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Review

Updated recommendations of the International Dengue Initiative expert group for CYD-TDV vaccine implementation in Latin America

J.R. Torres [a,*], L.H. Falleiros-Arlant [b], B.D. Gessner [c], I. Delrieu [d], M.L. Avila-Aguero [e,f], H.I.G. Giambernardino [g], A. Mascareñas [h], J. Brea [i], C.N. Torres [j], J.M. Castellanos-Martinez [k]

[a] Infectious Diseases Section, Tropical Medicine Institute, Universidad Central de Venezuela, Caracas, Venezuela
[b] Departamento de Salud de los Niños, Facultad de Medicina, Universidad Metropolitana de Santos, Brazil
[c] Agence de Médecine Préventive, Ferney-Voltaire, France
[d] Sciences and Technologies for Health EpiLinks, Saint-Genis-Pouilly, France
[e] Servicio de Infectología, Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", Caja Costarricense de Seguro Social (CCSS), San José, Costa Rica
[f] Affiliated Researcher Center for Infectious Disease Modeling and Analysis (CIDMA) at Yale University, New Haven, CT, USA
[g] Departamento de Inmunizaciones y de Control de Infección, Hospital Pequeño Principe, Curitiba, PR, Brazil
[h] Department of Pediatric Infectious Diseases, Hospital Universitario "José E. Gonzalez", Universidad Autónoma de Nuevo Leon, Mexico
[i] Centro Médico UCE, Santo Domingo, Dominican Republic
[j] Director Cafettor Medical, Universidad del Bosque, Bogotá, Colombia
[k] Hospital Regional de Alta Especialidad del Bajío, Secretaría de Salud, León Guanajuato, Mexico

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ABSTRACT

Dengue disease represents a large and growing global threat to public health, causing a significant burden to health systems of endemic countries. For countries considering vaccination as part of their Integrated Management Strategy for Prevention and Control of Dengue, the World Health Organization currently recommends the first licensed dengue vaccine, CYD-TDV for: individuals aged 9 years or above from populations with high transmission rates, based on either seroprevalence criteria or pre-vaccination screening strategies, and for persons with confirmed prior exposure to infection in moderate to lower transmission settings. This paper describes the main conclusions of the Sixth Meeting of the International Dengue Initiative (IDI) held in June 2018, following release of a new product label by the manufacturer, updated WHO-SAGE recommendations, additional scientific evidence on vaccine performance, and reports of experiences by implementing countries. Considerations were made regarding the need for improving the quality of epidemiological and surveillance data in the region to help define the convenience of either of the two vaccination strategies recommended by WHO-SAGE. Extensive discussion was dedicated to the pros and cons of implementing either of such strategies in Latin America. Although, in general, a seroprevalence-based approach was preferred in high transmission settings, when cost-effectivity is favorable pre-vaccination screening is a convenient alternative. Cost-effectiveness evaluations can assist with the decisions by public health authorities of whether to introduce a vaccine. Where implemented, vaccine introduction should be part of a public health strategy that includes the participation of multiple sectors of society, incorporating input from scientific societies, ministries of heath, and civil society, while ensuring a robust communication program.

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* Corresponding author.
E-mail addresses: torresj@iname.com (J.R. Torres), luizahfc@terra.com.br (L.H. Falleiros-Arlant), idelrieu@epilinks.net (I. Delrieu), heloisa.ihle@hpp.org.br (H.I.G. Giambernardino), catorres@uniandes.edu.co (C.N. Torres).

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1. Introduction

The 6th Expert meeting on dengue vaccine implementation in Latin America of the International Dengue Initiative (IDI), was held June 22 and 23, 2018 in Lima, Peru. The meeting convened a permanent group of Latin American and other international experts on dengue and vaccination. This group has been endorsed by the regional societies SLIPE (Latin American Society of Pediatric Infectology), ALAPE (Latin American Association of Pediatrics) and API (Pan American Association of Infectology).

The objective was to update the International Dengue Initiative group Position Paper on dengue vaccination in Latin America, based on a new product label by the manufacturer, revised World Health Organization's Strategic Advisory Group of Experts on Immunization (WHO-SAGE) recommendations, additional scientific evidence on vaccine performance, and reports of experiences by implementing countries.

This meeting included a series of lectures, workshops and discussions. The current report summarizes the main conclusions achieved and the group position on this subject.

