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Conference report

Pre-vaccination screening strategies for the use of the CYD-TDV dengue vaccine: A meeting report

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ABSTRACT

The first licensed dengue vaccine, CYD-TDV (Dengvaxia) is efficacious in seropositive individuals, but increases the risk for severe dengue in seronegative persons about two years after administration of the first dose. For countries considering the introduction of Dengvaxia, WHO recommends a pre-vaccination screening strategy whereby only persons with evidence of a past dengue infection would be vaccinated. Policy-makers need to consider the risk-benefit of vaccination strategies based on such screening tests, the optimal age to introduce the vaccine, communication and implementation strategies. To address these questions, the Global Dengue and Aedes-transmitted diseases Consortium (GDAC) organized a 3-day workshop in January 2019 with country representatives from Asia and Latin America.

The meeting discussions highlighted many challenges in introducing Dengvaxia, in terms of screening test characteristics, costs of such tests combined with a 3-dose schedule, logistics, achieving high coverage rates, vaccine confidence and communication; more challenges than for any other vaccine introduction programme. A screening test would require a high specificity to minimize individual risk, and at the same time high sensitivity to maximize individual and population benefit. The underlying seroprevalence dependent positive predictive value is the best indicator for an acceptable safety profile of a pre-vaccination screening strategy. The working groups discussed many possible implementation strategies. Addressing the bottlenecks in school-based vaccine introduction for Dengvaxia will also benefit other vaccines such as HPV and booster doses for tetanus and pertussis. Levels of public trust are highly variable and context specific, and understanding of population perceptions and concerns is essential to tailor interventions, monitor and mitigate risks.

1. Introduction

Dengue is a major public health problem with more than 3.6 billion people living in areas at risk for dengue virus (DENV) infection and an estimated 390 million infections annually in over 120 tropical and sub-tropical countries [1,2]. Effective vector control strategies that are easily scalable remain elusive [3], community-based approaches have had mixed results, but have been generally unreliable and unsustainable [4,5], compliance with personal protective measures is difficult on a daily basis [6,7], and novel vector control measures, such as Wolbachia [8,9], if effective,

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will take years to implement [9]. Dengue is also increasingly affecting travelers and migrants [10–14]. An effective vaccine could do much to reduce the global burden of disease.

The first licensed dengue vaccine, CYD-TDV by Sanofi Pasteur, is a live attenuated recombinant tetravalent vaccine that has been evaluated in Phase 3 efficacy trials as a 3-dose 0/6/12 month schedule [15]. It was first licensed in 2015 in Mexico, and is now registered in 20 dengue endemic countries for use in individuals 9–45 or 9–60 years of age living in endemic areas [16]. In 2017, new evidence emerged highlighting the serostatus-dependent vaccine performance of CYD-TDV. Serostatus refers to whether a vaccinee had been infected by dengue (seropositive) or not (seronegative) prior to receiving the vaccine. In seropositive vaccine recipients, the vaccine was efficacious and safe, but in seronegative vaccinees, CYD-TDV was associated with an excess risk of severe dengue observed from about 3 years after the first vaccine dose [17]. WHO's Strategic Advisory Group of Experts on Immunization therefore recommended that countries considering the introduction of CYD-TDV should only do so if minimization of risk in seronegative individuals could be assured [18]. Pre-vaccination screening was recommended whereby only persons with evidence of a past dengue infection would be vaccinated.

To support a pre-vaccination screening strategy, WHO highlighted the urgent need for rapid diagnostic tests (RDTs) to determine serostatus. In addition to target product profiles for such RDTs, and providing access to RDTs, policy-makers need to consider the risk-benefit of vaccination strategies based on such screening tests, as no test will be 100% sensitive and specific. What may be considered as an acceptable level of specificity will depend on risk perceptions in different countries, as well as background seroprevalence.

The Partnership for Dengue Control (PDC) [19], as part of the Global Dengue and Aedes-transmitted diseases Consortium (GDAC), organized a 3-day workshop in January 2019, hosted by the Mérieux Foundation at Les Pensières, Annecy, France. PDC has organised previous think-tanks on dengue such as on immune correlates for dengue protection and enhancement [20], best practices for vector control [21], dengue and other flavivirus diagnostics [22], and development of standard clinical endpoints for the use in interventional studies [23,24].

The pre-vaccination strategy workshop was attended by policy-makers from dengue-endemic countries, epidemiologists, modellers, public health and laboratory scientists, an ethicist, communication specialists, and representatives of vaccine manufacturers and diagnostic companies.

