Workshop Report

"Pre-vaccination screening for the use of dengue vaccines with differential performance dependent on serostatus: vaccine clinical updates, rapid diagnostic tests and implementation strategies."

Les Pensières Center for Global Health, Annecy, France

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Introduction

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 (1,2). In the absence of truly effective and sustainable vector control measures, a dengue vaccine is urgently needed. The first dengue vaccine was licensed in 2015; the live attenuated recombinant tetravalent vaccine CYD-TDV (Dengvaxia). However, new evidence highlighted the serostatus-dependent vaccine performance of Dengvaxia; 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 (3,4). The WHO recommended a pre-vaccination screening as the preferred strategy as with such a strategy predominantly persons with evidence of a prior dengue infection would be selected to be offered vaccination (based on serological test, or documentation of laboratory confirmed dengue infection in the past (5). To support the strategy, WHO and many expert panels highlighted the urgent need for rapid diagnostic tests (RDTs) to determine serostatus. To date, no RDT has been licensed for the indication of prior dengue infection status. Pre-vaccination screening strategies will benefit from RDTs that can be performed at point of care (POC), provide rapid test results, are sensitive and specific, as well as inexpensive for use in a population wide program.

In January 2019, the Partnership for Dengue Control (PDC) convened a first meeting of dengue experts, vaccinologists, country representatives, key opinion leaders and diagnostic manufacturers to discuss the pre-vaccination screening strategies and defined characteristics of screening tests, drafted a target product profile for a screening test, and developed implementation strategies (6). Since then, there have been significant developments such as new advances on RDT development and ongoing discussions on the practical challenges and opportunities in the implementation of the pre-vaccination screening strategy.

1. Objectives of the meeting

This 3-day workshop hosted by the Mérieux Foundation at Les Pensières, Annecy, France, from January 20-22, 2020, was organised to:

1. Provide updates on new clinical data for CYD-TDV
    - Discuss updates on recent clinical study results
    - Address the impact of such data in terms of WHO recommendations/guidelines and on field implementation

2. Discuss screening for prior dengue infection: rapid diagnostic tests(RDTs) development updates
    - Discuss RDT Target Product Profile(TPP) development status: where we are and next steps
    - Provide update on RDT development for pre-vaccination screening
    - Address qualified-RDTs access to countries
3. Discuss implementation strategies for pre-vaccination screening programs for dengue vaccines
    - Discuss practical issues for programmatic roll-out and get regional experiences feedback on CYD-TDV
    - Address programmatic challenges encountered by countries and the needs required for a successful implementation
    - Discuss communication strategies with regards to vaccine confidence, both for policy makers, the medical community and the lay public
    - Discuss cost-effectiveness data and modeling implementation approaches
4. Discuss public health strategy for outbreak response
5. Discuss the world dengue day target and expectations

The meeting was attended by 65 participants (academics, industries, research centers, health organizations) from Africa, Asia, Europe, Latin America and North America.

PDC and GDAC wish to thank all the participants for contributing to such an engaging and positive experience and Noah Fongwen (LSHTM) for preparing the workshop report.

The meeting was sponsored by Sanofi Pasteur, Roche and BluSense Diagnostics.

Updates, presentations and workshop

The meeting included a series of presentations and a workshop session. The presentations provided clinical updates on the dengue vaccine, desired characteristics for a screening test and how access to a new screening test can be increased, modelling studies of cost-effectiveness of pre-vaccination screening strategies, key questions on the implementation strategies, country experiences and considerations.

The key questions that were addressed part of implementation were:

- What is the best timing for vaccination after an acute confirmed dengue infection?
- What is the best timing to re-screen people who were tested sero-negative in high endemic countries?
- How to address communication and ensure parental acceptance and high coverage?

1. New clinical data

Now that the vaccine profile of CYD-TDV has been better characterized with a clear benefit-risk which is highly favorable for individuals with prior dengue infection, Sanofi Pasteur has further analyzed the data coming from the efficacy trials (CYD23/57, CYD14 and CYD15), plus the data from an ongoing trial (CYD65) assessing compressed vaccination schedule with less than 3 doses. These new data or analyses will be proposed to Regulatory Authorities to support the following label updates:

1. To optimize the vaccine schedule, moving from a 3-dose to a 2-dose schedule
2. To extend the indication for dengue seropositive individuals regardless of geographical considerations (ie, living or not in endemic areas
3. To extend the age indication, including dengue seropositive children from 6-8 years of age with a 3-dose schedule.

The vaccination schedule optimization is supported by:

- Clinical data from CYD14 and CYD15 efficacy trials showing in seropositive individuals 9-16 years of age, a vaccine efficacy of 82% against symptomatic virologically confirmed dengue (VCD) 6 months after the receipt of the second dose. This efficacy result was similar to that observed after 3 doses on the per-protocol analysis in this age group.
- Immunogenicity data from the efficacy trials showing that antibody levels met the superiority criteria for the 4 dengue serotypes when comparing at a 2 dose schedule 28 days post-injection against a 3 dose schedule in the seropositive population 9-16

years of age, and immunogenicity data coming from the CYD65 study showing that the non-inferiority criteria was met for the 4 serotypes when comparing a 2 dose schedule at 28 days and 1 year post-injection against a 3 dose schedule in the seropositive population 9-50 years of age.

- Safety data based on integrated safety analysis of multiple clinical trials showing an overall safety profile Post-Dose 2 similar to a Post-Dose 3 in seropositive individuals of any age.

CYD-TDV current indication targets individuals living in endemic areas only. Limiting the current indication to those living in endemic areas was justified by two reasons: a) Endemic areas represent the highest disease burden, and b) In non-endemic areas, the proportion of individuals truly infected by dengue is considered generally very low, which can negatively influence the Positive Predictive Value of a dengue serotest. Sanofi Pasteur will be proposing that the eligibility to vaccination changes from a geographical criteria '"living in endemic areas" to a serostatus criteria in all countries where the vaccine is registered. This proposed label simplification would allow to address the unmet medical need for specific populations living in non-endemic areas but which share the characteristics of populations living in endemic areas (that is, high probability of previous dengue infection). This will be aligned between the different countries where CYD-TDV is registered, understanding that there is an age indication variation from country to country.

The age extension indication from 6 years of age is supported by the clinical data coming from the efficacy trials (CYD14 and/or CYD23/57) showing that for seropositive individuals 6-8 years of age, efficacy was demonstrated on the 3 main clinical outcomes. The integrated analyses from both trials showed an efficacy of 66% against symptomatic VCD in the first 2 years of the trials, and a sustained efficacy of 64% measured the last 2 years of these 6-year long-term trials. For the protection against hospitalized and severe VCD, results showed a statistically significant Relative Risk of 0.21 and 0.22 respectively during the 6-year follow-up.

Following the updated WHO recommendations on the use of dengue vaccine and pre-vaccination screening, Sanofi Pasteur will seek Regulatory endorsement on these label updates in order to maximize individual and public health benefits (7).

2. Desired characteristics for a screening test: accelerating access to a new screening test

This talk focused on the desired characteristics for a screening test and how the access to a new screening test could be accelerated.

The ideal characteristics of a diagnostic test have been summarized by the acronym 'ASSURED', which stands for Affordable, Sensitive, Specific, User-friendly, Rapid, and robust, **E**quipment-free and **D**eliverable (8). This acronym has been revised to '**RE**-ASSURED' after adding **R**eal-time connectivity and **E**ase of use (9). These ideal characteristics can be further summarized into affordable, accurate, and accessible. It is important to note that no test is perfect and trade-offs need to be considered.

Affordability takes into account:

- The test and supplies.
- Transport and storage
- Training and supervision, quality assurance

Accuracy takes into account:

- Sensitivity: should be high for a screening test
- Specificity: consider potential risk in case of false positive result. (Consider a 2-test algorithm if acceptable sensitivity and specificity cannot be met with only one test. ELISA could complement in some settings)

Accessibility considers:

- Simplicity of use, 2-3 steps
- Time to result <30 min
- Ease of interpretation of results: mechanical readers may take away subjectivity and are more sensitive than the eyes.
- Minimal equipment – does not require electricity
- Possibility of storage at ambient temperature for > 1 year
- Connectivity for real time surveillance

Target Product Profiles (TPP) are developed to guide manufacturers in test development. Regarding a public health approach the following considerations need to be made:

- Should there be a unique TPP for all countries/settings? Consider accuracy requirements for populations of high, medium and low seroprevalence.
- The Delphi process versus regional consultations:
  - What we know
  - What we don't know
  - Health system constraints, including infrastructure and human resource constraints
  - Acceptability, values and preferences
  - Costs and cost-effectiveness

- Screening should maximise individual and public health benefits:
  - Embed dengue IgG screening as part of survey seroprevalence of arboviruses and surveys of other vaccine preventable diseases to lower costs

The access to diagnostics is usually lengthy, fragmented with gaps, duplication and uncertainties. It takes on average greater than 10 years between the development of the target product profile (TPP) to test adoption. There are three valleys of death, which may limit the access of diagnostics. These are regulatory, policy, financial and health systems barriers.

