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Workshop Report

Pre-vaccination screening for the use of dengue vaccines with differential performance dependent on serostatus: rapid diagnostic tests and implementation strategies

Les Pensières Center for Global Health, Annecy, France
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Table of contents

Foreword

Dengue is a major public health problem with more than 3.6 billion people at risk for dengue virus (DENV) infection and an estimated 390 million infections annually in over 120 tropical and sub-tropical countries. In the absence of truly effective and sustainable vector control measures, a dengue vaccine is urgently needed. The first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was first licensed in December, 2015 and registered for use in individuals 9-45 or 9-60 years of age living in endemic areas. CYD-TDV is a live attenuated recombinant tetravalent vaccine that has been evaluated as a 3-dose series on a 0/6/12 month schedule in Phase III clinical studies. New evidence highlighted the serostatus-dependent vaccine performance of CYD-TDV; a retrospective analysis of clinical trial data, stratifying participants according to their dengue serostatus before the first vaccine dose, revealed an excess risk of severe dengue in seronegative vaccine recipients, while in seropositive vaccine recipients, the vaccine was efficacious and safe. Whether this serostatus-dependent vaccine performance will also be observed for the second-generation dengue vaccines is currently unknown. However, a differential performance based on baseline serostatus is theoretically possible for all live dengue vaccines.

SAGE provided revised recommendations in April 2018 on how best to use this vaccine in populations at risk:[1] Countries considering the introduction of CYD-TDV should only do so if the minimization of the risk in seronegative individuals can be assured. The pre-vaccination screening is the preferred strategy as with such a strategy predominantly persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a laboratory confirmed dengue infection in the past).

To support a pre-vaccination screening strategy, WHO and many expert panels highlighted the urgent need for rapid diagnostic tests (RDT) to determine serostatus. To date, no RDT has been licensed for the indication of determining dengue serostatus, eg past dengue infection. Pre-vaccination screening strategies will require RDTs that can be done at point of care, provide rapid test results, are sensitive and specific, as well as inexpensive for use in a population wide programme.

In addition to target product profiles for such RDTs, policy-makers need to think through risk-benefit of diagnostic tests, given that there will always be a certain trade-off between sensitivity and specificity. What level of sensitivity and specificity is good enough, which trade-offs are acceptable by communities and governments, how much evidence is needed, and does one need standardized risk classification? Public acceptance of a certain level of specificity will depend on background seroprevalence, co-circulation of other flaviviruses, and

[1] http://www.who.int/immunization/sage/previous/en/index.html

the epidemiological situation of dengue in any given country. Optimal age targeting is another aspect that will differ from country to country depending on the peak of hospitalizations seen. Furthermore, both the pre-vaccination screening require careful planning around communication, implementation strategies, acceptability to stakeholders and communities, and cost-effectiveness studies.

In January 2019, the Partnership for Dengue Control (PDC) and the Global Dengue and Aedes-transmitted diseases Consortium (GDAC), with the support of Sanofi Pasteur, Bio-Mérieux, FIND and Chembio, organized a 3-day workshop hosted by the Mérieux Foundation at Les Pensières, Annecy, France.

The workshop was attended by NITAG experts, EPI managers, policy-makers with experience in vaccine introduction, front-line academic and public health scientists with expertise in vaccine introduction and mass vaccination, industry, diagnostics manufacturers, leaders of laboratory networks, regulatory authorities, WHO and CDC experts.

The overall meeting objectives were to:

(1) Assess rapid diagnostic tests (RDT) for screening for past dengue infection

(2) Discuss implementation strategies for pre-vaccination screening programmes for dengue vaccines

The meeting included a series of lectures as well as two workshop sessions which addressed questions on:

- Which thresholds for test sensitivity and specificity are acceptable by policy-makers and communities?
- Programmatic strategies for a CYD-TDV test and vaccinate program: school programmes versus other settings

The following report summarizes the main workshop outcomes.

PDC wishes to thank all the participants for contributing to such an engaging and positive experience. The meeting was sponsored by Sanofi Pasteur, bioMérieux and Chembio Diagnostic Systems, and with in-kind support by FIND.

Report prepared by Isabelle Delrieu, EpiLinks (www.epilinks.net). Final version 22 February 2019

Rationale for a Test & Vaccinate strategy for dengue vaccine implementation

Dengue vaccine trial results

CYD-TDV (commercial name Dengvaxia®) is a prophylactic, tetravalent, live attenuated, recombinant viral vaccine against dengue developed by Sanofi Pasteur. The chimeric vaccine is a mix of four viral recombinant, encoding for membrane and envelop structural proteins antigens of the four dengue virus strains, with a yellow fever 17D strain backbone. The dengue vaccination is indicated to prevent symptomatic dengue disease in individuals aged 9-45 years living in endemic areas and is given as a 3-dose regimen with 6-month intervals. Efficacy and safety have been evaluated in two Phase III clinical trials (**Hadinegoro, 2015**) in five countries in Asia (CYD14; 10 275 children aged 2–14 years) and five countries in Latin America (CYD15; 20 869 children, aged 9–16 years), and in one phase IIb trial in Thailand (CYD23/57; aged 4-11 years). Together, these trials included over 35,000 participants aged 2 to 16 years, randomized to vaccine and placebo in a 2:1 ratio.

After 2 years of follow-up from the first vaccine dose, in the 2-16 years participants, vaccine efficacy against symptomatic virologically confirmed dengue was estimated to be around 60%, with higher efficacies against hospitalized (73%) and severe dengue (79%). Vaccine efficacy increased with age, was higher against serotypes 3 and 4, and was higher among those with evidence of a prior dengue infection (seropositive) prior to vaccination, as measured by presence of neutralizing antibody against dengue. Because follow-up beyond 2 years showed an excess of hospitalized and severe dengue in children aged less than 6 years at vaccination, initial licensure of the vaccine was sought only for those aged 9 years and above.

Long term follow-up studies continued for safety analyses on disease leading to hospitalization (hospital phase), and active surveillance was reinstated from approximately month 50 onward. Because only a small subset of participants (13%) in the large Phase 3 trials had blood samples collected before vaccination, the serostatus of most trial participants was not known. Blood samples were collected during acute phase of confirmed dengue disease, whenever occurring from month 13 (one month after the 3rd dose was administered) onward and used to retrospectively infer dengue serostatus at the time of first vaccination. CYD-TDV contains genes encoding the NS1 protein from the yellow fever 17D vaccine virus rather than from dengue virus. A newly developed dengue anti non-structural protein 1 (NS1) IgG enzyme-linked immunosorbent assay (ELISA) was used to differentiate between anti-NS1antibodies induced by natural dengue infection and those induced by vaccination. To infer serostatus at baseline, the initial plaque reduction neutralization test (PRNT) results were used when available, otherwise, baseline status was imputed using 3 distinct methods: i) results from the anti NS1 assay at month 13, ii) Multiple Imputation (MI) by which PRNT50 results are inferred prior to vaccination using NS1 data and other predictors, or iii) Probability Weighted Targeted Minimum Loss-Based Estimation (TMLE). All 3 methods gave similar results.

The new data (**Sridhar, 2018**) confirmed that in the subset of trial participants, vaccine efficacy against symptomatic dengue was high (73%) in those who were inferred to be seropositive at the time of first vaccination, and modest (32%) in those seronegative. There was a significant excess risk of hospitalized and

severe dengue in seronegatives over the 6 years of follow-up. Thus, while, in this period, the vaccine gave about 70% protection against hospitalized dengue in those who were seropositive prior to vaccination, the risk of hospitalized disease was enhanced by about 75% in those who were initially seronegative.

If the vaccine were to be deployed in a population without prior serological testing for prior dengue infection, the overall effect of the vaccination programme would depend upon the seroprevalence in the population vaccinated. For example, for every 1 excess case of hospitalized dengue in vaccinated seronegatives, there would be 7 hospitalized cases prevented in vaccinated seropositives in a vaccinated population in which the seroprevalence is 70%, and nearly 13 hospitalized cases prevented if seroprevalence is 80% (**Table 1**).

