Analysis of the evidence about the efficacy and safety of the CYD-TDV dengue vaccine and its potential licensing and implementation within the Mexican Universal Vaccination Program

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Abstract

Dengue is a major global public health problem which affects Latin America and Mexico. The prevention and control measures focusing on epidemiological surveillance and vector control have been partially effective as well as costly; thus, the development of a vaccine against dengue has created great expectations among the health authorities and scientific communities worldwide. The CYD-TDV dengue vaccine produced by Sanofi-Pasteur is the only dengue vaccine evaluated in phase III controlled clinical trials.

However, despite the significant contribution to the development of a vaccine against dengue, the three phase III clinical studies of CYD-TDV and the meta-analysis of the long-term follow-up of those studies have provided evidence that this vaccine exhibited partial efficacy to protect against virologically confirmed dengue and lead to four considerations: a) adequate vaccine efficacy against infection by dengue viruses (DENV) 3 and 4, a lower vaccine efficacy against DENV 1, and null protection against infection by DENV 2; b) decreased vaccine efficacy in dengue seronegative individuals at the time of the initial vaccination; c) 83 and 90% protection against hospitalizations and severe forms of dengue, respectively, at 25 months follow-up; and d) increased hospitalization for dengue in the vaccinated group, in children under nine years of age at the time of vaccination, detected since the third year of follow-up. The benefit of CYD-TDV vaccine consists in protection against infection by DENV 3 and 4, as well as protection from hospitalizations and severe cases in individuals over nine years who have had a previous dengue infection, working mainly as a booster. In this review we identified elements of the efficacy and safety of this vaccine that must be taken into account in the licensing process and potential inclusion in the national vaccination program of Mexico. The available scientific evidence on the CYD-TDV vaccine shows merits but also leads to relevant questions that should be answered in order to properly assess the safety profile of the product and the target populations for potential benefit. In this regard we consider it would be informative to complete the 6-year follow-up after starting vaccination, according to the company's own studies protocol, as recommended by the World Health Organization. As with any new vaccine, the potential licensing and implementation of use of CYD-TDV in the Mexican vaccination program requires a clear definition of the balance between the expected benefits and risks.

Particularly in the face of a vaccine with variable efficacy and the presence of some signs of risk, in the probable case of licencing, this must be followed by the development of detailed protocols in order to immediately identify any risks or health events associated with the vaccination.

Keywords: CYD-TDV vaccine; dengue; Mexico

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Resumen

El dengue es un importante problema de salud pública global, que afecta a América Latina y México. Las medidas de prevención y control centradas en vigilancia epidemiológica y control de vectores han resultado parcialmente efectivas y costosas, por lo que el desarrollo de una vacuna contra el dengue ha creado grandes expectativas entre las autoridades sanitarias y las comunidades científicas en el mundo. Sólo la vacuna CYD-TDV, producida por Sanofi-Pasteur, ha sido evaluada en ensayos clínicos controlados fase 3. No obstante a pesar de la importante contribución que esto significa para el desarrollo de una vacuna contra el dengue, los tres estudios clínicos fase 3 de CYD-TDV y el metaanálisis de seguimiento a largo plazo derivado de los mismos proporcionan evidencia de que esta vacuna tiene una eficacia parcial para proteger contra dengue virológicamente confirmado. Al respecto, surgen cuatro consideraciones: a) eficacia adecuada contra infecciones por virus de dengue (DENV) 3 y 4, menor eficacia contra infecciones por DENV 1 y prácticamente nula protección contra infecciones por DENV 2; b) disminución de la eficacia en individuos seronegativos a dengue al inicio de la vacunación; c) 83 y 90% de protección contra hospitalizaciones y formas de dengue grave, respectivamente, a 25 meses de seguimiento, y d) incremento de hospitalización por dengue, en el grupo de vacunados, en niños menores de nueve años de edad al momento de la vacunación, detectado a partir del tercer año de seguimiento. El beneficio de la vacuna CYD-TDV se puede resumir en la protección contra infecciones por DENV 3 y 4, así como en la protección de hospitalizaciones y casos graves en individuos mayores de nueve años y en quienes han tenido infección previa por dengue, pues funciona principalmente como una vacuna de refuerzo. En esta revisión se identificaron elementos sobre eficacia y seguridad de esta vacuna que deben ser tomados en cuenta ante el potencial registro e inclusión en el programa de vacunación en la población mexicana. La evidencia científica disponible sobre la vacuna CYD-TDV demuestra méritos, pero también da lugar a preguntas relevantes que deberían ser contestadas para evaluar apropiadamente el perfil de seguridad del producto, así como las poblaciones blanco de potencial beneficio. Al respecto, consideramos que sería informativo completar el seguimiento indicado de seis años después de iniciar la vacunación, de acuerdo con el protocolo propuesto en los propios estudios del fabricante como una recomendación de la Organización Mundial de la Salud. Al igual que con cualquier nueva vacuna, el potencial registro e implementación de uso de CYD-TDV en el programa nacional de vacunación de México requiere una definición clara de cuál es el balance entre los beneficios y riesgos esperados. En particular, ante una vacuna con eficacia variable y algunas señales de riesgo, en caso de aprobar el registro, se deben desarrollar protocolos de manejo de riesgos detallados que permitan identificar de manera oportuna cualquier evento de salud asociado con la vacunación.

