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Roadmap for the Introduction of a New Dengue Vaccine

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<http://dx.doi.org/10.5772/67745>

“The impact of vaccination on the health of the world’s people is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth”

Stanley Plotkin

Abstract

Dengue remains the most common vector-transmitted disease in the world despite enormous prevention and control efforts by endemic countries and regions. Today, after decades of research, public health programs contemplate as part of the intervention to control the disease, a safe and effective vaccine against dengue. In this chapter, we review general principles for developing a safe and efficacious vaccine against dengue virus, the current vaccine candidates approved and under research, and the roadmap for the introduction of a new dengue vaccine, based on the procedures, carried out by Mexico, for the licensure and eventual adoption of CYD-TDV vaccine, which concluded with Mexico becoming the first country in the world to grant licensure to a Dengue vaccine in December of 2015. Finally, we discuss the rationale for the adoption of dengue vaccines a public health policy and the paradigm shift required for the efficient adoption of vaccines in low- and middle-income countries.

Keywords: dengue control, vaccine, prevention, public health

1. Introduction

Vaccination is one of the most successful preventive measures in public health; its relevance for the prevention and control of infectious diseases is beyond any doubt. Vaccines have been paramount in the eradication of human and animal diseases such as smallpox [1] and rinderpest [2] and have been a main driver for the eradication efforts of other diseases (**Table 1**).

Disease	Main public health measures	Conclusion of the International Task Force for Disease Eradication
Dracunculiasis	Water sanitation, vector control, surveillance and contention	Eradicable
Lymphatic filariasis	Pharmacological treatment, vector control	Potentially eradicable
Measles	Vaccination	Potentially eradicable
Mumps	Vaccination	Potentially eradicable
Poliomyelitis	Vaccination	Eradicable
Rubella	Vaccination	Potentially eradicable
Taeniasis/cysticercosis	Improved sanitation, pharmacological treatment, vaccination of cattle	Potentially eradicable

Table 1. Candidate diseases for eradication. Modified from Ref. [3].

As we all know, in public health, disease eradication through vaccination is an ultimate goal; nonetheless, this is not the only benefit of vaccines. Well-documented advantages such as elimination of diseases, control of mortality, morbidity and complications of disease are positive impacts of immunizations. Additional benefits can be attributed to vaccines such as mitigation of disease severity, protection of unvaccinated population through herd immunity, prevention of antibiotic resistance, extension of life expectancy, enhancement of equality and empowerment of vulnerable populations. These effects are perhaps not as recognizable as disease eradication, but they have certainly shaped the health profile of entire populations [4].

Vector-transmitted diseases (VTDs) are a heterogeneous group of human illnesses caused by viral, bacterial and parasitic agents. Unlike many other infections in which transmission occurs directly between humans, VTD transmission cycles require the involvement of different arthropods such as mosquitoes, ticks, fleas, flies and kissing bugs, which work as vectors by carrying pathogens from humans to humans. In some VTDs like malaria, zika or dengue, arthropods and humans are the only components of the cycles; however, other VTDs like Chagas disease or Yellow fever are also zoonoses, which means that their transmission cycles include intermediate hosts, usually mammals. The more complex these cycles are, the more difficult VTDs control is [5], since more interventions are required to interrupt transmission. As an example, lymphatic filariasis is potentially eradicable since it has few vectors, and there is a non-expensive and effective treatment, which administered regularly to population at risk in large endemic areas ensures the interruption of transmission independently of vector circulation. Chagas disease, on the other hand, is considered non-eradicable since it has multiple vectors and hosts, it is difficult to diagnose, and the treatment is not well tolerated by most patients.

To date, prevention and control of VTDs, especially those transmitted by mosquitoes, rely mostly on vector control strategies, usually insecticide spraying and physical denial of vector's ecological niches. In the case of dengue, preventive measures include focal approaches with different schemes of insecticide use for indoor and outdoor settings aimed at larvae and adults, and the physical removal or destruction of mosquito breeding sites. For outbreak control, the same two interventions are usually applied with intensive schemes. For other VTDs,

such as malaria, early identification and diagnosis of cases have proven to be an efficacious measure [6], but for a number of reasons such as cost, lack of point-of-care diagnostic tools and complicated logistics, this is not as applicable for dengue. Unfortunately, few vaccines have been developed successfully for this group of diseases, and nevertheless, examples such as the yellow fever vaccine show that, although challenging, vaccines can be essential for achieving or improving disease control. Thanks to the introduction of the vaccine, urban yellow fever is rare, and sylvatic yellow fever has been under control for decades.

Dengue virus (DENV) infection causes a broad spectrum of clinical manifestations ranging from asymptomatic infection to life-threatening severe dengue [7]. Each year, up to 390 million infections worldwide, resulting in about 96 million clinical cases, represent a huge burden of disease for health systems in endemic areas [8]. Although most cases are benign and only a minor fraction of these develop severe disease, the number of infections every year and consequently the number of severe forms of dengue continue to increase despite current vector control measures since there is no specific preventive measure focused on the host. The expenditure on vector control represents an enormous burden and a threat to health systems in low- and middle-income countries [9].