TABLE 1. NUMBER OF CASES PREVENTED IN SEROPOSITIVES FOR EACH ADDITIONAL CASE IN SERONEGATIVES. FOR VACCINEES AGED ≥ 9 YEARS IN 5 YEARS FOLLOWING VACCINATION.

Seroprevalence in population	Hospitalized cases prevented	Severe cases prevented
50%	3.15	1.76
70%	7.36	4.11
80%	12.61	7.04

Therefore, despite the population benefit of vaccination in such circumstances, there would be some potentially identifiable individuals (those seronegative) who would be disadvantaged by receipt of the vaccine.

WHO recommended implementation strategies for the dengue vaccine

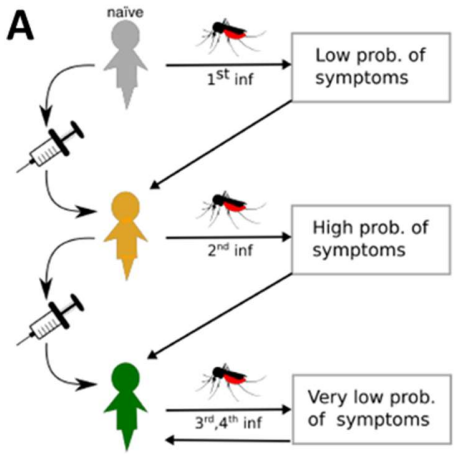
In November 2017, after the results of the retrospective analysis of data from clinical trials became available, Sanofi ask regulators to update product label to reflect new information. The WHO Strategic Advisory Group of Experts on Immunization (SAGE) revised its recommendations in April 2018, and in September 2018, an updated Position Paper replaced the 2016 WHO position paper on the use of the CYD-TDV dengue vaccine.

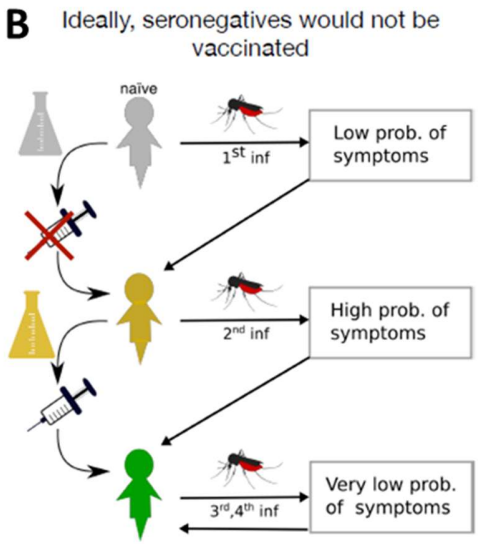
Given the serostatus-dependent performance of CYD-TDV, the WHO SAGE working group considered two options to maximize the public health impact of vaccination and minimize safety concerns: individual pre-vaccination screening strategy, versus population-based seroprevalence criteria without individual screening. The SAGE working group based its recommendations on a number of considerations, including population benefit versus individual risk, ethical considerations, risk perceptions and communication, programmatic challenges, population impact, and cost effectiveness.

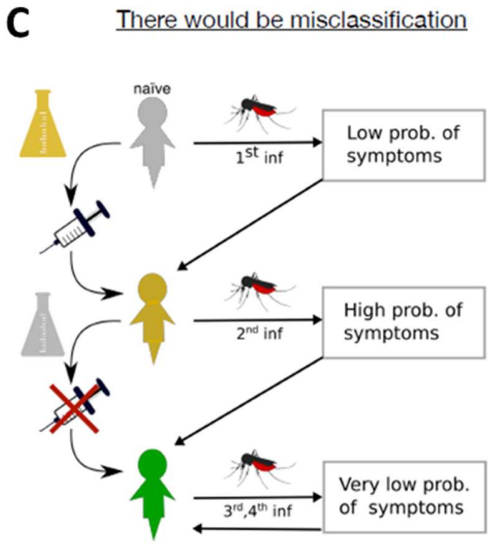
On one hand, the population seroprevalence criteria allows for mass vaccination campaigns and overall substantial population benefit in high seroprevalence identified areas. However, even when high seroprevalence is documented (e.g. 80% seroprevalence), a substantial proportion of the population will be put at risk (e.g. 20% of vaccinees will be seronegative). Moreover, there is a large heterogeneity of seroprevalence between and within countries, and subnational areas with seroprevalence >80% in 9-year olds are predicted by modelling to be rare. Consequently, multiple and repeated small-scale age-stratified serosurveys should be conducted to inform up-to-

date serostatus of the target age cohorts, which is costly and may be difficult to implement in resource limited settings. An informed individual may be reluctant to be vaccinated without knowing his/her serostatus, which may ultimately lead to a loss in vaccine confidence. Current diagnostic tests would require more validation work to estimate past dengue infections. A seroprevalence of 80% at age 9 is a proxy for force of transmission, and the recommended seroprevalence threshold increases with age (e.g. seroprevalence at age 16 should be greater than 90%). At a country level, the impact on the population may be low given the predicted rarity of areas with seroprevalence greater than 80%.

FIGURE 1. MODEL FOR CYD-TDV VACCINATION. A: SEVERITY OF DENGUE DEPENDS ON THE NUMBER OF PREVIOUS DENGUE INFECTIONS. CYD-TDV MIMICS A NATURAL INFECTION: IT PROTECTS SEROPOSITIVES AND INCREASES THE RISK IN SERONEGATIVES. B: WHO RECOMMENDS NOT TO VACCINATE SERONEGATIVES TO MINIMIZE THE RISK OF SEVERE DENGUE. C: DUE TO IMPERFECT TEST GIVING FALSE POSITIVE RESULTS, SERONEGATIVES WILL BE OFFERED VACCINATION AND PUT AT INCREASED RISK FOR SEVERE DENGUE







On the other hand, the pre-vaccination screening allows avoiding harm by not vaccinating seronegatives, while maximizing the benefit of vaccination in all seropositive persons in the population. Seropositive persons at any age in the label indication can receive the vaccination, and the strategy can be used in a range of transmission settings. However, as no test is 100% specific, some seronegative will still be put at increased risk of severe dengue after vaccination due to incorrect diagnostic test result. This risk needs to be evaluated by the authorities and explained to the patients and caregivers. Pre-vaccination blood sampling may lead to decreased acceptance of the vaccination programme and more complex and costly implementation strategies. At the moment, all rapid diagnostic tests (RDTs) are calibrated to detect current or recent infections, and there is no test validated or licensed for the indication of screening for past dengue infection. There is also a strong need to develop a highly sensitive and specific rapid diagnostic test to determine serostatus. High specificity will ensure that no truly seronegative will receive vaccination which guarantee best vaccine safety, while high sensitivity will ensure that the largest possible proportion of seropositives will benefit from vaccination, which maximize vaccine impact. Statistical models predict that the use of the vaccine would lead to a 20% reduction of hospitalized dengue over 30 years.

Given the elements described above, the WHO recommends that "for countries considering vaccination as part of their dengue control program, a pre-vaccination screening strategy is the recommended strategy, in which only dengue-seropositive persons are vaccinated. […] If individual pre-vaccination screening is not feasible, vaccination could be considered in areas with recent documentation of seroprevalence rates of at least 80% by age of 9 years."

Relevant countries experience with vaccine introduction

Dengvaxia was first licensed in Mexico, December 2015, quickly followed by the Philippines and Brazil. It is now registered in over 20 countries in Asia, Latin America, Australia and the European Union for use in endemic areas and has been introduced in two public health programmes in the Philippines and Brazil.