The objectives of the workshop were to

- review the rationale for the pre-vaccination screening strategy and to learn from the experience of countries where CYD-TDV had been introduced, and
- discuss rapid diagnostic tests (RDT) for screening for past dengue infection (dengue serostatus), including to:
  - o discuss a draft target product profile for RDTs to support a pre-vaccination screening strategy;
  - o present a landscape analysis on RDT characteristics, and their sensitivity and specificity in different flavivirus endemic settings;
  - o elaborate on population level benefit versus individual risk; and
  - o address policy-makers' perceptions and views on risk-benefit assessment of an RDT as a pre-vaccination screening tool under different scenarios (high versus low seroprevalence)
- discuss implementation strategies for pre-vaccination screening programmes for dengue vaccines, including:
  - o practical issues for programmatic roll-out;
  - o the optimal age for vaccine introduction;
  - o communication strategies with regards to vaccine confidence, both for policy makers, the medical community and the lay public; and
  - o school-based campaigns

2. Background

2.1. Country experiences with CYD-TDV to date

CYD-TDV dengue vaccine was first licensed in Mexico in December 2015, quickly followed by the Philippines and Brazil. It is now registered in 20 dengue-endemic countries in Asia, Latin America, and the Pacific. Furthermore, the European Medicine Agency (EMA) issued marketing authorization throughout the European Union in December 2018 (https://www.ema.europa.eu/en/documents/product-information/CYD-TDV-epar-product-information_en.pdf) for the indication of prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9–45 years of age with prior dengue virus infection and living in endemic areas. Although many Europeans travel to dengue endemic countries [19], and an increasing proportion of travelers are seropositive [25–28], due to lack of safety and efficacy data in travelers, EMA excluded travelers from the indication. On 1 May 2019, the US Food and Drug Administration (FDA) approved CYD-TDV for use in seropositive individuals 9 through 16 years of age living in endemic areas of the U.S. Despite widespread licensure, to date, CYD-TDV has only been introduced in two public health programmes: in the Philippines and Brazil.

In the Philippines, the plan was to administer CYD-TDV in schools to approximately one million 4th grade children (9–10 year olds) in highly endemic regions, starting April 2016. When Sanofi Pasteur announced the safety signal in November 2017 (https://mediaroom.sanofi.com/en/press-releases/2017/sanofi-updates-information-on-dengue-vaccine/), highlighting that seronegative persons should not receive the vaccine due to an increased risk of severe dengue, the programme was suspended. By then, over 830 000 children had received the vaccine, the majority three doses, but several hundred thousands had only received two doses or one dose. The public reaction in the Philippines to the press release was immediate outrage. Several deaths from dengue were claimed to be due to the vaccine. Political turmoil ensued, and several researchers, regulators and the former Secretary of Health were held to be responsible [29]. The result was broken public trust around the dengue vaccine and heightened anxiety around vaccines in general [30]. The Vaccine Confidence Project™ measured the impact of this crisis, comparing confidence levels in 2015, before the incident, with levels in 2018. The findings reflect a dramatic drop in vaccine confidence from 93% "strongly agreeing" that vaccines are important in 2015 to 32% in 2018 [30] with a subsequent resurgence of measles in the Philippines, in line with the global resurgence of measles [31–33]. Lessons learnt included the importance of communication around introduction of any new vaccine to avoid distrust and lack in vaccine confidence. In the case of the dengue vaccine, mistrust was greatly enhanced by the recognition of potential serious adverse effects that were not apparent at the time of vaccine introduction.

In Brazil, the state of Paraná decided to introduce CYD-TDV® in response to the state's largest dengue outbreak in history in 2015–2016. Municipalities were selected based on two criteria (i) municipalities that had three or more outbreaks in the previous 5-year period, with incidence rates >500/100,000; or (ii) an incidence rate above 8000/100,000 in the year of introduction (2016). Two municipalities fulfilled the latter criterion and 28 the former. In the first group of municipalities the target was the age group with largest incidence of reported cases, 15–27 years of age. In the second, the target was from 9 to 44 years of age, the entire age range for which the vaccine was licensed in Brazil. The target population was estimated to be 500,000. Three vaccine campaigns were carried out between 2016 and 2018. Vaccine uptake was 61% for the first dose, 43% for the second, and 22% for the third dose (personal communication, Dr Luna). The rapid decline in the uptake of the third dose was a result of the negative media messages around CYD-TDV after November 2017. To evaluate the effectiveness of the vaccination a case-control study of incident cases has been set up. However, a major limitation to the study has been the low transmission of dengue in Brazil during 2017–2018, possibly due to some degree of cross-protection from the preceding ZIka outbreak [34]. No risk of severe dengue was reported in vaccinees in Brazil, as dengue incidence was so low in the years following CYD-TDV introduction.

