions, Latin America and Asia-Pacific. Seropositivity rates were generally stable over time. The proportion of participants who had only experienced primary infection tended to be higher in younger children than adolescents/adults. These results will help inform and guide dengue control strategies in the participating countries.

Keywords: Dengue, PRNT, Seropositivity, Seroprevalence

Introduction

Dengue, a mosquito-borne viral disease, has rapidly spread across the tropical and subtropical regions of the world in recent decades. The disease is considered to be endemic and a major public health concern in over 120 countries in the Asia–Pacific region, Africa, and Latin America (including the Caribbean).[1] Worldwide, an estimated 390 million dengue infections occur every year, of which around 100 million are associated with clinical manifestations and the remainder asymptomatic.[2] Clinical manifestations range from mild febrile illness to severe disease requiring hospitalization and, in some cases, leading to fatalities.[3] There are four genetically divergent dengue virus serotypes with antigenic differences.[4] Infection with one serotype is generally believed to produce durable, even life-long, homotypic immunity against that same serotype, but generates initial partial and transient cross-protection against the other serotypes, allowing sequential dengue infections with other serotypes in an individual.[5]

Although dengue is a notifiable disease in many countries, constraints inherent in public health surveillance systems and challenges specific to dengue do not allow dengue cases to be fully captured.[6–8] These constraints and challenges are related to the non-specific nature and wide spectrum of dengue illness, and in part, to the lack of uniform case definitions, diagnostic ascertainment, laboratory capabilities and capacity, as well as a reliance on diverse public health practices and healthcare professionals for disease notification.[9] Consequently, the true number of dengue cases is probably substantially underreported.[10] Moreover, variability in underreporting both within and between countries[11,12] affects the interpretation and comparability of the disease profile and rates from different public health surveillance systems.

As there is a large reservoir of undetected dengue infections, asymptomatic and underreported cases, serological data are essential in determining the true extent of dengue exposure, and the role of both symptomatic and asymptomatic infections in dengue transmission dynamics.[13,14] Recent WHO SAGE recommendations and a subsequent WHO position paper on dengue suggested that seroprevalence data could be used to help define age groups and populations for dengue vaccination with the licensed Sanofi Pasteur's live, attenuated, tetravalent dengue vaccine (CYD-TDV).[15,16] However, robust age-stratified seroprevalence data are sometimes not available, or if available, generated with non-standardized laboratory methods,[17] which makes generalization or comparison of the limited available data beyond the locality where the data were gathered questionable.

Enzyme-linked immunosorbent assays (ELISAs) for anti-dengue IgG or IgM antibodies are widely used to assess dengue seroprevalence. These have several limitations including cross-reactivity with other flaviviruse, such as yellow fever, Japanese encephalitis and Zika, and their inability to distinguish between the different infecting serotypes.[18] The plaque reduction neutralization test (PRNT) is a sensitive and specific test for detecting neutralizing antibodies against dengue. It is also the recommended test for assessing immunogenicity in dengue vaccine trials.[19,20] However, the PRNT is costlier and technically more demanding than ELISA assessment and, as such, is typically not used for routine surveillance purposes.

The $PRNT_{50}$[20] was extensively used during the clinical development of the Sanofi Pasteur's CYD-TDV to determine baseline dengue serostatus and vaccine immunogenicity. Here we present an unprecedented summary of dengue seropositivity data across a range of age groups, countries and time periods, based on pre-vaccination $PRNT_{50}$ data from trials undertaken with CYD-TDV.

Materials and methods

Studies and study participants

During the development of CYD-TDV, between October 2005 and February 2014, 24 trials were undertaken across 15 countries. Enrolled participants were healthy and within the age range 12 months to 60 years (Table 1). Studies that excluded participants based on their baseline dengue status (assessed or self-reported; n=7) were excluded from the current analysis to limit selection bias. Two additional studies were excluded because of database incompatibility; CYD01 and CYD02 (the earliest studies) were excluded because their databases were in a different 'older format' that was not compatible with that used in the other databases for the latter studies. Therefore, our analysis was based on data from 15 studies across 14 countries (Table 1). Participants were excluded from the selected studies if they had febrile illness within the 7 days preceding inclusion, congenital or acquired immunodeficiency, or had received another vaccine in the 4 weeks before inclusion. Other specific inclusion and exclusion criteria have been described in the corresponding publications (citations listed in Table 1).