Climate change, urbanization and other anthropogenic factors facilitate transmission of dengue and other VTDs [10]. Current vector control strategies have not, with very few exceptions, provided the expected results in diminishing or stabilizing dengue transmission for long periods [11]. Case identification is not currently feasible and before the availability of dengue vaccines, no other preventive option existed for the host. Considering these perspectives, dengue vaccines are more than ever a true necessity for improving the health of the millions that inhabit dengue endemic regions.

2. Development of vaccines against dengue

Dengue virus (DENV) belongs to the *Flaviviridae* family. Vaccines against members of this family such as the yellow fever virus (YFV) [12], the Tick-borne Encephalitis virus (TBEV) [13], and the Japanese Encephalitis virus (JEV) [14] have been successfully developed; nonetheless, a reliable and efficacious vaccine against dengue remained an elusive goal for decades.

Some characteristics of the dengue virus and the disease it causes constitute a great challenge for the development of a dengue vaccine. Some of those related to the agent are the genotype divergence, which contrary to other members of the *Flaviviridae* family, is so wide that it translates into notable serotype divergence [15–17], therefore making difficult to identify immunogenic proteins that are widely conserved among serotypes. In the case of flaviviruses, the main immunogenic protein is located in the envelope (E protein), which as we will review below, it is the basis for the development of most of vaccine candidates against dengue.

Another important challenge lies in the pathophysiology of severe dengue, which is strongly associated with previous exposure to the dengue virus. A secondary exposure after initial “priming” is capable of triggering an exaggerated immune response characterized by a cytokine storm, which contributes to impaired endothelial function and plasma leakage as its

main pathologic characteristic. Because of this, any vaccine developed against dengue needs to achieve a balance between being protective enough to prevent the disease and being sufficiently safe to avoid a pathologic immune response after priming [18].

An additional difficulty arises with the fact that a natural dengue infection elicits two types of antibodies. One type of antibodies is specific against the infecting serotype; these are usually long-lasting and with neutralizing capacity. The other type is cross-reactive to other serotypes, short lasting and non-neutralizing. Short lasting, non-neutralizing antibodies contribute to limit dengue epidemics and the number of serotypes that cause outbreaks. It is believed that in the long term, these non-neutralizing antibodies might play a role in the pathophysiology of dengue by facilitating the infection of larger number of cells during secondary exposures to the virus, a phenomenon called “antibody-dependent enhancement,” or ADE [19]. Apparently, this phenomenon is not exclusive of dengue virus infections and has only been demonstrated in vitro; however, its real contribution to dengue pathophysiology is still under debate. Nonetheless, the risk of ADE needs to be taken into account when developing vaccines against dengue [20].

Based on these biological characteristics, it is desirable that any dengue vaccine developed be capable of immunizing simultaneously against each of its four known serotypes. Also, in order to avoid natural infections that might trigger secondary pathologic responses, the vaccine should be administered in a minimum-dose scheme and in a short period [21, 22]. Simulation studies have shown that even vaccines that do not elicit complete protection against all serotypes and require multiple-dose schemes would be valuable tools in the medium and long terms, since their positive impacts exceed the theoretical potential negative effects [23].

Table 2 shows a list of the most relevant vaccines against dengue, currently approved and under development. Although not a comprehensive list, we can observe the different types of vaccines, and as discussed below, their particular advantages and disadvantages. It is expected that in the near future, many of these vaccines will become available and will be introduced as part of national dengue control strategies in endemic countries and regions.

Vaccine	Manufacturer	Type	Serotypes included
CYD-TVD	Sanofi – Pasteur	Recombinant live-attenuated chimeric. PrM/E proteins cloned into a 17D YFV backbone	All four
DENVax	Takeda	Live attenuated. Recombinant PM/E proteins from DENV-1, DENV-3 and DENV-4 cloned into live-attenuated DENV-2	All four
TV003/TV005	NIAID/Butantan Institute	Live-attenuated admixture of mutated and chimeric viruses	All four
TDENV PIV	GSK	Purified, formalin-inactivated viruses	All four
V180	Merck	Recombinant subunit. Truncated E protein from each DENV serotype	All four
TVDV	NMRC	DNA. Plasmids encoding PrM/E genes	All four

Table 2. Vaccines currently used or under development against dengue [18, 22, 24, 25].

In general, live-attenuated vaccines are produced with viable viruses that have been modified from wild-type pathogenic viruses into less virulent or attenuated versions, which are unable to produce severe disease. They have the advantage of being capable of infecting cells and replicating, eliciting strong, long-term immune responses similar to natural infections. However, since these vaccines contain live viruses, reversion to pathogenic forms is always a possibility; therefore, surveillance is necessary to ensure the safety of the vaccine. These vaccines cannot be administered to pregnant women or immunosuppressed individuals [26]. The yellow fever and Japanese Encephalitis vaccines belong to this group.

