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A comparative study on active and passive epidemiological surveillance for dengue in five countries of Latin America

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SUMMARY

Background: Dengue is a notifiable infectious disease in many countries, but under-reporting of cases to National Epidemiological Surveillance Systems (NESSs) conceals the true extent of the disease burden. The incidence of dengue identified in a cohort study was compared with those reported to NESSs.
Methods: A randomized, placebo-controlled study was undertaken in Brazil, Colombia, Honduras, Mexico, and Puerto Rico to assess the efficacy of a tetravalent dengue vaccine (CYD-TDV) in children aged 9–16 years. The incidence of dengue in the placebo group was compared with that reported to NESSs in a similar age group (10–19 years) from June 2011 to April 2014.
Results: Three thousand six hundred and fifteen suspected dengue cases were identified in the study over 13 527 person-years of observation. The overall incidence of confirmed dengue was 2.9 per 100 person-years (range 1.5 to 4.1 per 100 person-years). In the NESSs combined, over 3.2 million suspected dengue cases were reported during the same period, corresponding to over 1 billion person-years of observation. The incidence of confirmed dengue reported by the NESSs in the same locality where the study took place was 0.286 per 100 person-years across Brazil, Colombia, and Mexico (range 0.180 to 0.734 per 100 person-years). The incidence of confirmed dengue was 10.0-fold higher in the study than that reported to NESSs in the same localities (range 3.5- to 19.4-fold higher).
Conclusions: There is a substantial under-reporting of dengue in the NESSs. Understanding the level of under-reporting would allow more accurate estimates of the dengue burden in Latin America.

1. Introduction

Dengue is an endemic disease caused by an arbovirus of the family *Flaviviridae*, transmitted to humans through the bite of female mosquitoes of the *Aedes* genus (mainly *Aedes aegypti*) infected by one of four dengue virus serotypes, DENV-1–4. Clinical manifestations range from a non-specific febrile illness to a potentially more severe or life-threatening disease, such as dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS), and in some cases may lead to death.[1]

Routine dengue surveillance in endemic countries is essential for monitoring disease trends and detecting outbreaks, thus allowing decision-makers and health systems to have timely information on which to act whenever needed. Previous studies have revealed considerable under-reporting in national surveillance systems in endemic regions, limiting their ability to quantify the incidence or provide reliable estimates of future trends.[2,3] Indeed, to provide more accurate estimates of dengue disease burden and costs, analysts use country-specific expansion factors derived from cohort study estimates to account for the under-reporting of cases from national surveillance data.[4–7] However, these estimates remain mostly speculative and are based on small populations. In a systematic review of dengue surveillance in endemic countries, Runge-Ranzinger et al. identified the need for further research to help identify strategies to strengthen surveillance systems and to allow the identification of appropriate thresholds of excess reporting.[2]

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All four dengue serotypes have been isolated in the Americas, and they circulate simultaneously in several countries.[8] Large epidemics have recently occurred in the Caribbean, Brazil, Colombia, Ecuador, Mexico, and Venezuela.[9] Despite concerted dengue control efforts, the disease has continued to increase substantially in Latin America.[10] The number of suspected dengue cases reported by the National Epidemiological Surveillance Systems (NESSs) in the region increased from 652 212 in 2000[11] to 2 386 836 in 2013,[12] and dengue-related registered deaths increased from 92[13] to 1318 in the same period.[12]

A phase III, randomized, placebo-controlled study (CYD15) was undertaken to evaluate the safety and efficacy of a recombinant live-attenuated tetravalent dengue vaccine (CYD-TVD) in healthy children aged 9–16 years (n = 20 869) over 25 months in five Latin American countries (Brazil, Colombia, Honduras, Mexico, and Puerto Rico).[14] The longitudinal follow-up of placebo recipients (n = 6939) provided a unique opportunity to examine the background incidence of dengue in this well-defined cohort. The incidence rates observed in the placebo group of the CYD15 study cohort were compared with data reported by the NESSs for a comparable age group and in the same geographic areas (locality/sites).