2.2. Evidence for serostatus dependent performance of CYD-TDV and WHO's recommendations on the use of CYD-TDV in 2018

The data that led to the 29 November 2017 Sanofi Pasteur press release were based on additional retrospective analyses of the Phase 3 trial data. An excess risk of severe dengue in those vaccinated had been detected in children aged 2–5 years [15], and this prompted further analyses using a new immunological assay to determine if the risk was associated with age per se or was due to a higher proportion in this age group having had no previous dengue infections. These latter analyses in blood samples taken at month 13 of the trial demonstrated that while the vaccine offered substantial protection among those who had been previously infected with dengue, dengue-naïve vaccinees were at increased risk for dengue hospitalization and severe dengue during the 5 year trial follow-up compared to similar children in the placebo group [17]. These retrospective analyses showed that in seropositive trial participants aged 9–16 years, over 66 months follow-up after administration of the first dose of CYD-TDV, hazard ratios (HRs), comparing vaccinated to placebo recipients, for hospitalized virologically confirmed dengue (VCD) and severe VCD were 0.21 (95% CI: 0.14–0.31) and 0.16 (95% CI: 0.07–0.37), respectively. Cumulative incidence of hospitalized VCD and severe VCD up to month 60 after the first vaccine dose were 0.38% (95% CI: 0.26–0.54%) and 0.08% (95% CI: 0.03–0.17%), respectively, in vaccine recipients and 1.88% (95% CI: 1.54–2.31%) and 0.48% (95% CI: 0.34–0.69%) in placebo recipients [17]. In seronegative participants aged 9–16 years, HRs for hospitalized VCD and severe VCD were 1.41 (95% CI: 0.74–2.68) and 2.44 (95% CI: 0.47–12.56), respectively. Cumulative incidence of hospitalized VCD and severe VCD up to month 60 after the first dose were 1.57% (95% CI: 1.13–2.19%) and 0.40% (95% CI: 0.22–0.75%) in seronegative vaccine recipients, respectively, and 1.09% (95% CI: 0.53–2.27%) and 0.17% (95% CI: 0.04–0.83%) in unvaccinated seronegative recipients [17].

Based on these findings, WHO's position published in 2018 is that for countries considering CYD-TDV vaccination as part of their dengue control programme, a pre-vaccination screening strategy, in which only dengue-seropositive persons are vaccinated, is the recommended strategy [35].

3. Desired characteristics of screening tests

A screening test would require a high specificity to minimize individual risk and the inadvertent use of vaccine in seronegative persons by reducing the number of false positive test results, and at the same time high sensitivity to maximize individual and population benefit by identifying a high a proportion of previously exposed persons who will benefit from vaccination. The required sensitivity to achieve a high positive predictive value (PPV) will depend on the seroprevalence in the population on which the test is conducted and on the test specificity. The PPV of a test would be a unifying indicator for an acceptable safety profile of a pre-vaccination screening strategy [36]. Furthermore, an additional reasonable criterion for the selection of a diagnostic test is that those who are deemed ineligible for vaccination as a result of the test, should be at a lower risk of hospitalized or severe dengue disease if they are left unvaccinated than if they are vaccinated [37]. In the Phase 3 trials of CYD-TDV, the 5-year cumulative incidence of dengue hospitalization in over 9-year-old vaccinees was reduced by 1.5 per 100 and elevated by 0.48 per 100 in comparison to their control arms for seropositive and seronegative participants, respectively [37]. Hence, if more than 25% of the test-negative, in a pre-vaccination screening strategy, are misclassified, then, on average, the test negative person would benefit from vaccination. In other words, a meaningful rapid diagnostic test will need a negative predictive value (NPV) of at least 75% [37].

Conventional dengue IgG ELISA diagnostic tests, which can be used to identify DENV IgG, are not the preferred option for large scale screening as they require the expertise of phlebotomists and can overwhelm laboratory capacities if used in national vaccine introduction programmes. Conventional dengue IgG ELISA should nevertheless not be discarded as a possibility, as they could be appropriate in certain settings such as school-based programs. However, RDTs would clearly offer a more convenient method for pre-vaccination screening at point-of-care, thus enabling single visits for both screening and vaccination.

3.1. Draft target product profile (TPP) for a dengue RDT for the diagnosis of previous dengue infection

An early draft TPP was presented at the meeting, and further refined through large group and individual discussions, along with semi-structured individual interviews with 16 dengue experts. The TPP defines medical and public health needs and makes them transparent to test developers. Collaborative development of TPPs ensures alignment between users, implementers, clinicians and technical experts. Desired characteristics mentioned by a majority of dengue experts were included in the TPP (Table 1), with median values used for quantitative responses. This process is being led by the Foundation for Innovative New Diagnostics (FIND), a not-for-profit global health organization focused on innovation, development, and delivery of diagnostics for diseases affecting the world's poorest populations.

Concern was raised about the feasibility of such high sensitivities and specificities. A number of suggestions were provided by audience members and focused around the characterization of reference samples, healthcare system requirements, and sensitivity and specificity. During the discussions, it became clear that each country will develop a tailored vaccination strategy and, therefore, developing a generalized TPP at this time may be premature. Experts from FIND therefore suggested that further country-specific discussions are needed with vaccine implementation partners within the government agencies to clarify how a vaccination campaign may be implemented, which populations will be prioritized and what types of testing facilities will be available in order to properly develop TPP that match the most frequent use cases. A final TPP will not be published until this work is completed. In order to bring dengue diagnostic tests to the market, appropriate studies will need to be conducted to evaluate critical TPP characteristics such as use of innovative formats for determining past infections, cross reactivity, and stability, and meet stringent regulatory authority approvals. In addition, implementation strategies and tailored toolkits will need to be developed to support priority

Table 1
Preliminary Draft Target Product Profile (TPP) for a dengue rapid diagnostic test (RDT): minimal and optimal characteristics of a test in the context of pre-vaccination screening.