2. Background information

2.1. Regional epidemiological review

According to the WHO, dengue is considered a worldwide menace to public health [1]. Globally, half of the population lives in areas at risk for dengue, representing a constant epidemic threat. Since the 1980s, the number of dengue cases in the Americas reported to the Pan American Health Organization (PAHO) has doubled each decade, reaching nearly 13 million accumulated cases since 2010 [2]. During 2015–2016, the number of cases increased substantially, followed by an unexplained drop during 2017–2018, except for major outbreaks in Peru and Paraguay [2].

The distribution of dengue-related mortality varies from one year to another across Latin America due to changing epidemiological trends in countries. Although the absolute number of deaths has increased over the years, driven primarily by rises in the number of dengue cases, new clinical guidelines to manage dengue (WHO definition of cases, 2009) and early diagnosis of unsuspected dengue cases may have contributed to an overall decrease in the dengue case fatality ratio despite its increase in some countries [3,4].

Dengue burden likely is greatly underestimated as true incidence rates could be 10–20 times higher than reported in some countries. Underreporting of dengue is frequent and may be due to various causes, including the failure of symptomatic persons to present for care, misdiagnosis by care providers, failure to obtain laboratory tests, and insensitive laboratory diagnostics. Better tools are needed to improve case detection using standardized case definitions, similar diagnostic algorithms, and tests [5–10].

2.2. Pathogenesis of dengue

Severe dengue disease is defined by at least one of the following criteria: shock due to plasma leak and/or fluid accumulation with respiratory distress, and severe bleeding or organ impairment [11].

The complex pathogenesis of severe dengue is not fully understood. Whereas there is not consensus regarding the physiopathology mechanisms involved in severe disease, several factors may play a role, such as the level, quality and type of antibodies, cellular response, serotype and in particular the genotype involved, as well as host factors like age and cellular receptors. Different organs play important roles [11–20].

3. Key aspects about Dengvaxia dengue vaccine

Despite a relative abundance of dengue vaccine candidates at various stages of development, the only currently available commercial product is the tetravalent chimeric yellow fever-dengue vaccine (CYD-TDV, Dengvaxia®, Sanofi Pasteur).

3.1. CYD vaccine effect by baseline serostatus

Here we summarize data for individuals of the age group 9+ years; that is, the vaccine target population, from the combined analysis of phase III studies (CYD 14, CYD 15 and CYD 23/57), grade I evidence, Active Surveillance Phase (25 months of follow-up after the first dose), and Hospitalized Phase (close to 4 additional years of follow-up after first dose) [21,22]. Of note, all VE and safety analyses according to basal serostatus were performed in the "immunogenicity" subset of participants comprising only 4003 subjects [21,22].

- Average Vaccine Efficacy (VE) 25 months after dose 3 for virologically confirmed dengue (VCD) was 65.6% (95% CI, 60.7–69.9).
- Overall VE against severe disease and hospitalization due to VCD were 92.9% (95% CI, 76.1–97.9) and 80.8% (95% CI, 70.1–87.7), respectively.
- VE against VCD varied by serotype, being lowest for serotype 2, but was statistically significant for each serotype.
- VE according to pre-vaccination serostatus, estimated from the immunogenicity subset (about 13% of the total trial population only), was statistically significant for both seropositives: 81.9% (95% CI, 67.2–90.0), and seronegatives: 52.5% (95% CI, 5.9–76.1).

After 4 years of long term follow-up (LTFU) in a meta-analysis that included the CYD 14, CYD 15 and CYD 23/57 studies, the Relative Risk (RR) of hospitalization and severe VCD remained below one, with a RR of 0.3 (95% I.C 0.2–0.4) in the target age population regardless of country or previous serostatus [22].

Data from LTFU stratified by pre-vaccination serostatus did not show an increased risk of hospitalized or severe VCD at any time point in seronegatives 9 years of age or older. However, data are limited by the number of cases that occurred in this subset for

Table 1
Overall observed or imputed dengue vaccine efficacy and risk reduction in seropositive participants over 9 years of age, from CYD14, CYD15 and CYD23/57 trials, according to clinical category and length of follow-up.