All studies included in our analysis were performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization—Good Clinical Practice. Study protocols and amendments were approved by the individual review board/independent ethics committee for each participating site. All participants or their parents/guardians provided informed written consent.

Laboratory tests

The participants' dengue serostatus was assessed at baseline using a validated $PRNT_{50}$[20] according to World Health Organization guideline recommendations.[19] For the phase I studies, several challenge viruses were considered for each serotype, before one of each serotype was selected for subsequent $PRNT_{50}$ use in phase II/III studies. Only results obtained with similar challenge viruses (i.e. DENV-1 strain PUO-359, DENV-2 strain PUO-218, DENV-3 strain PaH881/88 and DENV-4 strain 1228) in phase I through to phases II and III are included in our report. Titers were calculated and expressed as the highest reciprocal serum dilution (1/dil) that reduced the mean plaque count by 50% compared with the virus input control.[20,41] The detection threshold for the assay was a neutralizing antibody titer of 1:10 dil. The $PRNT_{50}$ was performed in two different laboratories: Sanofi Pasteur's Global Clinical Immunology laboratory (Swiftwater, PA, USA) and the Center for Vaccine Development at Mahidol University (Bangkok, Thailand). Both sites followed the same protocols and concordance was established between the two sites.

Dengue seropositivity was defined as $PRNT_{50}$ titer $\geq$10 1/dil to at least one serotype. Primary dengue infection was defined as $PRNT_{50}$ titer $\geq$10 1/dil to only one dengue virus serotype (i.e. a monotypic $PRNT_{50}$ profile).[42]

Statistical methods

All analyses were descriptive. Outcomes of interest were dengue seropositivity and the proportion of participants who had only experienced primary infection. We assumed that the proportion of participants seropositive for only one serotype would approximate to the primary dengue infection rate. These outcomes were described in terms of the number and percentage of participants, overall and by age group, and by country and study. Age groups defined for the analyses were <2 years, 2–8, 9–17, 18–45 and $\geq$46 years. Binomial approximation from the Clopper–Pearson method was used to calculate 95% CI.[43] Analyses were carried out using Stata v14 statistical software (StatCorp LP, College Station, TX, USA) or R statistical package v3.2.0 (R Development Core Team, Vienna, Austria).

Results

Study participant characteristics

Data for the <2-year age group were available for the Philippines, Mexico, Peru and Colombia. Data for both the 2–8- and 9–17-year age groups were available for several Asia–Pacific (the Philippines, Thailand, Vietnam, Malaysia, Indonesia and Singapore) and Latin American countries (Mexico and Peru); for 9–17-year-olds, data were additionally available for Colombia, Puerto Rico, Brazil and Honduras. Data for the 18–45-year age

Table 1. Summary of studies from the clinical development of the live, attenuated, tetravalent dengue vaccine that were considered for inclusion in this integrated summary; those excluded are highlighted as 'not included' in the Analyses column. The reason for exclusion of some studies from the current analysis (n=7) was to limit selection bias because these recruited participants were based on their baseline dengue status (assessed or self-reported) and thus, not representative of their respective populations in their countries.