2. Methods

2.1. Data sources

2.1.1. CYD15 study data

The Latin American CYD-TDV (CYD15) study has been described previously.[14] Healthy children aged 9−16 years were recruited at 22 centres in Colombia (nine centres), Brazil (five centres), Mexico (five centres), Puerto Rico (two centres), and Honduras (one centre) between June 2011 and April 2014. Active dengue surveillance started on the day of the first vaccination or receipt of placebo control and continued for 25 months for each participant. Participants were followed closely for acute febrile illness (temperature $\geq$38 °C on two or more consecutive days), and those who presented with fever were screened for signs and symptoms of dengue. Acute and convalescent blood samples were obtained and assessed using a quantitative reverse-transcriptase PCR (RT-PCR) assay for dengue amplified genomic sequences, and an ELISA for dengue non-structural protein 1 (NS1) antigen, in accordance with the guidelines of the World Health Organization (WHO).[15,16] Virological confirmation of suspected dengue was undertaken under blinded conditions at the sponsor's global clinical immunology laboratories (at the Centre for Vaccine Development of Mahidol University in Bangkok, Thailand) and at Focus Diagnostics (California, USA), permitting highly rigorous and comparable results across all study sites to be obtained. The illness episode was classified as virologically confirmed dengue if any of the tests was positive.

This article focuses on data obtained in the placebo group through to April 2014. All acute febrile episodes, confirmed dengue, and DHF or severe dengue (SD) cases were summarized by country for the entire placebo cohort over the whole follow-up period. Incidence rates for confirmed dengue and DHF/SD cases were obtained by dividing total numbers of these events by the person-years of follow-up, as reported elsewhere.[17] The 95% confidence intervals (CI) for incidence rates and proportions were computed with the exact binomial distribution for percentages (Clopper–Pearson method).[18]

2.1.2. Census data

The population census data for the country were obtained from the Instituto Brasileiro de Geografia e Estatística for Brazil,[19,20] Departamento Administrativo Nacional de Estadística for Colombia,[21] the National Institute of Statistics for Honduras,[22] Consejo Nacional de Población for Mexico,[23] and the US Census Bureau for Puerto Rico.[24] Population data were disaggregated into groups by age and regional jurisdiction (state and local level). The cumulative age-specific dengue cases for the follow-up study period (2011–2014) in the municipalities/sites where the study was undertaken in each country were used in the calculation of the country-specific dengue incidence rates.

2.1.3. NESS description

The NESS characteristics for the participating countries, as well as the clinical and laboratory criteria used for dengue notification, are summarized in the **Supplementary Material** (Appendix S1, Table S1). Physicians and other healthcare providers are required to report suspected cases meeting the WHO criteria. There are currently two WHO case definitions used: the 1997 classification (dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS)),[1] and the 2009 case classification (dengue without warning signs (D), dengue with warning signs (DWS), and severe dengue (SD)).[15] Each country has since adapted these definitions in line with their national experience; the country-specific case definitions for suspected dengue are summarized in the **Supplementary Material** (Table S2).

Each country has specific national guidelines/algorithms regarding the assays/tests to undertake and the proportion of suspected cases to assess, depending on whether the cases are identified during endemic or epidemic situations, as well as when they can declare suspected cases as confirmed by simple epidemiological association during epidemics when the virus is known to be circulating (**Supplementary Material**, Tables S1 and S2). Dengue diagnosis based solely on clinical symptoms is unreliable and the need for laboratory confirmation is emphasized by the WHO.[1] It is recommended that blood samples for suspected cases be collected within 5 days of fever onset (acute sample) and during convalescence (convalescent sample) about 10 days after the acute sample. A suspected case is considered confirmed with one of the following: isolation of the dengue virus, detection of dengue virus genomic sequences or antigens, or if there is a 4-fold or greater increase in dengue-specific IgG or IgM titres in paired serum.[1,15]

2.1.4. NESS data

Data on confirmed and suspected dengue cases were collected from the NESSs from June 2011 to April 2014, corresponding to the 9-month enrolment period plus 25 months follow-up for each participant in the CYD15 study. The number of suspected and confirmed dengue cases, DHF/SD cases, and deaths reported were summarized by age, time of occurrence, and by regional level (country, state/department, municipalities/sites). These data were used to calculate incidence rates of suspected and confirmed dengue cases and DHF/SD cases corresponding to each participating city/municipality, state, and country. Incidence rates were obtained by dividing total numbers of cases with the person-years of follow-up. The 95% CI for incidence rates and proportions were calculated using the binomial distribution for percentages.[25] The case-fatality rate (CFR) was estimated based on the ratio of dengue-related deaths to total confirmed DHF/SD cases, and to suspected cases.