Dengue vaccine implementation in the state of Paraná, Brazil

Soon after its largest dengue outbreak to date, the Brazilian state of Paraná decided to use Dengvaxia® as an additional tool to control the disease. To select the municipalities that would be targeted by the vaccination program two criteria were used: (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 8,000/100,000 in the current year (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 to 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. Doubts about the operational aspects of the vaccination campaign, fear of adverse events, and negative news on social networks were the main reasons not to vaccinate, according to an evaluation survey. To evaluate the effectiveness of the vaccination a case-control study of incident cases has been set up. A RT-PCR positive for dengue is required for the cases. Two asymptomatic IgM negative controls for each case are being recruited. The

vaccine registry is consulted to ascertain the exposure (vaccination). A major limitation to the study has been the low transmission of dengue in the whole country in the past two years. Since the beginning of the field work, more than 1,800 dengue suspect cases within the vaccine age have been screened and just three were confirmed by PCR.

Lessons learnt from the HPV school-based vaccination in Sao Paulo, Brazil

Brazil has a long and successful experience in implementing vaccinations. The Brazilian National Immunization Program (PNI) has implemented several adolescent vaccinations: Human Papilloma Virus, Meningitis C, dT, Hepatitis B, MMR and Yellow Fever. The HPV-4v vaccine was introduced into the PNI in 2014, initially for girls aged 11 to 13 years, in a 2-dose schedule. A school-based vaccination program was implemented for the first time in the country, in two annual campaigns (March and September), while the vaccine was also available in all Vaccine Rooms in healthcare facilities all year round.

During the first campaign, public awareness campaigns were conducted, mobilization was very high and vaccination coverage reached 85.7%, with 4.2 million doses administered nationwide in about 3 months, essentially in schools. However, soon after the start of the 2nd campaign, a cluster of adverse events following immunization (AEFI) occurred in a city in the coast of Sao Paulo state: dizziness, headache, weakness, malaise, tremors and fainting and paresis were observed in 13 girls two hours after vaccine administration. Despite the fact that all of them had full recovery and that after investigation, the reactions were classified as post-immunization anxiety, stories and photos were widely disclosed in the traditional and social media, and as a consequence, vaccine coverage declined drastically to 60%. In the following years, specific measures were implemented such as widening the target age of vaccination, and adopting a gender-neutral program (boys aged 12-13 years), vaccine coverage remained lower than initially observed.

In Brazil, vaccination strategy is the responsibility of each municipality, leading to large variations in implementation. In Sao Paulo state, in the Southeast of the country, most municipalities opted for a school-based strategy, either as the only setting for vaccination, or mobilizing schools to refer students to healthcare facilities to get vaccination. At schools, meetings were organized with the education staff, parents and students and a "Vaccine Authorization Forms" were sent to parents for consent and a Vaccination Day was scheduled, when the heath team go to the school, check the vaccination card and parents authorization and vaccinate the children. In other municipalities, the health teams had meetings with the education staff, parents and students, but prefer to refer the students to be vaccinated in healthcare centers and return to school with a "Certificate of Updated Vaccination". Although school-based vaccination is seen as a rewarding activity for schools, allowing for rapid high vaccine coverage and discussions of taboos and reasons for vaccine hesitancy, specific issues have emerged. In the event that a school-based implementation strategy is being considered in Brazil for the CYD-TDV vaccine, strong partnerships between health authorities and educational staff would be crucial, which depends heavily on the commitment of local officials. Program implementers should specifically consider the following challenges: lack of space for vaccination in schools, lack of structure for the immediate management of AEFI, disruption of school routine, and shortage of health workers. In addition, the concurrent implementation of other vaccination campaigns in response to epidemics (yellow fever and measles) can affect the success of dengue vaccination. Finally, the disclosure and exploitation of adverse events in media that is hostile to vaccination can have a strong negative impact on the program.

Situation in the Philippines

In the Philippines, the vaccine was given in schools to approximately one million of 4th grade children (9-10 year olds) in highly endemic regions.

After the latest trial results were announced, a major communication crisis took by surprise: myths, misconception and lies spread on social media, principal investigators were put in criminal charges, special task force and dengue vaccine patients wards were set up, which contributed to collective hysteria and jeopardized other vaccination programs.

Causality assessments are extremely challenging in such a context of communication crisis and political turmoil, but also because the serious adverse event (severe dengue) cannot be differentiated from vaccine/program failure, and it is almost impossible to know the child serostatus for dengue at the time of vaccination. Clinically, the risk of severe dengue in vaccinated seronegatives will be the same as the risk of severe dengue in non-vaccinated seropositives. In the Philippines, post marketing safety data are available and show that the vaccine is safe. There is no clusters of events and no evidence that any deaths have been causally linked to the dengue vaccine. Before the program was suspended, over 830 000 children had received the vaccine, among those 705 500 would be seropositives and 124 500 seronegatives. With a seroprevalence around 85% at age 9, and a vaccine efficacy of 72%, based on transmission model informed by NS1 study data, most severe dengue cases should be expected in presumably seropositives children.

The United States perspective

The United States of America (U.S.) are in the early stage of consideration for the use of Dengvaxia with the setting up of a new Advisory Committee Immunization Practices (ACIP) dengue vaccines workgroup in late 2018. The ACIP makes US vaccine recommendations on the U.S. Food and Drug Administration (FDA) licensed vaccines. Although the U.S. do not have a high dengue burden, some of its unincorporated territories are endemic. Puerto Rico is at high endemicity with simultaneous circulation of multiple serotypes. While dengue serosurveys are desirable and planned, current evidence suggest that most of the population has had at least one dengue infection by the age of 19, and the peak of hospitalized dengue is between 9 and 14 and in older persons. In this region, diagnosis may be challenging due to unspecific cross-reactions with other circulating arboviroses, in particular Zika. Various diagnostic tests perform differently to differentiate Zika infection from dengue infection. Test performance, but also risk communication and implementation costs including vaccine-related side effects, vaccine coverage or possible herd immunity, are key elements to consider for decision-taking.

Communication challenges

As for many vaccines, although high in seropositives, the CYD-TDV vaccine efficacy is not 100%; therefore, the population offered vaccination should receive clear information on the fact they are partially protected when vaccinated and that they should continue adhering to other preventive measures and to seek prompt medical

care in the case of dengue-like symptoms. In the context of a test and vaccinate strategy, given that no assay is 100% specific, some truly seronegatives will be tested positives and offered vaccination; consequently, the limitation of the test performances will need to be clearly communicated for informed consent of vaccinees or caregivers.

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. Conflicting information, misinformation and manipulated information undermine trust, contribute to persistent vaccine anxieties and refusals, and can jeopardize the preventive public health interventions. 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. Worldwide, false rumours over vaccine safety have impaired vaccination programs such as those for yellow fever, measles, rubella, polio, rotavirus, HPV, and more recently dengue. The Vaccine Confidence project conduct global research on vaccine confidence has developed multiple metrics to assess countries population attitudes towards vaccination, including a Vaccine Confidence Index.

Recommendations based on robust scientific and medical evidence are no longer sufficient to guarantee the population adherence to vaccination programs. Vaccine hesitancy ride 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). In the Philippines, where on average people spent nearly 4h a day on social media[2], the context of introduction of Dengvaxia combined most of those risk factors. Confidence in vaccine safety dropped from 82% in 2015 to 21% in 2018 (**Larson, 2018**), after concerns arose about the safety of the CYD-TDV dengue vaccine. The authorities reacted with outrage and political turmoil with naming and shaming of government officials and scientists involved in the vaccination. As a result, the vaccination program was stopped and public trust around the dengue vaccine and around vaccines in general was broken.

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.

[2] Source : GlobalWebIndex survey Q2-Q3 2017, on internet users aged 16-64.

What tests for the Test & Vaccinate strategy?