Study (CYD ID)	Immunosubset (planned)	Immunosubset (analysed)	Country	City/ municipality	Age group	Screening period	Study design	Analyses	References
CYD01	56	56	USA	Springfield	18–49 y	03/2002–06/2002	Mono	Not included	Guirakhoo et al. *Hum Vaccin* 2006[21]
CYD02	99	99	USA	Springfield	18–40 y	11/2003–11/2004	Mono	Not included	Data on file
CYD04	66	66	USA	Springfield	18–45 y	10/2005–02/2007	Mono	Included	Morrisson et al., *J Infect Dis*, 2010[22]
CYD05	126	126	Philippines	Muntinlupa	2–45 y	03/2006–10/2007	Mono	Not included	Capeding et al., *Vaccine*, 2011[23]
CYD06	126	126	Mexico	Tlalpan Valle del Chalco	2–45 y	01/2006–08/2007	Mono	Included	Poo et al., *Pediatr Infect Dis J* 2011; 30(1):e9–e17
CYD08	222	222	Philippines	San Pablo	12–15 m	01/2010–01/2012	Mono	Included	Crevat et al., *Pediatr Infect Dis J*, 2015[24]
CYD10	35	35	Australia	Adelaide	18–40 y	08/2006–03/2007	Mono	Not included	Qiao et al. *Am J Trop Med Hyg* 2011[25]
CYD11	155	155	Mexico	Tlalpan Valle de Chalco	18–45 y	08/2008–11/2008	Multi	Not included	Dayan et al., *Hum Vaccin Immunother*, 2014[26]
CYD12	260	260	USA	New Orleans San Diego Springfield Alabaster Vallejo	18–45 y	04/2008–14/2009	Multi	Included	Dayan G et al., *Vaccine*, 2013[27]
CYD13	600	600	Colombia Honduras Mexico Puerto Rico	Bucaramanga Tegucigalpa Temixco Carolina	9–16 y	10/2009–02/2010	Multi	Included	Villar et al., *Pediatr Infect Dis J*, 2013[28]
CYD14	2000	1994	Indonesia Malaysia Philippines Thailand Vietnam	Jakarta Bali Bandung Kuala Lumpur Penang San Pablo City Cebu City Ratchaburi Kampang Phae My Tho Long Xuyen	2–14 y	06/2011–12/2011	Multi	Included	Capeding et al., *Lancet*, 2014[29]

Continued

Table 1. *Continued*

Study (CYD ID)	Immunosubset (planned)	Immunosubset (analysed)	Country	City/ municipality	Age group	Screening period	Study design	Analyses	References
CYD15	2000	1995	Brazil Colombia Honduras Mexico Puerto Rico	Vitória Natal Goiania Campo Grande Fortaleza Yopal Aguazul Acacias Girardot La Tebaida Armenia Calarcá Bucaramanga Tegucigalpa Temixco Veracruz Tamaulipas Tizimin Valladolid San Juan Guayama	9–16 y	06/2011–03/2012	Multi	Included	Villar et al., *N Engl J Med*, 2014[30]
CYD17	715	712	Australia	Enoggera Westmead Herston Carina Heights Adelaide Subiaco Heidelberg	18–60 y	10/2010–06/2012	Multi	Not included	Torresi et al., *Vaccine*, 2015[31]
CYD22	252	252	Vietnam	Ho-Chi Minh	2–45 y	03/2009–07/2009	Mono	Included	Tran et al., *J Vaccines Vaccin*, 2012[32]
CYD23	299	299	Thailand	Ratchaburi	4–11 y	02/2009–02/2010	Mono	Included	Sabchareon et al., *Lancet*, 2012[33]
CYD24	367	367	Peru	Piura	2–11 y	09/2008–02/2009	Mono	Included	Lanata et al., *Vaccine*, 2012[34]
CYD28	585	585	Singapore	Singapore	2–45 y	04/2009–10/2009	Multi	Included	Leo et al., *Hum Vaccin Immunother*, 2012[35]
CYD29	786	784	Colombia Peru	Cali Lima	12–13 m	09/2011–09/2013	Multi	Included	Lopez et al., *Pediatr Infect Dis J*, 2016[36]
CYD30	150	150	Brazil	Vitória	9–16 y	08/2010–10/2010	Multi	Included	Dayan et al., *Am J Trop Med Hyg*, 2013[37]

Table 1. *Continued*

Study (CYD ID)	Immunosubset (planned)	Immunosubset (analysed)	Country	City/ municipality	Age group	Screening period	Study design	Analyses	References
CYD32	250	250	Malaysia	Kuala Lumpur Perak Negeri Sembilan Sarawak	2–11 y	12/2010–08/2012	Multi	Included	Amar-Singh et al., *Vaccine*, 2013[38]
CYD33	714	714	Mexico	Mérida Acapulco Monterrey	9–12 mm	07/2011–06/2013	Multi	Included	Rodriguez et al., *Pediatr Infect Dis J*, 2017[39]
CYD47	188	188	India	New Delhi Pimpri Ludhiana Bangalore Kolkata	18–45 y	03/2012–02/2014	Multi	Included	Dubey et al., *Hum Vaccin Immunother*, 2015[40]
CYD51	390	390	USA	Springfield Las Vegas Jacksonville Hoover Mile Fort Detrick	18–45 y	12/2012–11/2013	Multi	Not included	Kirstein et al., Submitted for publication

