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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

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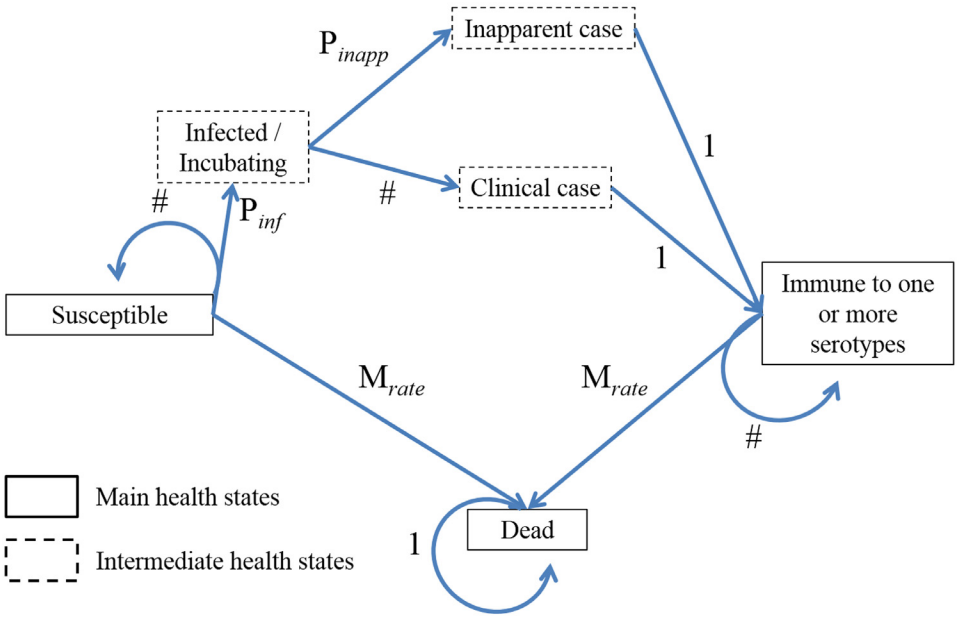

Fig. 1. Dependency diagram for the Markov model showing the main (solid line) and the intermediate health states (interrupted line) with the transition probabilities. #: complementary probability; P_{inapp}: probability of inapparent cases; P_{inf}: probability of infection; M_{rate}: mortality rate (all causes, age dependent).

because not all dengue cases are detected and notified by passive surveillance systems. This is because as the epidemics progress the mild cases (mainly adult cases) does not procure diagnosis or treatment. Accordingly, as different values of expansion factors are expected for ambulatory and hospitalized patients, the probability of hospitalization related to dengue illness was also considered; this probability was extracted from a study that uses data from the cohort of children that was included in the phase 3 trial of dengue vaccine efficacy in Latin America [22]. The value of P_{inf} was constrained to the range 0–1. The incidence of dengue from 2007 to 2016 as notified by the passive surveillance system was obtained from the National Ministry of Health. For year 2016, i.e. Argentina's worst dengue outbreak, the incidence was age-specific. For other years, the incidence was assumed to be uniform in all age groups. All parameters, ranges and bibliographic sources considered can be seen in Table 1 and Supplementary Tables 1–3. Supplementary Table 4 shows a summary of key assumptions of the model.

2.4. Sensitivity analyses

A series of one-way deterministic sensitivity analyses were conducted in order to evaluate the individual influence of each parameter in the outcome, within the considered ranges. These variations were represented by a tornado diagram [23]. Additionally, a threshold analysis was implemented in order to estimate the values of the parameters from which the seroprevalence would be higher than 50% and 70%, varying one parameter at a time. These thresholds were selected considering the WHO (2016) recommendations for dengue vaccination [9]:

- If prior infection with dengue virus of any serotype, as measured by seroprevalence, is approximately 70% or higher in national or sub-national levels, countries should consider the introduction of the dengue vaccine.
- If the seroprevalence is between 50% and 70%, the vaccination is acceptable but the impact of the vaccination program may be lower.
- If the seroprevalence is below 50% in the age group targeted for vaccination, the vaccine is not recommended.

In addition, a probabilistic sensitivity analysis was performed to evaluate the simultaneous variation of all parameters and to estimate the 95% confidence interval around the outcome. For this purpose, the distributions of probabilities of all parameters were assumed to follow a triangular distribution between the ranges (Table 1). This was a conservative assumption as little is known about the probability distribution of these parameters. The probabilistic sensitivity analysis was based on 10,000 Monte Carlo simulations.