The NESS dengue reports from Brazil, Colombia, and Mexico (but not from Honduras and Puerto Rico) were usually consolidated into 5-year age groups (with the exception of children <1 year of age and those aged >65 years). In order to be close to the age groups recruited in the CYD15 study (age 9–16 years) and considering that after 12 months of recruitment this population would have aged to 10–17 years and after 24 months to 11–18 years, it was decided to aggregate data from the NESSs in these three countries for two age groups: 10–14 and 15–19 years. Age-stratified data were not available for Honduras and Puerto Rico.

2.2. Comparisons of CYD15 placebo data with NESS data

Incidence rates from the placebo group of the CYD15 study were compared with their respective age-specific (10–19 years age group) incidence rates reported by the NESSs by country, as well as by state and by municipality/site level. Analyses of DHF (severe dengue) cases from the NESS Honduras were based on clinical features only because laboratory confirmation of severe dengue is not undertaken.

2.3. Role of funding source

Sanofi Pasteur had the opportunity to review and comment on this manuscript.

3. Results

3.1. CYD15 study data

In the CYD15 study, 6939 children and adolescents were enrolled at a mean age of 12.5 ± 2.1 years. During 13 527 person-years of follow-up, there were 3613 suspected dengue cases, of which 389 episodes were virologically confirmed to be dengue and 10 episodes were confirmed to be DHF, providing an overall incidence rate of 2.9 per 100 and 73.9 per 100 000, respectively (Table 1). Honduras had the highest incidence rate for febrile episodes (51.08 per 100 person-years) and virologically confirmed dengue cases (4.10 per 100 person-years). There were no virologically confirmed DHF/SD cases reported in Brazil or Mexico, and the virologically confirmed DHF/SD cases as a percentage of total virologically confirmed dengue cases across the other three countries ranged from 2.7% to 7.7%.

3.2. NESS data

Across the five countries, there were over 3.2 million suspected dengue cases reported to the NESSs across all age groups during the period June 2011 to April 2014, from over 1 billion person-years of observation. The numbers of suspected and confirmed dengue cases and DHF/SD cases reported, as well as the corresponding incidence rates, are summarized for each country in the **Supplementary Material** (Tables S3–S7). The incidence rate of suspected dengue ranged from 0.1 per 100 person-years in Colombia to 0.45 per 100 person-years in Brazil and Puerto Rico; the corresponding incidence rate of confirmed dengue ranged from 0.004 per 100 person-years in Honduras to 0.31 per 100 person-years in Brazil (Table 2). Although Brazil had the highest incidence rates for both suspected and confirmed dengue cases, it had the lowest incidence rates for confirmed DHF/SD (0.59 per 100 000 person-years). The overall incidence rate for confirmed DHF/SD was 4.89 per 100 000 person-years across all countries excluding Honduras. Honduras had the highest incidence rate for DHF (35.24 per 100 000 person-years), but this figure is based on clinical features without laboratory confirmation.

3.3. Comparison between the CYD15 study cohort and NESS data

There were consistently more cases identified in the CYD15 study than were reported via the NESSs in a similar age-stratified cohort at all levels in the three countries (age-stratified data were not available for Honduras or Puerto Rico) (Table 3). The incidence rates for confirmed dengue cases were on average 25.1-fold higher in the CYD15 study than reported in the NESSs at the national level across the three countries, and 12.0- and 10.0-fold higher at the state and local levels, respectively. The greatest disparity was found for Brazil with 16.9- and 19.4-fold higher confirmed dengue cases in the CYD15 study than at the state and local levels, and the lowest disparity was found for Colombia at 5.8- and 3.5-fold higher, respectively.

In a crude comparison, the incidence rates for confirmed dengue cases were 978- and 9.4-fold higher in the CYD15 study than reported across all age groups in the NESSs for Honduras and Puerto Rico, respectively.