mono, single-center; multi, multi-center.
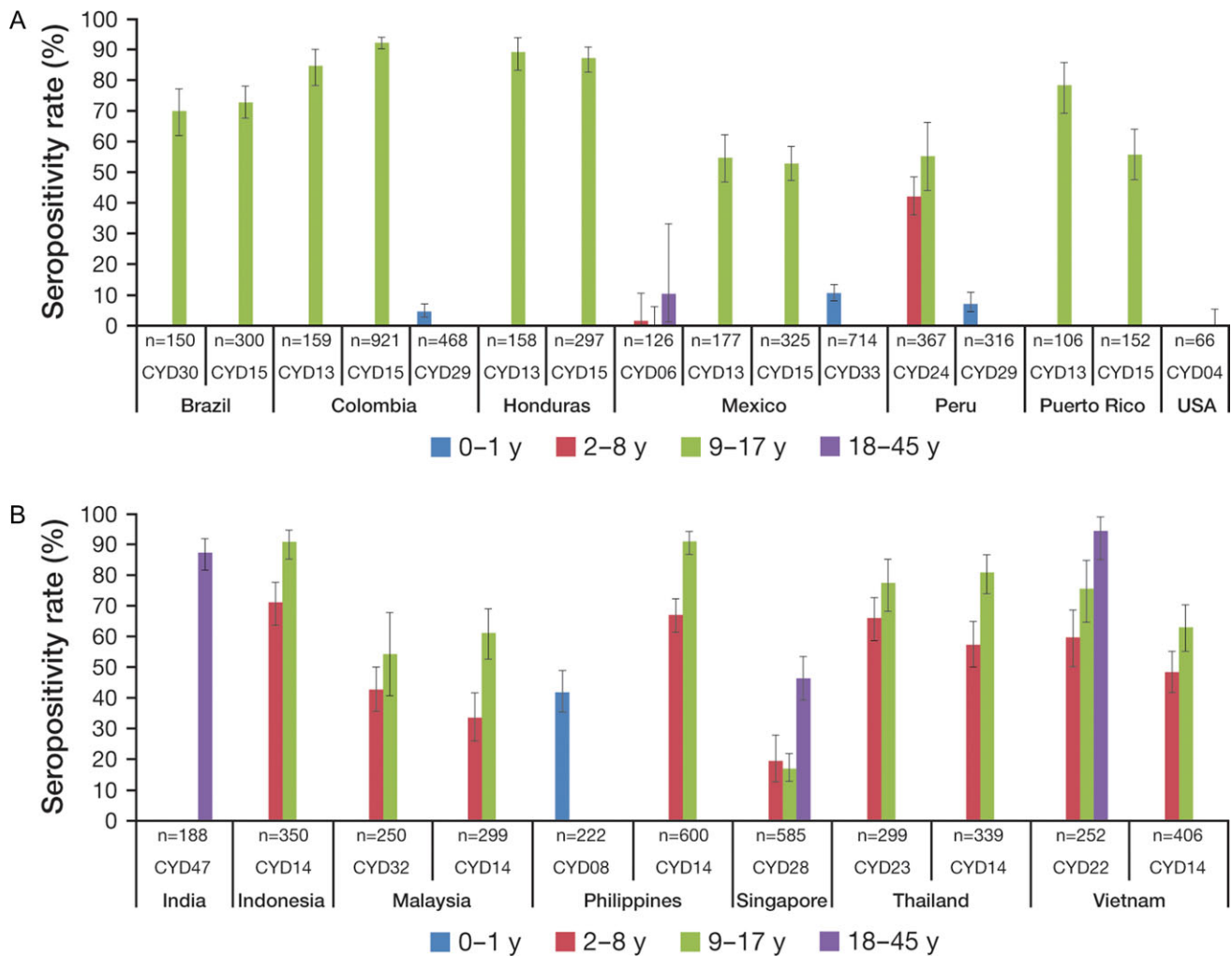
Figure 1. Seropositivity rate (as determined with the $PRNT_{50}$) and 95% CI at baseline in studies conducted in A) six Latin American countries and the USA, and B) seven Asia-Pacific countries. n, total number of tested samples.

group were available for Vietnam, Singapore, India, Mexico and the USA.

