Multi-country joint regulatory review: the dengue vaccine (Dengvaxia) marketing authorization process

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1. The Developing Countries' Vaccine Regulators Network (DCVRN)

National authorizations for Dengvaxia (Sanofi Pasteur), the first vaccine approved for Dengue Disease, happened from 2015 on, facilitated by World Health Organization (WHO), based on the idea that countries affected by neglected tropical diseases should be the first jurisdictions to issue marketing authorizations for products aiming at this category of diseases[1]:

> In December 2015, the first dengue vaccine, CYD-TDV (Dengvaxia), was licensed by three dengue-endemic countries, followed shortly by several others in 2016 throughout Latin America and Asia. This reflects an increasing trend of regulatory submissions for Phase 2 and Phase 3 clinical trials or for marketing authorizations for drugs and vaccines against neglected tropical diseases going first to the countries most affected by disease, rather than North American or European regulatory agencies. Such an

The facilitation effort coordinate by WHO involved, according to Mahoney et al.[2], the Pediatric Dengue Vaccine Initiative (PDVI), supported by the Bill & Melinda Gates Foundation, an initiative targeting the accelerate development and regulatory review of pediatric vaccines:

> The Pediatric Dengue Vaccine Initiative (PDVI) is a product development partnership (PDP) based at the International Vaccine Institute (IVI) in Seoul, Korea, and is supported by the Bill & Melinda Gates Foundation. PDPs are nonprofit entities that seek to accelerate the development, evaluation, and introduction of vaccines, drugs, devices, diagnostics, and other technologies to reduce the burden of disease in developing countries. They operate through partner-

[1] Vannice, K. et al., **The value of multi-country joint regulatory reviews: The experience of a WHO joint technical consultation on the CYD-TDV (Dengvaxia) dossier**, Vaccine 35 (2017) 5731–5733. Available on: https://www.sciencedirect.com/science/article/pii/S0264410X17309520?via%3Dihub

[2] Mahoney, R. et al. **Dengue Vaccines Regulatory Pathways: A Report on Two Meetings with Regulators of Developing Countries**. PLoS Med 8(2) (2011): e1000418.doi:10.1371/journal.pmed.1000418. Available on: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000418

PDVI collaborated, on the regulatory assessment of Dengvaxia's dossier, with the Developing Countries' Vaccine Regulators Network (DCVRN), a World Health Organization (WHO) initiative *"(…) involving nine countries: Brazil, China, Cuba, the Republic of South Korea, India, Indonesia, the Russian Federation, South Africa, and Thailand. (…)."*[3]

DCRVN, according to Mahoney et al.[4], "*provides a forum for discussion, advancement of knowledge, and exposure to policies and procedures pertaining to oversight of clinical trials and evaluation of clinical data for registration of vaccines*", and could count on the participation of the United States Food and Drug Administration (US/FDA) and the European Medicines Agency (EMA) for the Evaluation of Medicinal Products, as well as on the participation of additional dengue-endemic non-DCVRN member countries, as, for example, Philippines:

> Thailand. It provides a forum for discussion, advancement of knowledge, and exposure to policies and procedures pertaining to oversight of clinical trials and evaluation of clinical data for registration of vaccines. The United States Food and Drug Administration (FDA) and the European Union European Medicines Agency for the Evaluation of Medicinal Products (EMA) often participate in meetings of the DCVRN. In addition, regulatory staff from several additional dengue-endemic non-DCVRN member countries (Cambodia, Malaysia, Philippines, and Vietnam) have participated in the dengue vaccine sessions at the DCVRN meetings.

2. EMA's participation in the DCVRN

The participation of EMA in the DCVRN involved the elaboration and presentation to the DCVRN and non-DCVRN member countries, during the joint review process facilitate by WHO, of a Scientific Opinion regarding the evaluation of Dengvaxia's dossier. The Scientific Opinion is non-legally binding to DCVRN and non-DCVRN member countries, but was taken into consideration in the process that led to the marketing approval of Dengvaxia in different jurisdictions. According to Mahoney et al.[5], the "*[I]nvolvement of the US FDA and the EMA can be helpful in assuring a high level of regulatory review*", and was made possible by the article 58 of the Regulation (EC) No 726/2004, laying down

[3] Mahoney et al. Available on: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000418
[4] Mahoney et al. Available on: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000418
[5] Mahoney et al. Available on: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000418

Community procedures for the authorization and supervision of medicinal products for human and veterinary use:

- Manufacturers can submit a dossier to the European Medicines Agency for the Evaluation of Medicinal Products (EMA) for review (Scientific Opinion). This is possible due to the introduction of Article 58 of EMA's regulation 726/2004 (within which the example of dengue is specifically mentioned). This Opinion could facilitate the review process by NRAs in developing countries. Manufacturers may also obtain scientific advice and protocol assistance from the EMA, which may facilitate later Article 58 review.
- The Developing Countries' Vaccine Regulators Network recommends that consideration be given to agreements for joint reviews of clinical trial applications by similarly affected NRAs and also the review of applications for licensure in order to accelerate the launch and introduction of dengue vaccines. The NRAs would need to have access to the necessary expertise to review the quality and safety aspects of the license application.

