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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.