Inactivated vaccines are produced by exposing a pathogenic agent to chemicals, heat, or radiation in a process called inactivation. These vaccines are preferred over live-attenuated vaccines due to the absence of risks such as reversion of virulence, or limitations on its usage in selected population groups such as pregnant women and immunosuppressed individuals. Although they are generally very stable, sometimes, the inactivation process alters the structure of the pathogens, and possibly the immunogenicity of the viral proteins, diminishing its efficacy to elicit a protective immune response. Given the alteration caused by the inactivation process, the viruses from these vaccines are unable to replicate, and therefore, the viral proteins must be highly immunogenic on their own. Otherwise, the vaccine formulation needs to be added with a booster or adjuvant to increase its immunogenicity. The formalin-inactivated TDENV-PIV dengue vaccine under development belongs to this group [26].

Subunit vaccines are similar to inactivated vaccines, but they are formulated with incomplete agents, usually proteins from the original pathogenic strain. Since they are not whole pathogens, they cannot replicate, and the risk of reversion is absent, but they also lack the immunogenicity of whole pathogens. Therefore, the trick is to reach an acceptable immunogenic capability with truncated proteins that are unable to be infectious [26]. The V180 dengue vaccine is being formulated using a subunit of the E protein.

Recombinant vector vaccines, also known as chimeric vaccines, are based on attenuated viruses or microbes to introduce DNA from a pathogenic agent mimicking a natural infection and stimulating the immune system. The CYD-TDV dengue vaccine is a live-attenuated chimeric tetravalent vaccine constructed by cloning DENV Pre-M and E genes into a yellow fever Virus 17D strain backbone and belongs to this group [27]. Phase 3 clinical trials have demonstrated the vaccine's efficacy in preventing severe forms of dengue and admissions to hospital [28–30]. WHO has published a position paper describing the recommended procedures and conditions under which this vaccine is to be used by the international community [31]. To date, this is the only existing approved vaccine in the world. It was first licensed in Mexico in December of 2015 [32], and by late 2016, 12 additional countries from Latin America and Southeast Asia have also granted licensure to CYD-TDV.

Finally, DNA vaccines are theoretically the safest type of vaccines. They are formed by nucleic acids that encode fragments of the original pathogenic agent that are administered directly into the cells in order to produce immunogenic proteins that provide a protective immune response against infection. Nonetheless, the immune response that these vaccines produce is usually weak, and although promising, they still are in experimental phases [26]. This strategy is used in the TVDV dengue vaccine, which relies on fragments of DENV prM/E proteins expressed by a plasmid vector.

3. The vaccine introduction process

Traditionally, the introduction of vaccines in low- and middle-income countries (LMIC) occurs years or even decades after they have been introduced in high-income countries. With very few exceptions, vaccines are usually developed, tested and adopted according to the public health needs of high-income countries. LMICs seldom participate in the vaccine development process and only uptake products already tested in developed markets.

Because of this passive behavior, it takes a long time for public health officials in LMICs to incorporate new vaccines since there is a tendency to wait for licensure, introduction and phase 4 studies in high-income countries before beginning the introduction process. This delay in the adoption of innovation in public health technologies causes unnecessary suffering for populations in need of such scientific advances to address their health needs.

Recent events such as the emergence of infectious diseases like Zika and, Chikungunya in the Americas, or the re-emergence of Ebola in Africa have exposed the weaknesses of public health systems, and the need to change this passive behavior in order to accelerate access to the benefits provided by vaccines for those who need them the most [33]. The aim is for LMICs to participate in all phases of vaccine development, from their theoretical conception to all levels of clinical trials, and then to reduce the elapsed time between the moment a safe and efficacious vaccine is ready for commercialization and the moment the vaccine is licensed and eventually adopted.

As an effort to promote the early adoption of vaccines in LMICs, the authors have pushed forward for a paradigm shift in the introduction of new vaccines by designing and supporting the implementation of a new strategy for vaccine introduction based on scientific and technical analyses, and the accompaniment of public health authorities in the process. The aim of this strategy is to modify the general attitude toward vaccine introduction by involving all relevant actors (government, academia, industry, National Regulatory Agencies, etc.) in a proactive and anticipatory exercise.

These efforts led to the development of a roadmap for the Introduction of New Vaccines that has been instrumented in Mexico for the incorporation of the new dengue vaccine. In the following section, we will describe the process followed to promote the early adoption of these novel vaccines as a public health policy in the country.