CHARACTERISTICC	MINIMAL	OPTIMAL	COMMENTS
Scope			
Goal of Test	RDT for detection of dengue-specific IgG antibodies indicative of previous dengue infection		Detection of all 4 serotypes
Target Population	Individuals eligible for dengue vaccination		Vaccine licensed for 9–45 years old living in endemic areas
Target User	Minimally trained community health worker		Could be the same person who is giving the vaccine
Target Use Setting	Community based settings (schools, community vaccination campaign), clinics, hospitals		Should be usable in low to high endemicity settings
Healthcare System Requirements	Functioning vaccination program with clear understanding and ability to communicate the risks and benefits of vaccination	Same as minimal, plus: - Serosurveys - Risk/benefit analysis - Reference laboratory	
Assay Characteristics			
Specimen type	Fingerprick whole blood ≤100 µl	Fingerprick whole blood ≤25 µl	
Specimen handling	Maximum 2 handling steps after fingerprick	Direct application of whole blood without handling	
Time to result	30 min	15 min	
Result interpretation	Visual/qualitative	Automated reader/semi-quantitative grading of strength of positivity	
Price per test	≤USD 7.50	≤USD 2.50	
Biosafety and waste disposal	Simple waste biosafety disposal		
Assay stability: transportation	No cold chain	No cold chain, withstand transport stress	Use of vaccination supply chains may help facilitate transportation of test kits
Assay stability: operating conditions and shelf life	10–30 °C and 80% relative humidity, ≥12 month shelf life	5–40 °C and 95% relative humidity or individually sealed tests with desiccants to enable humidity proof packaging, ≥ 18 month shelf life	
Internal control	Internal process control line visually to indicate proper functioning	Presence of additional detection lines to identify cocirculating flavivirus antibodies for flow-type test formats, for example.	Future research may demonstrate if other flavivirus antibodies will affect the dengue vaccine performance
Resulting reporting and assay connectivity	No connectivity; manual result reporting in vaccination record	Automated reader with connectivity for transfer of results to electronic medical records/databases and patient result notification	Adequate result reporting can also facilitate repeat testing of negative individuals
Test performance			
Clinical Sensitivity	≥90%	≥95%	Specificity is a higher priority than sensitivityPerformance shall be determined in appropriate samplesDengue seroprevalence will impact the required specificity of the test
Clinical Specificity	≥90%	≥98%	
Positive Predictive Value	≥90%	≥95%	
Negative Predictive Value	≥90%	≥95%	
Cross-Reactivity	No cross-reactivity to other flaviviruses No cross-reactivity to circulating antibodies from other flavivirus vaccinations No cross-reactivity to endogenous substances and other pathogens		
Characterization of Reference Samples	Samples from individuals with: - proven past dengue infection - no known flavivirus exposure and no evidence of dengue IgG - proven previous infection with other flaviviruses - prior flavivirus vaccination	Samples from a well-characterized cohort including individuals with - virological confirmation of acute dengue infection with varying timepoints after resolution of acute infection - no known flavivirus exposure and no evidence of dengue IgG - proven asymptomatic past dengue infection - previous infection by other flaviviruses with varying timepoints after resolution of infection - previous infection by both dengue and another flavivirus with varying timepoints after resolution of infections - who have received other flavivirus vaccinations	

countries in rolling out successful and safe vaccination campaigns. Lastly, practicalities of RDTs such as training needed for interpreting RDT read-outs, the necessity of cold-chains, and storage needs for screening communities under field conditions of hot climates still need to be addressed.

3.2. Availability of RDTs for the purpose of pre-vaccination screening

Due to the high extent of homology between the flaviviruses, all IgG based assays are marred by cross-reactivity, which poses an increasing problem given the widespread co-circulation of Zika

(ZIKV), West Nile (WNV), yellow fever (YFV) and Japanese encephalitis (JEV) viruses in Latin America and Asia [38]. At the moment, no RDT is designed for detection of past dengue infection, nor evaluated in the context of co-circulating flaviviruses and flavivirus vaccinations. New RDTs or modifications to current RDTs are feasible and may optimize the performance of these tests for use in a pre-vaccination screening approach. A challenge will be to improve sensitivity to detect lower levels of IgG from past infection while not negatively impacting test specificity. A systematic review summarized the performance of 4 dengue IgG RDTs as determined in 3137 individuals across 10 studies conducted in 13 countries, with serum used in most of the studies [39]. The majority of studies demonstrated sensitivities and specificities between 80 and 100% for dengue IgG detection in samples from secondary infection or convalescent time points after recent infection, but data were limited with regards to testing cross-reactivity with other flaviviruses, in particular Zika virus.

Further evaluations were presented by Sanofi Pasteur representatives at the meeting to compare the performance of existing dengue IgG-detecting RDTs. Sanofi Pasteur's landscape analyses identified 20 companies with commercialized dengue IgG lateral flow tests, that are compatible with WHO-ASSURED criteria, and that take into account disease complexity (serotypes, cross-reactivity with other flaviviruses, and primary vs. secondary infection). Four RDT were sub-selected for laboratory evaluation to assess diagnostic sensitivity and specificity in detecting past dengue infection and two IgG ELISAs were selected as comparators (manuscript in preparation). All four tests evaluated showed high specificity (over 99%) and minimal antibody cross reactivity with other flaviviruses (Yellow fever and Japanese encephalitis), but evaluation was limited for Zika and West Nile virus due to the small number of positive samples available for testing (manuscript in preparation). Nevertheless, compared to ELISAs, IgG component of all tested RDTs was less cross-reactive to related flaviviruses, especially WNV and Zika. However, the RDTs showed relatively low sensitivity (40–70%). For three tests out of four, detection rates were comparable for documenting recent and remote infections. Dengue IgG detection appears to be durable though 3–4 years but durability beyond four years remains to be demonstrated.