The article 58 of the Regulation (EC) No 726/2004 on scientific opinions, in the context of cooperation with the WHO:

> *"Article 58*
> *1. The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.*
> *2. The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice."*

3. Dengue disease and vaccines candidate

It was known in advance that the development of vaccines against dengue disease was a complex enterprise, given the existence of four related viruses causing the disease and the risk of Antibody-Dependent Enhancement (ADE), a severe adverse immune response to vaccination[6]:

[6] Mahoney et al. Available on: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000418

Dengue diseases are caused by four related viruses (DENV 1, DENV 2, DENV 3, and DENV 4). In most countries, one virus tends to dominate during a season, but is replaced by other viruses over several years. Thus, a dengue vaccine must be effective against all four viruses, i.e., tetravalent. In addition, there is the theoretical possibility of an adverse immune response in individuals not protected against all four viruses. An individual protected against one or two of the four viruses may be subject to a severe immune response (antibody-dependent enhancement) if exposed to a virus against which the individual is not protected, although the only human studies to assess this possibility have not observed these events [8,9]. The challenge of tetravalent vaccine development is compounded because of interference among the viruses and by the lack of an animal model for dengue infection and disease [6].

Despite of the theoretical risk of adverse immune response (ADE), and the contradictory results of the clinical trials, Sanofi Pasteur maintained the decision of registering the product. A story published by NPR[7] on the marketing approval of Dengvaxia in the Philippines describes the negative repercussion of the clinical trial's safety results, involving the senior scientist Dr. Scott Halstead:

> *"When I read the New England Journal article, I almost fell out of my chair," says Dr. Scott Halstead, who has studied dengue for more than 50 years with the U.S. military. When Halstead looked at the vaccine's safety data in the clinical trial, he knew right away there was a problem.*
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> *For some children, the vaccine didn't seem to work. In fact, Halstead says, it appeared to be harmful. When those kids caught dengue after being vaccinated, the vaccine appeared to worsen the disease in some instances.* ***Specifically, for children who had never been exposed to dengue, the vaccine seemed to increase the risk of a deadly complication called plasma leakage syndrome, in which blood vessels start to leak the yellow fluid of the blood****.*
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> *"****Then everything gets worse, and maybe it's impossible to save your life," Halstead says. "A child can go into shock****."*

[7] Doucleef, M. Rush To Produce, Sell Vaccine Put Kids In Philippines At Risk. NPR, May 3, 2019. Available on: https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

"The trouble is that the disease occurs very rapidly, just in a matter of a few hours," he adds. "And there's nothing on the outside of the body to signify the person is leaking fluid on the inside."

The complication is rare, says Halstead. Still, he was so worried about the safety concerns that he wrote at least six editorials for scientific journals. He even made a video to warn the Philippine government about the problem.

"I just think, 'No, you can't give a vaccine to a perfectly normal, healthy person and then put them at an increased risk for the rest of their lives for plasma leakage syndrome,' " Halstead says. "You can't do that." (italics added)

Despite all the safety concerns raised by Dr. Scott Halstead and the fact that he wrote at least six editorials for scientific journals and even shot a video to warn Philippine authorities, Sanofi Pasteur replied to the criticism sustaining that Dengvaxia's safety profile was acceptable:

"The vaccine manufacturer disagreed with Halstead's interpretation of the study's results. The company wrote a rebuttal, asserting that regulatory agencies had approved Dengvaxia "on the basis of the vaccine's proven protection and acceptable safety profile."

The company also said it would perform additional studies to "further access the safety, efficacy and effectiveness" of the vaccine." [8]

4. The DCVRN's joint regulatory review process

The facilitation provided by WHO within DCVRN is described in terms of a response to Member States request, whose representatives have previously agreed with the concept of joint evaluation of the registration dossier[9]:

this risk subsequently diminished [7,8]. Due to these complexities and on request by countries, WHO in collaboration with the Dengue Vaccine Initiative-International Vaccine Institute (DVI-IVI) hosted a technical consultation with seven NRAs on the dengue vaccine dossier 28–30 July 2015, in Geneva, Switzerland [9].