3.1. A roadmap for the introduction of a dengue vaccine

It is necessary to recognize that the process for the introduction of any vaccine does not begin with the development of a candidate molecule by researchers. This path actually starts with the daily activities of epidemiologists and public health workers in the field, which generate and provide reliable epidemiological information, thus revealing health needs characterized as disease cases, fatalities, stress to health systems or any other negative impact. In Mexico, as in many other countries, dengue has become a major challenge for public health in the last three decades causing large outbreaks, mortality, and an increase in the demand of health services across the country. Its seasonal and oscillatory behavior makes it difficult to predict when or where there will be outbreaks in order to anticipate control interventions.

As vaccine candidates developed by the pharmaceutical industry began to show results from early clinical trials in recent years suggesting the availability of a safe and efficacious dengue vaccine in the short term, the authors presented to Mexican Health authorities a roadmap proposal for the eventual adoption of such technologies into the Mexican context. This roadmap includes a series of well-defined steps to be followed in anticipation to the licensure of the vaccine by the National Regulatory Agency in order to be ready for early implementation.

To lead the anticipatory exercise, an independent, multidisciplinary body of experts, called Mexican Dengue Expert Group (MDEG), was specifically convened. The MDEG included representatives from academic and research institutions, public health authorities and representatives of the private and social sectors (**Figure 1**).

The objectives of the MDEG were to analyze and discuss all relevant aspects related to the possibility of the introduction in Mexico of the different vaccines under development and also to evaluate their potential impact on the disease epidemiology and the implications on the National Immunizations and Vector-Borne Disease Prevention and Control Programs, in order to issue recommendations to the Mexican Public Health Authorities.

The roadmap was presented to and accepted by national health authorities in Mexico, which accepted the MDEG as the group that would officially lead the process.

The specific topics discussed and analyzed by the MDEG were epidemiological data and burden of disease: economic and financial aspects, operational and logistical issues, legal and regulatory aspects, strategic communications and clinical issues (**Table 3**). All these elements were reviewed taking into account the available evidence on safety and efficacy of the different candidate vaccines.

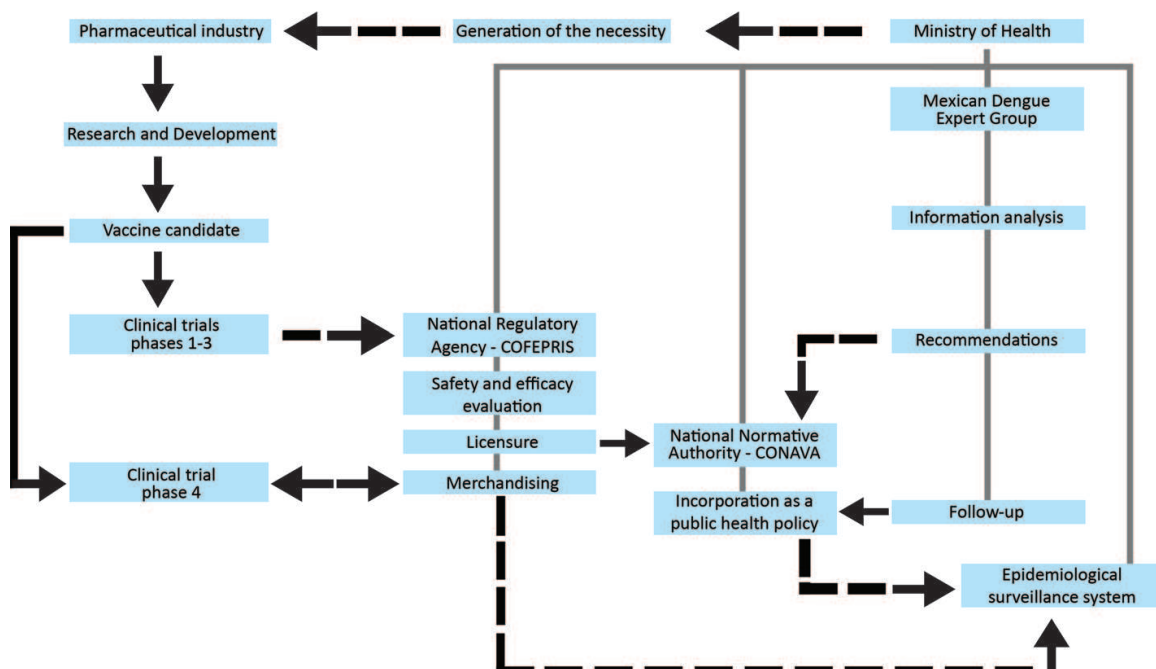


Figure 1. General roadmap for the introduction of a new dengue vaccine.

Subgroup of epidemiological information and disease burden

- I. To define geographic areas for the introduction of a vaccine.
- II. To define the target population.
- III. To establish impact scenarios of the vaccination scheme.

Subgroup of economic and financial aspects

- IV. To generate cost-benefit and cost-effective studies using modeling tools.
- V. To define the budgetary requirements for the introduction of the vaccine into the country.