Sanofi Pasteur is committed to work with manufacturers to develop an IgG-based RDT optimized for accurate identification of prior dengue infection, with the aim to achieve initial registration by end of 2020. Despite existing limitations, currently available dengue RDTs could be considered for identification of prior dengue infected individuals in endemic settings, assuming local assessment of performance and expanded evaluation of cross-reactivity, especially for Zika, yellow fever and West Nile viruses has been done.

3.3. Impact and cost effectiveness of a pre-vaccination screening strategy depending on RDT performance

The recent use of the NS1 assay in combination with multiple imputation techniques allowed calculation of the cumulative risk of dengue hospitalization and severe dengue over the 5-year trial follow-up and its stratification by serostatus [17]. Using these risks allows simple extrapolation of dengue risk to different seroprevalence settings and a test and vaccinate strategy with given sensitivity and specificity of a diagnostic test (Table 2).

To evaluate the potential impact and cost-effectiveness of a pre-vaccination screening strategy with CYD-TDV, vaccine introduction to a single age of nine years was simulated over a range of test sensitivities and specificities. An agent-based model of DENV transmission was applied to identify the conditions under which such a strategy would have positive impacts on health and be cost-effective, for given transmission settings, defined by the proportion of nine-year olds with previous DENV exposure (PE_9). As seen from Fig. 1, from a population perspective (Fig. 1 top panel), the public health impact is maximized at low PE_9 when both specificity and sensitivity are relatively high (first reduces negative impacts, and latest increases coverage among the few who should have been vaccinated). In high-transmission settings (the highest PE_9), public health impact depends primarily on the sensitivity of serological screening. The higher the seroprevalence of a setting, the higher the test sensitivity should be.

In low-transmission settings ($PE_9 \leq 0.3$), the risk benefits of vaccination depends on the sensitivity and specificity, with a significant reduction in risk (<0.6) with very high values of specificity (almost 100%). In very low transmission settings (PE_9 around 0.1), vaccinees are at higher risks than unvaccinated persons unless perfect test-specificity is achieved, which means that the pre-vaccination screening strategy should ideally only be used in high transmission settings.

In terms of cost effectiveness, if a pre-vaccination screening strategy is used, fewer vaccines will be used, however, there will be an additional cost for tests. Scenarios about the cost-effectiveness of screening and vaccination were chosen to be representative of Brazil and the Philippines. Results indicate that a pre-vaccination strategy could be cost-effective from both, public payer and individual perspectives in some economic settings only. Using an agent-based model to simulate DENV transmission with and without vaccination over a 10-year timeframe, Guido Espana presented his findings across a range of seroprevalence settings. They projected the proportion of symptomatic and hospitalized cases averted as a function of the sensitivity and specificity of the screening test [40]. Cost-effectiveness could be achievable from the perspective of a public payer provided that sensitivity and the value of a disability-adjusted life-year were both high, but only in high-transmission settings. Requirements for reducing relative risk and achieving cost-effectiveness from an individual perspective were more restricted, due to the fact that those who test negative pay for screening but receive no benefit. Their results predict that cost-effectiveness could be achieved only in high-transmission areas of dengue-endemic countries with a relatively high per capita GDP, such as Panama (13,680 USD), Brazil (8649 USD), Mexico (8201 USD), or Thailand (5807 USD), but not in the Philippines. In conclusion, vaccination with CYD-TDV following serological screening could have a positive impact in some high-transmission settings, provided that screening is highly specific (to minimize individual harm), at least moderately sensitive (to maximize population benefit), and sufficiently inexpensive (depending on the setting). Additional scenarios can be evaluated in a web-based application [41].

Eventually CYD-TDV introduction may be decided on the basis of affordability rather than cost-effectiveness, particularly since the latter is designed to prioritize the avoidance of life years lost which is rarely the case for dengue. A higher willingness to pay for vaccine will occur at times of outbreaks with increased community fear and media attention.

3.4. Implementation strategies for CYD-TDV dengue vaccine

At the country level, the decision about implementing a pre-vaccination screening strategy with the currently available tests will require careful assessment including considerations on dengue burden, local priorities, test performances, and affordability of both the vaccines and screening tests.