Palabras clave: vacuna CYD-TDV; dengue; México

Dengue is one of the infectious problems that have experienced the largest growth and geographical expanse in the last 50 years; it entails a high social, economic cost, as well as a considerable cost for the health care of the affected population. Dengue control programs have had limited sustainable success, as they involve complex elements at an operational level: a broad spectrum of clinical presentation of the disease, a wide distribution and adaptation of the vector to human environments, a need for community participation, as well as for epidemiological, virological and entomological surveillance, and the development of adequate laboratories and health care units for timely detection and quality care. This implies coordination between the various levels of the government, a close link with the national, regional and international institutions associated with the public programs and policies for the prevention and control of dengue[1], and encouragement to citizen participation. For these reasons, there is great need for the availability of better measures for direct prevention, such as a dengue vaccine.[2]

Several types of vaccines are currently being developed in the world: live attenuated, inactivated, recombinant subunit, DNA and viral vector based vaccines, among others. The only vaccine to have reached phase III of clinical trials is the CYD-TDV live attenuated chimeric vaccine, which contains structural genes of the dengue virus inserted in a skeleton of the yellow fever 17D virus strain, developed by Sanofi-Pasteur.[3-5]

The studies derived from the clinical trials of the CYD-TDV vaccine published so far[6-9] have provided useful information on the epidemiology of and immunity to dengue infection. At the same time, they have posed numerous questions and have evidenced the fact that there are still gaps in our understanding of the immunological response against this virus. Four conclusions stand out: a) adequate effectiveness against infections by the dengue virus (DENV) 3 and 4, a lower effectiveness against infections by DENV 1 and a virtually null effectiveness against infections by DENV 2; b) a lower effectiveness in dengue seronegative individuals at the onset of the vaccination; c) 83 and 90 % protection against hospitalizations and serious forms of dengue, respectively, at 25 months follow-up, and d) increase of hospitalizations due to dengue in vaccinated children under 9 years of age at the onset of the vaccination, detected after the third year of follow-up. For this reason, the published scientific evidence directly and indirectly related to this vaccine was thoroughly examined at the National Institute of Public Health (INSP).

This examination identified important elements related to the efficacy and safety of the CYD-TDV vaccine which must be taken into account in the face of its potential licencing and implementation within the national vaccination program of Mexico and which indicate the need for solid evidence to determine the balance between the benefits and the risks.

The relevant scientific evidence accumulated on the efficacy and safety of the CYD-TDV vaccine is the result of three controlled clinical trials, published between 2012 and 2015 in prestigious scientific journals and carried out in Thailand6 (CYD23), in five countries of Asia[7] (CYD14) and in five in Latin America[8] (CYD15), as well as a recent publication on an integrated analysis (meta-analysis) of the long-term follow-up of the previous trials.[9] This last study encompasses the third year of follow-up since the first dose of the vaccine in the Phase III CDY14 and CDY 15 trials, and the third and fourth years of the CYD23 trial (extension CYD57). The main findings of this examination are summarized below.