A previous meeting was organized by WHO on advancing Zika, dengue and flavivirus diagnostic tests, where over 80 diagnostic test stakeholders discussed about quality specimens, regularity clarity, shared research, market and investment, and Zika/dengue vaccine companion test including requirement for rapid test. The objectives of the meeting were to review assessments of current diagnostics tests, to identify key barriers for research, development, assessment, and availability of sensitive and specific diagnostic assays, and to develop a roadmap to address key barriers.

Among the most critical challenges identified were the availability and access to quality specimen for test development and assessment, the sporadic funding due to changing prioritization of diseases, and the discrepancy between tests assessment methods.

The recommendations were to commit to a long term sustainable infrastructure for diagnostic test from development to post marketing, including a quality specimen repository ensuring equitable access, to construct a strategic roadmap with short and long term actions to provide the support needed to advance diagnostic tests, to coalesce diagnostic test stakeholders as a consortium around information sharing, governance and shared agendas, and to create a GAVI- or CEPI- like private-public model for diagnostic tests.

For pre-vaccination screening for implementation of the CYD-TDV dengue vaccine, a test with a very high specificity (≥99%) would minimize individual risk and the inadvertent use of vaccine in seronegative persons by reducing the number of false positive test results, while a high sensitivity (≥90%) would maximize individual and population benefit by identifying a high a proportion of previously exposed persons who will benefit from vaccination. Although currently available dengue Rapid Diagnostic Tests (RDTs) have lower sensitivity and specificity to detect past dengue infection, conventional dengue IgG ELISA diagnostic tests are not the preferred option for large scale screening. Using ELISA testing can overwhelm laboratory capacities and requires blood sampling and handling which may cause additional safety constraints and reduced acceptance in the target population. Conversely, RDTs would offer a convenient method for pre-vaccination screening at point-of-care, which enable inexpensive, easy single visits for both screening and vaccination. Therefore, in high transmission settings where the pre-test probability of an individual being seropositive will be higher, the WHO recommendation is to consider using currently available RDTs until better tests are available.

Best available tests for the determination of dengue serostatus

Rapid Diagnostic Tests (RDTs) are currently available for the diagnosis of primary and secondary dengue infection and typically use a combination of dengue IgM, IgG, and NS1 antigen.

A systematic review was conducted by the International Diagnostics Centre and the London School of Hygiene and Tropical Medicine (LSHTM) to evaluate the performance of current dengue RDTs for determining dengue serostatus, using IgG antibodies against DENV as a marker of past infection.

The performance of 4 dengue IgG RDTs was determined in 3137 individuals across 10 studies conducted in 13 countries, with serum used in most of the studies. No studies reported data for determining dengue serostatus,

and limited data were available regarding cross-reactivity with other viruses. The majority of studies demonstrated sensitivities and specificities between 80-100% for dengue IgG detection in samples from secondary infection or convalescent timepoints after recent infection.

In parallel, additional assessment studies were conducted by Sanofi Pasteur to compare the performance of existing dengue IgG-detecting RDTs in identifying prior dengue infection. The 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. Blood was identified as the best body fluid for dengue antibody detection, and 804 archived serum were used, from both dengue negatives - as identified by PRNT50 and dengue NS1 IgG, and dengue-positive individual leaving in either non-endemic countries or Asia and Latin America endemic countries. Among dengue positive samples, some were from individuals having declared dengue during the past years, others were from subjects who had a confirmed dengue in the past three to four years.

All four tests evaluated showed highly specificity (over 99%) (Table 2) 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 little number of positive samples available for testing. Nevertheless, compared to ELISAs, IgG component of all tested RDTs was less cross-reactive to related flaviviruses, especially WNV and Zika.

However, the tests showed variable and limited 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.

TABLE 2. OVERALL SPECIFICITY AND SENSITIVITY OF SEROLOGICAL ASSAYS FOR PRIOR DENGUE INFECTION IDENTIFICATION (CONFIDENTIAL)

Assay Name	Maker	Specificity [95% CI] (n=534)		Sensitivity [95% CI] (n=270)	
		IgG only	IgG+IgM (IgA)	IgG only	IgG+IgM (IgA)
RDT Dengue IgA/IgG	Bio-Rad	99.4% [98.4-99.9]	83.7% [80.3-86.7]	69.6% [63.8-75.1]	74.1% [68.4-79.1]
OnSite Dengue IgG/IgM	CTK Biotech	98.9% [97.6-99.6]	97.2% [95.4-98.4]	67.0% [61.1-72.6]	67.0% [61.1-72.6]
SD Bioline Dengue IgG/IgM	Alere/Abbott	99.6% [98.7-100]	99.4% [98.4-99.9]	53.7% [47.6-59.8]	58.5% [52.4-64.5]
Dengue IgG/IgM	GenBody	99.1% [97.8-99.7]	98.9% [97.6-99.6]	39.6% [33.8-45.7]	40.7% [34.8-46.9]
Panbio Dengue IgG Indirect ELISA	Alere/Abbott	99.6% [98.7-100]	N/A[1]	90.0% [85.8-93.3]	N/A
Dengue Virus IgG DxSelect ELISA	Focus Diagnostics	94.6% [92.3-96.3]	N/A	90.7% [86.6-93.9]	N/A

[1]N/A – not applicable (test was IgG only).
RDT results in top rows (above dotted line), ELISA results in bottom rows (below dotted line).

Although current dengue IgG RDTs have shown reasonable performance compared to laboratory-based tests in secondary infection, additional research is needed to determine how RDTs would perform in relevant

populations targeted for vaccination. 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, nor designed for differentiating primary from secondary infection. 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 to improving sensitivity to detect lower levels of IgG that may be found in past infection while not negatively impact test specificity. Sanofi Pasteur has committed to work with a manufacturer 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 and West Nile viruses. As such, they can be recommended as a temporizing solution for decision making.

Target Product Profile for the dengue RDT

An early draft target product profile (TPP) was created based on semi-structured individual interviews with 16 dengue experts, along with a review of the dengue literature and similar TPPs. The TPP defines medical and public health needs and make them transparent to test developers. Collaborative development of TPPs ensure alignment between users, implementers, clinicians and technical experts. Characteristics mentioned by a majority of dengue experts were included in the TPP (**Table 3**), with median values used for quantitative responses. This process is led by FIND, the non-for-profit global health product development and delivery partnership.

TABLE 3. TPP FOR A DENGUE RDT: MINIMAL AND OPTIMAL CHARACTERISTICS OF A TEST IN THE CONTEXT OF A TEST AND VACCINATE STRATEGY

CHARACTERISTIC	MINIMAL	OPTIMAL	COMMENTS
Scope			
Goal of Test	RDT for detection of dengue-specific IgG antibodies indicative of previous dengue infections		Detection of all 4 serotypes
Target Population	Individuals eligible for dengue vaccination		License 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	Fingerprick whole blood	

	≤25µl	≤100µl	
Specimen handling	Maximum 2 handling steps after fingerprick	Direct application of whole blood without handling	
Time to result	30 minutes	15 minutes	
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 of consumables		
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 individual 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	Future research may demonstrate if other flavivirus antibodies will affect the dengue vaccine
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 sensitivity Performance as determined in appropriate samples Dengue seroprevalence will impact the required
Clinical Specificity	≥ 90%	≥ 98%	

			specificity of the test
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	

A number of suggestions were provided by audience members and focused around the characterization of reference samples, healthcare system requirements, and sensitivity and specificity. Further rounds of feedback will occur to refine and finalize the TPP to be published. To bring dengue diagnostic tests to the market, appropriate studies will be conducted to evaluate critical TPP characteristics such as cross reactivity, specificity or stability, appropriate regulatory pathways, likely the Food and Drug Administration (FDA), will be identified and implementation strategies and toolkits will be developed for priority countries.