The regulatory barriers include:

- Tests are sold and used in much of the developing world without evidence of effectiveness
- Duplication in clinical performance studies and manufacturing
- quality inspections pose major barriers to market entry, resulting in
- delay in access and unaffordable pricing
- Companies with quality tests unable or unwilling to compete in
- market flooded with low quality tests
- Smaller countries often do not have access to tests because
- companies do not bother marketing in small markets because of
- costs and effort
- Regulatory science has not kept pace with technological innovation

The paradigm of non-inferiority can no longer be used for the regulatory approval of accessible diagnostics. There is an urgent need for joint assessment of risks and benefits by regulators, policy makers and subject matter experts to accelerate the access pathway (**figure 1**).

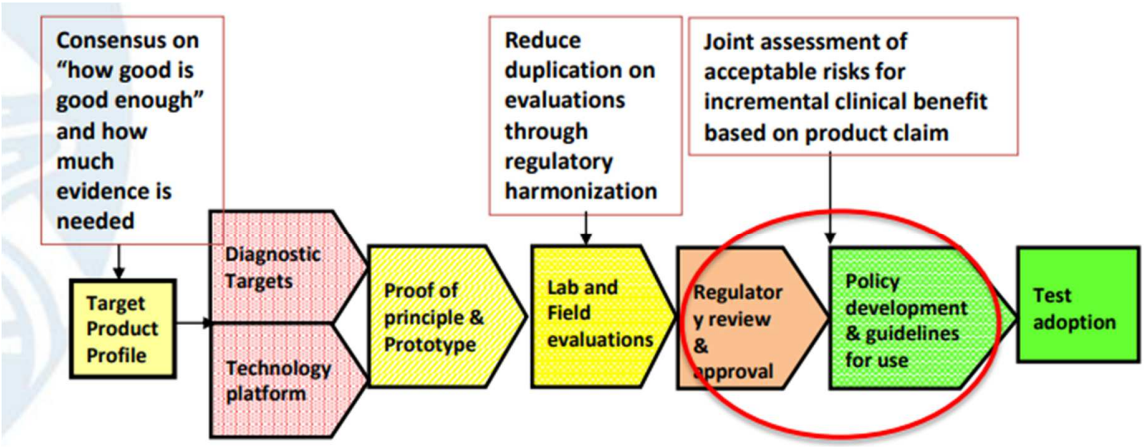

Figure 1 Proposed new regulatory policy framework to accelerate regulatory approval for In Vitro Diagnostics (IVD)

In summary:

- In each setting, the desired characteristics of a screening test need to take into account:
  - Affordability vs accuracy vs accessibility
  - Health system constraints, including human resource constraints
  - Acceptability, values and preferences
- The paradigm of non-inferiority can no longer be used for the regulatory approval of accessible diagnostics.
- There is an urgent need for joint assessment of risks and benefits by regulators, policy makers and subject matter experts to accelerate the access pathway.
- Successes in implementation of new diagnostics depends on engaging policy makers early in determination of test performance in settings and populations to maximize individual and public health benefits.
- In this digital age connectivity solutions provide opportunities to monitor quality of tests and testing, provide alerts of outbreaks, increase the efficiency of health systems and improve patient outcomes.

3. Update on the status of development and evaluation of a Dengue IgG Rapid Diagnostic Tests for pre-vaccination screening

CYD-TDV vaccination is associated with a benefit-risk profile which is highly favorable for individuals with prior dengue infection (PDI) and unfavorable for those who are dengue naïve. WHO has recommended pre-vaccination screening to identify and propose vaccination to dengue seropositive individuals. In addition WHO called for the development of point-of-care (POC) tests

with adequate performance characteristics to identify prior dengue infection, ie high specificity and sensitivity in order to minimize vaccine risk and maximize individual and public health benefits (7). Until tests specifically designed for that purpose become available, WHO considered the use of IgG ELISAs and IgG-containing RDTs as temporizing tools depending on the epidemiological setting.

In this context, Sanofi Pasteur undertook the evaluation of existing dengue IgG immunoassays (10,11) and in partnership with an IVD manufacturer, initiated development of a dengue IgG RDT designed specifically for identifying PDI. To complement published evidence on performance of existing dengue serotests in identifying PDI, Sanofi Pasteur recently performed a retrospective analysis from the immunogenicity subset of the CYD-TDV Phase III trials, CYD14 and CYD15. This analysis was conducted to determine vaccine efficacy (VE) against VCD over 25 months and hospitalized VCD over 6 years from first injection in subjects 2-16 years of age assessed as seropositive by different dengue IgG serotests (3 RDT and 2 ELISA). This analysis confirmed for each serotest assessed that vaccination of test-positive subjects was associated with high VE against VCD and against hospitalized VCD, as already demonstrated with other methods (ie, PRNT50 and NS1 Elisa). These data are unpublished at the time of this meeting report release.

Sanofi Pasteur's co-development of a dengue pre-vaccination screening IgG RDT has been guided by an internally approved target product profile (TPP) that prioritizes first very high specificity (to minimize the risk of vaccination of false positive individuals), minimal to no flavivirus cross-reactivity, and high sensitivity to ensure detection of a high proportion of true dengue seropositive individuals. Lead prototypes emerging from development studies exhibit specificity, sensitivity, and cross-reactivity that are in agreement with the desired TPP performance targets. Based on current projections, the first country registrations of the optimized RDT are expected by the end of 2020.

4. Development of RDTs by diagnostic developers

During the meeting four diagnostic companies presented on the status of development of RDTs for dengue. These companies were BIORAD, BluSense, Chembio and CTK Biotech. The methods they used, their findings and the next steps are summarized in the appendix section. In general, the developers reported candidate assays of high specificities with some compromise on their sensitivities. The assays have unique advantages and disadvantages. The Chembio assay is a multiplex assay for dengue, Zika, and Chikungunya, with quantitative detection and a digital reader. The BluSense immunomagnetic assay has connectivity capabilities and quantitative detection. The CTK Biotech assay has a long shelf life. The BIORAD assay is a lateral flow assay, easy to use with whole blood, serum and plasma. For most manufacturers except currently CTK Biotech, there is a lack of proper evaluation of cross reactivity with other flaviviruses.

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

By design, pre-vaccination RDTs are meant to select the population eligible for vaccination. Additionally, these tests should have very high specificity to exclude those individuals not eleigibile for vaccination (dengue seronegatives). This typically comes at the cost of test sensitivity and hence a loss in detecting those previously exposed to dengue and who are the most likely to benefit from vaccination. Different modelling approaches show that in settings with high endemicity (SP9>70%) this trade-off will typically result in little net change in vaccination impact if compared with vaccination without prior screening. However, in settings with lower dengue transmission the screen and vaccinate strategy would improve impact of vaccination versus a no testing strategy. PPV and NPV which combine positive and negative pre-test probability and performance characteristics of a given test, have been proposed as alternative and more meaningful cross-setting indicators. While PPV constraints RDT accuracy in low prevalence settings, NPV constraints do so for high prevalence settings. To fulfil both criteria generally a highly specific (>95%) and very sensitive (>85%) RDT is required.

In the low and moderately endemic settings, a screen and vaccinate strategy would streamline the use of vaccine and reduce drastically the number of doses used, however, additional expenses from testing a whole birth cohort could occur. Cost-effectiveness is likely most sensitive to the specificity of the test, as a lack thereof will result in additional vaccine costs that are used to generate a net negative health impact through the vaccination of seronegatives. Published models diverge on their prediction of cost effectiveness of a test and vaccinate strategy spanning not cost effective to highly cost effective for endemic countries including the Philippines and Brazil. The assumed case fatality ratios may be a key driver of these differences.

6. Multiple testing: re-screening people who were tested sero-negative in high endemic countries

In terms of multiple testing, the results of a mathematical model of environmentally acquired dengue infection with one or more pre-vaccination tests, examining averted disease outcomes in age-eligible birth cohorts in Puerto Rico between the ages of 9 and 16 years were presented. A secondary analysis, which reduces the minimum age of testing and vaccination to 2 or 6 years, was considered. A range of seroprevalences from 30% to 70% and vaccination both with and without a Rapid Diagnostic Test (85% sensitivity, 95% specificity), assuming similar coverage to the Puerto Rican HPV program was considered.

Modelling indicates that it is possible to reduce hospitalisation in the age-eligible cohorts by at least 15% and that from a societal perspective, it may be at least cost effective to do so (under incremental cost-effectiveness ratios and return on investment). This cost effectiveness remains when considering multiple testing, and the use of a web-based app developed at LSHTM was demonstrated to aid public health officials in assessing whether an annual testing programme is cost effective based on the relative cost of the test and vaccine to the cost of a secondary infection, https://samclifford.shinyapps.io/Denvax_demo/.

7. The timing of vaccination after an acute confirmed dengue infection

When a diagnostic of prior dengue infection has been firmly established and the decision to vaccinate has been taken, one following question is then to know when it is possible to start vaccination, *i.e.* how early can vaccination be performed after wild type dengue infection?

To address this question, Guy and colleagues reviewed the immunological and practical considerations in the context of CYD-TDV vaccination. Specifically, the following issues were discussed:

- Firstly, the nature and kinetics of immune responses triggered by primary or secondary wild type dengue infection may positively or negatively impact subsequent live vaccine take and associated clinical benefit, depending on when vaccination is performed after infection
- Secondly, regarding practical aspects, the “easiest” situation would correspond to a confirmed acute dengue infection, and then one only needs to know when the patient should come back for vaccination. However, it is likely that in most cases, it will not be possible to firmly establish the actual date of prior infection. In this scenario, likely to be the most common scenario, not only do individual practitioners need guidance when to vaccinate, but also health authorities establishing vaccine policies at the country level

The following suggestions were given as per the timing of vaccination with CYD-TDV after an acute confirmed dengue infection:

- Immune responses triggered by dengue wild type infection should have no impact on vaccine reactogenicity/safety, regardless of the timing of vaccination after infection.
- To be fully efficient, first vaccination should not take place before 1-month post-infection, and preferably not before 6 months. Performing vaccination after 3 months could nevertheless provide some benefit. Immune responses triggered by dengue wild type infection may induce a “refractory period” during which vaccine efficacy could be limited or even absent.