Virologically Confirmed Dengue (VCD)	Hospitalized dengue	Severe dengue
Vaccine Efficacy M0–M25 (95% CI)	Risk reduction M0–M66 (95% CI) inferred from 1 – HR or RR	Risk reduction M0–M66 (95% CI) inferred from 1 – HR or RR
76% (64, 84)	79% (69, 86)	84% (63, 93)

Imputation: MI-M0 estimate, pooled analysis of CYD14 (9–14-year-old group), CYD15 (9–16-year-old group) and CYD23/57 (9–11-year-old group) studies (VCD 2 year follow-up; hospitalized VCD and severe VCD 5–6 year follow-up). CI, confidence interval; HR, hazard ratio; RR, relative risk; MI-M0, Multiple Imputation at month 0.
Modified from: Sridhar S. Luedtke A, Langevin E, Zhu M, et al, N Engl J Med 2018, 379: 327–340.

which baseline serostatus was known [21–23]. After the initial data release and published results, WHO-SAGE, as well as various Scientific, Public Health, and Regulatory agencies indicated that there was an important knowledge gap in CYD vaccine safety among the seronegative population, and that very limited information was available from the efficacy studies, due to the small size of the immunogenicity subset.

Subsequently, Sanofi Pasteur conducted a complex post hoc analysis to assess CYD-TDV performance according to previous immune status [24,25]. This analysis was based on a case-cohort study derived from the phase III and IIb studies. This approach considered all cases of VCD, hospitalization due to VCD, and severe VCD that occurred during the follow-up period. The cohort was randomly selected and comprised 10% of the entire study population, including 10% of the immunology subset. In the absence of samples at baseline from all subjects, samples from month thirteen (one month after the third vaccine dose), which were available in all 31,000 participants, were used to estimate previous dengue serostatus. A recently developed dengue anti–nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay (ELISA) was used to differentiate between anti-NS1 antibodies induced by wild-type dengue infection and those induced by vaccination, since the CYD-TDV contains genes encoding NS1 of yellow fever 17D vaccine virus instead of those encoding NS1 of dengue virus. The analysis included 1258 cases with symptomatic VCD, 644 hospitalizations due to VCD, and 142 cases of severe VCD. The investigators used different approaches to define serostatus. The full methodology is described by Sridhar et al. [25].

Table 2
Long-term (5–6 year follow up) incidence proportion of hospitalized and severe dengue in unvaccinated seropositive and vaccinated seronegative participants of CYD14, CYD15 and CYD23/57 trials, after one or more virologically confirmed infections.

	Unvaccinated seropositives, Secondary Infection	Vaccinated seronegatives, Secondary-like* Infection
Incidence of Hospitalized Dengue (%)	1.88	1.57
Incidence of Severe Dengue (%)	0.48	0.40

Source: WHO background paper on dengue vaccines, March 23rd, 2018 https://www.who.int/immunization/sage/meetings/2018/april/2_DengueBackgrPaper_SAGE_Apr2018.pdf.
* Vaccination in seronegative individuals would act as a primary-like infection, transiently increasing the risk of both hospitalized and severe illness after the occurrence of infection by any of the dengue virus serotypes.

The main results can be summarized as follows:

- Among seropositive participants aged 9–16 years:
  a. In the active surveillance phase (initial 25 months of follow-up after administration of first dose of the vaccine), vaccine efficacy was 76% (95% CI, 64–84) against symptomatic VCD, 79% against hospitalized dengue (95% CI, 69–86), and 84% (95% CI, 63–93) against severe dengue. (See Table 1).
  b. The relative risk among dengue vaccine recipients compared to controls after 60 months of follow-up was 0.2 (95% CI, 0.13–0.30) for dengue hospitalization, and 0.14 (95%CI, 0.05–0.33) for severe dengue.
- Among seronegative subjects of the same age group:
  a. VE against symptomatic VCD was 39% (95% CI, −1–63), with relative risks of 1.40 (95%CI, 0.70–2.80) for dengue hospitalization and 2.29 (95%CI, 0.44–11.92) for severe dengue.
  b. Vaccinated seronegative subjects developed less hospitalized VCD than non-vaccinated subjects until month 30, at which point case accumulation became greater among vaccinated subjects.

As depicted in Table 2, the similar incidence of hospitalization and severe dengue in vaccinated seronegative and unvaccinated seropositive subjects, is consistent with the hypothesis that vaccination of the former mimics a primary infection [23,24]. Therefore, due to the waning of protection, after 30 months vaccinated seronegative subjects would eventually be at the same risk as those with a natural primary infection.