Impact and cost effectiveness of a test and vaccinate approach 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 into both serostatus and trial arm. Using these risks allows simple extrapolation of dengue risk to alternative seroprevalence settings and a test and vaccinate strategy with given sensitivity and specificity of a diagnostic test.

TABLE 4. DIRECT MODEL OF TRIAL DATA

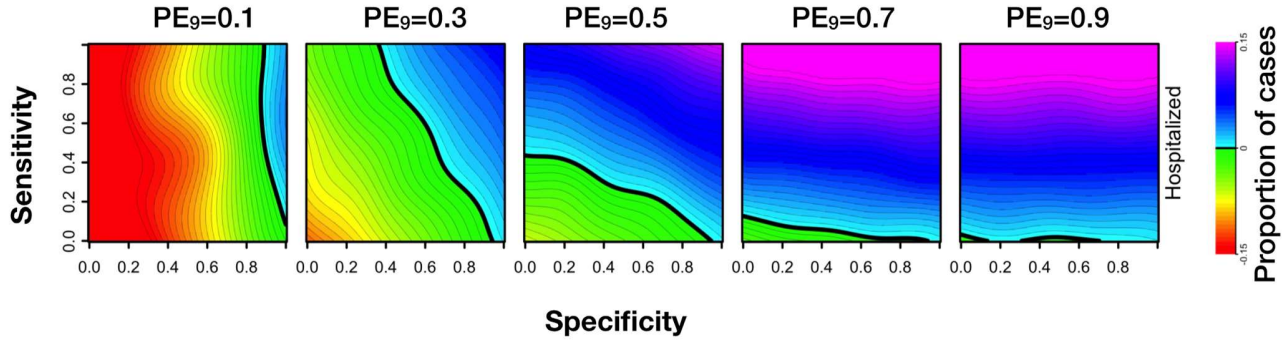
Seroprevalence	Sensitivity	Specificity	Hospitalized Cases averted			
			In seropositives	In seronegatives	In total	Averted / Caused
90%	100%	0%	1.357	-48	1.309	28.4
	100%	100%	1.357	0	1357	Inf
	90%	100%	1221	0	1221	Inf
	90%	90%	1221	-5	1217	255.5
70%	100%	0%	1056	-143	912	7.4
	90%	90%	950	-14	936	66.3
50%	100	0%	754	-239	515	3.2
	90%	90%	679	-24	655	28.4

While high specificity limits the number of dengue cases attributable to vaccinating false positive seronegative individuals, high sensitivity ensures that the population benefit is maintained by vaccinating true positive seropositive individuals. The optimal trade-off between sensitivity and specificity for optimizing the net population impact hereby depends on dengue seroprevalence in the target population. In settings with high seroprevalence test sensitivity gains priority whereas in settings with lower seroprevalence high specificity limits additional cases in false positive vaccinees and thereby ensures highest net population impact (**Table 4**). It should be noted that this is a simplified extrapolation and ignores that in other seroprevalence settings the risks observed in the trial would likely change as well.

To further evaluate the potential impact and cost-effectiveness of a pre-vaccination screening strategy with CYD-TDV, a strategy of routine vaccination applied to a single age of nine years old 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).

From a population perspective (**Figure 2**), 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 highest test sensitivity should be.

FIGURE 2. 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)



In terms of cost effectiveness, if a pre-vaccine test is used, there will be less seronegative and seropositives vaccinated and therefore less vaccine 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. With the baseline assumptions of 70 USD for a fully vaccinated child, and 10 USD for screening, vaccination is only cost-effective in the economic scenario of Brazil, not in the Philippines. From a public payer perspective in Brazil, the interventions are cost-effective in high-transmission settings (SP9≥70%) with a sensitivity above 60%. From a societal perspective, cost-effective scenarios are found in moderate- to high-transmission settings (SP9 ≥50%) and highly specific tests (≥0.8). In the Philippines cost-effective scenarios are found from a public payer perspective only if the costs per fully vaccinated child can be dropped below 23 USD. Additional scenarios can be evaluated in a web-based application[3].

In the base case scenario assessed in the 2015 Dengvaxia impact model comparison work developed by the LSHTM, Dengvaxia at the price of 21 USD per dose was not cost-effective. Even if an RDT was available free of charge and with the assumptions that a test and vaccinate would not reduce vaccine impact but would reduce vaccine cost by 30% through not vaccinating seronegatives, Dengvaxia remains not cost-effective in the base case scenario. This is substantially altered justifiable alternative assumptions for the cost-effectiveness analyses. These include a societal perspective, a higher willingness to pay or vaccine procurement at reduced prices. However, eventually Dengvaxia 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.

[3] http://denguevaccine.crc.nd.edu

Implementation of a Test and Vaccinate strategy

At the country level, the decision about implementing a T&V 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.

The transmission intensity in the target areas and the age at vaccination are critical factors. If selecting too young population, 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. As monotypic seropositives are the target group for vaccination, the optimal age for receiving the first vaccine dose can be informed by the age at which dengue hospitalizations due to severe dengue peaks.

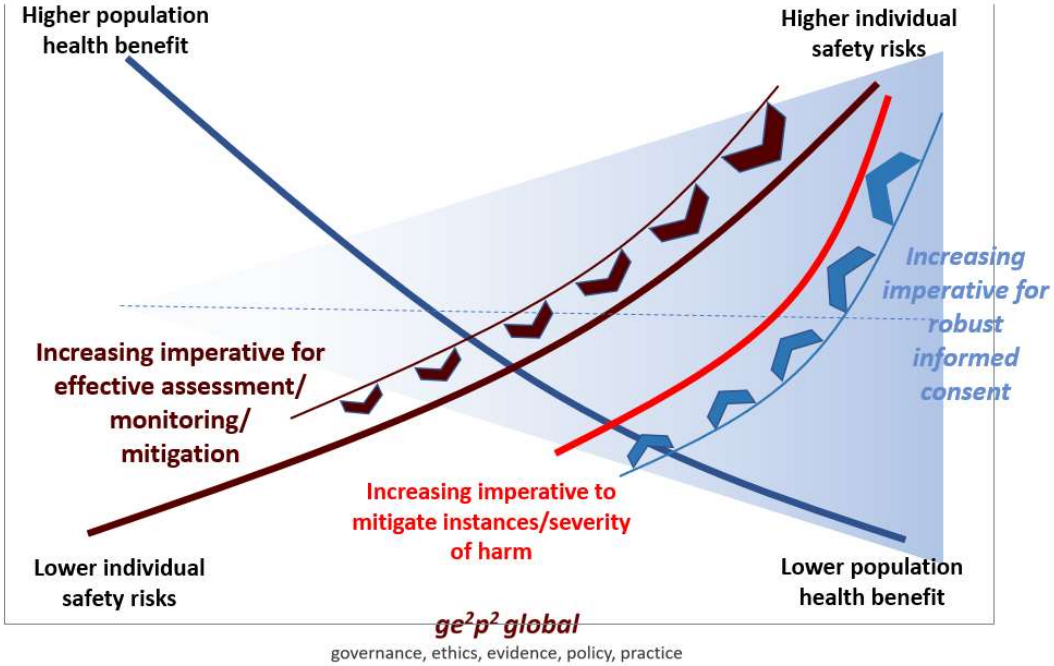
Ethical challenges with the dengue vaccination

As almost no vaccine is perfect, notably in terms of efficacy and safety, and growing tensions develop between global guidance and national realities, there is a strong need to develop mature communication plans taking into account patients' autonomy of choice based on risks and articulated benefits. In addition, if using imperfect RDTs in support of vaccination campaigns with the current dengue vaccine, seronegative people will be potentially put at risk.