Sex ratio (male to female) was generally balanced except in Puerto Rico (in the CYD13 study, 0·6:1), India (CYD47, 4·2:1) and the USA (CYD04, 0·3:1). Baseline participant demographic characteristics are shown for each included study by country in supplementary Table S1.

Seropositivity rates

Data were obtained from 8592 participants overall. Seropositivity rates as measured by $PRNT_{50}$ are shown by country, study and age group in Figure 1 and supplementary Table S2.

The Americas

Baseline seropositivity rates and 95% CIs for participants in studies undertaken in the Americas are summarized in Figure 1 (A). Three studies conducted in three different countries enrolled

young children, aged <2 years, with seropositivity rates below 11%. Two studies included data for 2–8-year-olds: Mexico in 2006 (CYD06) and Peru (Piura city) in 2008 (CYD24), with seropositivity rates of 2% and 42.6%, respectively. Most of the available data pertained to 9–17-year-olds (five studies in six countries). Seropositivity rates in this age group were relatively high, excluding the USA; these ranged from 53.1% in Mexico in 2011 (CYD15) to 92.4% in Colombia 2011 (CYD15).

In Mexico, variations in baseline seropositivity were observed across studies. The baseline seropositivity rate among participants in the CYD06 study conducted in Mexico City's metropolitan area (Tlaplan and Valle del Chalco municipalities) in 2006 was low at 2.4%, which contrasted with the higher rates in other Mexican states in 2009 (Morelos, Mexico and Veracruz in CYD13) and 2011 (Morelos, Yucatan, Tamaulipas and Veracuz in CYD15), reported at 54.8% and 53.1% in the two studies, respectively, in the 9–17-year age group.

In countries where different studies were conducted over different time periods in similar age-groups, seropositivity rates were generally not significantly different (overlapping 95% CI)

between the years considered (in 9–17-year-olds in Brazil in 2010 and 2011, in Honduras in 2009 and 2011, in Mexico in 2009 and 2011). However, seropositivity rates in the 9–17-year age group increased between 2009 (CYD13) and 2011 (CYD15) in Colombia (2009: 84.6% [95% CI: 78.4–90.1]; 2011: 92.4% [95% CI: 90.5–94.0]) and decreased in Puerto Rico (CYD13 in 2009: 78.3% [95% CI: 69.2–85.7] vs CYD15 in 2011: 55.9% [95% CI: 47.6–64.0]).

In the 18–45 years age group, low baseline seropositivity rates (10.5% [95% CI: 1.3–33.1]) were reported in Mexico in 2006 (CYD06) as the study was conducted in the non-dengue-endemic area of Mexico City. The seropositivity rate in this age group in the study in the USA in 2005 (CYD04) was 0%.

Asia–Pacific countries

Baseline seropositivity rates and 95% CI for participants in studies undertaken in the Asia–Pacific countries are summarized in Figure 1(B). In the one study that included participants aged <2 years the seropositivity rate reported was 42.3% [in the Philippines in 2010 (CYD08)]. Five studies included data for 2–8-

year-olds and 9–17-year-olds in six different countries. In 2–8-year-olds, seropositivity rates ranged from 19.8% in Singapore in 2009 (CYD28) to 72.7% in Indonesia in 2011 (CYD14). In 9–17-year-olds, these ranged from 17% in Singapore in 2009 (CYD28) to 91.3% in Indonesia in 2011 (CYD14).

In Malaysia, the Philippines and Vietnam, two different studies were conducted at different time periods in similar age-groups (2–8- and 9–17-year-olds); here also the 95% CI of the seropositivity rates overlapped, indicating no significant differences between the different years considered.

There were three studies in the 18–45-year age group, seropositivity rates were high in Vietnam (94.5% in 2009 [CYD22]) and India (87.2% in 2012 [CYD47]), with lower rates observed in Singapore (48.7% in 2009 [CYD28]).