No significant differences were observed during the 25 months active efficacy phase or during LTFU among 9+ years old vaccinated seronegative compared to unvaccinated seropositive subjects for length of hospitalization, duration of fever, clinical picture, viremia or cytokine patterns [21,24–28].

There were no differences between vaccinated and control subjects – regardless of baseline serostatus – in relation to incidence of non-dengue severe adverse events (SAEs) and fatal SAEs after 5 years of LTFU [23].

The combined CYD trials analysis revealed a marked reduction in the attributable risk of hospitalized and severe dengue among vaccinated seropositive subjects aged 9–16 years. Based on attributable risk estimations over a 5-year follow-up period, the numbers of hospitalized and severe cases prevented among vaccinated seropositive subjects would be 7 and 4 respectively, for each additional case occurring among vaccinated seronegative subjects. If vaccination occurs in a population with 70% seropositivity level, 7 hospitalized and 4 severe cases would be adverted, 13 and 7 cases with 80% seropositivity, and 28 and 16 cases with 90% seropositivity level [22–25].

1. Advantages of this design where a sub-cohort is selected from the original total cohort are: It allows for retrospectively testing new hypotheses from time 0; not all subjects from the original cohort require diagnostic tests; the selection bias is reduced since cases and the cohort belong to the same population; and the risk can be measured at any time. Disadvantages include: exposure information is collected at different times with potential for reduction in data quality over time; bias can still occur since the sub-cohort is established after time 0; statistical analysis requires assuming distributions and is based on imputations
2. For the CYD dengue vaccine trial, in the analyzed seronegative population older than 9 years of age, the case cohort study has a power of only 25% to show an increased risk of dengue hospitalization in the vaccine group over the placebo group (see Supplementary Appendix in Sridhar S, Luedtke A, Langevin E, et al., 2018) [25].

3. Evaluating serostatus at month 13 after initial vaccination has some limitations in establishing the immunological status at baseline since it may be influenced by asymptomatic infections with a wild type virus over the previous 12 months. In addition, some amount of cross-reactivity of anti-dengue antibodies with the NS1 protein of yellow fever, were identified during the data analysis. The correlation between the level of antibodies against NS1 at month 13 with the gold standard PRNT at month 0 was acceptable but not perfect, and misclassification, dependent on the NS1 threshold that was considered indicative of previous dengue exposure, affected the vaccine subgroup more than the placebo cohort.
4. The decision was made to choose the lowest threshold, not to miss any possible seropositive; however, this also resulted in an NS1 test specificity of 70–79%, implying that at least 21–30% of the subjects classified as seropositive at baseline would be false positive.
5. To avoid misclassification, the investigators imputed antibodies against NS1 at month thirteen to PRNT50 at month 0 via logistic regressions and a super learner. When available, serostatus at baseline PRNT50 results were used; otherwise, baseline status was imputed. However, it must be pointed that neither of these two analyses provided a perfect correlation, affecting more vaccinated than placebo arm, and VCD more than hospitalized cases; in such a way, that LTFU vaccine efficacy and safety could be artificially influenced in a negative way.
6. Extrapolating the estimates of attributable risk to a population of 1 million people aged 9–16 years in a high seroprevalence area (≥80%) suggests that over a period of 5 years, vaccination would prevent around 11,000 hospitalizations (12,000 avoided among seropositive persons and an excess of 1000 among seronegative persons), as well as around 2500 severe cases (3000 avoided among seropositives and an excess of 500 among seronegatives) [25].
7. The NNV (number needed to vaccinate) is a public health surveillance outcome expressing how many people need to be vaccinated to prevent a single disease case [29]. To prevent one case of hospitalization with VCD 201 subjects need to be vaccinated, while NNV equals 661 for severe dengue. In comparison, the NNV for influenza hospitalization among children 6–23 months of age is 2040, and NNV for vaccine serotype invasive pneumococcal disease is 1779 and for rotavirus hospitalization 200, in young Latin American children [30,31]. Therefore, NNV figures for dengue vaccine are similar to or better than other widely used vaccines.
8. Most VCD cases in the CYD trial were classified as grade I and II severity, conforming to WHO 1999 criteria. However, according to the new WHO classification, most of the severe cases will be labeled as dengue with alarm signs instead of severe dengue. There were no deaths due to dengue during the CYD study [24,25,27].
9. The case-cohort method and use of NS1 testing at month 13 to impute baseline serostatus had low power, used as a conservative anti-NS1 assay threshold, and had imperfect correlation between baseline PRNT and month 13 NS1, all of which could identify a falsely high association between dengue vaccine and severe dengue among baseline seronegative persons.
10. This vaccine, as with all vaccines, needs to be evaluated in the context of its overall impact on public health.