(1) Optimal age for the introduction of CYD-TDV:

The transmission intensity in the target areas and the age at vaccination are critical factors. If selecting too young a population,

Table 2
Impact of pre-vaccination screening tests with different sensitivity and specificity scenarios at different seroprevalence settings on number of hospitalized dengue cases averted or triggered, stratified by serostatus.

ivaSeroprevalence	Sensitivity	Specificity	Hospitalized Cases averted out of 100,000 vaccinees			
			In seropositives	In seronegatives	In total	Averted/Caused
90%	100%	0%	1357	−48	1309	28.4
	100%	100%	1357	0	1357	Inf
	90%	100%	1221	0	1221	Inf
	90%	90%	1221	−5	1217	255.5
70%	100%	0%	1056	−143	912	7.4
	90%	90%	950	−14	936	66.3
50%	100	0%	754	−239	515	3.2
	90%	90%	679	−24	655	28.4

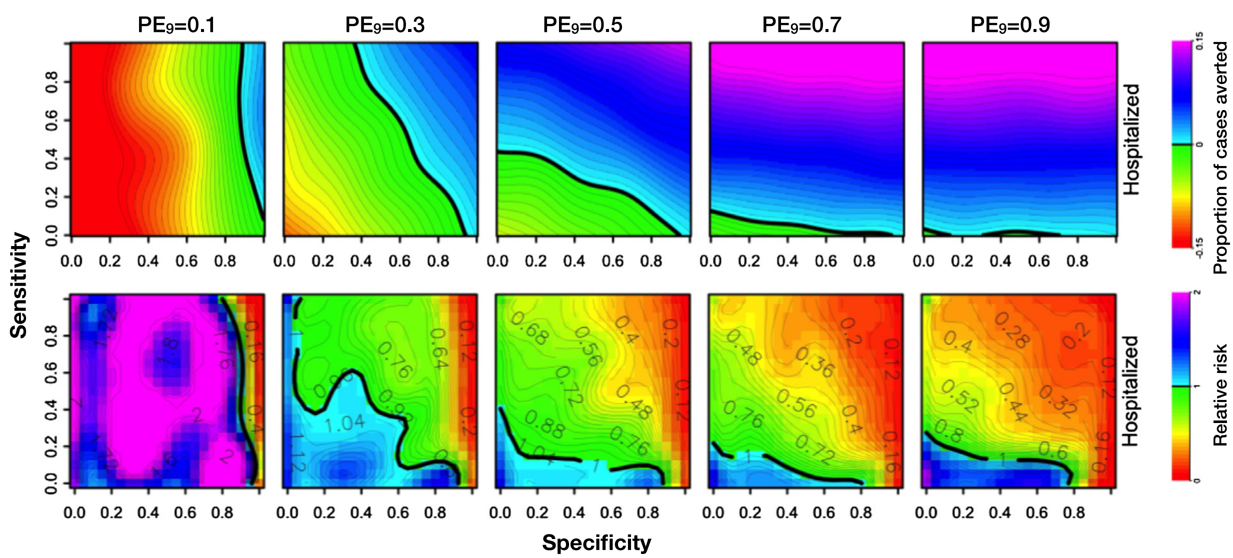

Fig. 1. Conditions for positive impact from a population perspective. cumulative proportion of hospitalized cases averted in the population over a 30-year period. y-axis: sensitivity; x-axis: specificity; each column shows results for a given transmission setting defined by the proportion of 9 year olds with previous dengue infection (PE9).

a high proportion of individuals may still be seronegative, which will be costly in the case of the test-and-vaccinate strategy and will increase risks related to seronegative vaccination. If selecting older age groups, a high proportion may already have had two infections, which minimize vaccine impact on preventing severe dengue [42].

Individuals who had only one past dengue infection (monotypic past infection) will benefit most from CYD-TDV. The likelihood of having had only one past dengue infection depends on age and transmission intensity. The age at which severe dengue (for which hospitalizations is a proxy) peaks can be used to guide the optimum age for vaccine introduction, as the aim is to target those who have had monotypic infections. The optimal age target for vaccination in a given area is just before the age group in which the highest dengue hospitalization incidence is observed. Fig. 2, extracted from the SAGE background paper depicts the optimal age for dengue vaccine introduction [42].

(2) School-based introduction:

Schools are an increasingly attractive setting for delivery of these new immunisations because of their ability to reach large numbers of children in a short period of time [43]. Experience with HPV vaccinations at schools can be used to guide dengue vaccination programs. While HPV or TT-containing vaccines could be co-administered based on age indication, there are currently no co-administration data, however, Sanofi Pasteur has several ongoing studies to this regard. Experiences with new visits/school-based campaigns suggest substantial programmatic costs, unless integrated with existing school-based programs (http://amp-vaccinology.org/activity/dengue-vaccination-program-toolkit). However, there are many challenges to school-based programmes, including lack of space for vaccination in schools, lack of facilities for the immediate management of AEFI, disruption of school routine, and shortage of health workers.

Although RDTs would render a school-based campaign easier, it would not be inconceivable that schools would allow for an initial blood taking session, combined with a second session after an interval of a week or more to vaccinate those school children whose blood tests identified them as seropositive.

Understanding the facilitators and barriers is important for improving the delivery of future school-based vaccination programmes. These factors included programme leadership and governance, organisational models and institutional relationships, workforce capacity and roles particularly concerning the school nurse, communication with parents and students, including methods for obtaining consent, and clinic organization and delivery [43]. Strong partnerships between health authorities and educational staff would be crucial, which depends heavily on the commitment of local officials.