Proportion of participants who had only experienced primary infection

In studies with data available for both the 2–8 and 9–17-year age groups, the proportion of participants who had only
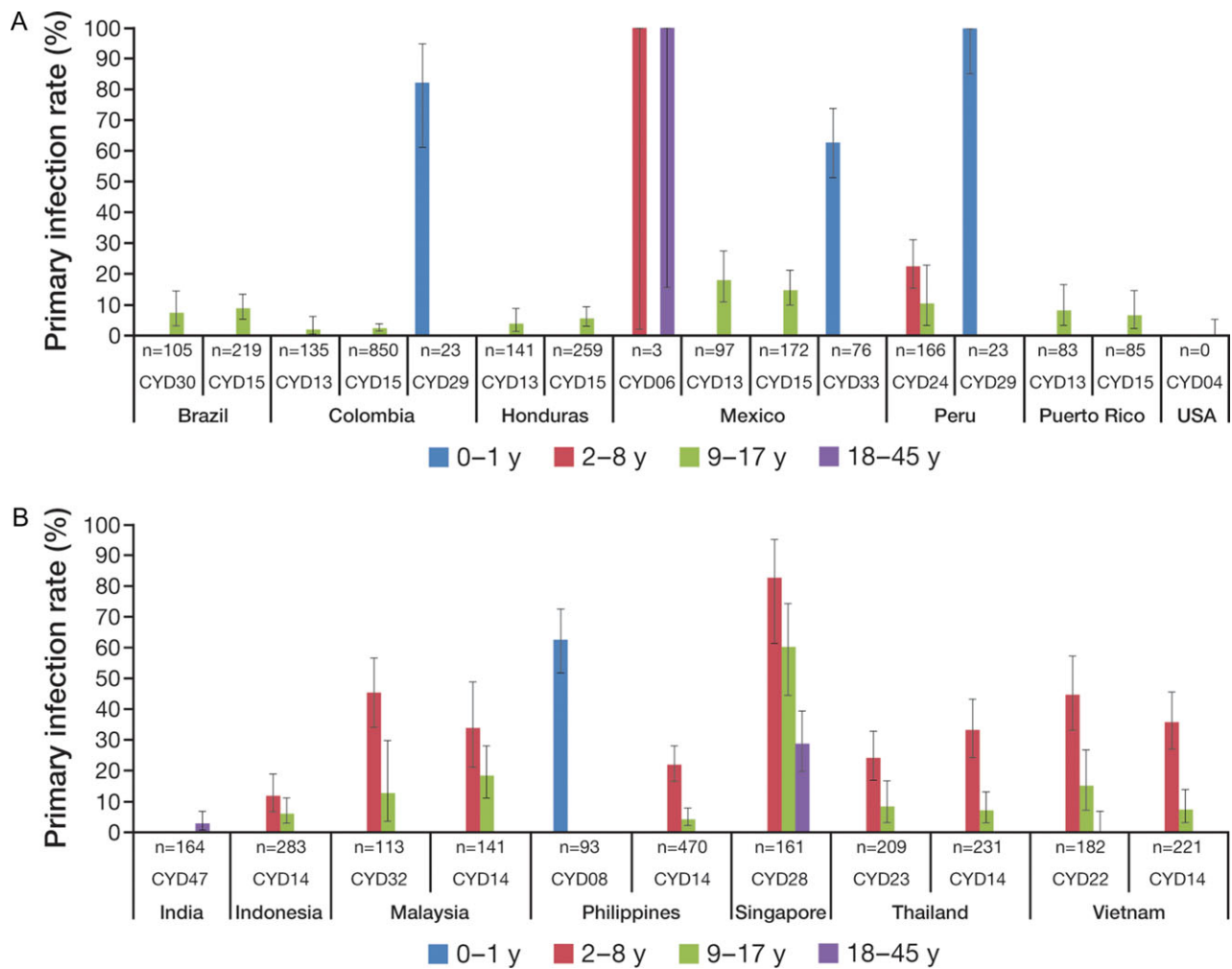

Figure 2. Proportion of participants who had only experienced primary infection (as determined with the PRNT$_{50}$) and 95% CI at baseline in studies conducted in (A) six Latin American countries and the USA, and (B) seven Asia-Pacific countries. n, total number of tested samples.