Efficacy of the vaccine

The three clinical trials mentioned above were designed to compare the efficacy and safety of three doses of the CYD-TDV vaccine —administered at six-month intervals— to prevent virologically confirmed symptomatic dengue occurring within13 to 25 months after the third dose of the vaccine, against a placebo. A minimum effectiveness was determined for the conclusion of interest in the Phase III trials when the lower limit of the 95% confidence interval (CI) of the estimated mean efficacy was equal to or above 25.

In the first multicentric Phase III clinical trial —CYD14, performed in Asia,[7]— a mean efficacy of 56.5% (95%CI 43.8-66.4) was estimated. Finally, in the multicentric Phase III clinical trial CYD15, carried out in Latin America,[8] the estimated efficacy was 60.8% (95%CI 52.0-68.0).

In the trials performed in Asia and Latin America,[7,8] mean efficacies of 78.4 (95%CI 52.9-66.4) and 74% (95%CI 61.9-82.4) were estimated for DENV 3, and of 75.3 (95%CI 54.5-87.0) and 78% (95%CI 60.2-88) for the DENV 4, respectively. In contrast, the efficacy against DENV 1 was 50% (95%CI 24.6-66.8) in Asia, and 50.3% (IC95% 29.1-65.2) in Latin America; the efficacy against DENV 3 was only 35% (95%CI -9.2-61.0) in Asia, and 42.3% (95%CI 14.0-61.1) in Latin America. Both studies coincide in that the lower CI limit for the efficacy of this vaccine is above 25% in the case of DENV 3 and 4, and the limit for DENV 1 and for DENV 2 are lower than the efficacy goal, determined at 25%. According to the experimental design, these results allow concluding that this vaccine is effective to protect against the disease caused by DENV 3 and 4, limited for DENV 1, and ineffective against DENV 2. Table I summarizes this information.

Although stratification by countries was not considered in the primary design of the trials, according to the results in Latin America[8] —in an electronic supplement—, the estimated efficacy was poor in those countries where DENV 1 and 2 were in circulation. In Mexico, 3 464 study subjects (18% of the total Latin American sample) were included; 58 (15%) out of the 396 confirmed cases of dengue occurred in the region, and the estimated efficacy was only 31% (95%CI 1.3-52%). The available evidence suggests a suboptimal efficacy for the epidemiological context prevailing in our country at the time when the study was carried out. The variations in the efficacy of the CYD-TDV vaccine between studies and by country can be accounted for by the variability of circulating DENVs and by the differences in the proportion of dengue seronegative participants at the time of the administration of the vaccine.

Table I.
A SUMMARY OF THE DATA ON THE GENERAL EFFICACY* AND OF THE EFFICACY ACCORDING TO THE SEROTYPE OF THE CYT-TVD VACCINE, BY TRIAL

Trial	*Sabchareon A, et. al.*[6]		*Capeding MR, et.al.*[7]		*Villar L, et. al.*[8]	
Serotype	*Percentage*	*(IC95%)*	*Percentage*	*(IC95%)*	*Percentage*	*(IC95%)*
General	30.2	(-13.4 to 56.6)	56.5	(43.8 to 66.4)	60.8	(52.0 to 68.0)
Serotype 1	55.6	(-21.6 to 84.0)	50.0	(24.6 to 66.8)	50.3	(29.1 to 65.2)
Serotype 2	9.2	(-75.0 to 51.3)	35.0	(-9.2 to 61.0)	42.3	(14.0 to 61.1)
Serotype 3	75.3	(-375.0 to 99.6)	78.4	(52.9 to 90.8)	74.0	(61.9 to 82.4)
Serotype 4	100	(24.8 to 100)	75.3	(54.5 to 87.0)	77.7	(60.2 to 88.0)

* >28 days after the administration of three doses (protocol analysis)

In Brazil, Colombia and Honduras, where DENV 3 and 4 are predominant, and the proportion of dengue seronegative participants was 36, 8 and 14%, respectively, the respective estimated effectiveness was 78, 68 and 71%. On the other hand, in Mexico and Puerto Rico, where DENVs 1 and 2 prevail, and where the proportion of baseline DENV seronegative participants was 47 and 44%, the efficacy of the vaccine was considerably lower: 31 and 58%,[8] respectively. This is consistent with the poor effectiveness, of 31%, estimated in the Phase IIb study carried out in Thailand,[6] where DENV 2 prevailed. These data show that the CYD-TDV vaccine does not offer a good protection for primary dengue infections but works as a reinforcement of the immunity already acquired as a result of previous natural dengue infections. These observations suggest that generalization and the consequent direct application of the results to all the regions where dengue is endemic should be taken with caution.