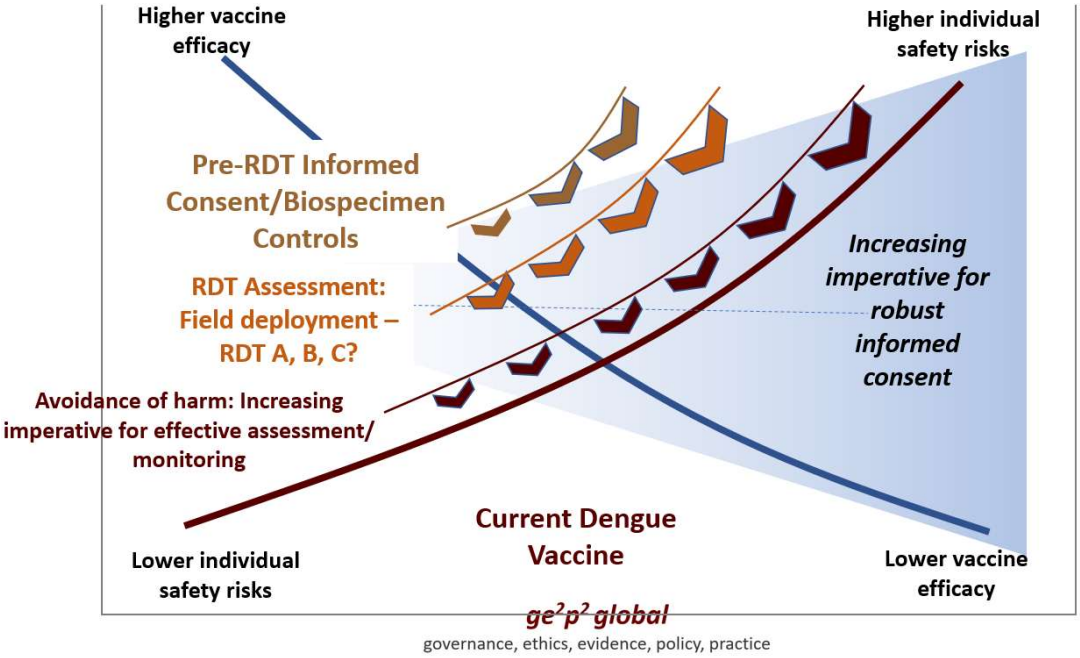
In an attempt to conceptualize the ethical dimensions of population benefit versus individual risk, a map can be drawn, that portrays the increasing imperative to implement robust informed consent and risk communications as vaccine efficacy - and therefore population benefit - declines and individual risk increases (**Figure 1A**). With the obligation to actively monitor and assess potential harms, comes the concomitant obligation to provide robust “rescue” and health system support for individuals/communities when harm is experienced. The conceptual map approach is enhanced (**Figure 1B**) to reflect the additional imperative for informed consent around use of such a diagnostic test.

FIGURE 1. VACCINE ETHICAL MAP: POPULATION BENEFIT VS. INDIVIDUAL RISK.

A. "CLASSIC" VACCINATION



B. TEST AND VACCINATE STRATEGY USING IMPERFECT TESTS

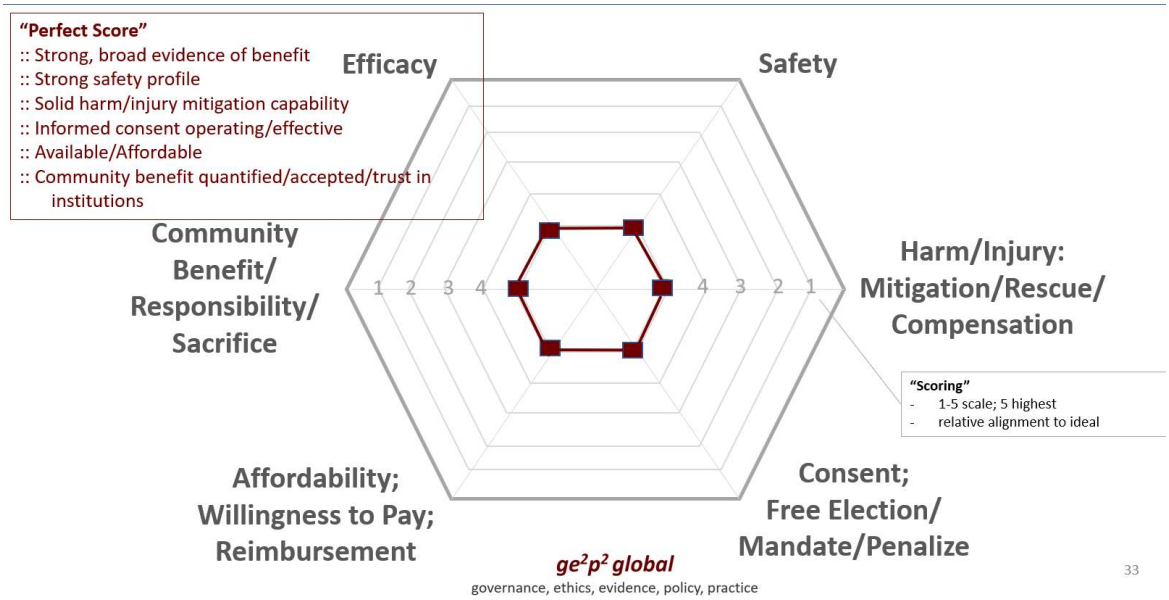


A second approach to understand the dynamics of the ethical question involves a hexagonal radar chart (**Figure 2A**) to depict decision factors around the use of the vaccine at three decision-making levels: the individual/parental level (**Figure 2B**), the Ministry of Health/Health Authority level and the global governance

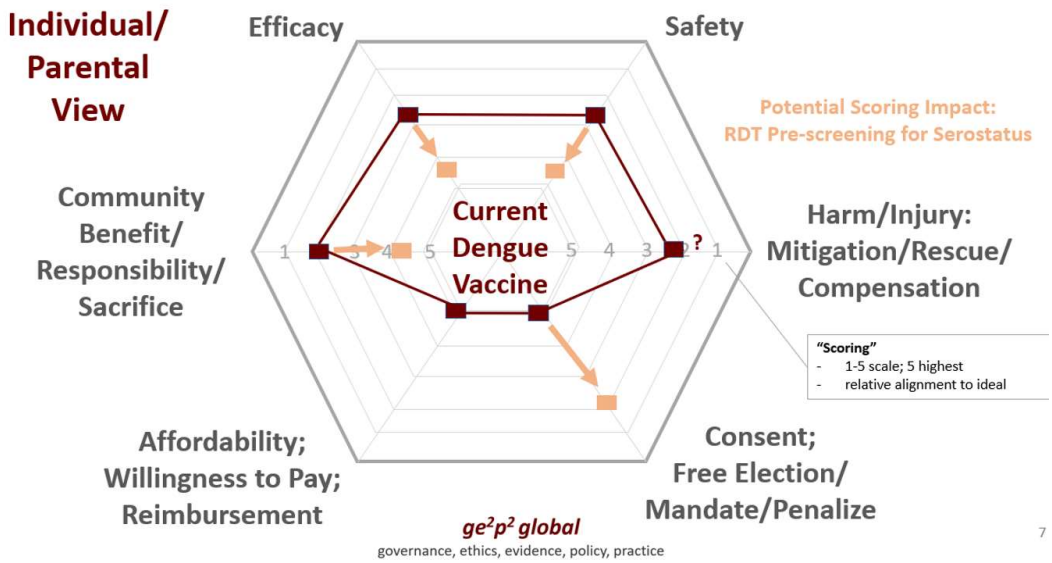
level (**Figure 2C**). This draft approach utilizes 1-5 scoring against six decision dimensions; vaccine efficacy; vaccine safety; mitigation, rescue or compensation of harm; consent dimension; affordability and community benefit. The radar chart approach is enhanced to depict the impact of adding an RDT assessment capability to an immunization campaign as per the current WHO SAGE guidance.