4. Discussion

This analysis is one of the few studies to compare active surveillance with passive surveillance in different countries. There was a much higher incidence of confirmed dengue identified during active surveillance in the cohort study than reported to the NESSs, even when considering comparable data at the state level and at the municipality/site level. The expansion factors calculated (Table 3), indicating the level of under-reporting, varied considerably by country. However, these expansion factors should be interpreted with caution, as the study locations and age groups assessed in the CYD15 study were not selected randomly and as such, may not necessarily be representative of their respective countries overall.

It is generally recognized that there is a tendency for passive NESSs to under-report dengue cases, particularly for less severe non-hospitalized cases.[2] The variability in under-reporting makes it difficult to compare the incidence rates both within and between countries. There are a number of factors that contribute to under-reporting in passive NESSs. Many people or parents do not usually seek treatment for a mild febrile illness (including mild dengue) unless they have cause for concern. Under-reporting may also occur to a greater extent among the older age groups, where febrile illnesses may easily be dismissed. There is also the possibility of misdiagnosis, especially with less severe dengue, with other infectious diseases confounding the diagnosis. In addition,

Table 1
Data from the CYD15 study cohort (aged 9–16 years) for the period June 2011 to April 2014

	Brazil	Colombia	Honduras	Mexico	Puerto Rico	Overall[a]
Number of participants, *N*	1174	3245	931	1149	440	6939
Population observation, person-years	2290	6313	1799	2280	845	13 527 (11 728)
Number of febrile episodes, *n*	552	1486	919	473	185	3615
Febrile episodes, IR per 100 participants	24.10	23.54	51.08	20.75	21.89	26·72
Number of confirmed dengue episodes, *n*	81	165	73	57	13	389
Confirmed dengue episodes, IR per 100 person-years	3.50	2.60	4.10	2.50	1.50	2.87
Number of confirmed DHF/SD episodes, *n*	0	7	2	0	1	10 (8)
Proportion of confirmed DHF/SD episodes, %	0.00	4.24	2.74	0.00	7.69	2.57
IR of confirmed DHF/SD episodes per 100 000 person-years	0.00	110.88	111.17	0.00	118.34	73.93 (68.21)

IR, incidence rate; DHF, dengue haemorrhagic fever; SD, severe dengue.
[a] Numbers shown in parentheses are for the adjusted denominator (i.e., without Honduras because it does not report laboratory-confirmed DHF cases in the National Epidemiological Surveillance System, to allow for the necessary comparative analyses; the diagnosis of DHF is based on clinical features only).

Table 2
Summary of national dengue cases (all age groups) reported to National Epidemiological Surveillance Systems for the period June 2011 to April 2014

	Brazil	Colombia	Honduras	Mexico	Puerto Rico	Overall[a]
Population observation, person-years	564 937 700	132 453 602	23 927 087[b]	332 795 595	10 351 002	1 064 464 986 (1 040 537 899)
Number of suspected dengue cases, *n*	2 522 527	126 959	63 873	470 692	47 001	3 231 052
Suspected cases, IR per 100 population	0.45	0.10	0.27	0.14	0.45	0.30
Number of confirmed dengue cases, *n*	1 750 307	114 225	831	134 931	16 489	2 016 783
Confirmed cases, IR per 100 population	0.310	0.086	0.004	0.041	0.16	0.189
Number of confirmed DHF/SD cases, *n*	3320	4054	8432[b]	43 355	114	59 275 (50 843)
DHF/SD from confirmed cases, %	0.19	3.55	0.00	32.13	0.69	2.94
DHF/SD from suspected cases, %	0.13	3.19	13.20[b]	9.21	0.24	1.83
Number of deaths, *n*	1328	256	35	369	22	2010
CFR (deaths/confirmed DHF/SD cases)	40.00	6.31	0.42[b]	0.85	19.30	3.39
CFR (deaths/No. suspected cases)	0.05	0.20	0.05	0.08	0.00	0.06
IR confirmed DHF/SD (DHF/SD/ population) × 100 000	0.59	3.06	35.24[b]	13.03	1.10	5.57 (4.89)