- If the actual date of infection is unknown or if for practical reasons vaccination would be performed before this 6-month period of time (i.e. 3-5 months),this would not be an issue in the case of multidose vaccination schedules, in which doses are given 6 months apart, as the second dose would induce a proper and efficient immune response outside of the refractory period.
- Waiting for 6 months would also not be an issue regarding induction of protection, as wild type infection induces at least a 6 month to 1- year cross-protection

8. Communication: The Philippines' experience

The story: After a 5-year period of continuous high dengue from 2012-2016, the department of health launched vaccination campaign in highly endemic regions which coincided with the national and local elections, causing it to be viewed as an electioneering issue. The program started as a school-based program and was later extended to the South as a community-based program. Few hours after the Sanofi announcement in November 2017, there was a social media frenzy, which led to the opening of an inquiry by the Senate and the Congress within a week. This appeared to be more of like an inquisition rather than an inquiry. This led to immediate withdrawal of the program and the product by the department of health (DoH) and a demand for reimbursement of funds. Criminal charges were brought on experts, including FDA officers.

The inquiry focused on the product registration and procurement and funding source, the "lack of transparency", existence of a "mafia" in department of health, industry "bad behaviors", cost–effectiveness of the vaccine and the relationship between the program and the elections and if it was rushed to "favour the regime implementation", the delivery strategy with- no "parental consent obtained".

Factors associated with public scare were:

- Media reports (media took a bias side against vaccine). Live feed of autopsies.
- Social media became a platform for an invisible war
- Some health care experts took the side of the antivax movement to spread false information
- Confusion resulting from arguments between health care experts on media outlets
- Poor communication: the use of term severe dengue was poorly interpreted by the public
- Politicians muddled up and the department of health made no statement.

Consequences were:

- Mistrust and damage to the credibility of institutions, program, product and individuals. Health care workers were no longer trusted.

- Inability of the accused to defend due to conflict of interest
- Attack on health experts who tried calming down tensions
- Distrust of preventive national programs leading to outbreaks of measles and other diseases. More deaths registered in dengue outbreak

Lessons learned included:

- Revising the code of conduct for health professionals as to what can be said in public.
- Code of conduct of media
- Need to improve knowledge about vaccines even among health care professionals
- Don't assume decision makers can do an appropriate risk-benefit assessment to make good judgement using scientific guidelines
- Decisions of parents is about vaccines are mainly emotional

Questions to address when moving forward:

- With hyperendemicity (89%) and CFR (0.48%) in Philippines–knowing what we know now, should a public health program be undertaken (with pre-vaccination screening or no screening)?
- How do we rebuild trust in this vaccine? Or is this trust in the system that we need to rebuild?
- Reframing the question: How to increase vaccine uptake while preserving parental autonomy to choose
- What is the scenario like to re-introduce this vaccine for public and for private clinic use with pre-vaccination screening? (What will doctors and parents accept?)

Key dilemmas expected:

- Governance dilemma:
  1-knowing what we know now, in the absence of reliable pre-screen tests, given the outbreaks, what should the government decision be?
  2-Given there is election, should the program be postponed?
- Ethical dilemma: Having thrown the baby out with the bath water, and government will not bring back the vaccine, how shall we protect the majority and will be at the expense of sero-negatives? (Is it really true that 75% have had first dengue but did not know?)
- Equity dilemma: Is Dengvaxia only for the rich folks?
- Clinical dilemma: Is the risk of "severe" dengue in vaccinated seronegatives the same as the risk of unvaccinated seropositives who contracted dengue?
- Do we know how soon someone will get a second dengue infection?

The following suggestions were given on how communications should be tailored:

- Improve the value chain of message owner–message–delivery–Listener
- Understand the target listener & their pain points
- Put ourselves in the shoes of the parent: (imagine the conversation): "Your child has been screened positive for previous dengue, he can be vaccinated with Dengvaxia", "his brother at the same time has been tested and negative for dengue, we cannot vaccinate him, because if we do, he will..
- Tailor messages to win over vaccine hesitant people and not necessarily consider every one of them as die-hard anti-vax. Some of them are well educated and just seeking answers If possible, be a step ahead of the anti-vaxx movement and be pro-active and not reactive to them.
- Consider who the decision maker is. Is it the government or the parents? In the Philippines, the mother-in-law appears to be the main influencer. Neighbours are also important influencers. Not just the parents as independent decision makers, also the community.
- Re-evaluate what is taught in health schools in terms of communication and vaccines
- Is the nudge theory the right way to go?: consider the transcript from parents below

If nudging is to be considered in future communications, the following quotes from parents should be considered:

'I feel that if I vaccinated my kid, if he did, I will be more responsible for his death than if I hadn't vaccinated him and he did.I will not be willing to take a high risk with vaccine as I would with the disease'.

'I would rather take my chance that the child would not catch flu than to be responsible for giving my child a vaccine which could be fatal'.

'I did not want to risk killing child with vaccine that is optional. It would therefore be my fault if the child died from that vaccine'.

9. Country/regional experiences

9.1. Brazilian experience in public & private vaccination center settings

The Unified Health System ("Sistema Único de Saúde"- SUS, in Portuguese) was established in 1989. It provides universal health care free of charge to all people. In parallel to SUS, there is also a private sector, mostly funded by private health insurances. Some 20% of the 210 million Brazilians are covered by the private sector. The National Immunization Program ("Programa

Nacional de Imunizações"- PNI) is one of the programs within the SUS. It provides a wide range of vaccines and biologicals free of charge to the Brazilian population. In 2019 there were 36,458 health care units that provided vaccines registered by the Ministry of Health, 95% public services, and just 5% private (approximately 1,800). The public vaccine providers are usually primary care clinics, where there is a "vaccine room". The private ones include vaccine clinics, hospitals, travel medicine clinics, and some pediatricians' offices. The PNI implemented since 2014 an online vaccine registry (SI-PNI). The individual vaccine file may be accessed and updated by any provider. The SI-PNI should be used also by the private sector, but the type of service (public or private) is not among the routine outputs of the system. One way to use the SI-PNI to assess the number of vaccine doses provided by the private services would be the selection of vaccines provided only by the private ones. In 2018, just 382,000 doses of such vaccines had been registered in SI-PNI, a result that made clear that not all private vaccine providers in the country were in fact using the system. The PNI administered more than 112 million vaccine doses in 2019, excluding influenza. The number of vaccine doses administered by the private sector was not available, but we did find the number of doses sold to the private sector by the four vaccine manufacturers operating in Brazil, approximately 2 million doses. The participation of the private sector is higher in influenza vaccines (around 5 to 6 million doses), while the public campaign vaccinated 62 million people in 2019. It is important to note that the private health insurances in Brazil usually do not cover vaccine expenses. As for the dengue vaccine, CYD-TDV was licensed by the national regulatory agency (ANVISA) in late 2015. It was used in a public campaign conducted in 30 high-risk municipalities of the State of Paraná, where some 300,000 people were vaccinated between 2016 and 2018. Anecdotal reports account for a very little use of this vaccine by the private sector. Considering the size of the vaccine private sector in Brazil, its participation in scaling up the use of the dengue vaccine would likely be limited.

9.2. Recommendations for Latin America (LATAM) from the International Dengue Initiative

The International Dengue Initiative (IDI) experts working group is a permanent group of Latin America and other international experts. This talk presented the updated recommendations of the IDI expert group for CYD-TDV implementation in LATAM. The recommendations take into consideration the main conclusions of the Sixth Meeting of the IDI (Lima, June 2018), the updated WHO-SAGE recommendations, additional scientific evidence on vaccine performance and experiences reported by implementing countries.

The key recommendations regarding the implementation of the dengue vaccine were:

The characteristics of dengue transmission in target populations should be evaluated in advance of immunization to help define the efficiency of either a mass vaccination based on high

seroprevalence or a vaccination strategy based on point-of-care screening to target seropositive individuals.

- In areas of high endemicity in which seropositive subjects predominate, the benefit of mass vaccination outweighs the risk to seronegative individuals at a population level. In high seroprevalence areas, studies to determine detailed information on seroprevalence over time or pre-vaccination serologic assessment would significantly increase the costs of vaccination programs and delay vaccine implementation for populations that would have substantial benefit from vaccine use. However, in countries of the region with relatively high per capita GDP pre-vaccination strategy might be cost-effective from both, public payer and individual perspectives.
- Countries should consider vaccination in municipalities or other defined areas that already have robust seroprevalence data and fulfil the above mentioned epidemiological criteria.
- In areas of intermediate or low endemicity, where the risk of vaccinating seronegative individuals potentially could outweigh the benefit of vaccinating the entire population, pretesting to establish the patient's serostatus before vaccination is mandatory. This strategy would increase trust in the vaccination program and improve coverage. In addition, it will generate seroprevalence data enabling subsequent decision-making.
- Dengue serostatus ascertainment considerations include:
    1. The ELISA capture would not be practical due to the time it takes to obtain results, in addition to cross-reactivity with other flaviviruses.
    2. RDT implementable at the POC need to be easy-to-use, qualitative, applicable to whole blood, and validated to indicate past dengue infection at any age in any endemic setting.
    3. The ideal RDT needs to be highly specific and highly sensitive avoiding vaccination of seronegative subjects and maximizing the impact of vaccinating a higher number of seropositive individuals.
    4. A reasonable option would be to use a test with the highest specificity currently available, even with imperfect sensitivity, while newer tests are developed.
    5. Countries should use the best available tests, and help develop new ones by sharing epidemiological data and biological samples, and conducting demonstration projects with current tests.
- The current vaccine is not indicated for outbreak response but may assist with outbreak prevention.
- Countries should implement a robust and documented vaccination information strategy, and optimal program planning.