In the combined analysis of all the studies on effectiveness and long-term safety and effectiveness,[9] the global effectiveness of the vaccine was 60.3% (95%CI 55.7-64.5). However, stratification of the results by age showed a combined efficacy of 65 % (95%CI 60.7-69.9) in Phase III studies in subjects aged nine or more years, which is significantly higher than the effectiveness of 44.6 % (95%CI 31.6-55.0) reported for children under nine years. The latter figure was estimated only for the population that participated in the studies carried out in Asia, since no children under the age of nine were recruited in Latin America.

Furthermore, this last publication describes the results stratified by age and with the presence of antibodies against dengue at the time of the vaccination. The global effectiveness in dengue seropositive individuals was 81.9 % (95%CI 67.2-90.0) for the group of subjects aged nine years or more, and of 70.1% (95%CI 32.3-87.3) for the children under nine. In contrast, for individuals aged more than nine years who were DENV seronegative at the time of vaccination, the efficacy was 52.5% (95%CI 5.9-76.1), and for children under nine years, it was 14.4% (95%CI −111.0- 63.5). I.e. even in children over nine, who were dengue seronegative, the vaccine was less effective, and the 95%CI values were much lower than the 25% established in the experimental protocol for an acceptable vaccine efficacy.

These data confirm the tendency observed in individual studies (CYD14 and CYD15)[7,8] of the vaccine to vary significantly according to the baseline dengue seroprevalence at the time of vaccination. Moreover, the probability of a previous natural dengue infection increases with age. Therefore, the differences observed in the efficacy of the vaccine in relation to the age reflect an efficacy indicator that depends on previous exposure to the dengue virus, rather than on a mere biological effect ascribable exclusively to age. In this study[9] the results of the variable efficacy of the vaccine by circulating DENV serotype in the region remained constant.

Another relevant aspect shown by the results of the Phase III studies on the efficacy of this vaccine is 80.3% protection against hospitalizations, and 95% protection against serious cases.[7,8] The study performed in Latin America reports 17 hospitalizations due to virologically confirmed dengue after at least one dose in the group of vaccinated patients, versus 43 in the control group (with an efficacy of 80.3, 95%CI 64.7-89.5); the control versus vaccinated patients ratio is 2:1. This same study registered a serious case of dengue in the group of vaccinated patients, and 11 in the control group, which results in an effectiveness of 95.5% (95%CI 68.8-99.0) against this type of dengue.

In the integrated long-term monitoring study,[9] the results for efficacy in preventing hospitalizations are encouraging, but they vary with age. Thus, efficacy in children aged nine years or more was 89.8% (95%CI 70.1-87.7), versus 56.1% (95%CI 26.2-74.1) in children under nine years. As for protection against serious cases of dengue, the results were 93.2% (95%CI 77.3-98.0) for the group of children aged nine or more years and non-informative for children under the age of nine [44.5% (95%CI −54.4-79.7)]. Efficacy against hemorrhagic dengue was 92.9% (95%CI 76.1-97.9) for nine or more years, and unconclusive for children under nine [66.7% (95%CI −4.7-90.2)]. For hospitalizations and hemorrhagic events in children under nine years, the lower value of 95%CI is negative, which is indicative of suboptimal efficacy.