IR, incidence rate (by 100 population); DHF, dengue haemorrhagic fever; SD, severe dengue; CFR, case-fatality rate.
[a] Numbers shown in parentheses are for the adjusted denominator (i.e., without Honduras because it does not report laboratory-confirmed DHF cases in the National Epidemiological Surveillance System, to allow for the necessary comparative analyses; the diagnosis of DHF is based on clinical features only).
[b] Due to a lack of data for confirmed cases for 2011. Only years with complete data were taken into account. Severe dengue cases are not laboratory-confirmed in Honduras; the number of DHF cases reported here for Honduras represents suspected DHF cases.

although reporting of dengue is required by law in the countries assessed, there is usually no practical way of ensuring compliance with surveillance requirements. Other factors that may contribute to under-reporting include limited laboratory capabilities or infrastructure, as well as difficulties (or inconsistencies) in applying the WHO dengue case definition. Under-reporting rates may also differ depending on the epidemiological scenario—the occurrence of outbreaks with increased disease awareness among the population may reduce the rate of under-reporting,[26,27] but conversely may lead to over-reporting.[28]

The overall level of under-reporting for confirmed dengue cases (Brazil, Colombia, and Mexico) ranged from 10.0- to 25.1-fold in this study, depending on whether the comparison was with the local, state, or national level. These observations appear consistent with those reported in another study comparing paediatric (age 2–12 years) cohort-based data with NESS data in Nicaragua, in which the expansion factor indicated the level of under-reporting to be 14–28-fold for confirmed cases reported by the NESS.[4] An earlier analysis undertaken for Puerto Rico based on available data and on expert opinion suggested that 10- and 27-fold more cases occur in paediatric and adult populations, respectively, than are reported.[5] Empirical estimates from several countries in Latin America suggest under-reporting of 1.4–3.4-fold for hospitalized and fatal cases, and of 2.1–28-fold for ambulatory cases.[6] The level of under-reporting estimated at the local level in Brazil (19.4-fold), Colombia (3.5-fold), and Mexico (8.4-fold) in the present study may be considered the closest to the real-life situation in these countries.

The difference in dengue incidence rates reported in the NESSs relative to the CYD15 study appeared to decrease progressively from the national level through to the state and municipality/site levels. The sites/regions selected for the study were based, in part, on their capacity to undertake research and on the availability of health staff to perform the fieldwork in a timely manner, which may indirectly reflect the efficiency or capability/infrastructure of the healthcare system in the local area to report cases to the NESS. In addition, the CYD15 study was a major, well-publicized study, and it is possible that physicians and other healthcare providers in the area where it was conducted may have been more aware or reminded of the need to report suspected cases for laboratory confirmation. Alternatively, as the sites in the CYD15 study were selected with the knowledge that they had a high dengue burden,[29] the difference in incidence rates reported at the national level compared with the study cohort may simply reflect the geographical variability in the burden of dengue across these countries.

The variation in the incidence rates of cases reported to the NESSs may also reflect differences in healthcare systems or differences in the case definition used. Although the Pan American Health Organization (PAHO)—the regional office for the Americas of the WHO—provided standardized case definitions based on the 1997 WHO publication, later revised in 2009 according to disease severity,[1,15] each country has since adapted these definitions in line with their national experience (**Supplementary Material**, Table S2). This has led to some inconsistencies in case definitions between countries. For instance, in Mexico, only laboratory-confirmed cases

Table 3
Comparison between the CYD15 study cohort (aged 9–18 years) and National Epidemiological Surveillance System data (for those aged 10–19 years) for the period June 2011 to April 2014[a]