This consultation also built off of a series of regular meetings organized by DVI starting in 2013, with this same group of seven NRAs from countries where the first registration of CYD-TDV was anticipated, and which had agreed with the concept of participating in a joint evaluation of the registration dossier. These meetings

[8] Douclef, M. Available on: https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

[9] Vannice, K. et al. Available on: https://www.sciencedirect.com/science/article/pii/S0264410X17309520?via%3Dihub

According to Vannice, K. et al.[10], representatives of EMA and US/FDA, independent experts from other regulatory authorities or experts in dengue and WHO members took part in DCVRN technical debates, as well as representatives of the sponsor, allowed to participate in select sessions, called open sessions:

> In addition to the WHO, DVI-IVI, and 2–3 representatives from each participating NRA, eight independent experts from other regulatory authorities or experts in dengue were invited as advisors. Experts were selected by WHO such that the full range of topics covered in the dossier could be addressed, including quality, non-clinical, and clinical. These experts were also provided access to the dossier by the sponsor in advance of the meeting. The sponsor was present during select sessions. The roles and responsibilities of each participant type were outlined and agreed to ahead of the consultation.

> The consultation was conducted in open and closed sessions over 3 days: open sessions included the sponsor, whereas the closed sessions were limited to the participating country regulatory authorities, independent technical advisers, DVI-IVI, and WHO Secretariat. The meeting agenda was structured according to each of the four sections of the dossier: Quality, Non-clinical, Clinical and Risk Management Plan. Following a detailed presentation from the company on each of the above areas, the company was excused and regulators from the countries discussed their interpretation and considerations, including with peers and invited experts and prepared a consolidated list of questions and requests for clarifications. WHO transmitted the lists to the sponsor immediately after, and the agenda was structured in order to provide the sponsor sufficient time to prepare a presentation of responses to the questions and requests for clarifications for an open session. Most queries raised during the meeting could be addressed by the sponsor and/or experts, and NRAs were able to further discuss bilaterally if desired. After the meeting the presentations were provided to the participants from the NRAs that received the registration file, for their further review and consideration.

WHO is classified, by Vannice, K. et al.[11], as a neutral body facilitating the interaction of regulatory players, with no opinion on the final decisions taken by national regulatory agencies:

> As the convening body, WHO (1) ensured that participating countries received the same submission file in advance of the consultation, including the most recently available clinical data [8], (2) coordinated the participation and support of the external independent technical experts to assist in the discussion, and (3) managed the collection and coordination of questions raised by the countries for discussion by technical experts and for response by the sponsor. WHO was a neutral convening body without opinion in the outcome by individual NRAs.

[10] Vannice, K. et al. Available on: https://www.sciencedirect.com/science/article/pii/S0264410X17309520?via%3Dihub

[11] Vannice, K. et al. Available on: https://www.sciencedirect.com/science/article/pii/S0264410X17309520?via%3Dihub

Important to stress though that classifying WHO as a neutral body facilitating the interaction of players, with no opinion on the final decisions taken by national regulatory agencies remarks the understanding that WHO has no liability in any outcome arising from DCVRN initiatives. A configuration that doesn't induce WHO to act as cautiously as possible when issuing recommendations on the impacted products, and that, on the other hand, prevent any interpretation of WHO's role as inducive or influential in DCVRN and non-DCVRN member countries' final regulatory decisions.

5. Outcomes of the DCVRN's joint regulatory review process

Based on the common ground arising from the inputs provided by the DCVRN meetings, the DCVRN and non-DCVRN member countries - while collaborating with PDVI, an initiative supported by the Bill & Melinda Gates Foundation - took their own regulatory decision, on the national level, concerning Dengvaxia's marketing authorization[12]:

> The primary objective of this technical consultation was to assist NRAs with informed decision-making on the registration of the dengue vaccine through discussion on the scientific elements of the dossier, as well as to contribute to capacity building, quality of the review, and efficiency. The aim was for the regulators from various agencies to have a common scientific understanding of the file that would inform their own regulatory processes. With this approach, each regulator was able to independently come to its own decision on registration in accordance with its own scientific review, legislation, and timelines. This consultation preserved the principles of joint reviews, in which regulators perform a preliminary evaluation, discuss and validate their findings with other regulators with support from technical experts, present a consolidated list of questions to the sponsor and receive answers, and finally make their independent decisions afterwards.

An alleged demonstration of the sovereignty of the multi-country joint review process adopted by WHO, according to Vannice et al.[13], is the fact that the DCVRN and non-DCVRN member countries end up with considerable distinct final regulatory decisions, on the national level:

> five months of the consultation. As NRAs had independent authority in their decisions in alignment with national laws and regulations, regulatory decisions by the participating NRAs came

[12] Vannice, K. et al. Available on: https://www.sciencedirect.com/science/article/pii/S0264410X17309520?via%3Dihub
[13] Vannice, K. et al. Available on: https://www.sciencedirect.com/science/article/pii/S0264410X17309520?via%3Dihub

at varying time points, as full or conditional approval, and with variable age indications. For example, the first registrations came in December 2015; as of June 2017, one NRA of the seven has yet to make a decision on the CYD dossier. The indication in the license is typically individuals 9–45 years of age living in endemic areas, but one country licensed the vaccine for those 9–16 years, and another country provided conditional approval.