4. Safety data of the dengue vaccine in Parana State, Brazil

In Parana, the community-based dengue vaccination campaign started in August 2016. Thirty municipalities were selected based on disease incidence criteria and past epidemics. No seroprevalence studies were performed prior to the introduction of the vaccine. Based on the dengue burden by age identified by the Parana State Surveillance System, the vaccine was administered to 15–27 years old persons in 28 municipalities, and to 9–45 years old persons in 2 municipalities, with a total target population of 500,000 inhabitants. Three doses were administered at 6-month intervals [32,33].

In total, 674,681 doses were administered with a vaccine coverage of around 62% for the first dose (311, 058 vaccines), close to 44% (219, 078 vaccinated) for the second dose, and 29% (144,545 vaccinated) for the third dose completed in April 2018 [32,33]. Of the 30 municipalities listed to receive the vaccine, 24 immunized more than 50% of their target audience with three doses, and 10 cities reached more than 80% of coverage [34].

Databases from vaccination records (Vaccine Registration system) and dengue surveillance (Sistema de Informação de Agravos de Notificação, SINAN), were linked to assess vaccination status among persons with confirmed dengue illness. By 2017, a total of 311,053 subjects had been vaccinated in Parana, among whom, 49 (0.01%) had confirmed dengue. None of these cases required hospitalization. Overall, the number of confirmed dengue cases reported in the population of Parana was 1108 out of which 47 (4.2%) were vaccinated [32–34].

There were no deaths attributable to dengue vaccine. Although the vast majority of adverse events were mild and reported SAEs were not related to vaccination, it should be noted that follow-up period might be too short to see a potential detrimental effect of the vaccine and information is too scanty to be interpreted. No data on vaccine efficacy in this setting are yet available [32–34].

5. A dengue serotest as a complementary diagnostic to support vaccine implementation

As the CYD-TDV vaccine 5-year follow-up studies suggest that vaccinated seronegative persons have a higher risk of severe dengue and hospitalization the need has emerged for a rapid diagnostic test capable of detecting past dengue infections at the point of vaccination.

Ideally, a test with very high specificity (≥99%) would minimize individual risk and the inadvertent use of the vaccine in seronegative persons. A test with high sensitivity (≥90%) would maximize population benefit. In a 70% seroprevalence setting, there will be seven cases of severe dengue possibly caused by vaccination of test false positive individuals compared to 1050 cases if the vaccination is not given to those tested seropositive [35].

Among the two types of tests that could be considered (serological assays such as the dengue IgG ELISA, and rapid diagnostic tests (RDT)) only the later provides point-of-vaccination information.

A recent systematic review of studies assessing RDT performance showed that most demonstrated sensitivities and specificities between 80% and 100% for dengue IgG detection in samples from secondary infection or convalescent time-points after recent infection [36].

Additional research is needed to determine how RDTs would perform in relevant populations targeted for vaccination. Modifications to current RDT may optimize the performance of these tests for use in a pre-vaccination screening approach [36].

A preliminary evaluation of four commercially available RDTs (RDT Dengue IgA/IgG Bio-Rad, OnSite Dengue IgG/IgM CTK Biotech, SD Bioline Dengue IgG/IgM Alere/Abbott, Genbody Dengue IgG/IgM GenBody Inc.) and two conventional enzyme-linked immunosorbent assays (ELISA) to determine prior dengue infection was performed. Results showed a favorable specificity of >98% for the IgG component of RDT and ELISA. The rate of false positives due to Japanese Encephalitis or Yellow Fever cross reactivity was ≤3%

for the RDT, and higher for ELISA. Sensitivity varied from 40 to 70% for RDT and 90% for ELISA. Despite existing limitations in sensitivity, the high specificity of currently available RDT would justify their use in endemic settings, until better tests become available [37].