- Vaccine-implementing countries should have a robust surveillance for monitoring adverse events.
- Dengue Committees should be strengthened and adequate information on vaccine and other prevention strategies given to those in charge of the program
- Surveillance should include number of doses given, epidemic situation, and clarification on aspects of potential confusion for decision-makers, implementers, and patients.
- Age:
    1. The vaccine is currently indicated por persons 9 years of age or older.
    2. Among those 9+, the target age of implementation needs to be in accordance with the local regulatory agency recommendations.
    3. For public campaigns, the age targets should be in the age groups with higher seroprevalence of higher hospitalizations incidences.
    4. Previous vaccine adherence should be considered when identifying target age groups.
    5. Vaccination of larger or complementary cohorts could be implemented to have a higher and faster impact. The extension of such campaigns will depend on modelling information using local data for optimal impact.
- Countries should be empowered to take their own decisions based on evidence-based information and support from local and international experts.
- The guidelines developed by scientific and medical societies (e.g. SLIPE) should be given more visibility and should help country decision-making.
- In summary, dengue vaccination, where implemented, should be part of a public health strategy that includes the participation of scientific societies, the MOH and civil society.
- These recommendations need to be updated regularly, as new scientific evidence becomes available.

9.3. French Territories: deliberations on introduction

Arbo-France is a multidisciplinary and multi-institutional surveillance and research network, working on dengue vaccine implementation to provide a scientific research framework to the potential introduction of the dengue vaccine in the French West Indies.

The speaker started by presenting the findings of seroprevalence study that provides background epidemiological data on dengue and arboviruses circulating in the French West Indies. In this study, L'Azou et al used an anti-dengue immunoglobulin G (IgG) indirect enzyme-linked immunosorbent assay, to determine the seroprevalence among 783 adult blood donors in the French Caribbean islands of Guadeloupe and Martinique in 2011. The findings revealed that:

- Overall, 93.5% [91.5; 95.1] samples were positive for dengue antibodies, 90.7% (350 of 386) in Martinique and 96.2% (382 of 397) in Guadeloupe.
- Only 30% of these adults recalled having had dengue disease before.
- Serotype-specific neutralization assays applied to a subset of IgG-positive samples indicated that a majority (77 of 96; 80%) reacted to the four serotypes.
- In addition, 87% of 18/19-year-old blood donors were anti-dengue IgG seropositive.
- These seroprevalence findings were the first reported for Guadeloupe and Martinique and are consistent with the dengue epidemiology in these territories

With respect to a potential introduction of the dengue vaccine in these French territories, the speaker highlighted the following points:

- No plan of large vaccination implementation is currently considered
- As per national recommendation, Vaccination should be considered only based on individual lab-confirmation of past dengue infection (not on epidemiological data)
- Planned epidemiological and clinical studies in the French Antilles would primarily address tolerance, and then social sciences, previous flaviviral immunity and long term clinical & biological follow-up
- Sickle cell patients may have a higher risk for severe dengue, hence there is a high demand from sickle cells disease patients to be vaccinated.
- The priority ranking of planned clinical studies will include the following: patients with Sickle Cell Anemia, patients >60 yrs of age and post-dengue vaccination programme
- There are also remaining questions such as the possibility of a 2 vs 3 dose regime.

9.4. US Territories: deliberations on introduction

The U.S. Advisory Committee on Immunization Practices (ACIP) makes recommendations and provides guidance on the safe use of civilian vaccinations in the U.S. The ACIP Dengue Vaccines Workgroup convened in October 2018 to review evidence CYD-TDV. CYD-TDV was licensed by the U.S. Food and Drug Administration (FDA) in May 2019 for children 9-16 years of age living in endemic areas with laboratory confirmed evidence of prior dengue infection. Endemic areas include U.S. territories in the Caribbean (Puerto Rico, U.S. Virgin Islands) and the Pacific (American Samoa). The workgroup has reviewed data on the epidemiology of dengue in the U.S. safety, efficacy, available laboratory tests pre-vaccination screening, quality of the evidence, cost effectiveness, and feasibility. The workgroup is the process of gathering information on acceptability of the vaccine to physicians and parents in Puerto Rico, the U.S. territory with the highest burden of dengue disease. Modeling suggests that CYD-TDV could be cost effective in Puerto Rico depending on the price of the vaccine and laboratory test. The availability of an independent fully evaluated highly specific and sensitive IgG screening test for prior dengue

infection poses the major challenge to making an ACIP recommendation for CYD-TDV. Additional challenges include the logistics of pre-vaccination screening and how to clearly communicate risk and benefits to parents for this partially effective vaccine. Pilot testing would be an asset.

10. Implementation of a dengue screen-and-vaccinate strategy & operational guidelines to support dengue vaccine implementation

Dengue vaccination has been already implemented in two public programs: in 30 municipalities of the Parana state in Brazil and in five regions in the Philippines. Vaccine introduction was mostly decided based on dengue burden (number of cases, recent outbreaks, serosurveys) as documented by existing surveillance data. Depending on the targeted population, school-based programs or community outreach interventions were used to deliver the 3 doses of the vaccine. There were programmatic challenges to achieve a high coverage for all 3 doses, 6 months apart. Lessons can be learned from these experience that can help future implementation, including the need for: early joint planning and responsibilities sharing between national immunization program, education sectors, local administrations and professional societies; robust coordination of field activities using devoted mobile teams; strong systems and tools for tracking out-of-school children and 2nd and 3rd dose defaulters; triggering adherence through the delivery of other interventions.

The recommended Screen and Vaccinate strategy brings new challenges that need to be answered locally, depending on the specific epidemiology, health care access, logistic, administrative, financial and political contexts of the settings targeted. The new strategy aims at vaccinating those (age and area) who have been infected once and outside the refractory period. Implementers can consider i) a one-step approach where everything is done in one-go using the best RDT available, or ii) a two-step approach where sampling, screening and vaccinating are performed at different times and in different places. A complementary approach consists of screening existing clinical registers or identifying prospectively clinical cases and offering vaccination (after the refractory period) to those having a positive laboratory dengue test result. The vaccine offer could be integrated into the national case management procedure.

When considering a Dengue Screen and Vaccination for public health programs, a range of delivery scenarios can be considered, using various settings for each step of the intervention (**Figure 2**). If schools are the starting point of the intervention, the full strategy can be done in one step (a), or the vaccination can be done at the health care center on those tested seropositives (b), or the samples can be sent in a laboratory and vaccination later given at schools (c) or in health care facilities (d). If a health facility-based strategy is used, the whole procedure can be done in one-step (e), or the samples may have to be sent to a laboratory before vaccination can be offered on seropositives (f). When a community outreach strategy is preferred, everything can be done in the same community setting (g), or individuals screened

positives can be invited to health care centres for vaccination (h), or samples can be sent to laboratories and seropositives invited to vaccination in community posts (i) or at the clinic (j). The strengths and challenges of using different approaches and settings are described elsewhere and should be evaluated and tested locally before taking a decision. Mixed delivery strategies can be implemented in the same country or region, depending on target age group, school enrolment rate, previous experience of school-based interventions or community-based intervention, access to quality health services, but also dengue epidemiology/burden, logistical and financial capacities.

Acceptance and adherence towards the screen and vaccination approach and the selected delivery strategy need to be assessed and ensured across the "full" target including the population (vaccinee and community), key decision makers at local and national levels, health care providers, laboratory technicians, school staff, social mobilizers and opinion leaders.

The Dengue Screen and Vaccinate strategy is a new and challenging intervention for countries wishing to engage in dengue prevention through vaccination. Therefore, there is a strong need for developing information and operational tools, to support country decision makers and program planners make decisions on implementation and evaluation. EpiLinks is currently developing such a Toolkit for Dengue Vaccine implementation, based on scientific evidence, tailored to countries realities and experiences, and reflecting the range and diversity of thoughts and solutions. So far, eight modules have been produced on 1) general information, 2) implementation strategies, 3) organization of immunization sessions, 4) vaccine public health impact, 5) safety of the dengue vaccine, 6) dengue outbreak and evaluation, 7) dengue diagnostic strategies, 8) communication for the dengue vaccine, all of which will be soon revised and published.