3. Results

The point estimate of the expected seroprevalence in 9–year-old children was 97% for Misiones province, 25% for Salta province, and 9% for Buenos Aires city. The point estimates by age and health state can be seen in Table 2. The parameters that most influenced this outcome were the P_{inapp} and the EF_{amb}, followed by the P_{hosp} and finally the EF_{hosp} in all settings (Fig. 2). The composed EF considering the combination of the EF_{amb} and the EF_{hosp} was 13.095. The cut-off condition of $P_{inf} \leq 1$ was only needed during the 2015–2016 outbreak in Misiones. In this case, an incidence of 1492 cases per 100,000 pop leaded to an expected incidence of 19,539 clinical cases per 100,000 pop and 102,837 infections per 100,000 pop, considering a multiplication factor of 5.26 due to the probability of inapparent cases of 0.81 (see Eq. (1)).

Regarding the threshold analyses, in Misiones the expected seroprevalence was higher than 70% in a wide range of parameter values, for example in all the range of P_{hosp} and EF_{hosp}. Further, the seroprevalence was higher than 70% for an EF_{amb} higher than 10. In Salta and Buenos Aires, the individual variation of any parameter led to a seroprevalence lower than 50%. The probabilistic sensitivity analysis showed that the mean and 95% confidence interval for the expected seroprevalence was 79% (95%CI: 46–100%) for Misiones, 22% (95%CI: 14–30%) for Salta, and 7% (95%CI: 3–11%) for

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Table 1
Transition probabilities of the Markov model and related parameters: values, ranges and bibliographic sources.

Parameter	Symbol	Value	Range	Reference
Number of cases by year and place[a]	C	See Supplementary Tables 1 and 2		[18,46]
Probability of inapparent cases[b]	P_{inapp}	0.81	0.58–0.86	[42]
Probability of dengue hospitalization	P_{hosp}	0.15	0.05–0.45	[22]
Expansion factor for ambulatory patients	EF_{amb}	15	9–28	[33]
Expansion factor for hospitalized patients	EF_{hosp}	2.3	1.4–3.3	[33]
All cause mortality rate (by age group)	M_{rate}	See Supplementary Table 3		[47]

[a] This figure includes cases diagnosed by epidemiological nexus or laboratory-confirmed cases.
[b] The value and range were calculated as median and quartiles for different countries in children less than 16 years old.

Table 2
Point estimates of the Markov model for Misiones, Salta, and Buenos Aires, showing values of the cohort by age and main health state.

	Misiones			Salta			Buenos Aires		
Age	Su (%)	Se (%)	De (%)	Su (%)	Se (%)	De (%)	Su (%)	Se (%)	De (%)
0	100	0	0	100	0	0	100	0	0
1	99	0	1	98	1	1	99	0	1
2	98	0	2	97	1	2	99	0	1
3	98	0	2	82	16	2	98	1	1
4	93	5	2	82	16	2	98	1	1
5	93	5	2	82	16	2	97	1	1
6	93	5	2	81	16	3	97	1	1
7	92	5	3	77	21	3	97	1	2
8	92	5	3	75	22	3	97	1	2
9	92	5	3	75	22	3	97	1	2
10	0	97	3	72	25	3	89	9	2

Su: susceptible; Se: seropositive; De: dead.

Buenos Aires. The distributions of the expected seroprevalence in the 10,000 Monte Carlo trials for each location are shown in Fig. 3.