Although that same outcome (distinct final regulatory decisions and marketing authorizations scopes) could be an indication of independence of the national regulatory decisions, it can also be a sign that the safety and efficacy profiles of Dengvaxia weren't clear enough for homogeneous registration across different jurisdictions. Meaning that the data provided was not subject to technical and regulatory consensus, given the uncertainties identified by national regulators.

6. Dengvaxia's mass vaccination in the Philippines

As mentioned before, Philippines took part into the DCVRN process as a non-DCVRN member country. Philippines was also the first country to authorize the use of Dengvaxia, starting in April 2016 a mass vaccination campaign that reached 800,000 children.

That regulatory decision soon demonstrated to be a massive public health mistake, leading to criminal charges against many national officials, even though the design of the clinical trial that supported the national marketing authorization was, according to Dr. Scott Halstead, elaborated by Sanofi Pasteur in collaboration with WHO. As reported by Science[14]:

> *"(…) Halstead says the trials Capeding helped conduct were not well designed; if the researchers had looked separately at outcomes for children who did and didn't have dengue before the shot, they would have identified the ADE risk, he says. He notes that Sanofi and WHO committees designed the trials, however, not Capeding. He declined to say whether criminal charges are warranted: "This is a very complex ethical and scientific question that needs to be handled carefully."*

Also according to Science[15], the former head of the dengue department of the Research Institute for Tropical Medicine (RITM), Rose Capeding, could face up to 48 years in prison, given the mass vaccination with Dengvaxia in the Philippines:

[14] Arkin, F. **Dengue vaccine fiasco leads to criminal charges for researcher in the Philippines.** Science, 24th of April, 2019. Available on: https://www.science.org/content/article/dengue-vaccine-fiasco-leads-criminal-charges-researcher-philippines

[15] Arkin, F. Available on: https://www.science.org/content/article/dengue-vaccine-fiasco-leads-criminal-charges-researcher-philippines

"A prominent pediatrician and medical researcher in the Philippines has been indicted over the failed—and many say premature—introduction of Dengvaxia, a vaccine against dengue that was yanked from the Philippine market in 2017 because of safety issues. If convicted of accusations leveled at her by the national Department of Justice (DOJ), Rose Capeding, 63, former head of the dengue department of the Research Institute for Tropical Medicine (RITM) here, could face up to 48 years in prison.

In February, prosecutors concluded there is probable cause to indict Capeding and 19 others for "reckless imprudence resulting [in] homicide," because they "facilitated, with undue haste," Dengvaxia's approval and its rollout among Philippine schoolchildren.

Also charged are Capeding's former boss, former RITM head Socorro Lupisan; former Department of Health (DOH) Secretary Janette Garin; other officials at DOH and the Philippines Food and Drug Administration (FDA); and current and former officials of Sanofi Pasteur, the French company producing the shots. The first of eight criminal cases—which could be consolidated—are now pending in five courts throughout the northern island of Luzon, where the vaccination campaign took place."

The publication also adds that the mass vaccination of children in the country was based on researches leaded by Rose Capeding and funded by Sanofi Pasteur:

"(…) The Philippine FDA greenlighted the vaccine in December 2015, based on research funded by Sanofi Pasteur in which Capeding played an important role. For example, she was the first author on a 2014 paper in The Lancet detailing a study among more than 10,000 children in five Asian countries that showed Dengvaxia worked and had a good safety profile. In April 2016, the Philippine government launched a $67 million public school–based immunization program for Dengvaxia." [16]

Science[17], as described by NPR, also mentions the concerns raised by Dr. Scott Halstead regarding the risk of children with no previous contact with the dengue virus to develop severe immune response related to ADE:

"That alarmed some scientists, because the dengue virus is peculiar: A first infection is rarely fatal, but a second one with a different virus type can lead to much more serious disease, because of what is called antibody-dependent enhancement (ADE), in which the immune response to the first virus amplifies the effect of the second type. Scott Halstead, a retired dengue expert formerly at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, argued that dengue vaccines could have the same effect, and warned that Dengvaxia should not be given to children never infected with dengue. But a

[16] Arkin, F. Available on: https://www.science.org/content/article/dengue-vaccine-fiasco-leads-criminal-charges-researcher-philippines

[17] Arkin, F. Available on: https://www.science.org/content/article/dengue-vaccine-fiasco-leads-criminal-charges-researcher-philippines

vaccine panel at the World Health Organization (WHO) concluded in 2016 that Dengvaxia was safe for children aged 9 and older

Halstead's concerns proved valid. In November 2017, Sanofi Pasteur announced that the vaccine could indeed exacerbate cases of dengue in children never previously infected, and the Philippines halted the campaign immediately. (WHO now recommends the vaccine be used only after a test to be sure children have had at least one brush with dengue.)