experienced primary infection was higher in the younger age groups in Peru (22.7% vs 10.6% [CYD24]), the Philippines (22.2% vs 4.6% [CYD14]), Thailand (24.4%–8.5% [CYD23]; and 33.3% vs 7.1% [CYD14]), Vietnam (45.1% vs 15.2% [CYD22]; 36.0% vs 7.5% [CYD14]), Malaysia (45.1% vs 12.9% [CYD32]; 34.0% vs 18.7% [CYD14]), Indonesia (12.0% vs 6.3% [CYD14]) and Singapore (82.0% vs 60.0% [CYD28]; Figure 2 and supplementary Table S3). These proportions remained stable over time (2009 vs 2011) for the same age groups, in Vietnam (22.5% [95% CI: 16.7–29.3] vs 22.2% [95% CI: 16.9–28.2]; CYD22 vs CYD14), Thailand (18.2% [95% CI: 13.2–24.1] vs 19.0% [95% CI: 14.2–24.7]; CYD23 vs CYD14) and Malaysia (36.3% [95% CI: 27.4–45.8] vs 24.1% [95% CI: 17.3–32.0]; CYD32 vs CYD14). Among infants and toddlers (aged <2 years), the proportion who had only experienced primary infection ranged from 62.4% in the Philippines (CYD08) to 82.6% in Colombia (CYD29). In adults, the proportion who had only experienced primary infection, where available, was mostly low (Vietnam: 0% [CYD22], India: 3.0% [CYD47]), except in Singapore where the proportion was 29.0% (CYD28) among 18–45-year-olds (Figure 2B).

Discussion

We determined underlying dengue seropositivity rates in populations encompassing a wide age range, across multiple geographical locations with varying dengue endemicity and temporal settings, using $PRNT_{50}$ data that were determined at two concordant centralized laboratories following the same validated methodology. We showed that seropositivity rates generally increased with age in endemic settings as a result of cumulative exposure over time. In addition, seropositivity was variable across geographical areas, from one given country to another, but also within a country by locality. However, no major differences were observed for given age groups between the two endemic regions, Latin America and Asia-Pacific, with the exception of Singapore, where lower seropositivity rates were observed in general, relative to other countries in the region. Seropositivity rates were also generally stable over time, where data were available.

Transmission intensity and history of primary infection among populations varied both between and within countries. This phenomenon may have been amplified in our analysis as countries were selected for participation depending on the purpose of the studies to include either low/non endemic (e.g. USA) or endemic areas (e.g. Latin America and Asia-Pacific). Interestingly, some countries like Mexico have regions with different endemicity—the CYD06 study was conducted in an area with very low dengue transmission (Mexico City's Metropolitan area, at 2240 m above sea level on average and thus with a low vector density), while CYD15 was conducted in highly endemic regions of Mexico. As well as geographic factors, urbanization and the quality of sanitary infrastructures may also have an impact on the extent of vector infestation and, hence, viral circulation. Differences in vector control policies may also contribute to variability in transmission intensities between countries. For example, in the current analysis, we observed lower seropositivity rates in Singapore where effective control measures have been launched,[44] compared with other Asian countries.

Conversely, several studies did not find an association between vector indices and dengue seroprevalence.[45,46]

Dengue virus has circulated in the Asia Pacific region since the 1960s. In 2010, this region accounted for 70% of global disease burden,[2] with co-circulation of the four serotypes in different proportions and with different predominant serotypes.[47] In contrast, Latin American countries experienced a vector re-infestation after the diminution of the yellow fever eradication program in the 1980's,[48] and serotype distributions vary according to country with patterns observed, from a single predominating serotype to co-circulation of the four serotypes.[47] However, crucially, our seropositivity analysis did not show distinct differences in regional trends between Asia Pacific and Latin America. This is probably due to the persistence and increased intensity of dengue circulation in the absence of efficient vector control measures in Latin American countries in recent decades.

Comparison with other seroprevalence data from literature is difficult due to the limited number of studies conducted to date, and is further limited by the different survey designs and serological tests used. Nevertheless, the same increased trend in seroprevalence with age observed in our study has also been previously reported in surveys conducted in Mexico, Singapore and India.[49–55] In 2009, a Mexican survey reported a dengue seroprevalence rate of 52.2% in 10–14-year-olds in Morelos, which is consistent with that reported in the CYD13 study (between October 2009 and February 2010)—54.8% in 9–17-year-olds.[51] In Singapore, seroprevalence in 2009 was reported to be between 16.1% and 57.3% in 16–45-year-olds, which is also consistent with that reported in the CYD28 study (17.0–48.7% in 2–45-year-olds) during the same year.[54] In the Indian city of Chennai (east coast), a household-based serosurvey conducted in 2011, reported a seroprevalence rate of 97.3% among 18–45-year-olds,[55] compared with a seroprevalence rate of 87.2% in adults reported in the CYD47 study (between March 2012 and February 2014).

