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Estimation of expected dengue seroprevalence from passive epidemiological surveillance systems in selected areas of Argentina: A proxy to evaluate the applicability of dengue vaccination

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ABSTRACT

Background: Current recommendations about dengue vaccination by the World Health Organization depend on seroprevalence levels and serological status in populations and individuals. However, seroprevalence estimation may be difficult due to a diversity of factors. Thus, estimation through models using data from epidemiological surveillance systems could be an alternative procedure to achieve this goal.
Objective: To estimate the expected dengue seroprevalence in children of selected areas in Argentina, using a simple model based on data from passive epidemiological surveillance systems.
Methods: A Markov model using a simulated cohort of individuals from age 0 to 9 years was developed. Parameters regarding the reported annual incidence of dengue, proportion of inapparent cases, and expansion factors for outpatient and hospitalized cases were considered as transition probabilities. The proportion of immune population at 9 years of age was taken as a proxy of the expected seroprevalence, considering this age as targeted for vaccination. The model was used to evaluate the expected seroprevalence in Misiones and Salta provinces and in Buenos Aires city, three settings showing different climatic favorability for dengue.
Results: The estimates of the seroprevalence for the group of 9-year-old children for Misiones was 79% (95%CI:46–100%), and for Salta 22% (95%CI:14–30%), both located in northeastern and northwestern Argentina, respectively. Buenos Aires city, from central Argentina, showed a likely seroprevalence of 7% (95%CI: 3–11%). According to the deterministic sensitivity analyses, the parameter showing the highest influence on these results was the probability of inapparent cases.
Conclusions: This model allowed the estimation of dengue seroprevalence in settings where this information is not available. Particularly for Misiones, the expected seroprevalence was higher than 70% in a wide range of scenarios, thus in this province a vaccination strategy directed to seropositive children of >9 years should be analyzed, including further considerations as safety, cost-effectiveness, and budget impact.

1. Introduction

Among all vector-borne diseases affecting humans, dengue is considered the most important due to its high incidence and dispersion [1]. Nearly 390 million people are infected every year, and approximately 500,000 patients develop severe dengue and require hospitalization [2]. The main dengue vector, the mosquito *Aedes aegypti*, is widely distributed from temperate to tropical regions of the world, being the northern half of Argentina its southern distribution fringe in America [3]. During the last decades, the main efforts to control dengue epidemics worldwide were based on the elimination of the mosquito, because the absence of an effective vaccine.

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Several dengue vaccine candidates have been under development [4]. One of these vaccines, the chimeric yellow fever–dengue virus (DENV) tetravalent dengue vaccine CYD-TDV from Sanofi-Pasteur, is the one that have reached further development at present [5]. This vaccine has demonstrated promising results from two phase 3 trials in Asia and Latin America, with pooled rates of efficacy of 65.6% and 93.2% for symptomatic and severe dengue, respectively, although with unequal efficacy among serotypes (from 47.1% for serotype 2 to 83.2% for serotype 4) [6]. In Latin America, the CYD-TDV was licensed during 2016 in Paraguay, Mexico, Brazil, El Salvador, and Costa Rica [7]. However, some studies have postulated that vaccination in low-transmission settings with a high population of seronegatives will increase the number of hospitalized dengue cases [8], specifically in seronegative children <9-year old [9]. In this context, the World Health Organization (WHO) recommended that countries consider introduction of the vaccine only in settings with high endemicity, defined by a seroprevalence of at least 70% in the target age group [9], and refrain from deploying the vaccine for values lower than 50% [10]. In a recent publication, the WHO has also suggested that the current licensed dengue vaccine should only be administered to individuals that are known to have been infected with dengue prior to vaccination, as a precautionary and interim measure until the full review of data [11]. In countries where dengue serostatus of general populations is unknown, the WHO recommends a combination of seroprevalence, surveillance data, and programmatic factors to define the target population in a sub-national level [9]. Controversially, as far as 2016, the Pan American Health Organization (PAHO) did not recommend the introduction of the dengue vaccine into routine national immunization programs of America until more information about safety and effectiveness is available [12].