The news enraged and frightened the parents of some 830,000 schoolchildren who had already received one or more Dengvaxia shots. Given the high prevalence of dengue in the Philippines, most probably already had the disease at least once, and thus are not at risk of ADE—but some had not. In September 2018, DOH Undersecretary Enrique Domingo told reporters that 130 vaccinated children had died; 19 of those had dengue, meaning ADE possibly played a role. The case triggered "mass hysteria," says Edsel Salvaña, an infectious disease physician at the University of the Philippines here. "Parents thought their kids were all going to die."

Despite all the concerns raised by Dr. Scott Halstead, in July 2016, WHO went ahead and recommended the vaccine for all children ages 9 to 16[18]. The recommendation came three months after the Philippines launched its mass vaccination campaign in April 2016[19].

But a year and half after the WHO recommendation, the mass vaccination campaign in the Philippines was interrupted, given, in November 2017, Sanofi Pasteur's announcement on its website stating the company had new information about Dengvaxia's safety, precisely related to the risk of ADE development:

"Halstead's fears were confirmed. Sanofi had found evidence that the vaccine increases the risk of hospitalization and cytoplasmic leakage syndrome in children who had no prior exposure to dengue, regardless of age.

"For individuals who have not been previously infected by dengue virus, vaccination should not be recommended," the company wrote.

Panic hit the Philippines. In news reports, parents said that the vaccine contributed to the deaths of 10 children. Protests erupted. The Congress of the Philippines launched investigations into the vaccine's purchase and the immunization campaign. And Philippine health officials started performing autopsies on children who died after receiving the vaccine. "In total, the deaths of about 600 children who received Dengvaxia are under investigation by the

[18] Dengue vaccine: WHO position paper – July 2016.
Available on: https://www.who.int/wer/2016/wer9130.pdf?ua=1
[19] Douclef, M. Available on:
https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

Public Attorney's Office, " the South China Morning Post reported last month. Investigators have not yet released their results." [20]

As a consequence, in September 2018 WHO changed its recommendation[21]. The organization now states the vaccine is only safe for children who have had a prior dengue infection:

"By the time Sanofi acknowledged this problem with the vaccine, about 800,000 Philippine children had been vaccinated. The Sanofi study estimated that more than 100,000 of them had never been infected with dengue and should not have received the shot, according to WHO's revised recommendation." [22]

7. WHO recommendations on Dengvaxia

Given the warning posed by Dr. Scott Halstead and the fact that WHO recognized, in July 2016, that the *"[U]se of CYD-TDV in populations in which seroprevalence is low in the age group considered for vaccination is not recommended because of low efficacy* ***and potential longer-term risks of severe dengue in vaccinated seronegative individuals***", shouldn't WHO, from the beginning, have recommended the introduction of Dengvaxia only if the minimization of risk among seronegative individuals could be assured, as stated in its second recommendation issued in September 2018?

Bearing in mind that Dengvaxia targeted mass vaccinations in developing countries, would it still be feasible to implement, in 2016, mass vaccination campaigns if the necessary precautionary approach of pre-vaccination screening of the population for past dengue infection were adopted? According to WHO's 2018 recommendation, the policy to be implemented is complex, since "*Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated*."

Bellow, the core issues of both WHO recommendations:

1. **2016[23]:**

[20] Douclef, M. Available on: https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

[21] Dengue vaccines: WHO position paper – September 2018. Available on: https://www.who.int/publications/i/item/WER9335-457-476

[22] Douclef, M. Available on: https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

[23] Dengue vaccine: WHO position paper – July 2016. Available on: https://www.who.int/wer/2016/wer9130.pdf?ua=1

WHO position

Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.

In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost-effectiveness. Vaccination of populations with seroprevalence between 50% and 70% is acceptable but the impact of the vaccination programme may be lower. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination.

The seroprevalence criteria for vaccine introduction are based on the differential performance of CYD-TDV in seronegative compared to seropositive persons. Seroprevalence of 50% and above reflects the settings in which the Phase 3 clinical trials were conducted. The overall seroprevalence in trial participants aged 9–16 years in the Phase 3 studies was approximately 80%. Use of CYD-TDV in populations in which seroprevalence is low in the age group considered for vaccination is not recommended because of low efficacy and potential longer-term risks of severe dengue in vaccinated seronegative individuals. While age-stratified serosurveys are currently the best method for selecting populations suitable for vaccination, subnational, age-stratified surveillance data may be used to help guide vaccine decision-making. Preferably a combination of seroprevalence, surveillance data, and programmatic factors should define the target population.