Subgroup of operational aspects

- VI. To analyze the age groups for the application of the immunization scheme.
- VII. To generate strategies and scenarios for vaccine application depending on the selected target population.
- VIII. To discuss the relevance of strengthening the immunization information system in order to accurately measuring the coverage of the target population.
- IX. To analyze the impact in the cold chain caused by the introduction of a new vaccine.
- X. To develop the operational training strategy for the Universal Vaccination Program in the areas of vaccine introduction.

Subgroup of legal and regulatory aspects

- XI. To ensure the readiness of the registration and licensure procedures for the vaccines.
- XII. To orchestrate an automated pharmacosurveillance system to ensure the monitoring of adverse events following immunization (AEFI's) attributable to the vaccine introduction.

Subgroup of strategic communication

- XIII. Generate strategies that allow the appropriate communication on the rationale behind a Dengue vaccine introduction to all relevant groups.
- XIV. Develop specific communication channels for the new vaccine's target population.
- XV. Ensure that messages on the general population inform on the importance of strengthening vector control, and the role of the new vaccine as part of an integral strategy, not as a substitute of prevention and control activities.

Subgroup of clinical aspects

- XVI. Analyze the elements of clinical care in patients with Dengue that might result affected by the introduction of the vaccine.
- XVII. Strengthen the health personnel capabilities in clinical scenarios for detecting and reporting AEFI.
- XVIII. Strengthen the clinical personnel capacity for differential diagnosis of regional febrile diseases related to DF.

This figure describes the specific objectives from each working subgroup.

Table 3. Specific objectives for each subgroup in the Dengue Mexican Expert Group.

The roadmap included two phases. The first phase reviewed the existing evidence in order to analyze vaccine developments and the feasibility and requirements for the eventual adoption of such vaccines into the dengue control and immunization programs. This phase took place between 2011 and 2013 and resulted in an initial set of recommendations for the introduction of the vaccine in Mexico [34]. Evidence from a number of vaccine candidates in light of national epidemiological data quickly demonstrated that the adoption of any dengue vaccine in the future would require major improvements in many aspects.

With regard to epidemiological surveillance, the MDEG identified the need for strengthening the capacity of surveillance systems, networks, classification of cases and diagnostic protocols. Evidence of differential vaccine efficacy against the four dengue serotypes requires the improvement of virological typing and mathematical modeling capabilities to correctly evaluate the impact of vaccine introduction on the population.

Economic and financial issues were discussed as a basic element in the context of constrained resources such as those prevalent in LMICs; therefore, it was necessary to establish common methodologies for economic burden studies and those for cost-effectiveness of preventive and control interventions.

The analyses concerning the operational aspects required for the introduction of new vaccines concluded on the necessity for establishing baseline measurements to evaluate impact, feasibility of population selection from endemic areas with high risk of transmission and adoption of vaccines using currently available strategies in the country.

Regulatory issues were not essential before the beginning of the registration process; nonetheless, the MDEG was able to continuously review industry data, particularly results from phase II and III studies and also to participate in the development of post marketing surveillance systems that would be necessary in the event of the vaccine licensure.

Finally, social communication and health promotion had to be addressed in order to transmit clear messages on the safety and efficacy of vaccines, the implementation of vaccines into current integrated strategies for dengue control and not as an isolated intervention, and more important to clarify the regionalized strategy for these vaccines in contrast to universal vaccination schemes used regularly in the country.

After the first phase, the MDEG produced the following recommendations.

- I. Strengthen epidemiologic, entomologic and virological surveillance and obtain data necessary for impact modeling of dengue vaccine introduction.
- II. Carry out studies of the economic burden of dengue in Mexico, necessary for cost-benefit and cost-effectiveness analyses to support financial decisions.
- III. Introduce the vaccine as soon as it becomes available.
- IV. Invite potential vaccine producers to engage with the national regulatory authority to facilitate registration and licensing procedures.
- V. Integrate the immunization schedule defined by the National Vaccination Council of Mexico and approved by COFEPRIS with pre-existing National Health Weeks.
- VI. Define vaccination age groups according to epidemiologic risk and producers' recommendations.
- VII. Collect data to support national information campaigns to facilitate introduction.

The second phase of the roadmap began in 2015 when the results from the phase 3 studies of the CYD-TDV vaccine were published and the licensure process for this vaccine by the Mexican National Regulatory Agency (COFEPRIS—National Commission for the Protection of Health Risks) began. The availability of these results raised the necessity for the MDEG to review the data derived from the CYD-TDV phase 3 trials [30], focusing on this occasion, on the analysis of the feasibility of introducing the vaccine as a public policy, considering the special characteristics of dengue as a disease and those of the vaccine as a preventive tool. As

part of the work carried out in this phase, it was decided to incorporate an external perspective by extending an invitation to the Partnership for Dengue Control (PDC), an international organization integrated by world-class experts on dengue with the aim of supporting global elimination efforts for the disease, to participate in the proceedings. PDC experts participated actively in the discussions and issued specific recommendations that were included in the final document prepared by the MDEG.