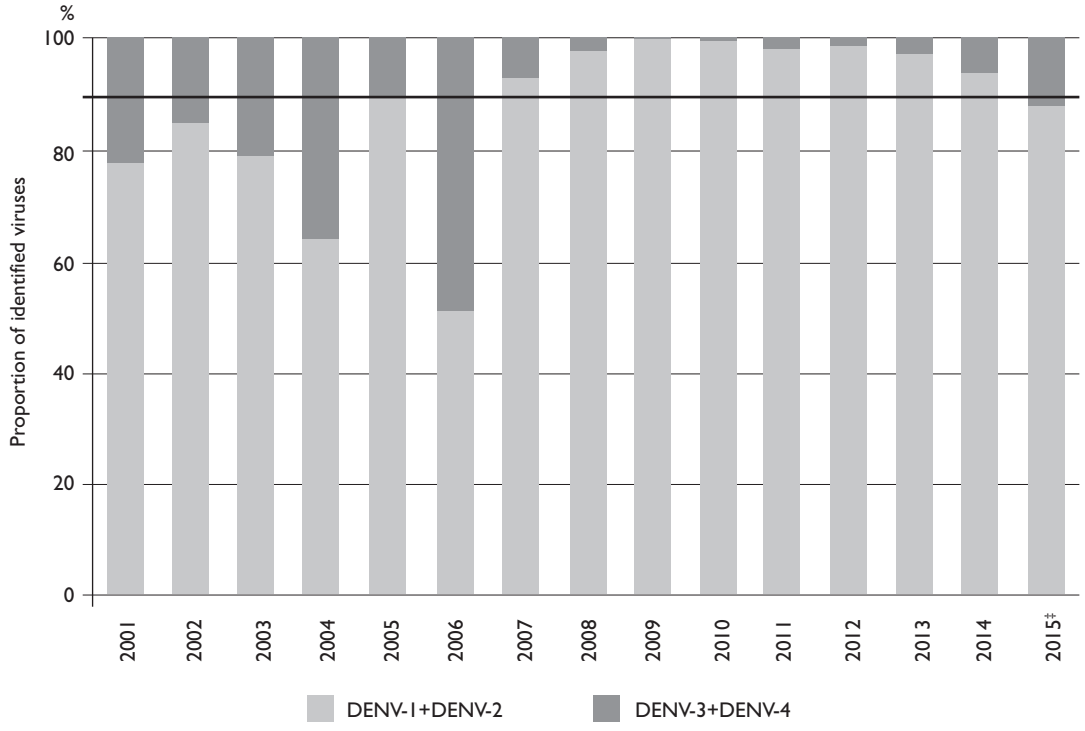
Data on efficacy to prevent hospitalizations and serious cases in relation to the baseline dengue immune status have not been presented in publications. Since the effectiveness of this vaccine depends upon immunity previous to the dengue infection and varies according to the circulating DENV serotypes, it is expected that protection against serious forms and hospitalizations will also depend on this variable. Therefore, the benefit associated to the global analysis must be taken with caution, as it may present variations by region, age groups, prevalence of antibodies against dengue among the population, etc. The data published in the Latin America study and the information that complements them online are of extraordinary interest for Mexico and must be carefully analyzed by the Federal Commission for Protection against Health Risks (Cofepris) and the National Vaccination Council (Conava), since, regardless of whether or not the requesting pharmaceutical enterprise covers global markets, the effectiveness of the vaccine in Mexico was limited; at the same time,

this was the country with the lowest baseline dengue seroprevalence of all the participating Latin American countries8 (electronic supplement).

An aspect that must be considered in Mexico in relation to effectiveness is that DENV 1 and 2 are currently prevalent across the country, with some variations between states. During the last 3 to 4 years, an increase in the number of cases of infection by DENV 3 and 4 particularly in the Yucatan peninsula and in Chiapas has been detected; however, the virological vigilance of dengue in the country indicates that nearly 90% of the cases are invariably caused by DENV 1 and 2 (figure 1).[10-11] The dynamics of DENV circulation in Mexico during over fifteen years suggests that the introduction of serotypes takes 5 to 6 years to establish the prevalence of a DENV serotype at a national scale.[9] This suggests that DENV subtypes for which the vaccine showed suboptimal results are prevalent in Mexico. One might argue that, since DENV 3 and 4 have been absent for several years, their generalized reintroduction may be imminent. This would be a reason to urgently implement CYD-TDV vaccination. However, it is hard to predict the conditions and times in which such reintroduction may occur.