6. Public health impact of dengue vaccination: insights from recent information on safety and efficacy data

On the 29th November 2017, Sanofi issued a warning that Dengvaxia posed a risk when given to people not previously exposed to dengue [38]. Whereas other countries that have used this vaccine chose to advise relevant local authorities, changing the guidance and revising the label, the Philippines, where more than 830,000 children had received the vaccine, reacted with a dramatic public and political outcry. Despite no solid evidence, several deaths were claimed to be due to the vaccine. Among political turmoil, accusations of impropriety were directed at health authorities who had launched the vaccination campaign, and several researchers, regulators and the former Secretary of Health were held to be responsible. As a consequence, public anxiety and fear around the dengue vaccine, and vaccines in general, prevailed [35,39].

As part of post marketing surveillance, a recently published safety analysis by the Global Advisory Committee on Vaccine Safety (GACVS) evaluated dengue associated deaths in The Philippines [27,28]. GACVS members concluded that according to the WHO classification system for vaccine adverse events, 11 out of 14 fatal case reports were in fact indeterminate, coincidental (i.e., not related to the dengue vaccine) or unclassifiable. GACVS concluded that there was insufficient evidence available to make a final determination on the association between CYD-TDV receipt and deaths in The Philippines [27,28].

A yet unpublished model-based approach, using anti-NS1 serum level results to assess potential benefits and risks associated with dengue vaccination in different transmission settings and time horizons, with or without inclusion of vaccine indirect protection, has been developed and was discussed during the last IDI meeting by Sanofi Pasteur representatives (Coudeville L et al., personal communication).

Several results from the model were reported at the meeting. Persons seropositive when vaccinated had long-term and sustained benefit. Seronegative persons a) experienced a transitory period of risk due to higher severity of natural infection following immunization but, b) would still benefit from vaccination if they were more likely than not to have two subsequent natural infections with different dengue serotypes. Besides serostatus, other drivers of efficacy were age at the time of vaccination and viral serotype. In addition, unvaccinated seronegative individuals could benefit from indirect protection if vaccinating seropositive [40,41].

The potential impact of dengue vaccination was estimated with and without pre-vaccination screening in various transmission settings and using current (sensitivity 70%; specificity 99%) or optimized (sensitivity 90%; specificity 99%) RDT test characteristics. With pre-vaccination screening, the impact depended on test sensitivity for detecting past dengue exposure. Pre-vaccination screening enabled the implementation of larger programs associated with a higher impact, unless a large portion of the population was known to live in high transmission settings. In moderate transmission settings (50% at age 9 years), pre-vaccination screening was more efficient (and potentially more cost-effective) than a seroprevalence-based approach, provided that the screening cost was lower than the vaccine cost (<75% of the cost of administering a vaccine dose). In very high transmission settings (90% at age 9 years), seroprevalence-based vaccination remained more efficient than pre-vaccination screening (unless serotesting was very inexpensive, i.e. 10% or less of the cost of administering a vaccine dose).

In conclusion, this model suggests that in known high transmission settings (≥80% seroprevalence at age 9 years), seroprevalence-based vaccination was associated with the largest impact and is expected to be more cost-effective than pre-vaccination screening. In other settings or in the context of heterogeneous transmission, pre-vaccination screening would enable the implementation of larger vaccination programs and a broader impact on health, is potentially more cost-effective than a seroprevalence-based approach if testing is not too costly, and reduces the risks for seronegative individuals. RDT optimized for pre-vaccination screening should improve impact and cost-effectiveness of dengue vaccination programs.

Other modeling have calculated the expected PPVs for tests with varying sensitivity and specificity, and across a range of levels of seroprevalence. In high-transmission settings, where the true dengue seroprevalence is more than 70%, it is possible to achieve a PPV of more than 90% with screening tests across a range of sensitivities and specificities. This PPV would mean that less than 10% of individuals who test seropositive will be misclassified and erroneously vaccinated. By contrast, in settings with moderate or low transmission, higher sensitivity and specificity are required to achieve a PPV of 90%: where seroprevalence is 50%, the sensitivity and specificity of the assay must be greater than 90%; and where seroprevalence is less than 30%, tests with near perfect specificity (>98%), not yet available, would be needed [42,43]. Furthermore, in populations where the expected seroprevalence is very low (<5%), such as among travelers from non-endemic areas, even tests with very high specificity (95%) will misclassify more than half of those who test positive. In high-transmission settings, less than perfect tests might provide some benefit nevertheless [42,43].