4. Discussion

Our model allowed the estimation of dengue seroprevalence in 9-year-old children in sub-national scenarios of Argentina using data from the passive epidemiological surveillance system. This estimation was achieved by using a Markov model that simulates a cohort of children exposed to dengue infections from birth, and considering different parameters as the number of clinical cases reported by the surveillance system, expansion factors, probability of hospitalizations, inapparent rates, and general mortality. It is generally accepted that passive surveillance systems underreport dengue cases [24,25], especially in non-hospitalized cases [26]. Two possible reasons for this underreporting of cases are that older age groups do not usually seek treatment for mild dengue [26], probably because the lay knowledge on dengue symptoms and drug-based therapies spread among the population, and misdiagnosis is commonly observed in non-severe dengue. Other possible reasons for underreporting are problems with the surveillance system design (especially when is not through electronic forms), the burden of healthcare professionals and laboratory staff, and lack of reporting in the private health sector. Even in well-established surveillance systems like Brazil and Puerto Rico, there is some evidence of underreporting in fatal cases [27,28]. The estimation of this underreporting of cases by passive surveillance systems is important to measure the disease burden, to guide control programs decisions, and to assess the impact of new interventions such as dengue vaccination [29]. To accomplish this objective, EFs were defined as the number of underreported dengue cases for each case reported to the passive epidemiological surveillance system. These factors can vary between different continents and countries, leading to values as high as 282 for India [30], and as low as 1 for Colombia [24]. According to a recent systematic analysis for Southeast Asia, the underreporting of symptomatic dengue cases is substantial, and only about 13% of all symptomatic dengue episodes are reported to surveillance systems [31]. In Argentina, estimations about EFs are a pending matter, but the underreporting is supposed to be serious [32]. In order to be conservative, we used average values of EFs previously assumed for American countries without empirical estimations [33], differentiating EFs for hospitalized dengue patients and for cases managed in ambulatory settings, being consistent with previous studies [26,31]. For example, Sarti and colleagues [26] observed a 10-fold increase in the incidence of cases detected by the study when compared to the incidence reported by the local surveillance system. As for Argentina the number of dengue cases registered by the surveillance system is not distinguished between hospitalized and ambulatory cases, an assumption about the proportion of ambulatory and hospitalized patients was needed. Other parameter that influenced the likely number of people that were exposed to the dengue virus was the rate of inapparent infections. It is accepted that the proportion of inapparent and sub-clinical cases is considerable [34], and this fact has many implications for the estimation of the real number of persons infected with dengue viruses.

Our results are closely related to the assessment of the suitability of dengue vaccination in Argentina, a country currently considered as non-endemic because the transmission is interrupted during winters [3,32]. It is worth noting that this situation may be changing, as the first autochthonous dengue cases during the cold season were confirmed in 2016 [19], and vertical transmission of the dengue virus in mosquitoes from northern Argentina was reported in 2014 [35]. A problem in Argentina for the estimation of dengue seroprevalence is that the yellow fever vaccine is being administered in mass vaccination campaigns and is also included in the regular schedule of the national immunization program in

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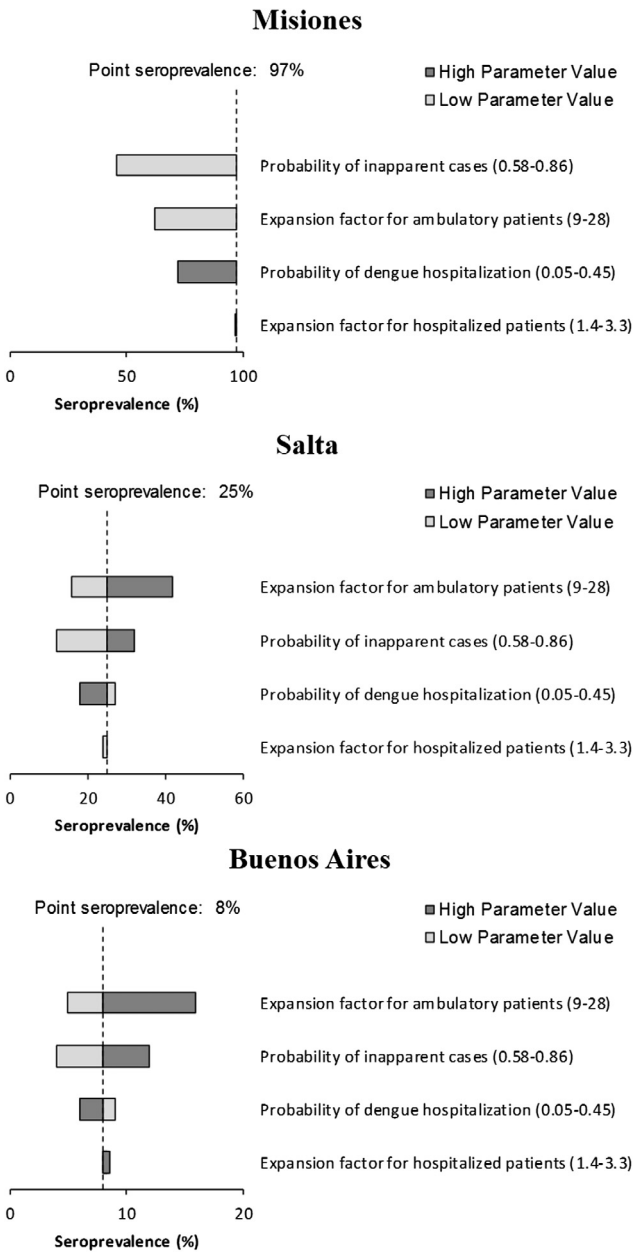

Fig. 2. Tornado diagram representing the univariate influence of parameters in the expected seroprevalence. The interrupted line represents the central value.