After deep analysis of the available evidence, the MDEG presented to the Mexican Ministry of Health its final recommendations for the introduction of the dengue CYD-TDV vaccine [35]. The MDEG reiterated its support for the adoption of the vaccine and developed the criteria shown in **Table 4**.

In parallel, and recognizing the existence of a viable vaccine candidate, international institutions such as the World Health Organization began similar exercises, and in April of 2015, the Strategic Advisory Group of Experts on Immunization (SAGE) issued the first recommendations on the use of Dengue vaccines [36], which were followed by the emission of WHO's Position paper on dengue vaccination in July of 2016 [31]. These official documents recognize the availability of a licensed dengue vaccine and establish the conditions under which the introduction of CYD-TDV is to be considered. As observed, MDEG's recommendations are fully consistent with those issued by WHO, which consequently validate this innovative approach to vaccine introduction.

-
1. The following epidemiological criteria must be considered for the introduction of the new dengue vaccine into municipalities. At least four out of the six following conditions must be met:
 - a. Cumulative incidence above national mean during at least one of the last 5 years.
 - b. Notification of dengue confirmed cases for at least 20 continuous weeks in the immediate prior year.
 - c. Annual proportion of severe cases equal or above 1%, considering the total reported cases of severe dengue and dengue with warning signs.
 - d. At least one confirmed dengue fatality during the last 5 years.
 - e. Co-circulation of at least two serotypes, and/or circulation of serotype 3 and/or 4.
 - f. Seroprevalence above 60%.
 2. To apply the vaccine on population aged 9, using current immunization strategies.
 3. To use the three-dose immunization scheme established by the manufacturer.
 4. To develop a communication strategy that allows informing the population on the adoption of this vaccine.
 5. Logistic and operational aspects for the introduction of the vaccine must be guaranteed.
 6. At the end of the first cohort, impact evaluation should be started.
 7. Based on the previous points, the information generated by the MDEG, and its six subgroups will be sent to CONAVA for the feasibility analyses on the introduction of the dengue vaccine into the immunization scheme.
-

Table 4. MDEG recommendations for the introduction of a Dengue vaccine in Mexico.

The criteria developed by the MDEG cover epidemiological, operational and communication issues that are applicable to other endemic regions in the world. It is important to notice that additionally to seroprevalence, these criteria include other measurable health impacts such as cumulative incidence, outbreak duration, proportion of severe cases, fatalities and hyperendemicity. The inclusion of these effects grants flexibility to the decision-makers while considering or not the adoption of dengue vaccines taking into account the particular characteristics and resources of the region. Having additional criteria is an advantage, since seroprevalence studies are very expensive and time-consuming, while basic data on disease burden using confirmed cases are usually available for the vast majority of health systems.

Simultaneously to the anticipatory introduction exercise, the Mexican National Regulatory Agency (COFEPRIS—National Commission for the Protection of Health Risks) began the licensing process for the CYD-TDV dengue vaccine. As stated in international protocols, COFEPRIS followed a scrupulous evaluation process that included the vaccine's safety, efficacy and quality of the candidate vaccine and, according to the country's regulatory criteria. Although independent, these proceedings and those performed by the MDEG were not separately carried out, since representatives of the two bodies met regularly in order to feedback from each other's analyses. This feedback helped both parts to align their criteria, sources and information, and also contributed to optimize procedures while shortening the time for discussions. At the end of the registration processes, COFEPRIS issued a favorable resolution granting the licensure in December 2015 (**Figure 2**).

Having obtained the licensure for marketing the vaccine in the private sector, the next natural step is the procedure for the adoption of the vaccine as a health policy. It is now the responsibility of the National Vaccination Council (CONAVA—Consejo Nacional de Vacunación) to decide if, when and how to introduce the new dengue vaccine in Mexico. The final MDEG