Paradoxically, with currently available commercial RDT a pre-vaccination screening strategy would work better in high transmission settings, as in such scenery its public health impact depends primarily on the sensitivity of serological screening. In terms of cost effectiveness, although fewer vaccines will be used, there will be an additional cost for tests, which may not be affordable for low-income endemic countries. On the other hand, at low transmission settings both specificity and sensitivity need to be relatively high to minimize negative impacts, and increase coverage among the few who should be vaccinated [35,42,43].

It has been rightfully stressed that in some Latin American countries few locations would have seroprevalences >80% in 9 year olds, and that the spatiotemporal heterogeneity of dengue transmission, combined with the need for high seroprevalence thresholds, would necessitate large scale, costly serosurveys to identify suitable areas at micro scale. Thus, adding complexity and cost to any public vaccination program and limiting the overall public health impact potentially [24,35].

However, other regional experts have recently underlined the fact that pre-testing strategy in Latin America is highly context-specific and should be decided at the country level or even at sub-national levels, with interventions targeting very high endemicity areas only. Cost represents the main barrier. Moreover, in their opinion this approach would not be desirable in settings with very high seroprevalence (above 90%) since pre-screening would not add much value [35].

Finally, dengue transmission maps may prove useful to identify geographical areas in which populations would benefit the most from public dengue vaccination campaigns, by means of:

a. Identification of indicators likely to be associated with transmission intensity through simulation exercises (e.g. relative incidence in <15 year-old and +15 year-old).

b. Estimation of the relationship between these indicators and observed seroprevalence for areas where both data are available.
c. Elaboration of a set of criteria capturing the level of dengue burden and the environmental conditions (such as climatic criteria).
d. Prediction of seroprevalence at a fine geographical scale.

7. IDI recommendations for dengue vaccine use in Latin America

1. The disease should be better documented in each country and sub-region, in terms of:
   o Endemicity: specific areas where the disease occurs continuously and with a predictable regularity in a population, or sustained notification of dengue cases for 20 weeks or more in at least one of the last 5 years [34,44].
   o Severity.
   o Burden by age groups.
2. Each country should define local dengue transmission maps according to their epidemiological data, including incidence by age and hospitalization status, serotype circulation, frequency of outbreaks.
3. To define high transmission areas a combination of two or more of the following criteria may be useful [44]:
   o At least 2 dengue epidemics over the past 5 years.
   o Cumulative incidence over 500 per 100,000 population in the past 5 years.
   o Reports of dengue deaths in at least one of the past 5 years.
   o Co-circulation of at least 2 serotypes.
   o Higher hospitalization rates in adolescents as compared to other age groups.
4. Currently, many countries already have small-scale detailed maps describing the recent epidemiology of dengue, including seroprevalence data. These maps should continue to be used for prioritizing vaccine intervention areas, where immunization programs should be started, as soon as possible.
5. For seroprevalences studies, countries should use the guidelines developed by the WHO to design and conduct dengue serosurveys [45].
6. While vaccination is an important component of the integrated strategy for dengue prevention and control, other preventive measures need to be maintained, such as vector control, prevention of mosquito bites, information and communication training. Research activities on prevention measures need to be continued.
7. The characteristic of dengue transmission in target populations should be evaluated in advance of immunization, to help define the efficiency of either a mass vaccination based on high seroprevalence or a vaccination strategy based on point-of-care screening to target seropositive individuals.
8. In areas of high endemicity in which seropositive subjects predominate, the benefit of mass vaccination outweighs the risk to seronegative individuals at a population level. In high seroprevalence areas, studies to determine detailed information on seroprevalence over time or pre-vaccination serologic assessment would significantly increase the costs of vaccination programs and delay vaccine implementation for populations that would have substantial benefit from vaccine use. However, in countries of the region with a relatively high per capita GDP pre-vaccination strategy might be cost-effective from both, public payer and individual perspectives [46].
9. Countries should consider vaccination in municipalities or other defined areas that already have robust seroprevalence data and fulfil the above mentioned epidemiological criteria.
10. In areas of intermediate or low endemicity, where the risk of vaccinating seronegative individuals potentially could outweigh the benefit of vaccinating the entire population, pretesting to establish the patient's serostatus before vaccination is mandatory. This strategy would increase trust in the vaccination program and thus improve vaccination coverage, as well as generate seroprevalence data enabling subsequent decision making.
11. Dengue serostatus ascertainment considerations:
    o The ELISA capture test would not be practical due to the time it takes to obtain results, in addition to cross-reactivity with other flaviviruses. Consequently, it likely does not have a role in dengue vaccine implementation.
    o RDT implementable at point-of-care need to be easy-to-use, qualitative, applicable to whole blood, and validated to indicate past dengue infection at any age in any endemic setting.
    o The ideal RDT needs to be highly specific to avoid vaccination of seronegative subjects and highly sensitive to maximize the impact of vaccinating a higher number of seropositive subjects.
    o A reasonable option would be to use a test with the highest specificity currently available, even with imperfect sensitivity, while newer RDTs are developed.
    o Countries should use the best available tests, and help develop new ones by sharing epidemiological data and biological samples, and conducting demonstration projects with current tests.
12. The current vaccine is not indicated for outbreak response but it may assist with outbreak prevention.
13. Countries should implement a robust and documented vaccination information strategy, and optimal program planning. HPV vaccination strategies can serve as examples, and lessons learnt from HPV vaccine implementation should help dengue vaccination [47].
14. Vaccine-implementing countries should have robust surveillance for monitoring adverse events.
15. Dengue Committees should be strengthened and adequate information on vaccine and other prevention strategies given to those in charge of the program.
16. Surveillance should include number of doses given, epidemic situation, and clarifications on aspects of potential confusion for decision-makers, implementers, and patients.
17. Age:
    o The vaccine is currently indicated for persons 9 years of age or older.
    o Among those 9+ years of age, the target age of implementation needs to be in accordance with local regulatory agency recommendation.
    o For public campaigns, the age targets for vaccination should be in the age groups with higher seroprevalence or higher hospitalization incidences.
    o Previous vaccine adherence should be considered when identifying target age groups.
    o Vaccination of larger or complementary cohorts could be implemented to have a higher and faster impact. The extension of such campaigns will depend on modeling information using local data for optimal impact.
18. Countries should be empowered to take their own decisions based on evidence-based information and support from local and international experts.