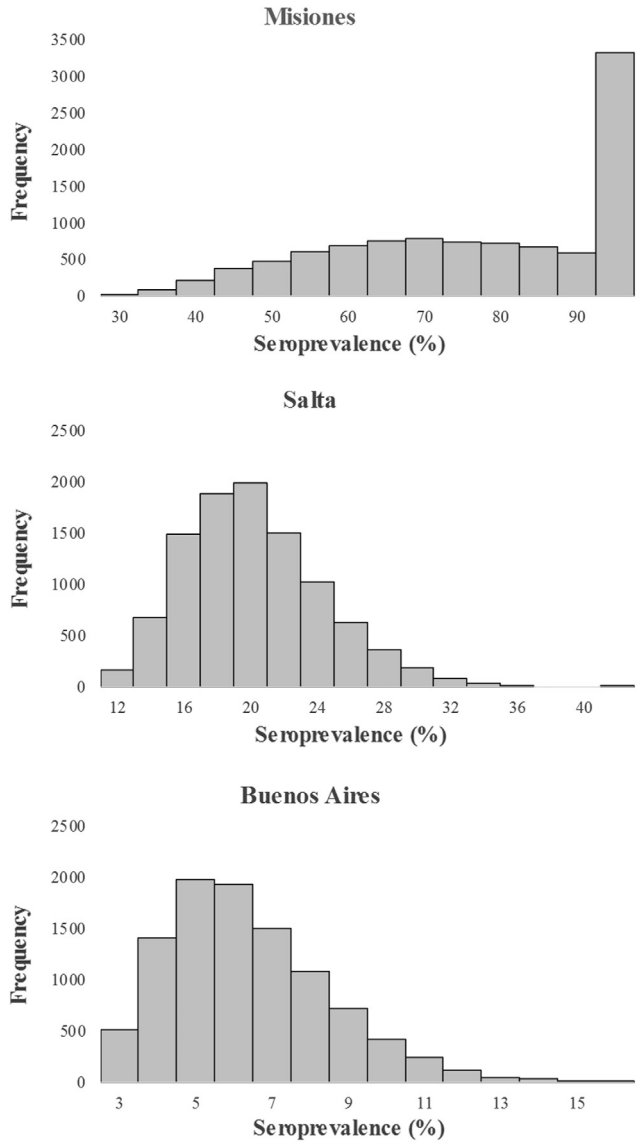

Fig. 3. Distribution of the Monte Carlo simulations for the expected seroprevalence.

Northern provinces. Moreover, the circulation of several flaviviruses has been detected, often producing small outbreaks, as the case of Saint Louis encephalitis [36]. Both, history of yellow fever vaccination [15] and co-circulation of other flaviviruses [14], are factors that make difficult the use of IgG antibodies to estimate dengue seroprevalence, since cross-reaction between anti-flavivirus IgG antibodies cannot be excluded [14,37]. The dengue plaque reduction neutralization test (PRNT) is a more specific assay and may be used to distinguish between cross-reactive and pathogen-specific responses [14]. However, the implementation of population surveys with this technique is difficult because it is burdensome and is not widely available [9,38]. In these contexts, the WHO suggests studies involving epidemiologic data based on high-quality age-stratified surveillance to infer likely seroprevalence by age [9]. This expected seroprevalence should be regarded as a basal level from which the real seroprevalence can be assumed.

This study showed that in the three studied areas of Argentina the seroprevalence in 9-year-old children could have a wide range. Particularly in Misiones, the expected seroprevalence was higher than 70%, thus a mass vaccination strategy directed to children >9 years should be analyzed. In fact, the government of Brazil implemented in 2016 a dengue vaccination program in the southern state of Paraná, an area bordering Misiones [7]. However, as we have previously mentioned, the PAHO did not recommend the introduction of the dengue vaccine into routine national immunization programs of America [12]. Moreover, due to evidence of increased severe dengue risk in seronegative individuals related to the phenomenon called antibody dependent enhancement (ADE), the vaccination to seropositive individuals can be considered as a more appropriate strategy than mass vaccination [39], even in endemic regions. In Salta the likely seroprevalence was below 20%, and therefore a vaccination strategy should not be recommended. It is interesting to note that in Salta, the spread of dengue is limited to certain areas, mainly with humid tropical and subtropical climates, while a vast territory comprising a dry forest eco-region is free of disease transmission due to the absence of the vector. This fact could explain the low expected seroprevalence in