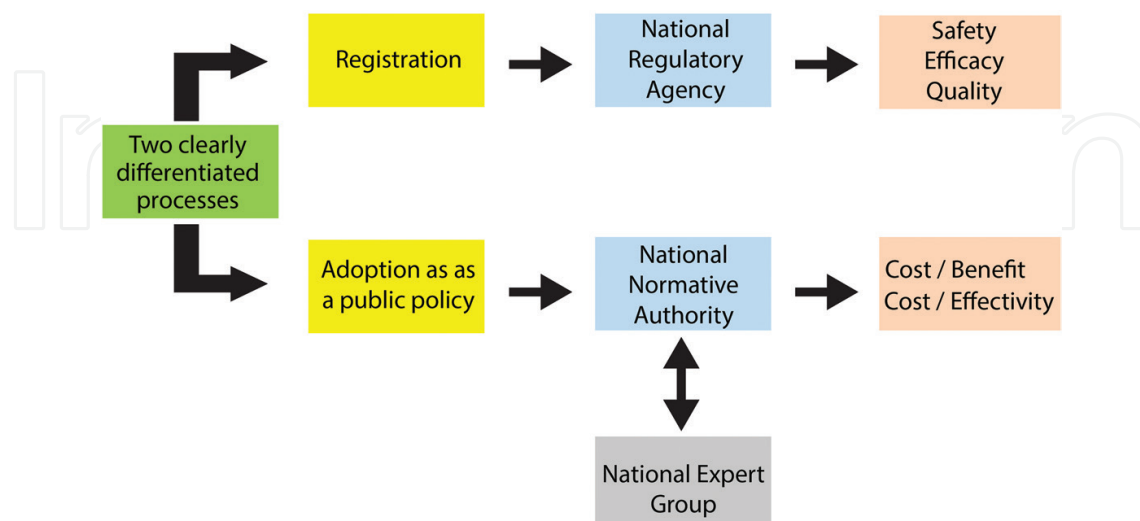


Figure 2. Processes of licensure and adoption as a public health policy.

recommendations were presented to the Council after the vaccine was licensed, and the proposed criteria were adopted as the basis for the document published as the interim policy regarding the CYD-TDV vaccine. The policy establishes a series of criteria for introduction of the vaccine by public health institutions (**Table 5**). At this point, the only remaining criterion to be fulfilled is the inclusion of CYD-TDV in the National Basic Catalogue of Medicinal Products, which has to be authorized by the General Health Council (Consejo de Salubridad General), the nation's top authority in Public Health matters.

The introduction of a tetravalent dengue vaccine as a public policy is to be considered under the following conditions:

- I. To fulfill at least four, out of the following six epidemiological criteria:
 - a. Population of states, municipalities or localities must have a demonstrable seroprevalence desirably equal or higher than 60%.
 - b. Cumulative incidence above the national mean, during at least one of the last 5 years.
 - c. Laboratory-confirmed cases of Dengue for at least 20 continuous weeks, during the last year.
 - d. Annual proportion of severe dengue equal or higher than 1% considering total notified cases.
 - e. At least one fatality recorded during the last 5 years.
 - f. Co-circulation of at least two serotypes and/or circulation of serotype 3 and/or 4.
- II. To be applied in population aged 9–16.
- III. To be applied using a three-dose immunization scheme: 0, 6 and 12 months, subcutaneously.
- IV. To ensure sufficient budget in order to guarantee the acquisition of the three-dose scheme for the cohorts to be immunized.
- V. To guarantee financial capacity for logistics, human and operational resources for vaccine introduction.
- VI. To develop a social communication strategy that allows informing the population on the introduction of this vaccine.
- VII. To develop a nominal registry of vaccinated individuals, preferably with an electronic vaccination card.
- VIII. The vaccine must be included in the Mexican basic catalogue of medicinal products.
- IX. The vaccine will not be universally applied in the country.
- X. States and social welfare institutions that wish to introduce the vaccine must define their strategies through their State Vaccination Councils, and present them to the national normative bodies for validation, in order to guarantee the compliance of the previously described conditions. Final approval must be obtained from the National Vaccination Council (CONAVA) and include all health institutions to comply with normative frame in order to guarantee notification and follow-up of adverse effects following immunization (AEFI), and the impact evaluation that includes cases, hospital admissions and averted deaths at the end of the first vaccination cohort. Vaccination strategy must be performed in a comprehensive manner, meaning that all public health institutions in the state should introduce the vaccine simultaneously.
- XI. Seroprevalence studies for the target group are proposed, after assessing budgetary and operational feasibility.
- XII. Resources for acquiring the vaccine must not be taken from the budget of the National Dengue Program or have any impact on the total budget allocated to health institutions, considering the budget of the year immediate prior to the vaccine introduction.

Table 5. National Vaccination Council's criteria for the introduction of a Dengue vaccine in Mexico [37].

4. Rationale for the adoption of a dengue vaccine as a public health policy

4.1. The paradigm shift

Existing epidemiological evidence shows that current surveillance and preventive and control measures are just not enough to reverse the currently increasing tendency of disease burden caused by DENV infection [8]. Newly recognized factors such as the contribution of human mobility on dengue transmission, its impact on control interventions [38] and the threats posed by the recent emergence of zika, chikungunya, and other VTDs are also important arguments to consider. To be able to curb the tendencies, vector control strategies need to evolve and adapt to new knowledge and technological developments in a way that has never occurred in the past but that is imperative in the face of the current challenges.

As discussed in this chapter, development and introduction of a dengue vaccine are a complex, challenging and demanding process for public health systems that requires the participation of all relevant actors. To finally have a safe and effective vaccine against this disease is a major breakthrough in the prevention and control of one of the most important VTD in the world, therefore, the necessity of health systems in endemic areas to be prepared for the adoption of this technology according to their particular needs and epidemiological characteristics.