19. The guidelines developed by scientific and medical societies (E.g. SLIPE) should be given more visibility and should help country decision-making.
20. In summary, dengue vaccination, where implemented, should be part of a public health strategy that includes the participation of scientific societies, the MOH and civil society.
21. These recommendations need to be updated regularly, as new scientific evidence becomes available.

Members of the International Dengue Initiative

- Arbo Antonio – Paraguay
- Leite Jose Geraldo – Brazil
- Arrendondo José Luis – Mexico
- López Eduardo – Colombia
- Avila María Luisa – Costa Rica
- López María Graciela – Venezuela
- Belaunzaran-Zamudio Pablo F – Mexico
- López Pío – Colombia
- Betancourt Cravioto Miguel – Mexico
- Luna Expedito – Brazil
- Bonvehí Pablo – Argentina
- Macías Alejandro – Mexico
- Bosco Joao – Brazil
- Macías Mercedes – Mexico
- Brea del Castillo José – Dominican Republic
- Mariño Cristina – Colombia
- Carrasquilla Gabriel – Colombia
- Martínez Cuellar Celia – Paraguay
- Casapía Martín – Peru
- Martínez Jose Guadalupe – Mexico
- Cassio De Moraes José – Brazil
- Mascareñas Abiel – Mexico
- Castellanos Javier – Mexico
- Melgar Mario – Guatemala
- Castro Hector – Paraguay
- Moreira Duarte Edson – Brazil
- Deseda Carmen – Puerto Rico
- Moreno Sarbelio – Mexico
- Dueñas Miriam de Lourdes – El Salvador
- Mosqueda Juan Luis – Mexico
- Esparza José – Venezuela
- Orduna Tomás – Argentina
- Falcón Lezama Jorge – Mexico
- Pascale Juan Miguel – Panama
- Falleiros-Arlant Luiza – Brazil
- Ramos Castañeda José – Mexico
- Freire De Andrade Jacy – Brazil
- Ramos Nicolas – Colombia
- Bradford D. Gessner – USA
- Reynales Humberto – Colombia
- Giglio Norberto – Argentina
- Rivera Doris – Honduras
- González Ayala Silvia – Argentina
- Rocha Crisanta – Nicaragua
- Hernández Marte – Mexico
- Rodríguez Hernán – Paraguay
- Giambernardino Heloisa – Brazil
- Salgado Doris – Colombia
- Isabelle Delrieu – France
- Torres Martínez Carlos – Colombia
- Lachira Arnaldo – Peru
- Torres Rojas Jaime – Venezuela

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.010.

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