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an area with yearly autochthonous transmission of dengue, historical circulation of the four serotpypes, and several recent epidemics. In any case, estimations at locality level should be carried out within Salta province before concluding about vaccination applicability. In Buenos Aires, the expected seroprevalence was close to 6%, and in all scenarios analyzed in the deterministic and probabilistic sensitivity analyses the expected seroprevalence is below 50%. In this context, a vaccination strategy in temperate Argentina is not suitable. It is worth noting that the seroprevalence in Misiones would be lower than in Salta until 2016. After that, the seroprevalence in Misiones increases remarkably from 5% to 97% of the initial cohort (i.e. 6% and 100% of the living cohort) due to the 2015–2016 outbreak. These extreme variations are typical from countries showing heterogeneous spatio-temporal risk and epidemic behavior, adding uncertainty to the results from the decision-maker perspective. All these analyses are relevant as a starting point for the assessment of the suitability of dengue vaccines for Argentina. According to a recent economic evaluation, from a societal perspective the vaccination in Argentina could be expected to be cost-effective if targeted to areas showing the highest transmission risk [40].

Our approach was subject to some limitations. First, expansion factors are subject to regional and local variations, as they depend on multiple factors, e.g. the inter- or intra-epidemic period, the health system awareness, or the reporting experience. Moreover, during the course of large outbreaks the passive surveillance system can overestimate the real dengue incidence [41]. Consequently, the EFs can have null or even negative values. Thus, the 2015–2016 outbreak in Misiones, which lead to an expected seroprevalence of 100% of the living cohort, should be interpreted considering this framework and a deep assessment of the sensitivity analyses. In this study, the same expansion factor was assumed despite of the previous experience of dengue outbreaks in the different settings. Local surveys should be carried out to measure the level of underreporting of cases, and therefore estimating more realistic expansion factors. Second, the inapparent rate is known to vary in response to different scenarios, genetic factors of humans and viruses, disease incidence [42], and the time interval between successive infections [43]. In this study a unique value of inapparent rate was used, but considering a possible range to account for the uncertainty. A local or national estimation of this parameter was not available, and therefore it was assumed to be similar from those observed in other settings. Moreover, due to the sparse evidence on inapparent rates in children of Latin America, we needed to include also values from Southeast Asia. Third, the yearly variation of dengue incidence in Argentina added uncertainty to this model, and this could be observed in the highly skewed distributions of the Monte Carlo simulations, especially for Misiones, where the 2016 epidemic had a strong impact on the disease burden. Finally, the dengue surveillance system in Argentina is relatively new, as the transmission of the disease occurred only after the late 1990s. Thus, detailed age-specific clinical reports are available only since the last national epidemic, while cumulative incidence of clinical and laboratory dengue cases without distinction of age-group can be obtained in a reliable way. The 2016 outbreak had the mode in younger ages, thus if we use that distribution in the previous years the expected seroprevalence would be inflated. Using a conservative approach, we used a uniform distribution of age for cases before 2016, instead of the age structure reported during the last outbreak. This decision is also related to the fact that the age-structure depends on the years considered [44].

As conclusion, our model served as a straightforward procedure to estimate the likely dengue seroprevalence using data from the passive surveillance system. This approach could be especially useful in settings where seroprevalence surveys are difficult to implement for different reasons. As for the areas evaluated in this study, only Misiones province has demonstrated an expected seroprevalence higher than 70%, while in other settings the expected seroprevalence was lower than 20%. These results are useful as a complementary tool to evaluate the appropriateness of dengue vaccinations, but including further considerations as safety, cost-effectiveness, budget impact, and others. Moreover, these results should be interpreted with caution, due to the wide uncertainty and variability in the outcome estimates. On the other hand, our model is useful for the evaluation of currently licensed vaccine of Sanofi-Pasteur but also for future dengue vaccines. Among the later, two vaccines under development have demonstrated encouraging results in phase 2 and phase 3 trials, i.e. the Takeda's tetravalent dengue vaccine (TDV) and the TetraVax-DV from the Instituto Butantan and the US National Institutes of Health, respectively [45]. Finally, in order to be useful for epidemiologists and decision makers, our model should be calibrated and validated in settings with known real seroprevalence provided by serosurveys to allow the comparison of the number of effective and estimated seropositives.

Conflicts of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.01.007. These data include Google maps of the most important areas described in this article.

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