In Colombia, an increase in seropositivity rates between 2009 and 2011 was observed. This was probably due to increased exposure among dengue-naïve individuals during the outbreak of 2010, when 120 918 cases were reported in the Orinoquía region, where the Acacias and Yopal municipalities (CYD15) are located, and the central regions, particularly among those aged under 15 years.[56] In Puerto Rico, in contrast, we observed a decrease in seropositivity rates between 2009 (CYD13) and 2011 (CYD15), despite an outbreak in 2010. During this outbreak, cases were mainly reported in the north of the island,[57] whereas the majority of participants (82%) in CYD15 were from areas in the south-eastern municipality of Guayama. Thus, it is likely that the decrease in seropositivity rate reported in CYD15 relative to CYD13 was due to the inclusion of a high number of participants who were not exposed in the 2010 outbreak. These data reflect the notion that dengue epidemics fluctuate over time—such fluctuation may be due to changes in natural herd immunity, host-virus interactions and virus virulence, as well as heterogeneity in the spatial distribution of the host/vector populations and climatic shift.

We observed that the proportion of participants who had only experienced primary infection tended to be higher in the younger age groups than in adolescents and adults. This is indicative

of the limited cumulative dengue-exposure in the younger age group. It also corroborates observation that seroprevalence increases with age, with age being a surrogate for cumulative exposure. Comparison with data from the literature is also difficult because of the lack of data and limited temporal correspondence. However, a dynamic school-based study of a cohort of Vietnamese children aged 2–15 years, which used IgG seroconversion to determine annual seroprevalence, reported the same stable trend over time for the proportion who had only experienced primary infection among given age groups as observed in the CYD studies where temporal data were available. Although not directly comparable with our study, between 2004 and 2007, the school-based cohort study revealed an average annual crude incidence risk of primary infection equal to 11.4% (range: 7.9–13.6%).[58] The rarer, but evident occurrence of adults living in endemic countries who have only experienced a primary infection may be explained by low virus circulation in some areas within these countries; this may simply reflect the geographical variability in the burden of dengue within these endemic countries.

Limitations of these analyses arise mainly from the fact that selected participants in the vaccine trials may not be representative of the respective nationwide populations from which the trials were undertaken:

- sites were not randomly selected;
- limited age groups were represented in some studies, in particular in Latin America.

Although the strict definition of primary infection used here ensured the detection of definitive primary infections only, this may lead to an under or over estimation of the true primary rate. For instance, when the serum sample is taken shortly after primary infection, responses against multiple serotypes can be observed.[59] However, in countries of low endemicity with large time intervals between epidemics, PRNT titers may wane with time in the absence of natural boosting, and neutralizing antibody responses detectable against only one serotype may be observed despite the overall multitypic dengue exposure profile. In addition, the numbers of seropositive samples in our analysis were sometimes too small to permit accurate determination of observed rates and meaningful comparisons with other studies. Flavivirus-induced antibody cross-reactivity exists due to antigenic epitopes common to flaviviruses and may result in some false positives, where the viruses co-circulate or as a result of vaccination. However, there is no evidence to date that yellow fever vaccination could influence dengue PRNT results, as observed with DENV-2.[60] In addition, the studies undertaken in Latin America were started prior to Zika introduction and circulation in the region.[61]

Conclusions

This study is the first to provide a consistently derived overview of dengue seropositivity data from different countries, at different times, using a validated neutralization assay at centralized laboratories. With such a unique dataset per country and over time, these results represent the largest collection to date of comparable standardized dengue seropositivity data across countries. Given that the majority of dengue infections are clinically asymptomatic, and that the disease is greatly underreported, these results provide distinctive information on dengue transmission per age group in the 14 participating countries, and will be invaluable in future modeling studies that explore the temporal and spatial distribution of dengue infection. Together with information on the characteristics of vector, virus and host populations, information on seroprevalence helps to determine the exposure history of populations, and the temporal and spatial dynamic of virus circulation. These results will help define the level of dengue endemicity, a key factor in informing and guiding dengue control strategies.

Supplementary data

Supplementary data are available at Transactions online (http://trstmh.oxfordjournals.org/).

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