2. 2018[24]:

WHO position

The live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be efficacious and safe in persons who have had a dengue virus infection in the past (seropositive individuals), but carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals). Countries should consider introduction of the dengue vaccine CYD-TDV only if the minimization of risk among seronegative individuals can be assured.[62]

[24] Dengue vaccines: WHO position paper – September 2018. Available on: https://www.who.int/publications/i/item/WER9335-457-476

For countries considering vaccination as part of their dengue control programme, pre-vaccination screening is the recommended strategy.[63] With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past). If pre-vaccination screening is not feasible, vaccination without individual screening could be considered in areas with recent documentation of seroprevalence rates of at least 80% by age 9 years.

Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated. Conventional serological testing for dengue virus IgG (e.g. dengue IgG ELISA) is available in most dengue endemic countries, and could be used to identify persons who have had a past dengue infection. However, such laboratory-based assays do not provide results at the point of care. Point-of-care tests, i.e. RDTs, would facilitate the implementation of the pre-vaccination screening strategy, but to date none have been validated or licensed specifically for the detection of past dengue infection. Use of currently available IgG-containing RDTs – despite their lower sensitivity for detection of past dengue infection compared with conventional dengue IgG ELISA – could be considered in high transmission settings until better RDTs for determing serostatus become available.

No screening test is likely to be 100% specific due to potential cross-reactivity with other flaviviruses. In settings with high dengue seroprevalence, a test with lower specificity might be acceptable as the proportion of seronegative individuals incorrectly vaccinated would be low. A pre-vaccination screening strategy may also be considered in low-to-moderate transmission settings. In settings with low seroprevalence a test with high specificity is needed. Given the limitations regarding specificity, some seronegative individuals may be vaccinated because of a false positive test result. Furthermore, as vaccine-induced protection against dengue in seropositive individuals is high but not complete, breakthrough disease will occur in some seropositive vaccinees. These limitations will need to be communicated to populations offered vaccination.

Decisions about implementing a pre-vaccination screening strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

8. Questions involving Dengvaxia's multi-countries joint regulatory procedure

It's interesting to note that WHO's recommendation on the use of Dengvaxia for all children ages 9 to 16 came only three months after the Philippines launched its mass vaccination campaign in April 2016, meaning that the first health authority to effectively take responsibility on the marketing authorization of a knowingly complex and potentially dangerous vaccine was the small health regulatory authority of a developing country that isn't itself a DCVRN member[25].

Moreover, questioned about the mistake of recommending a vaccine to healthy children that were under the risk of developing a potentially fatal condition, WHO alleged that its recommendation was a "conditional recommendation", pointing out the theoretically risk involved of hospitalization or severe dengue illness[26]:

> *"Yes, we did. It was what we call a 'conditional recommendation' with the emphasis to minimize potential risks," says Dr. Joachim Hombach, who led WHO's review of the vaccine. "We saw the problems. We also clearly pointed to the data gaps."*
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> *WHO recommended that Sanofi do more experiments to better understand the vaccine's safety issues. In its assessment, WHO pointed out that the vaccine "may be ineffective or may theoretically even increase the future risk of [being] hospitalized or severe dengue illness" in people who have never been exposed to dengue — which is about 10% to 20% of Philippine children."*

In order words, WHO, as a mere neutral body facilitating the interaction of regulatory players, with no opinion on the final decisions taken by national regulatory agencies, published a conditional recommendation that made it no clear that the countries should not vaccinate children that had no previous contact with the dengue virus, given the potential (in their words, theoretical) risk of developing ADE. And, most important, WHO is not legally bind to any of its activities related to the DCVRN multi-countries joint regulatory procedure.

Because of WHO's decision of not making it clear that pre-vaccination screening of the population for past dengue infection should be put in place, according to Science, 100,000 children in Philippines that had never been infected with dengue and should never have received the shot were vaccinated.

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[25] "The DCVRN was established in September 2004 in a meeting in Bangkok, Thailand. The nine countries represented in the 2002 meeting in Geneva became network members by fulfilling the criteria of having at least one manufacturer with a prequalified vaccine for supply through UN agencies, for use in national immunization programs and its NRA fulfilling the six critical regulatory functions required by the WHO, or having a government-endorsed work plan to achieve this. (…)"
Nishioka, S. et al., **Helping each other regulate clinical trials: a network of vaccine regulators from developing countries.** Clin. Invest. (2013) 3(2), 113–117.
Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8325038/

[26] Douclef, M. Available on:
https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

Summing it up, WHO and Sanofi Pasteur exposed 800,000 children to a well-known "theoretical" risk that could be identified through well-designed clinical trials, and, even more important, totally avoid by the adoption of pre-vaccination screening for past dengue infection.

A situation that raises additional pivotal questions. Was the clinical trials sponsored by Sanofi Pasteur poorly designed exactly to cover-up the well-known "theoretical" risk? Would Dengvaxia be commercially viable if its use were from the very beginning conditionate, by WHO or Sanofi Pasteur, to the pre-vaccination screening of the population for past dengue infection?