3.5. Communication challenges

There is a strong need to develop mature communication plans taking into account patients' autonomy of choice based on risks

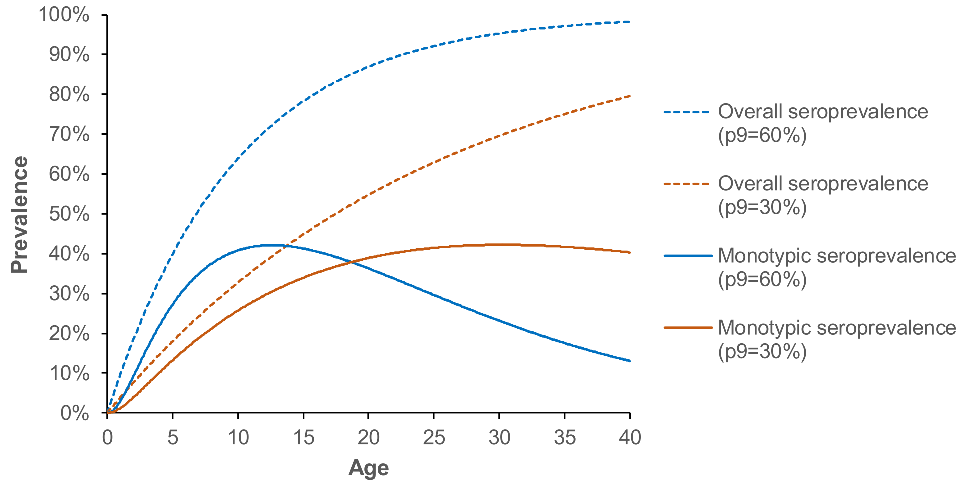

Fig. 2. Optimal age for the introduction of CYD-TDV (from the WHO SAGE background paper: https://www.who.int/immunization/sage/meetings/2018/april/2_DengueBackgrPaper_SAGE_Apr2018.pdf. Illustrative profiles of overall seroprevalence (1 or more past dengue infection) by age (dashed lines) and monotypic seroprevalence (only one prior dengue infection) by age (solid lined) for two transmission settings, corresponding to seroprevalence in 9 year-olds of 60% (blue) and 30% (orange). Single round screen and vaccinated policies need to target the age of peak monotypic seroprevalence for maximal impact (Figure prepared by Neil Ferguson for the SAGE background paper 2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and articulated benefits. Full disclosure of the risks of vaccination should therefore be ensured. Some seronegative individuals would be unintentionally vaccinated based on a false positive test result, as it is unlikely that any test will be 100% specific. In addition, although the efficacy against dengue infections in seropositive individuals is good, it is not complete. Therefore, transparent communication is needed to inform vaccinees that they are still at risk of dengue and should adhere to other disease preventive measures, and should seek treatment if they develop dengue-like symptoms.

Communication to the public regarding the rationale for pre-vaccination screening, including blood taking, will be complex. The fact that vaccination is only appropriate for those who have had a past dengue infection may be counterintuitive to the general public, and could also lead to confusion among health-care providers [18].

A major challenge with the implementation of a new vaccine with limited efficacy and controversial safety profile is how to communicate risks while building vaccine confidence. Fake news are largely and quickly amplified by social media and anti-vaccination groups are very organized and efficient in spreading doubts in population, using all kind of communication channels, from organized website to road-side billboards questioning vaccination. This trend is observed in a vast range of settings, from high- to low-income countries [44]. The Vaccine Confidence project conducts global research on vaccine confidence and has developed multiple metrics to assess attitudes towards vaccination, including a Vaccine Confidence Index [45–47]. Recommendations based on robust scientific and medical evidence are no longer sufficient to guarantee the population adherence to vaccination programs. Vaccine hesitancy rides the waves of emotions, religious or philosophical beliefs, imperfections of vaccines, uncertainties on AEFI, global environment of distrust, populism and political agendas. New research on a vaccine, new recommendations and policy change can also cause concern and suspicion in a population, as well as the organized effort of various protest groups (e.g. anti-vaccine, anti-big business, anti-system, anti-government).

The Philippines experience showed the speed of social media and public outcry which led to major collateral damage: public trust around the dengue vaccine and around vaccines in general was broken. Major measles outbreaks are now occurring in the Philippines [30]. The spill-over to other countries may have deleterious effects on measles resurgence globally, at a time when vaccine uptake is already low in many endemic populations and migrants [48–52].

Levels of public trust are highly variable and context specific, and understanding of population perceptions and concerns, historical experiences and religious, political and socioeconomic context is essential to tailor interventions, monitor and mitigate risks. Routinely identifying gaps or breakdowns in public confidence seems essential to avoid major crisis, rebuild trust and preserve national and global public health. Vaccine communication on social media should be also strengthened to deliver accurate information and counter rumours as they arise.

4. Interactive workshop on countries opinions and preferences on the pre-vaccination screening strategy

Workshops were conducted with regional country representatives to discuss acceptable test performance thresholds and programmatic strategies.