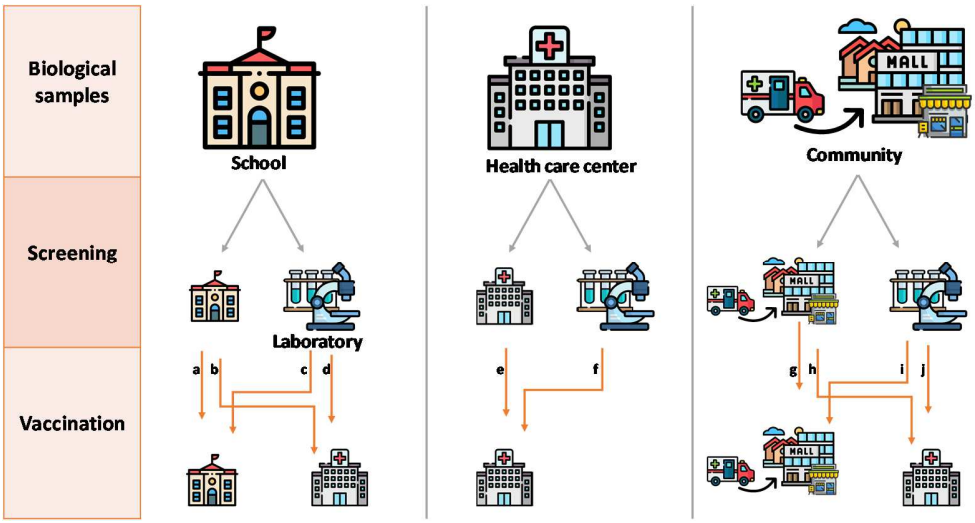

Figure 2 Various scenarios for dengue screening and vaccination implementation strategies

10.1. Feedback from the workshop session (case studies from LATAM and Asia)

The workshop session addressed two main questions:

- What are the needs to support a successful vaccine introduction in my country /region?
- How to address programmatic challenges?

To answer the two questions above, each workshop group(Latin America and Asia) was advised to use table 1 as a guide, which shows the strengths and challenges in the implementation of the pre-vaccination strategies(school-based, facility-based and community based). Each group was given the following steps as a guide:

- choose a country in their region that could be used a case study
- make necessary assumptions
- choose a strategy and justify why based on the strengths and challenges in table 1
- describe how the strategy will be implemented and risks will be mitigated
- propose an appropriate communication strategy

The discussions from each group were summarized in table 2.

Table 1 Strengths and challenges of pre-vaccination strategies

	School-based strategy	Health facility based strategy	Community based strategy
Program			
Strengths	Mobile teams. Opportunity for school-based health education	Where all programs are based, including teams and materials. Included in routine health services	Mobile teams. Reach older target age groups and out-of-school children. Facilitate catch-up campaign
Challenges	Requires strong commitment, coordination and training between health and education sectors. Need complementary strategy for reaching out-of-school children	Extra burden: HR, patient rooms, storage, cold chain, waste management	Need of strong training and coordination of health staff and social mobilizers. Extended availability of staff (7/7; morning to nigh
Logistics			
Strengths	Secured and closed environment	Lowest logistical constraints	

	School-based strategy	Health facility based strategy	Community based strategy
Adherence			
Strengths	High where school enrolment high. More "captive" target, better adherence over the 3 doses	Pro-active process so likely to follow the 3-dose regimen once they enter the program. Accurate and comprehensive information given by trained health staff.	Pro-active process with robust promotion/advocacy possibilities
Challenges	Complemented by other strategies for out-of-school, absents, moving or leaving- schools' children. State/region/nation-wide registry allowing follow-up of vaccination for children changing schools	Requires that population has easy access to health services. Active segment of the population not used to go.	Requires strong social mobilization and mobile teams' commitment for 3-dose regimen
Acceptance			
Strengths	Advocacy from trained and equipped trusted people (teachers). Identify key school leaders (PE teachers).	High for those presenting at health care facility: proactive process and trusted staff through existing health system	Other health interventions proposed
Challenges	Teachers may complain about additional workload. There's need to promote staff understanding and motivation	Achieve less impact where no history of adolescents/adults presenting for immunization	Largely relies on national/local communication and social mobilization
Affordability			
Strengths	Limited effort to reach a target population and administer the 3 doses	Least costly option: already integrated into existing system (transport, cold/waste management)	Can achieve better coverage. Other co-interventions are possible to improve cost-effectiveness
Challenge	Can be costly		Can be the most expensive option (mobile teams, various locations, unusual times)

Table 2 Feedback from groups on implementation strategies

Items	Asia group	Latin America group
Case study	The Kamphaeng Phet province in Thailand. This province has 11 health districts and 78 subdistricts with a total population of 729,133. The seroprevalence of dengue in 9yr olds is 60%. There are provincial hospital, district hospitals, Healthcare centers/ Primary care hospitals/Health clinics (both public and private)/ Community Health Volunteers and one private hospital.	No consensus reached on the particular country to use as case study because of extreme diversity. Puerto-Rico could have been ideal given that the US FDA clearance of the vaccine but its epidemiology and socio-economic profile are different from other countries in the region. Mexico was the first country to register the product but the public program is not yet possible because the government is reluctant to deal with the pharmaceutical industry. In this case, private use was suggested as a potential means to nurture a culture of vaccination.
Strategy	School-based (chosen mainly because of the age of the children). Not clear if a one-step or two-step approach will be feasible. A pilot study was proposed to assess the feasibility in terms of time, cost, and personnel.	School-based and one-step.
Implementation	• Letter and consents to be sent to all parents/guardians with some contents/ check list well ahead of time. • Opt-in option. Opt-out not recommended for live vaccines • At school, no assent is required. • Two-dose regime was preferred. Start campaign before the rainy season. First dose can be given in October so that the second dose is given before the rainy season. Logistics/adherence only over one grade. • Appropriate documentation. Both result of the RDT and vaccine administration need to be recorded electronically or on the vaccine card. If the result is positive, the vaccine should be given and if negative, the test should be repeated at age 11. No catch up plan was recommended due to limited budget.	• Change PAHO's position- through ACIPWHO and regional scientific societies recommendation and WHO Prequalification. • Vaccine registration to be granted in all countries • Map of prioritization. Define hot spot areas based in epidemiological criteria defined by IDI • School base screening – Permission for the parents for all procedures. • Two doses recommended. One-step approach. Vaccination of 9-16 yr olds • School base vaccination • Vaccination and test records- electronic data capture – review best way to ensure both. • Choose the best context for the decision- after an outbreak

Items	Asia group	Latin America group
Communication strategy	• Should be pro-active involving the education of all stakeholders: parents, community, teachers, and health personnel of every levels. • Reframe the message to state that vaccine is to prevent severe dengue and hospitalization in those have already had dengue infection. • Ensure the establishment of an AEFI surveillance system for early detection of adverse events and a rapid response team for intervention and or stopping rumor if any. Training of health care workers and school staff is important.	• Deep training for Health care professionals, teachers and students. • Specific strategy for parents, community, media, politicians, Journalists • Content: Burden of disease and cost effectiveness of the vaccine. Customize the language. By professionals. Focus vaccination benefits-relevance of immunization program • Use updated technology: Video – social media. Use influences • Be one step ahead: device a strategy against anti vaccines-in advance.
Strengths	• Mobile teams and Opportunity for school-based health education. • Advocacy from trained and equipped trusted people (teachers). Identify key school leaders (PE teachers). • The school administration is very much aware of the underlying co-morbidities of the children, making it easier avoid vaccinating children who are immunocompromised.	
Challenges	• Requires strong commitment, coordination and training between health and education sectors. • Extra burden: HR, patient rooms, storage, cold chain, waste management-Manageable as the program exists. • Need of strong training and coordination of health staff and social mobilizers. • Extended availability of staff (7/7; morning to night). • Need to promote staff understanding and motivation. • Can be costly but other co-interventions possible to improve cost-effectiveness. For example the HPV vaccine program. Some studies have been carried out to assess the impact of co-interventions but the data are yet to be made available. • The cost of the IEC should be included in the cost analysis.	

10.2. Suggestions on additional/alternative strategies

Apart from the discussions on the implementation strategies, proposals on additional strategies were made. In order to suggest additional strategies that can be used to get more people vaccinated, it was important to have some key questions in mind:

- How do we create or use encounters/windows of opportunity?
- How do we apply the nudge theory and create the 'ah-ha moment'?
- How can we incentive people?
- What are the immediate 'low hanging fruits'? Who is easy to convince?

The key suggestions are summarized in table 3.

Table 3 Additional implementation strategies

• For the Philippines, a low hanging fruit will be immediately target those who have just had clinical disease. They have just been through the pains and the aches and would likely be more willing to prevent severe disease in the future. They can also serve as advocates • Take advantage of any encounter in health facilities such as consultations, visits and hospitalisations • Make dengue rapid test widely available even in the offices of physicians • Consider a vaccine package for families so that there can be discounting • Identify leaders and influencers in the community to use their position and spread the message about the vaccine • Get business to sponsor vaccination. For example in Hawaii, a 10% discount on groceries has been used to increase uptake of flu vaccine (no data on impact available yet) • Make an investment case to companies that vaccination for dengue would lead to fewer hospital days and better productivity for their workers. Human resource can consider vaccination as a requirement to travel to endemic areas • Reimbursement of vaccinations by companies given that hospitalisation for dengue is expensive. Consultations about this strategy show it could be feasible. • Make companies understand the have a liability to protect their workers if they do not send them for dengue testing and vaccination, in countries where dengue vaccine is licensed. • Link insurance premiums to how active workers are in preventing disease. People can earn more points if they engage in prevention such as testing and getting vaccinated for dengue • Clinicians should counsel patients when they travel back to endemic countries on the need to take be vaccinated for dengue. • Take advantage of outbreaks to increase uptake of vaccine. • Reminders for dengue vaccination. Using Apps for reminder. • Take advantage of the dengue day to empower communities using a top bottom approach. From the people and for the people.