Sanofi Pasteur, in its turn, denies its responsibility alleging that the company followed all WHO guidelines while developing the vaccine and kept on communicating honestly throughout the entire process, stressing, besides this, that the product was approved by several regulatory agencies.

In other words, Sanofi Pasteur infers reasonable safety of Dengvaxia from the fact that the product received marketing approval from regulatory bodies involved in the DCVRN meetings facilitated by WHO (in connection with PDVI, an initiative supported by the Bill & Melinda Gates Foundation), and technically supported by experts and regulatory agencies (of reference, according to WHO's own language) that have no legal liability arising from the ultimate results (deaths of healthy children in other jurisdictions) of their own "scientific opinions":

> *"Dr. Su-Peing Ng, global medical head of Sanofi Pasteur, says the company followed all World Health Organization guidelines while developing the vaccine and communicated honestly throughout the process. "We've always been very transparent in sharing the results of our research," Ng says. "And I just want to stress that we have full confidence in our vaccine as it's been approved by regulatory agencies in over 20 countries."*

Put in other words, should WHO facilitate regulatory decisions in developing countries based on mere opinions of experts and regulatory bodies that will face no legal consequence in the case of their "scientific opinions" are wrong and has deadly consequences? Is it a model that WHO should keep on promoting when dealing with potentially dangerous health products?

Moreover, since the WHO guidelines mentioned by Sanofi Pasteur as an indication that the company followed the best regulatory practices possible while developing its product are infiltrated by pharmaceutical multinationals' influences, through ICH[27]

[27] "NEW DELHI: The World Health Organisation's (WHO) work of setting up norms and standards for production of medicines seems to be flawed by a fundamental conflict of interest. At the heart of its standard setting work is an entity the International Conference on Harmonization (ICH) in which majority of the WHO member countries have no voting rights and which is dominated by pharmaceutical industry groups. This glaring conflict of interest seems to fly in the face of WHO's policy on engagement with private entities which states that the development of norms, standards, policies and strategies which lies at the heart of WHO's work would be protected from influence by any form of vested interest.

(former “International Conference on Harmonization”, currently “International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use”[28]), and the WHO Member States never provided WHO the necessary mandate, through the World Health Assembly (WHA), to adopt ICH guidelines or regulatory standards, are WHO guidelines in fact a valid criteria to evaluate Sanofi Pasteur’s actions and risk management in the Dengvaxia case?

Given the fact that later in September 2018 WHO changed its own recommendation and that the well-known “theoretical” risk of ADE was mentioned by the Organization in its recommendation in 2016, it is very clear that WHO suppressed the right of Philippine parents have access to information about the real risks involved in the vaccination campaign their children were exposed to:

> *“Given the concerns by Halstead and the initial unknowns about the vaccine's safety, Philippine parents should have been warned about a potential risk, says Dr. Isabel Rodriguez at the University of California, San Francisco.*
>
> *"What bothers me most about this story is risk communication," says Rodriguez, who studies dengue in South America. "There was a lot of uncertainty from the beginning [about the vaccine's safety]. That needed to be communicated explicitly. You need to be honest about what evidence is out there."* [29]

It´s also important to note that US/FDA and EMA granted marketing authorization for Dengvaxia after the interruption of the mass vaccination of children in the Philippines. Taking that fact into consideration, the vaccination of 800,000 children in the Philippines functioned as a large experiment that gathered additional information on the safety profile of Dengvaxia to the same regulatory agencies that provided scientific opinions that supported the use of the product in the Philippines itself and other developing countries endemic for dengue disease:

> *“Here in the U.S., the approval of the vaccine — to be used in Puerto Rico, the U.S. and British Virgin Islands and Guam — comes with an important restriction: Doctors must have proof of a prior dengue infection to ensure the vaccine will not pose any risks to the child. That's a safeguard Philippine families never had.”* [30]

To begin with, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), closely involved with ICH since its inception, hosts the ICH secretariat in Geneva. So, the two share the same address --15, chemin Louis-Dunant, PO Box 195, 1211 Geneva-20. IFPMA participates in the steering committee of the ICH as a non-voting member.”
Nagarajan, R. **Conflict of interest in setting norms for pharmaceuticals in WHO.** The Times of India, May 17, 2014. Available on: https://timesofindia.indiatimes.com/city/delhi/Conflict-of-interest-in-setting-norms-for-pharmaceuticals-in-WHO/articleshow/35261958.cms

[28] https://www.ich.org/

[29] Douclef, M. Available on: https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

[30] Douclef, M. Available on: https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

EMA, responsible for the "scientific opinion" analyzed by DCVRN and non-DCVRN member countries - with WHO facilitation (incentive?), in connection with PDVI, an initiative supported by the Bill & Melinda Gates Foundation -, granted marketing authorization for Dengvaxia in December 2018[31]. In the US, the marketing authorization was issued in May 2019[32].