In the case of Argentina, dengue transmission has been notified almost yearly in subtropical and temperate areas of the country with a seasonal behavior since 1998 [3,13]. However, there is no available information on dengue serostatus of general populations. The main problem to estimate dengue seroprevalence through surveys is the possibility of cross-reaction, due to the circulation of other flaviviruses [14] and the previous history of yellow fever vaccinations [15]. This fact may result in an uncertain overestimation of the real dengue seroprevalence. To overcome this issue, we developed a novel approach that consist in the simulation of a cohort of children 0–9 years via a Markov model, that can estimate the number of seropositive individuals based on the number of clinical cases by year, the inapparent rate, the hospitalization rate and expansion factors (EF). With the goal to estimate the expected dengue seroprevalence in children of selected areas in Argentina, a simple model based on data from passive epidemiological surveillance systems was applied. This estimation could serve as a proxy of the applicability of dengue vaccination and the risk of severe dengue. It also could be a good measure of the actual burden for those regions where seroprevalence surveys are difficult to implement or the results are supposed to be subject to uncertainty.

2. Material and methods

2.1. Settings

In Argentina, dengue vector *Ae. aegypti* is distributed throughout the north half of the country, between the latitude 38° and 25° south. Salta and Misiones provinces (the province is the first sub-national jurisdiction) in the northwest and northeast, respectively, and Buenos Aires city in the center were selected for the estimation of the seroprevalence. Misiones province, bordering with Paraguay and Brazil, has a population of 1,189,446 inhabitants distributed in 29,801 km^2 and shows a warm and humid climate with abundant rainfall throughout the year. Salta is a large province with 1,333,365 inhabitants in 155,488 km^2 and different climates and eco-regions, from warm and humid subtropical to arid climates depending on the altitude. Buenos Aires is the capital city of Argentina and the largest urban conglomerate of the country. It has 3,054,267 inhabitants in 230 km^2 and the climate is temperate and humid without dry season [16,17].

All the national territory is considered as non-endemic by Argentinean health authorities, because dengue transmission is interrupted during winter. In Salta, since the first dengue outbreak in 1998, transmission has been notified almost every year [18]. Meanwhile in Misiones, the first dengue outbreak was detected in 2000, leading to outbreaks occurring in some years [18]. On the other hand, Buenos Aires has shown transmission only from 2009 [13], with two large outbreaks in 2009 and 2015–2016. After winter, dengue transmission is apparently dependent of the introduction of the virus from neighboring countries, i.e. Brazil, Paraguay and Bolivia, and until the present year-round dengue transmission was never detected [3]. However, the first autochthonous dengue transmission during winter was recently confirmed in Misiones [19].

2.2. Model overview

A simple Markov model was developed to simulate the dynamics of past dengue transmission according to available epidemiological surveillance data from 2007 to 2016. This period was defined to estimate the seroprevalence in 9-year-old children (see below). Three main health states were considered: susceptible, immune to one or more serotypes, and dead. In addition, three intermediate health states (infected/incubating, clinical case and inapparent case) were also considered between susceptible and immune, because the duration of these transitional states is less than one year (Fig. 1). The cycle length of the Markov model is assumed to last one year for main health states, while the intermediate states have a shorter extent. The population immune to one or more serotypes was assumed to be the population that would be seropositive if a serological survey was going to be applied, and this is the main outcome considered. Probabilities describing the likelihood of transitions among the health states included probability of dengue virus infection, proportion of inapparent cases, dengue incidence and all-cause mortality. Dengue-related mortality was not considered, as only 16 fatal cases were detected until now in Argentina, 6 during the 2009 epidemic [20] and 10 in 2016 [21]. A cohort of individuals starting at birth and aged 9 years at present was simulated, as this is the minimum age for vaccination suggested by the WHO (2016) [9]. As previously described, all-cause mortality was taken into account, but migration was not considered.

2.3. Equations and parameters

The probability of dengue virus infection (P*inf*) was back-calculated from the incidence notified by the passive surveillance system, using the Eq. (1). This parameter is defined as the probability of acquiring the infection, regardless of whether the outcome is symptomatic or asymptomatic.

$$P_{inf} = (P_{hosp}\ EF_{hosp} + (1 - P_{hosp})EF_{amb})/(1 - P_{inapp}) \quad (1)$$

Eq. (1) takes into account the probability of dengue hospitalization (P_{hosp}), expansion factors for cases managed in an ambulatory setting (EF_{amb}) and for hospitalized patients (EF_{hosp}), and the probability of inapparent cases (P_{inapp}). The probability of inapparent cases was considered for children of different countries of America and Asia, provided that this probability depends on the number of previous dengue infections. Expansion factors (*EFs*) are needed