Discussion

1. Limitations

Since the last meeting on the pre-vaccination strategies for dengue, there have been much improvement in the development of an 'ideal' test to be used, and in the knowledge about:

- the efficacy of different doses of vaccine (1, 2 or 3);
- cost-effectiveness of implementation strategies, the timing of vaccination;
- and best strategies to implement a dengue vaccination program.

However, several challenges or limitations exist, that will have to be considered in the future on how and when the dengue vaccine should be implemented.

Cost-effectiveness studies were presented which showed the strategy could be cost-effective and cost saving depending on the test performance and the prevalence of dengue. The cost-effectiveness can be estimated to improve with the 2-dose regimen and with multiple testing. However, one analysis also suggested that from a public payer perspective the program would not be feasible. The main obstacle appeared to be the price of the vaccine and test. Affordability varied from one country to another and was more important than cost-effectiveness. Furthermore, a major limitation of cost-effectiveness studies is that they did not consider the cost of communication. Well-tailored communication strategies that target the key stakeholders are expected to make up a significant part of any future dengue vaccination program. To improve on the cost-effectiveness, co-intervention has been suggested and studies have been conducted to confirm or refute the claim, but the data are still to be published.

The availability of a 'specific RDT' that can be used in the pre-vaccination screening strategy is a major determinant for many countries to start considering a roll-out of a dengue vaccination program. Despite the modelling scenarios, end-users will tend to go for a diagnostic test that has a very high specificity (of almost 100%) to guarantee safety. The currently available RDTs and those in development seem highly specific but suffer in terms of lower sensitivity in monotypic detection than ELISAs. In addition, there are questions about the impact of yellow fever vaccination and validity of samples used in evaluating the cross-reactivity of the RDTs. An industry-led TPP has been a good step but there is need to match the TPP to one that is independently developed by experts. To develop this new region/country specific TPP, the Delphi process was criticized for being too passive and biased. To overcome this limitation, an approach that would involve the policy makers, regulators and subject matter experts in a roundtable, was proposed by Rosanna Peeling from the London School of Hygiene and Tropical Medicine (LSHTM). This approach would also include regional consultations, led by the International Diagnostics Centre at LSHTM. Such an approach will be very important in the

current scenario where no "ideal" TPP can be applicable to all epidemiological settings. Meanwhile, a working TPP was updated from consensus during the meeting, that favors on the side of a desired high specificity at the expense of sensitivity (see table 4)..

In terms of implementation strategies, the two groups in the workshop chose a school-based intervention. The limitations of this strategy can be found in tables 1 and 2. Some of the limitations of the school-based strategy could be overcome by using a two-step approach in which screening takes place in schools while children are vaccinated in health care facilities. This would reduce the burden on schools, require less vaccine, reduce the cost for mobilization and vaccine transport, as well as better acceptance since vaccinations would take place in a trusted environment. However, there might be low vaccine coverage as vaccination becomes pro-active and dropouts between doses might occur. Furthermore, catch up strategies for those tested sero-negative will also have to be considered. Indeed, severe dengue is increasingly seen in adults and there might be a need to expand vaccinations for this age group. Studies that could be conducted in French overseas territories in three main risk groups which are adults >45 yrs, adult expatriates and sicklers, may provide some useful clinical evidence in this context.

During the discussions, it was suggested that an outbreak would be a suitable time for vaccination. On one hand, such approach could facilitate vaccination program implementation as the population could more easily accept vaccination. This can be useful in preparing for the next outbreak. However, during an outbreak, the health system is usually overwhelmed, and the government might not tolerate any additional cost. Furthermore, using the vaccine as an outbreak response tool has never been evaluated, in particular, the potential impact of cross-reactive immunity which might markedly reduce the efficacy of the vaccine if given too late. Therefore it would be advisable to assess feasibility of vaccination implementation before the start of the epidemic season

Table 4 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.

CHARACTERISTIC	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

CHARACTERISTIC	MINIMAL	OPTIMAL	COMMENTS
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 ll	Fingerprick whole blood ≤25 ll	
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 ºC and 80% relative humidity, 12 months shelf life	5–40 ºC 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

CHARACTERISTIC	MINIMAL	OPTIMAL	COMMENTS
Test performance			
Seroprevalence above 90%			Specificity is a higher priority than Sensitivity. Performance shall be determined in appropriate samples. Dengue seroprevalence
Clinical sensitivity	≥90%		
Clinical specificity	≥98%		
Area Under Curve	0.988		
High seroprevalence: 70-89%:			
Clinical sensitivity	≥85%		
Clinical specificity	≥99%		
Area Under Curve	0.99		
Moderate seroprevalence: 50-69%			
Clinical sensitivity	≥80%		
Clinical specificity	≥99%		
Area Under Curve	0.987		
Low seroprevalence: 20-49%			
Clinical sensitivity	≥70%		
Clinical specificity	≥99%		
Area Under Curve	0.98		
Cross-Reactivity	No cross-reactivity to other flaviviruses. No cross-reactivity to other flaviviruses No cross-reactivity to circulating antibodies from other flavivirus vaccinations		
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 time points 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 time points after resolution of infection - previous infection by both dengue and another flavivirus with varying time points after resolution of infections - who have received other flavivirus vaccinations	

Moving forward: the next steps

- The International Diagnostics Centre (IDC), LSHTM, to lead the development of region specific TPPs for a screening test for dengue.
- Development of a 'specific RDT' for pre-vaccination screening a priority. RDT available now with high specificity at the expense of a little bit of a lower sensitivity. The RDT still needs to go through regulatory approval.
- Ensure increased accessibility by streamlining the regulatory approval of the RDT
- Development of dengue vaccine implementation Toolkit
- Planning for the World Dengue Day. Using this opportunity to raise awareness about dengue.

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Appendix

1. Diagnostic developers and their test performance

1.1. BIORAD

Presented the performance evaluation of an RDT dengue IgG assay for pre-vaccination status determination. They developed a prototype of the RDT Dengue IgG assay to be used in the context of a pre-vaccination strategy that has the following specifications:

- Lateral Flow Format Assay
- Qualitative detection of Anti-Dengue Virus IgG
- Human whole blood, serum and plasma samples
- Result obtained in 20 min
- Simple 3-step protocol

The conducted specificity, sensitivity and cross-reactivity studies. The specificity study included 127 blood donor's specimens and 97 clinical anti-Dengue IgG negative specimens from a non-endemic area. Each specimen found positive with RDT was confirmed using 2 ELISA assays The Sensitivity study included 206 seropositive anti-Dengue IgG samples and samples came from different endemic areas (either commercial or clinical specimens). The Cross-reactivity study included 5 anti-Yellow Fever IgG positive samples (France) and 3 anti-Zika IgG positive samples (Florida). They concluded that the performance assessment of the prototype RDT Dengue IgG assay demonstrated data in agreement with FIND's draft TPP for pre-vaccinal testing with 99,1% specificity and 96,1% sensitivity, and suggested it could be a good candidate pre-vaccinal assay for serostatus determination.

RDT Dengue IgG Assay description

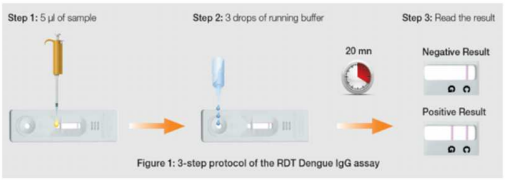


Figure 1: 3-step protocol of the RDT Dengue IgG assay

- Lateral Flow Format Assay
- Qualitative detection of Anti-Dengue Virus IgG
- Human whole blood, serum and plasma samples
- Result obtained in 20 min
- Simple 3-step protocol

3

BIO-RAD

Specificity study on RDT Dengue IgG

Blood Donor Specimens	Sera (n=52)	52/52 100% [100;100]
	Plasma EDTA K2 (n=50)	50/50 100% [100;100]
	Whole Blood (n=25)	25/25 100% [100;100]
Clinical Specimens	Sera (n=97)	95/97 97,9% [95,11;100]
Total specificity (n=224)		**222/224** **99,1% [97,88;100]**

- Two clinical specimens were found positive with RDT and negative with ELISA assays.
- Specificity of RDT Dengue IgG is higher than 98%, target for a pre-vaccinal anti-Dengue IgG assay .

Sensitivity study on RDT Dengue IgG

A total of 206 specimens from several endemic areas (Peru, Singapore, Burkina Faso, India).

	RDT Dengue IgG	DENV Detect IgG ELISA	Panbio Dengue IgG Indirect ELISA
Sensitivity	198/206 96,1% [93,48;98,75]	202/206 98,1% [96,17;99,94]	204/206 99% [97,69;100]

- On the tested population sensitivity of RDT Dengue IgG is slighty lower than the ELISA assays and is compliant with FIND's draft TPP.