Finally, it is important to mention that, despite the problems and the paradoxical regulatory conjecture arising from the lack of liability involving the "scientific opinions" supporting DCVRN and non-DCVRN member countries' regulatory decisions, WHO has gone further on approving guidelines on international reliance mechanisms.

In 2021, the Fifty-fifth Report[33] of the "WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)" adopted, through its 10th Annex, the first WHO guideline on international reliance mechanisms: the "Good reliance practices in the regulation of medical products: high level principles and considerations". The official document, never scrutinized by Member States, defines "reliance" as:

> "The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others." (italics added)

The guideline, as the sentence stressed on the aforementioned definition, makes it clear that the relying authority (Philippine FDA, in the Dengvaxia case) remains responsible and accountable for decisions taken based on another authority's assessment (EMA's scientific opinion, in the Dengvaxia case), whereas no recommendation or debate on the legal liability of the regulatory authority performing and endosing the assessment taken into consideration (mainly by developing countries lacking of full capacity of appraising the technical information and its real-world consequences), is presented or discussed by WHO. Not a single statement on possible legal liabilities involving "agencies of reference", neither in cases of bad faith, fraud or careless regulatory review, especially when products aiming exclusively at third countries' markets are involved (products targeting tropical neglected diseases, as dengue disease, for example).

Its also important to emphasize that ECSPP is the very Committee utilized by WHO to incorporate ICH documents and standards in its own guidelines and standards aiming at impact all the WHO Member States and the international trade of medical products, even though this very Member States never provided the required mandate for such

[31] https://www.ema.europa.eu/en/medicines/human/EPAR/dengvaxia
[32] https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-dengue-disease-endemic-regions
[33] https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

adoptions, through the World Health Assembly[34]. According to the NGO "Third World Network" (TWN)[35]:

> *""There are concerns that the World Health Organisation (WHO)'s alliance with an industry-led body facilitates regulatory capture of medicine regulation by pharmaceutical multinational corporations (MNCs).*
> *(…)*
> *The very participation of WHO in ICH activities* de facto *legitimises guidelines developed by the pharmaceutical multinational industrial association and developed country regulators together, with a primary objective of serving the interest of pharmaceutical MNCs.*
> *(…)*
> *Apart from this push for formal adoption of ICH guidelines, WHO has facilitated the backdoor entry of ICH guidelines into WHO's various guidelines adopted through the WHO's Expert Committee on Specifications for Pharmaceutical Substances (Expert Committee).*
> *(…) the important question is how regulatory agencies and WHO set norms in a body where the industry has a veto power through voting?*
> *Thanks to the alliance with WHO, many ICH guidelines found a place in the Report of WHO's Expert Committee on Specifications for Pharmaceutical Substances.*
> *In other words, the norms and standards set by ICH without the participation of a substantial majority of Member States got imported to the WHO Expert Committee process and adopted as norms and standards for the regulation of medicines."*

In sum, when adopting a guideline on "Good reliance practices in the regulation of medical products: high level principles and considerations", through the 10th Annex of the Fifty-fifth Report of the ECSPP, despite all the legal and strategic impact of such a theme, WHO is one more time using ECSPP to adopt high economic and regulatory impact policies with no due transparence and in-depth debate with its Member States. A persistent detrimental conduct that jeopardizes the global and local public health interests, as well as developing countries specific necessities, especially when the

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[34] "The WHO has continued with the ICH process for more than 24 years without the close scrutiny of Member States because the issues of norms and standards are considered as technical subjects; therefore, the World Health Assembly never deliberates the merits of the Expert Committee Reports, which contain norms and standards for the regulation of medicine.
The Report of the Expert Working Group is placed before the WHA Executive Board to take note of the Report along with many other expert reports. Normally, the Executive Board takes note of expert reports without any discussion.
The ICH adopts guidelines with political and economic considerations and successfully projects these guidelines as science-based and exported to WHO Expert Committees. The WHO's alliance with ICH facilitates this repackaging."
Gopakumar, K. WHO: **Alliance with industry raises concerns over medicine regulation**. Third World Network, SUNS #7807, 20th of May, 2014.
Available on: https://www.twn.my/title2/health.info/2014/hi140502.htm

[35] Gopakumar, K.
Available on: https://www.twn.my/title2/health.info/2014/hi140502.htm

regulatory perspective presented by pharmaceutical multinational corporations[36] see the covid-19 context as an opportunity to further accelerate marketing authorization reviews of medical products, as well as provide more flexibilities, despite juridical and ethical concerns related to the progressive decline on the adoption of precautionary approaches, to the regulatory environment controlling clinical trials, preclinical safety requirements and the acceptable clinical evidence generation.

[36] Stweart, J. et al., **Covid-19: A Catalyst to Accelerate Global Regulatory Transformation.** Clinical Pharmacology & Therapeutics, v. 109, n. 6 , 2021.
Available on: https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2046