	IR confirmed cases per 100 (95% CI)				Ratio of CYD15/ $NESS_{(National)}$	Ratio of CYD15/ $NESS_{(State)}$	Ratio of CYD15/ $NESS_{(Local\ sites)}$
	CYD15 study (control arm)	$NESS_{(National)}$	$NESS_{(States)}$	$NESS_{(Local\ sites)}$			
Brazil	3.5 (2.8–4.4)	0.131 (0.1312–0.1314)	0.207 (0.2069–0.2074)	0.180 (0.1797–0.1807)	26.7 (21.7–33.4)	16.9 (13.8–21.2)	19.4 (15.8–24.2)
Colombia	2.6 (2.2–3.0)	0.204 (0.2042–0.2045)	0.445 (0.4450–0.4464)	0.734 (0.7320–0.7361)	12.7 (11.0–14.8)	5.8 (5.0–6.7)	3.5 (3.0–4.0)
Mexico	2.5 (1.9–3.2)	0.055 (0.0554–0.0556)	0.197 (0.1973–0.1980)	0.297 (0.2957–0.2989)	45.5 (33.8–56.5)	12.6 (9.8–16.3)	8.4 (6.5–10.9)
Overall	2.9 (2.6–3.2)	0.11 (0.1143–0.1145)	0.239 (0.2388–0.2392)	0.286 (0.2857–0.2868)	25.1 (21.9–27.3)	12.0 (10.5–13.0)	10.0 (8.8–11.0)

IR, incidence rate; CI, confidence interval; NESS, National Epidemiological Surveillance System.
[a] Brazil and Mexico only include laboratory-confirmed cases. Confirmed cases in Colombia are based on their own definition (laboratory confirmed cases + epidemiological association and clinical findings). 'National' includes all information from the whole country; 'States' includes only the states where the CYD15 study was performed; 'Local sites' includes the same localities (municipalities/sites) where the CYD15 study was performed.

are notified, but in Brazil and Colombia epidemiological association is also used as a criterion for confirmation even in non-epidemic circumstances. However, the Brazilian data can be disaggregated into laboratory-confirmed cases and laboratory-confirmed plus epidemiological association cases (official case definition). Considering only laboratory-confirmed cases in Brazil at the site level, the CYD15 study data were 19.4-fold higher than those reported to the NESS (Table 3), but were only 3.6-fold higher than the respective NESS data when the official case definition was used (official incidence rate was 0.98 per 100 at the site level) (data not presented).

Data compared here were collected during a period that included a dengue outbreak in Brazil in 2013. This was reflected by the >2-fold higher incidence rate for confirmed dengue cases reported to the NESS during that year compared with the other years of the study (**Supplementary Material**, Table S3). Similarly, there was an outbreak in Honduras in the same year, reflected in the data by a higher number of suspected dengue cases reported, but which were not supported by the confirmed incidence rate (**Supplementary Material**, Table S5). As a consequence, the cautious use of expansion factors obtained from different epidemiological settings is recommended.

This study has a number of other limitations that also need to be considered. The main limitation is that data obtained from a cohort study undertaken at selected geographical settings in a selected healthy paediatric population were compared with national data, and as such are unlikely to be fully nationally representative or even fully representative of the same age-stratified paediatric population in the region where the study was undertaken. In addition, age-stratified data were not available for Honduras and Puerto Rico. Case reporting was much lower in Honduras, and in particular, the low rate of dengue confirmation makes the data from that country difficult to interpret. This may, in part, be related to the lower sensitivity of the laboratory techniques used in Honduras for confirmation of dengue, based on IgM and/or viral isolation, compared with the WHO recommended combination of NS1 ELISA and/or RT-PCR used by the other countries and in the CYD15 trial.[15,30] Finally, the case definition for suspected dengue cases in the study cohort was objectively defined as acute febrile illness with a temperature ≥38 °C for two or more consecutive days, and differs from the symptomatic definition used in the NESSs (**Supplementary Material**, Table S2).

In conclusion, there is an increasing need for better estimates of the burden of dengue in order to better assess the impact of new technologies for dengue control. This analysis shows that the rate of reporting of confirmed dengue varies considerably by country, and that there is likely under-reporting of the number of cases reported in the NESSs, which varies considerably by country. This study should assist with more accurate estimations of the burden of dengue determined from passive NESSs. Such estimates would be useful when modelling dengue disease dynamics or in health economics assessments.

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Conflict of interest: Elsa Sarti, Maïna L'Azou, Erick Solis, Fernando Noriega, and Leon Ochiai are employees of Sanofi Pasteur. Marcela Mercado, Pablo Kuri, and João Bosco Siqueira Jr have no relevant conflict of interest to report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.01.015.

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