Cross-reactivity study on RDT Dengue IgG

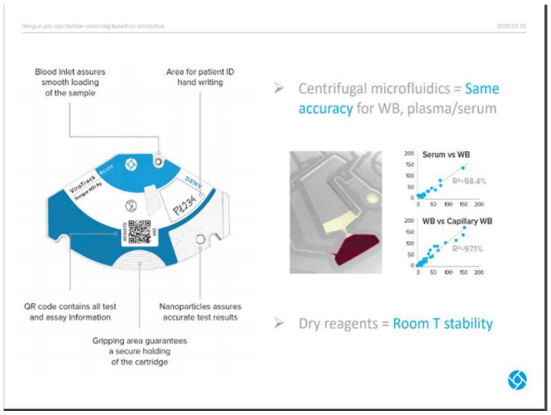
A total of 8 specimens was evaluated. Specificity is as follows:

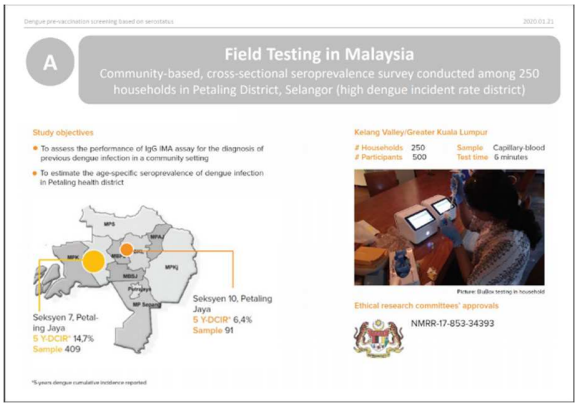
Ratio of Cross-reactive specimens	RDT Dengue IgG	DENV Detect IgG ELISA	Panbio Dengue IgG Indirect ELISA
Anti-YFV IgG (n=5)	2/5	Not tested	2/5
Anti-ZIKV IgG (n=3)	1/3	2/3	2/3

- On the tested population cross reactivity of RDT Dengue IgG is in the range of the ELISA assays.

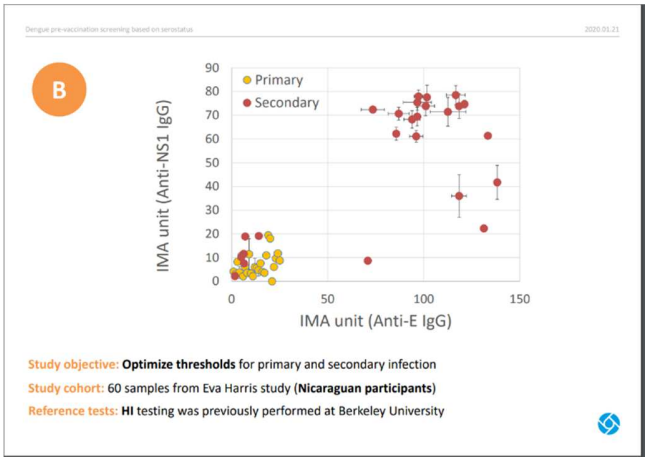
1.2. BluSense

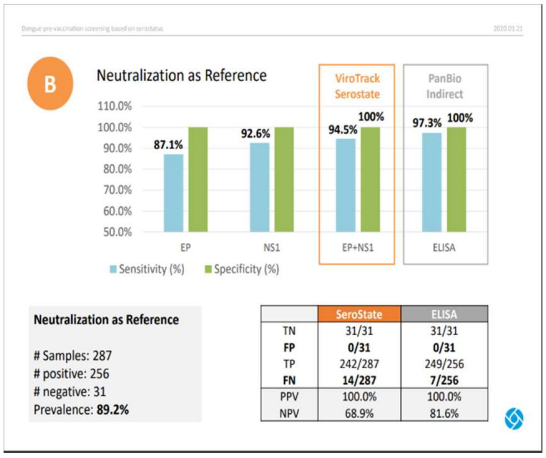

21 Jan 2020
BLUSENSE DIAGNOSTICS
ViroTrack Serostate
Fast quantification of dengue serostatus biomarkers
Filippo Bosco, PhD – CEO
Marco Donolato, PhD - CSO


Blood inlet assures smooth loading of the sample
Area for patient ID hand writing
Centrifugal microfluidics = Same accuracy for WB, plasma/serum
Serum vs WB
WB vs Capillary WB
QR code contains all test and assay information
Nanoparticles assures accurate test results
Gripping area guarantees a secure holding of the cartridge
Dry reagents = Room T stability


A
Field Testing in Malaysia
Community-based, cross-sectional seroprevalence survey conducted among 250 households in Petaling District, Selangor (high dengue incident rate district)
Study objectives
Kelang Valley/Greater Kuala Lumpur
Seksyen 10, Petaling Jaya
Seksyen 7, Petaling Jaya
Ethical research committees' approvals
NMRR-17-853-34393


A
Overall Dengue Seroprevalence by method
74.17%
75.20%
72.76%
ViroTrack
Indirect ELISA
HI Assay
Age-specific sensitivity for ViroTrack SeroState and ELISA indirect (HI as reference)
Cumulative Age-specific Dengue Seroprevalance


B
Primary
Secondary
IMA unit (Anti-NS1 IgG)
IMA unit (Anti-E IgG)
Study objective: Optimize thresholds for primary and secondary infection
Study cohort: 60 samples from Eva Harris study (Nicaraguan participants)
Reference tests: HI testing was previously performed at Berkeley University


B
Neutralization as Reference
ViroTrack Serostate
PanBio Indirect
87.1%
92.6%
94.5%
100%
97.3%
100%
EP
NS1
EP+NS1
ELISA
Sensitivity (%)
Specificity (%)
Neutralization as Reference
Samples: 287
positive: 256
negative: 31
Prevalence: 89.2%
SeroState
ELISA
TN 31/31 31/31
FP 0/31 0/31
TP 242/287 249/256
FN 14/287 7/256
PPV 100.0% 100.0%
NPV 68.9% 81.6%

1.3. Chembio

Chembio Commercially Available Products

Multiple commercial products serving unique customer requirements

Key Advantages

- Small sample size
  - 2.5-15µL fingerstick blood sample
- Rapid results
  - ~15 minute test time
- Reliable performance
  - Sensitive and Specific
- Advanced multiplexing*
  - HIV-Syphilis
  - Syphilis Screen & Confirm

Chembio sold 25MM POC worldwide 2018

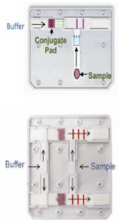
Product	U.S.	Int'l[1]
DPP® HIV 1/2	✓	✓
DPP® HIV-Syphilis*		✓
DPP® Syphilis S&C*		✓
DPP® Zika	✓	✓
DPP® Leishmania		✓
DPP® Ebola	✓	✓
DPP® ZCD (Zika, Chik., Dengue)		✓
STAT-PAK® HIV 1/2	✓	✓
STAT-PAK® Chagas		✓
SURE CHECK® HIV 1/2	✓	✓
SURE CHECK® HIV Self Test		✓

[1] International markets require specific country registrations

Patented DPP® Technology Platform

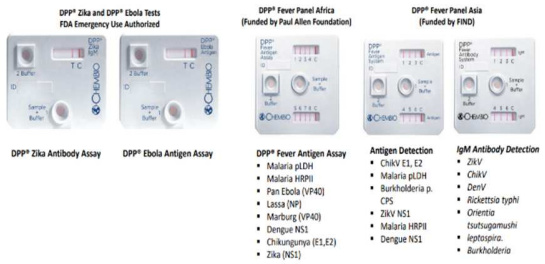
Advantages of dual sample and buffer paths

- Separate sample path and conjugate path
- Control of sample flow and order
- Incubation allows pre-binding of the analyte to the test line
- Buffer releases conjugate that clears the background
- Quantitative results when used with Chembio's optical reader
- Simultaneous analysis of the top and bottom strips allow detection of IgM and IgG antibodies, or detection of antibodies and antigens, with a single sample
- Enable broad sample matrixes (e.g., whole blood, plasma, serum, oral fluid, fecal, urine)



Patented DPP® Technology Platform

Examples of analyzer-based single and multiplex tests



DPP® Zika Antibody Assay

DPP® Ebola Antigen Assay

DPP® Fever Antigen Assay
- Malaria pLDH
- Malaria HRPII
- Pan Ebola (VP40)
- Lassa (NP)
- Marburg (VP40)
- Dengue NS1
- Chikungunya (E1,E2)
- Zika (NS1)

Antigen Detection
- ChikV E1, E2
- Malaria pLDH
- Burkholderia p. CPS
- ZikV NS1
- Malaria HRPII
- Dengue NS1

IgM Antibody Detection
- *ZikV*
- *ChikV*
- *DenV*
- *Rickettsia typhi*
- *Orientia tsutsugamushi*
- *leptospira.*
- *Burkholderia*

Advanced Multiplexing: DPP® Tropical Assays

Solution for Dengue, Zika, Chikungunya (IgM, IgG, Antigen detection)

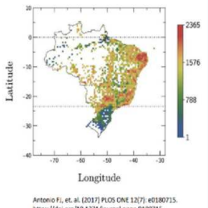
Why Dengue, Zika, Chikungunya, and Yellow Fever
- ✓ Co-circulation
- ✓ Co-infection
- ✓ Cross reactivity
- ✓ Similar symptoms
- ✓ Differential care