Having achieved this milestone, the challenges now lie in operational aspects for the introduction into immunization schemes and public health strategies. Dengue vaccines have unique characteristics that make them different to other existing vaccines. For this reason it is required that health personnel and general public have access to complete reliable information to understand the indications, capacities and limitations of this vaccine, and more important, to recognize this tool as an integral piece of dengue control strategy. In order to facilitate this process, it is desirable to develop introduction guidelines for specific topics such as the vaccine, application procedures, surveillance, and mass communication among others.

As a theoretical argument, it is valid to expect that a vaccine is completely reliable, efficacious and safe, but in real life, vaccines are usually adopted considering a balance between positive and adverse effects. However, in reference to the development of this new vaccine, it has been recognized by leading experts in dengue that *“the era when most vaccines provided efficacy well beyond 90% is over. Many of the more recently developed vaccines only provide partial efficacy. Although vaccines are typically licensed on the basis of demonstrated efficacy, the ultimate goal of vaccination goes far beyond efficacy”* [39].

The availability of a licensed, safe and efficacious vaccine provides VTD prevention and control programs with a new tool to be added to the current arsenal. Vector control strategies should no longer be considered as the sole preventive measures for dengue control, and it must be acknowledged that the development of dengue vaccines constitutes an important milestone that needs to be thoroughly evaluated in scientific terms and not with dogmatic positions.

Unnecessary delays in the introduction of CYD-TDV or any other dengue vaccine will have important consequences for the population of endemic areas. The first and most obvious is the persistence of the current epidemiological trend with more and more people suffering

from the disease and its consequences. Not introducing the vaccine will obstruct individuals from their right to obtain the protective benefits of the vaccine, benefits not currently provided by any other available measure.

Lacking hosts other than humans, being transmitted only by a specific and highly anthropophilic mosquito species, and being a predominantly urban disease, dengue elimination is theoretically feasible, but it requires a paradigm shift in prevention and control strategies that integrates additional approaches such as the introduction of a new vaccine to existing policies and approaches.

5. Conclusions

The use of vaccines has been critical in the control and eventual eradication of major epidemic diseases, especially those with direct transmission. Vaccines for VTDs such as the yellow fever vaccine have proven their value both as preventive tools and as control measures in the case of outbreaks.

The newly available dengue vaccine and those currently under development are valuable tools intended to complement, not replace, current and future dengue prevention and control strategies [40]. In the operational scope, this integration needs to be performed in a comprehensive manner in order to maximize the positive effects of individual measures [41], and to avoid the collateral effects of excessive usage of those currently available [42]. This approach will undoubtedly be essential for reaching the WHO's strategic goal of 25% reduction in morbidity and 50% reduction in mortality due to dengue by 2020 [43]. Delaying decisions regarding the introduction of dengue vaccines could have important public health and economic implications.

Just as with any other vaccine, the most important safety and efficacy evaluation will begin once it is used in a real-life environment, when the vaccine must demonstrate a measurable impact on the disease. This impact can be estimated through changes in age-stratified indicators such as total number of cases, incidence or lethality. Additionally, the introduction of a new vaccine needs to further evaluate its safety through pharmacosurveillance in order to identify any adverse effects attributable to the vaccine. With proper follow-up, it will be possible then to define the real usefulness of the vaccine as a public health measure.

As an exercise, the roadmap here described has provided valuable experiences and the expected results in a short period. The formation of National Expert Groups for the analysis of feasibility for the introduction of dengue vaccines was fundamental for achieving such goals and should be a requisite for any country willing to explore the adoption on any existing or future vaccines.

Acknowledgements

The authors wish to thank the representatives of the institutions that participated in The Mexican Dengue Expert Group (in strict alphabetical order):

Government institutions: Centro Nacional de Excelencia Tecnológica en Salud, Centro Nacional de Programas Preventivos y Control de Enfermedades, Centro Nacional para la Salud de la Infancia y la Adolescencia, Comisión Coordinadora de Instituto Nacionales de Salud y Hospitales de Alta Especialidad, Comisión Nacional para la Protección contra Riesgos Sanitarios, Dirección General de Calidad y Educación en Salud, Dirección General de Comunicación Social, Dirección General de Epidemiología, Instituto Nacional de Diagnóstico y Referencia Epidemiológicos, Dirección General de Promoción de la Salud, Hospital Infantil de México, Instituto de Seguridad Social y Servicios para los Trabajadores del Estado, Petróleos Mexicanos, Instituto Mexicano del Seguro Social, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán,” Instituto Nacional de Pediatría, Instituto Nacional de Salud Pública, Servicios de Salud de la Ciudad de México, Servicios de Salud de Nuevo León, Servicios de Salud de Tamaulipas, Servicios de Salud de Veracruz, Unidad de Análisis Económico—Secretaría de Salud.

Academic and research institutions: Centro de Investigación y Estudios Avanzados, Instituto Politécnico Nacional, Universidad Autónoma Metropolitana, Universidad Nacional Autónoma de México.

Social and private sectors: Fundación Carlos Slim, Sociedad Mexicana de Salud Pública A. C.

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