FIGURE 2. VACCINE ETHICAL RADAR CHART: POPULATION BENEFIT VERSUS INDIVIDUAL RISK

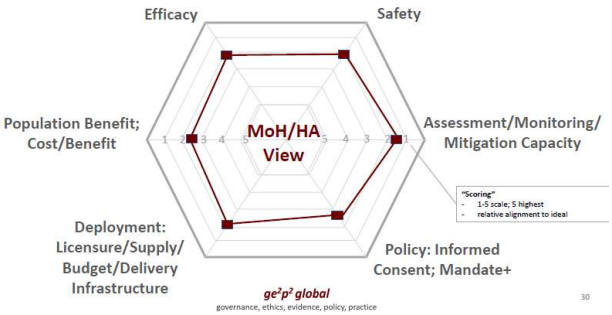
A. "CLASSIC" VACCINATION

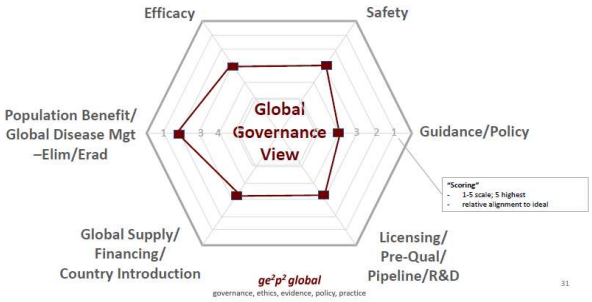


B. TEST AND VACCINATE STRATEGY USING IMPERFECT TESTS: THE INDIVIDUAL AND PARENTAL VIEW



C. TEST AND VACCINATE STRATEGY USING IMPERFECT TESTS: THE NATIONAL AUTHORITIES VIEW AND THE GLOBAL GOVERNANCE VIEW





An ethical framework can be considered to address the issues involved:

i. The overarching ethical imperative is to "do no harm", and where harm is unavoidable, to minimize it/mitigate it

ii. In contexts where there is anticipated risk but imperfect means to quantify individual risk, harm may be unavoidable. Here, the ethical imperative is to assure that robust clinical mitigation of/rescue from harm is available, competent, and delivered — and that harm that cannot be mitigated is compensated.
   - Where effective diagnostic testing and other assessment strategies can materially improve the ability to predict individual risk, they should be deployed in advance of immunization programming.
   - Assessment strategies deployed to improve the ability to predict and therefore mitigate individual risk should integrate robust risk communications and informed consent strategies.
   - Assessment strategies which involve biospecimens should address issues of privacy, controls on further use for secondary/complementary testing for other health assessments, and storage/disposal/destruction protocols.

iii. Equally, proceeding under varying known risk can be ethically sound if risk and known harms are freely accepted via "informed consent" or its equivalents in local contexts. Assessment, monitoring and harm mitigation capability and capacity must be in alignment to the quality of risk/harm.

iv. In contexts of epidemics or health emergencies, defined and affirmed by local law, sovereign action or global determination, state power may well be exercised and involve inform risk/harm "consent" may not be operative but "informed" continues as an ethical imperative as such power is employed.

A glimpse of countries decision making

Small workshops were conducted with regional country representatives to discuss accepted test performance thresholds and programmatic strategies.

Latin America group

For the purpose of a test and vaccinate strategy in Latin America, the minimum test performance thresholds for sensitivity and specificity would be 85% and 95% respectively. The experts questioned the feasibility of

improving current tests to obtain ideal performances. They recommended using current tests while waiting for optimized one in the short term.

The Latin America group recognized that the implementation approach is highly context-specific and should be decided at the country level. Subnational implementation is feasible in Latin America, with interventions targeting different age groups in different areas. The experts would favour a school-based strategy if the campaign targets young adolescents. The age group to target should be informed by age stratified seroprevalence data by municipality, and age group for which hospitalization peaks.

Using a test of 70% sensitivity and 98% specificity would allow to go on the side of safety; however, public health impact would be reduced. A test and vaccinate strategy would not be desirable in settings with very high seroprevalence (above 90%) as most of the population would be seropositive. 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 economic factor is probably the most important challenge a country would face to implement dengue vaccination in the public sector.

Asia Pacific group

For the Asia Pacific group, experts recommended that serosurveys should be done prior to implementing the test and vaccinate strategy since the trade-off depends on the background seroprevalence. In a 70% seroprevalence setting, a test with 85% sensitivity and 95% specificity may be acceptable. Using this figure, there will be 7 cases of severe dengue possibly caused by vaccination of false seropositives compared to 1050 cases if the vaccination is not given to those tested seropositive. Ideally, tests should allow identifying primary infections, since these population will be the one benefiting from the vaccination.

While Malaysia and Singapore restrict dengue vaccination to the private sector, Thailand would rather consider a national implementation. Assuming hospitalization for severe dengue would peak at the age of 14 years, it would be advisable to target age group 13 years-old. However, it may be difficult to deliver the third vaccine dose in this population, as 20% of adolescents of this age will not continue to secondary schools at the age of 13. The age of 12 years old was recommended.

If the test is not sensitive enough, the pre-vaccination strategy may become irrational as many seronegatives will be true seropositives, especially in high transmission settings. In this case, decision of implementation may be done on the basis of high seroprevalence only, as documented by previous studies.

If it is recognized as having an expected substantial impact and cost-effective Thailand would implement dengue vaccination without testing in areas where seroprevalence is high enough (over 70%).

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Annexes

- Meeting agenda
- Next generation of diagnostic tests: manufacturers panel
- World Dengue Day Petition
- Participants list

Meeting agenda

	DAY 1	
13:45-14:00	Welcome	Fondation Merieux Chair : Duane Gubler
14:10-14:30	CYD-TDV dengue vaccine: Long-term safety data stratified by serostatus	Peter Smith, LSHTM
14:30-15:00	Rationale for pre-vaccination screening strategy for dengue vaccine: WHO recommendations	Annelies Wilder-Smith
15:00-15:15	Situation in the Philippines	Annelies Wilder-Smith
15:15-15:35	Dengvaxia considerations from the U.S. perspective	Steve Waterman
15:35-16:00	BREAK	
16 00-16:20	HPV introduction in Brazilian schools: lessons learnt for dengue vaccine introduction	Ana Sartori, MoH Brazil
16:20-17:00	Communicating risk while building confidence in dengue vaccines the context of a pre-vaccination screening strategy	Heidi Larson, LSHTM
17:00-17:30	Population benefit versus individual risk of vaccines	David Curry, Center for Vaccine Ethics and policy, NYU School of Medicine
	DAY 2	
	POC RDTs and their implementation : TPP	Chairs : In-Kyu Yoon and May Chu
8:30-8.50	WHO meeting on flavivirus diagnostics advancement: a summary report	May Chu, University of Washington, US
8:50-9:10	Systematic Review on available RDT for diagnosing dengue serostatus	Robert Luo, FIND, US
9:10-10:30	Available test landscape analysis : Manufacturers`panel (Chembio, SD Biosensor, Roche, Blusense) Panel discussion	
10:30	BREAK	
11:00-11:30	Sanofi Pasteur`s validation efforts for different RDTs against existing panels	Steven Savarino, Sanofi Pasteur
11:30-11:45	Discussion	
11:45-12:30	Panel discussion: Target Product Profiles for RDTs for dengue serostatus	Robert Luo, FIND, US