DPP® Micro Reader

Next Generation Analyzer

Future Development

Test Result Transmission and Storage

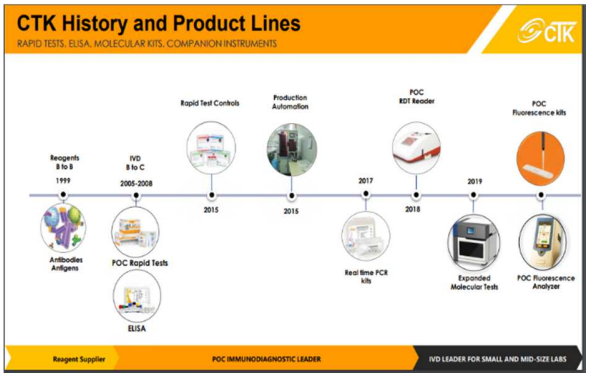


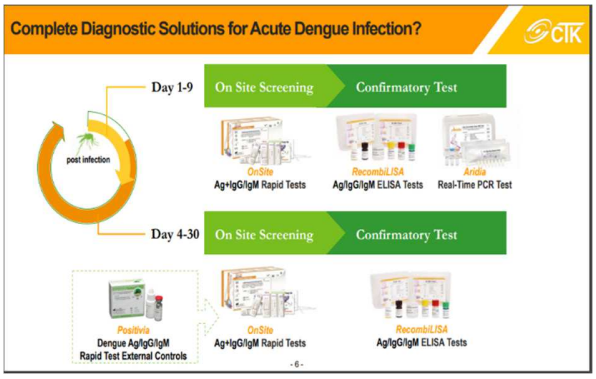
Antonio FJ, et. al. (2017) PLOS ONE 12(7): e0180715. https://doi.org/10.1371/journal.pone.0180715

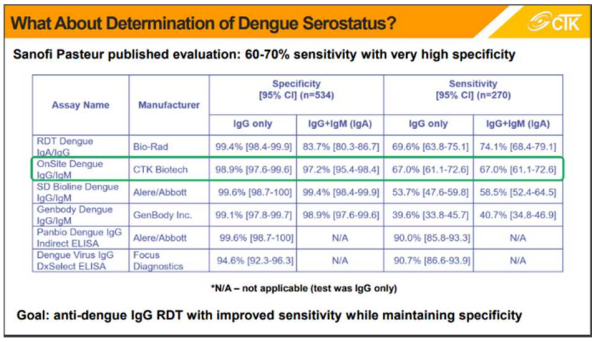
DPP ZCD IgM/IgG System

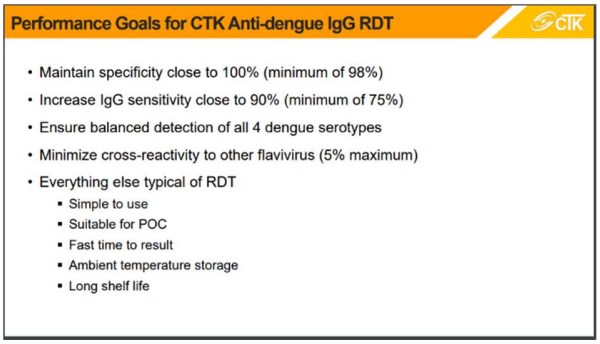
DPP Fever Panel Asia Antibody/Antigen

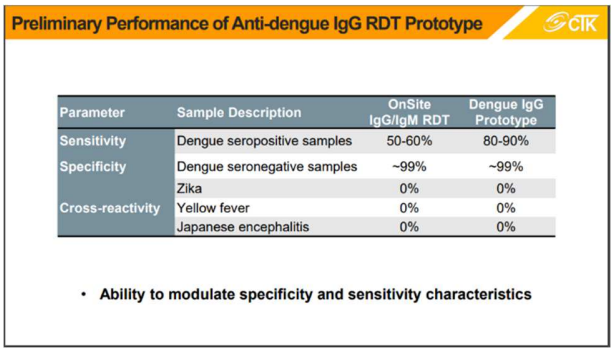
1.4. CTK Biotech











2. Questions/comments/answers from the sessions

2.1 The Philippines' experience

Question: How do you see things moving forward in the Philippines? Do you see a pathway?

Response: Even if the WHO including the vaccine in the essential medicines list and many other countries registering the product, we do not believe the Philippine government at this stage is going to re-instate the vaccine. This also puts at risk, the other industry product in the pipeline. The narrative about the vaccine that it will lead to death is very prevalent now. More time is needed to engage with the public, get their feedback that can help change this narrative.

However, there is one way this can be tackled. Interesting that after the US FDA approval of Dengvaxia, there was a lot of interest among private sector users who are willing to travel to Singapore to get the vaccine. Seen as a luxury product, it might gradually become more desirable. This might be a marketing strategy.

Radio commentators were using Dengvaxia as a verb, which was associated with harm. There's even the Dengvaxia looked used by women. These need to be factored in when planning a communications strategy. For the moment, it will be good to wait until the tsunami of negative energy and skepticism subside and then come back later with a better communication and community engagement plan.

Question: A key dilemma now is how do we strike a balance the democratization of public health and at the same allow public health decisions to be made experts. How do we convince the public about this balance?

Response: Traditional communication may work but not at this stage. The landscape has changed drastically. Collaborative governance can be applied (with some risks) by bringing on board community leaders and decision makers to make a joint decision. This may not work in all situation but can there is some willingness to test this approach.

Question: How much was the EPI program affected?

Response: Measles and pertussis case went up. Health workers were called out as child killers and were not welcomed in houses. The EPI program staff felt they were left on their own.

2.2 US territories: considerations for introduction

Question: If you happen to introduce this vaccine, what is your strategy going to be?

Response: There needs to be further discussions with parents and physicians. The initial survey results there is a fair amount of support for a pilot program, considering that there is a vast database of those with prior infections in Puerto-Rico. However, this will be a small number because very few people get laboratory confirmation compared to the total number of those infected.

Question: Fifty four percent (54%) of people said they accept if the specificity of the test was <5%. What did the remaining 46% say?

Response: A small number said 0% while others said a high specificity of 90% would be acceptable.

Comment: Puerto-Rico will set the pace in Latin America.

3. Meeting agenda

JANUARY 20 – DAY 1

Vaccine & RDT updates	
12:00 - 13:45	**Lunch**
14:00 - 14:15	**Welcome – Opening** *Mérieux Foundation* *Chair: Duane Gubler*
14:15 - 14:40	Recap of the previous meeting *Annelies Wilder-Smith*
14:40 - 15:15	CYD-TDV dengue vaccine: clinical data updates *Cesar Mascareñas*
15:15 - 15:45	Impact and cost-effectiveness of a pre-vaccination screening strategy depending on RDT performance *Stefan Flasche*
15:45 - 16:00	**Break**
16:00 - 16:45	Desired characteristics for a screening test: accelerating access to a new screening test *Rosanna Peeling*
16:45 - 17:15	RDT for pre-vaccination screening: a status update *Stephen Savarino*
17:15 - 17:45	Discussion
19:30	**Dinner**

JANUARY 21 – DAY 2

Implementation strategies for pre-vaccination program for CYD-TDV Chairs: TBC	
8:30 - 9:15	Updates on Dc tests determining past infection Diagnostic developers TBC (3*15')
9:15 - 9:45	Cost-effectiveness data and modeling implementation approaches *Laurent Coudeville*
9:45 - 10:45	Key questions to address as part of the implementation: • Timing for vaccination after an acute confirmed dengue infection • What is the best timing to re-screen people who were tested seronegative in high-endemic areas? • How to address communication and ensure parental acceptance and high coverage rate? (3*20') *Bruno Guy* *Sam Clifford* *Kenneth Hartigan-Go*
10:45 - 11:15	Discussion
11:15 - 11:30	**Break**
11:30 - 12:00	Public health perspective of dengue vaccine introduction base in pre-test, general guidelines and practical considerations *Brad Gessner (remotely)*
12:00 - 12:30	Implementation of a test-and-vaccinate strategy & operational guidelines to support implementation *Isabelle Delrieu*
12:45 – 14:00	**Lunch**
14:00 - 14:20	Brazilian experience in public & private vaccination center settings *Expedito Luna*
14:20 – 14:40	Recommendation for LATAM from the international dengue initiative *Carlos Torres (remotely)*
14:40 - 15:10	French Territories: deliberations on introduction *Xavier de Lamballerie*
15:10 - 15:30	US Territories: deliberations on introduction *Steve Waterman*

JANUARY 21 – DAY 2

15:30 - 15:45	**Break**
15:45 - 17:30	Workshop sessions (running in parallel): • What are the needs to support a successful vaccine introduction in my country/region? • How to address programmatic challenges? Working Group 1 Working Group 2
19:30	**Dinner**

JANUARY 22 – DAY 3

8:30 - 9:30	Reports from Working Groups 20' each, plus discussion
09:30 - 9:50	Dengue outbreaks 2018-2019 *Raman Velayudhan*
9:50 - 10:10	Economic burden of dengue *Till Baernighausen*
10:10 - 10:30	**Break**
10:30 - 11:45	Workshop session: 'Additional' vaccine implementation strategies (Hospital/Labs databases, Private settings, Travel clinics, after outbreak programs, etc.) *Chair: Hoe-Nam Leong*
11:45 - 12:15	World Dengue Day: target & expectation *Kamran Rafiq*
12:15 - 12:30	Closing *Duane Gubler & Annelies Wilder-Smith*
12:30	**Lunch – End of meeting**