4.1. Latin american group

For the purpose of a "test and vaccinate strategy" in Latin America, the conclusion of the group was that the minimum test performance thresholds for sensitivity and specificity would be 85% and 95% respectively, assuming that any higher standards will not be achievable. They recommended using currently available dengue IgG ELISA in the short term while waiting for an optimized RDT. The Latin America group recognized that the implementation approach is highly context-specific and should be decided at the country level or even at subnational levels, with interventions targeting very high endemicity areas only. The age group to target should be informed by age stratified seroprevalence data by municipality, and age group for which hospitalization peaks. The experts favored a school-based strategy.

It was also discussed that a pre-vaccination screening strategy would not be desirable in settings with very high seroprevalence (above 90%) as most of the population would be seropositive, and pre-screening would not add much value. Conversely, it would be difficult to obtain public funding for such a strategy if the seroprevalence was below 50%, as only a few would benefit from vaccination. The group concluded that costs are the main barrier. The costs of dengue vaccine introduction is exacerbated by the costs of the programme, the test itself, and a 3 dose vaccine schedule, with a cost of the individual dose being higher than most of the standard childhood vaccines.

4.2. Asia Pacific group

The group stated that population serosurveys should be done prior to implementing the "test and vaccinate strategy" since the trade-off for the sensitivity and specificity of RDTs depends on the background seroprevalence. In a 70% seroprevalence setting, a test with 85% sensitivity and 95% specificity may be acceptable. Using this scenario, there will be 7 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.

While Malaysia and Singapore restrict dengue vaccination to the private sector, Thailand would rather consider a school-based national implementation. As Thailand's surveillance data record highest incidence of severe dengue among those aged 10–14 years, it would be advisable to target the age range of 10–12 years, preceding the peak incidence of severe dengue. The third dose of vaccination should be done before children graduate from primary school, as many children will change schools and some will dropout from the school system. The group confirmed that high sensitivity of the test is needed for the pre-vaccination strategy especially in high transmission setting. With poor sensitivity, the pre-vaccination strategy may become unfeasible as many seronegatives will be true seropositives. After all exhaustive efforts, if a test with high sensitivity is technically not feasible, then the decision of implementation may be done on the basis of high seroprevalence only. The government would need to consider a combination of factors before deciding to introduce the vaccine such as the expected impact, cost-effectiveness and public acceptance. The Thai representatives believed the country is still open for that consideration.

Singapore's low intensity in dengue transmission has resulted in a low seroprevalence of only 14% at 16–20 years old age group [53]. National implementation is clearly not cost-effective; even with a pre-screening test, in a low seroprevalence setting the number of false-seropositives in large scale screening programmes would be unacceptably high.

5. Conclusions and outlook

Both working groups highlighted many challenges in introducing CYD-TDV, in terms of costs, logistics, achieving high coverage rates and communication; more challenges than for any other vaccine introduction programme. Implementation of a pre-vaccination screening strategy in all dengue-endemic countries is delayed due to the fact that a screening test is not yet available. Among the most critical challenges and rate-limiting steps to bringing new diagnostic tools to the market are the availability and access to quality specimens for test development and validation, the sporadic funding due to changing prioritization of diseases, and the discrepancy between test assessment methods [54,55]. Given that a 100% specific or sensitive test is technically not achievable, high seroprevalence rates are crucial to decide on the best trade-off between sensitivity and specificity, with the PPV as a the most suitable indicator for an acceptable safety profile of a pre-vaccination screening strategy. In a high seroprevalence area, a test with a very high sensitivity is required. In a low seroprevalence area, very high specificity is the most important feature.

Research is also needed to evaluate vaccine schedules with fewer doses in seropositive individuals, and to assess the need for booster doses for CYD-TDV [35]. The working groups discussed many possible implementation strategies and the advantages and disadvantages thereof, but operational and implementation research will now be needed to provide better guidance. Addressing the bottlenecks in school-based vaccine introduction for CYD-TDV will also benefit other vaccines such as HPV and booster doses for tetanus and pertussis.

The development of a safe, effective, and affordable dengue vaccine for use irrespective of serostatus remains a high priority.

Contributions

AWS, DJG, RL, MC, CK-C, AD, IKY served on the organizing committee for this workshop. All authors gave presentations during the workshop. AWS wrote the first draft. All authors contributed to the final draft.

Disclaimer

AWS serves as consultant to the World Health Organization (WHO), Initiative for Vaccine Research. SF and PGS served as members of the WHO SAGE working group on dengue vaccines. I-KY is an ad-hoc expert invited to the SAGE working group. CK-C is employed by FIND, RL serves as a consultant to WHO and FIND.

The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO or FIND.

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Declaration of Competing Interest

AWS, HL, RL, MC, CK-C, SF, PT and DC have nothing to declare. PGS is a member of the Independent Data Monitoring Committee for trials of the Sanofi-Pasteur dengue vaccine (Dengvaxia). I-KY's institution received unrestricted grants from Sanofi Pasteur related to dengue vaccines. AD is the Principal Investigator of several trials and studies related to the TV003/005 dengue vaccine. DJG holds shares with Takeda. DC's institution has received restricted grants from Sanofi Pasteur for its weekly vaccine news digest which is unrelated to dengue vaccines.

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