12:30	LUNCH	
		Chairs : Peter Smith and Duane Gubler
14 :00-14 :25	Modelling different sensitivity/specificity scenarios in different seroprevalence settings : impact on cost and effectiveness of dengue vaccines	Stefan Flasche, LSHTM
14:25-14: 55	Model-based assessment of public health impact and cost-effectiveness of routine pre-vaccination screening strategy with Dengvaxia®	Guido Camargo España, University of Notre Dame US
14:55-15:15	Ethical deliberations on imperfect RDTs that could lead to inadvertently vaccinating seronegative persons	David Curry, Centre for vaccine Ethics and Policy, US
15 :15-15 :30	Discussion	
15 :30	BREAK	
		Working group : Asia
16:00-16:45	Break-out session: Which thresholds for test sensitivity and specificity are acceptable by policy-makers and communities?	Working group : Latin America
16 :45-17 :30	Feedback from Working Groups	
	DAY 3	
08:30-9.00	Bringing RDTs for dengue serostatus into the market	Sabine Dittrich, FIND Geneva
9 :00-10 :30	The state of Parana experience with Dengvaxia	Luna Apres, Institut de Medicina Tropical, Universidade de Sao Paulo, Brasil
10:30-11:00	Programmatic strategies for a CYD-TDV test & vaccinate program : school programmes versus other settings	LatAm: Brazil, Colombia, Peru, Panama, Mexico WPRO/SEARO: Thaïland, Indonesia, Singapore
10:30	BREAK	
11:00-12:00	Presentation by groups Action plan Comments/Recommendations for a CYD-TDV « test & vaccinate program strategy »	
12:00-12:15	World dengue day: petition	Kamran Rafiq, The International Society for Neglected Tropical Diseases

Next generation of diagnostic tests: manufacturers panel

Chembio Diagnostic Systems, Inc.

http://chembio.com/

A patented Next Generation DPP® (Dual Path Platform) technology offers advantages over lateral-flow technologies including:

- Improved sensitivity
- Multiplexing
- Applications in a number of sample types (blood, saliva, serum, plasma etc.)

Today the DPP® technology is the basis of multiple collaborations worldwide spanning infectious diseases such as HIV, Dengue, Zika, Ebola, syphilis, malaria and other febrile illness, as well as cancer and brain injury. In addition, Chembio's products include an inexpensive, battery-powered handheld reader, capable of reading and quantifying test results in a few seconds.
The DPP® DZC IgM/IgG (Dengue/Zika/Chikungunya IgM/IgG) System is a single-use, rapid immunochromatographic test intended for the detection and differentiation of Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies to dengue (DENV), Zika (ZIKV) and chikungunya Virus (CHIKV) in fingerstick whole blood, EDTA venous whole blood, serum, or EDTA plasma samples. The DPP DZC IgM/IgG System is intended for use in clinical and point-of-care (POC) settings to aid in the diagnosis of infection with DENV, ZIKV or CHIKV in patients with clinical symptoms consistent with these arboviruses.
The DPP ZCD IgM/IgG Assay System distributes sample onto two test strips. The top test strip is for the detection of IgM antibodies to DENV, ZIKV and CHIKV and the bottom test strip is for the detection of IgG antibodies to DENV, ZIKV and CHIKV. The test uses a 10µL specimen and takes 15 minutes to run. At the time of reading the results, the Micro-reader is used and provides for each test line position a numerical value proportional to the intensity of the test line, guiding the decision process and removing subjectivity in interpreting test results.

SD BIOSENSOR

http://www.sdbiosensor.com/xe

SD BIOSENSOR is a Korean manufacturer specialized in POCT based on immunoassay. With the accumulated immunoassay technology since 1999, SD BIOSENSOR launched STANDARD™ Q – accurate & reliable / easy-to-use / single & multi immunochromatographic tests. The STANDARD™ Q includes various infectious parameters such as HIV, Hepatitis, STD, respiratory disease, gastrointestinal disease and vector-borne disease. Especially STANDARD™ Q vector-borne disease product portfolio is still evolving with simultaneous detection and differentiation of Dengue NS1, Dengue IgM/IgG, Chikungunya IgM/IgG, Zika IgM, and Yellow fever IgM by selecting combinations that suits in each market.

STANDARD™ F is a fluorescent immunoassay (FIA) system introduced for more sensitive detection of infectious disease and precise quantitative analysis of biomarkers by using fluorescent particle 'Europium'. The system includes 3 different models of analyzer, STANDARD™ F100/F200/F2400, which are suitable for any healthcare settings. The STANDARD™ F system is easy-to-use like rapid test, more sensitive & objective and easier to

manage the data via LIS/HIS connectivity. In addition, STANDARD™ F has various menu for infectious disease such as HIV, Hepatitis, respiratory disease, gastrointestinal disease and vector-borne disease, and for biomarkers such as cardiovascular, hormone, tumor, inflammation, and metabolite markers. STANDARD™ F Dengue NS1 is suitable for the acute dengue infection diagnosis with its outstanding sensitivity, and it also provides cut-off-index (COI) value along with the qualitative results. STANDARD™ F Dengue IgM/IgG performance showed good correlation with ELISA, which is suitable for diagnosis of past/present dengue infection also with COI value.

Both STANDARD™ Q and STANDARD™ F vector-borne parameter require 100ul of specimen (whole blood/serum/plasma) for antigen tests and 10ul of specimen (whole blood/serum/plasma) for antibody tests, and take 15 minutes for each test. (Early detection (in 5 minutes) of strong positive specimen using STANDARD™ F100/F200)

Blusense Diagnostics

https://www.blusense-diagnostics.com/

Blusense has developed the BluBox, a tool for dengue and zika diagnostics.

BluBox is a portable and affordable device specifically designed for single drop of full blood diagnostics operations. BluBox is compatible with the single-use tests for dengue and zika diagnostics applications which are under development. It has been designed and developed strictly following the global organizations' target product profile for diagnostics equipment. It is easy to use, the sample-to-answer is 9 minutes and includes 3G/Wi-Fi connectivity and automated case reporting. There will be a publication coming soon showing high sensitivity compared to other RDTs.

MIKROGEN

https://www.mikrogen.de/english/home.html

With *recom*Line Tropical Fever IgG, IgM MIKROGEN has developed the first global immunoblot assay for simultaneous detection and differentiation of Dengue, Chikungunya and Zika infections (CE marked, Patent Pending).

In contrast to ELISA test systems, the separate line-up of the antigens, allows the identification of specific antibodies against single antigens from Dengue, Chikungunya and Zika viruses. Virus-like particles (VLP) are used to detect CHIKV. To detect and differentiate the flaviviruses DENV and ZIKV, NS1 (non-structural protein 1) and a variant of the envelope (E) protein (Equad), which has a higher specificity due to targeted mutations, are used. The unique setup allows the differentiation of DENV and ZIKV by an interpretation scheme in two steps, which takes the NS1 antigen reactivities and in their absence the Equad antigen reactivities into account.

With respect to Dengue IgG testing and the recommended Dengue pre-vaccination screening this assay format shows a clearly better specificity than commercial ELISA test systems and allows the discrimination of primary and secondary flavivirus infections.

EUROIMMUN

https://www.euroimmun.com/startseite.html

EUROIMMUN focus on development of ELISA systems on dried blood spots that would permit for self-collection of sample, comfortable time storage and allow sending sample by post mail with reliable detection after 4 weeks. This would help patient to accept diagnostic.

World Dengue Day - Petition

https://www.isntd.org/world-dengue-day

The International Society for Neglected Tropical Diseases (ISNTD) and Break Dengue (BD) have joined forces to form a global collective with the clear goal of reducing the burden of dengue around the world and devising ambitious action plans and collaborations to contribute to the fight against dengue in communities and countries where dengue is a public health concern

Now, this collective is spearheading the call for a World Dengue Day with an Open Letter to the United Nations General Assembly, which will be presented at the 74th UNGA on September 17-30th 2019 in New York.

Participants list

NAME Firstname	Institution / Company, country
ATAMAN-ONAL Yasemin	Sanofi Pasteur, France
BATO Joan	Research Institute for Tropical Medicine, The Philippines
BERTELS Nele	Agence Fédérale des Médicaments et des Produits de Santé, France
BESADA-LOMBANA Sandra	Sanofi Pasteur, Colombia
BOSCO Filipo	BluSense Diagnostics ApS, Denmark
BOUNIORT Fabrice	Roche, Switzerland
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