DENVs show more genetic and antigenetic heterogeneity than the rest of flaviviruses. Within the four DENV serotypes there is a considerable genetic and structural heterogeneity referred to as genotypes or lineages. Such heterogeneity may imply key sites in protein E, conferring the possibility of escape by certain variants of the virus from the neutralizing action of the antibodies.[12] The poor effectiveness displayed by the vaccine against the DENV 2 serotype may be a result of a mismatch between the lineage of the vaccine and the lineages of the circulating DENV 2 in the regions where it was evaluated. According to a recent description,[13] although DENV isolates which differed genetically, geographically and temporally were generally grouped by serotype, they had genetic similarities with both heterologous and homologous viruses.

This study reveals the lack of homogeneity between the classic DENV serotypes and, above all, that there remains much to be understood about immunological protection against dengue and its implications in terms of vaccination, the dynamics of the emergence and reemergence of various DENV serotypes through time and across geographic regions.



* 90% of the dengue serotypes identified through the virological surveillance of dengue accumulated in the last 15 years in Mexico are DENV-1 and 2
‡ Up to the 43th epidemiological week of 2015

Figure 1. Proportion of serotypes identified in the virological surveillance of the dengue virus in Mexico, in the last 15 years*,‡

The risk-benefit and cost-effectiveness studies required to guide the policies regarding whether or not to introduce this vaccine in Mexico must realistically consider the relative frequency of the circulating DENV serotypes and explore, based on scientifically founded assumptions, a gradual model of the relative prevalence of serotypes and the potential short- and long-term temporal changes. I.e., the nearly 60% global effectiveness described for Latin America cannot be automatically extrapolated to the national reality. These cost-effectiveness studies should also consider that the vaccine offers a variable effectiveness depending on the dengue immunological status at the time of vaccination. The two Phase III studies included for its estimations those subjects who received the vaccine, regardless of whether or not they had completed the three-dose scheme (intention of treatment). In Asia,[7] the mean effectiveness of the vaccine estimated in those who received three doses (by protocol) was 57% (95%CI 44-66), and the intention of treatment was 55% (95%CI 47-62). In the case of Latin America,[8] these estimates were 61% (95%CI 52-68) and 65% (95%CI 59 to 70), respectively. The two efficacies are qualitatively and statistically equal, although the difference between the population that received three doses and the one that received an incomplete scheme was only 10%. These results make it essential to analyze whether or not three doses are really required to attain the proposed efficacy.

These three studies have also evidenced that the increase of dengue-neutralizing antibodies after vaccination, at least for DENV 2 and, partially, for DENV 1, are not correlated with protection against the disease,[6-8] since adequate immunogenicity has been reported in vaccinated patients against these serotypes, although the efficacy of the vaccine against them was low.[6-8] The lack of a consistent protection indicator makes it difficult to define protective immunity for any study related to candidate vaccines, and therefore it is still necessary to search for better surrogate markers for this purpose. This also represents a challenge for any regulating agency that must evaluate the potency of any candidate vaccine against dengue, without the possibility of having an indicator that fully relates to the protective capacity of the vaccine.

The scientific evidence of the variable efficacy of the CYD-TDV vaccine obliges to document and carry out a rigorous analysis of the variables that make it possible to determine the critical coverage threshold required to stop or significantly mitigate the transmission of dengue and how long it might take to attain this threshold in the light of an explicitly defined control goal.

Correct interpretation of the results of these controlled clinical trials requires awareness of the conceptual difference between efficacy (impact under experimental or controlled conditions) and effectiveness (impact on the real conditions in which the health care services operate). For most interventions –health and otherwise–, the observed magnitude of these two impact measures often differs.[14] Usually, the efficacy is greater than the effectiveness, which may induce false expectations, particularly in the short and medium term, regarding the usefulness of an intervention or supply.[15] In the case of vaccines, the effectiveness is lower than the efficacy, which is accounted for by a large set of requirements and potential failures in the vaccination operation (e.g. cold chain, application quality, selection of the subjects, etc.) or by incomplete or untimely schemes.

The CYD-TDV has been tested in a scheme of three initial doses with six-month intervals between doses. On another note, the meta-analysis[8] showed that the highest efficacy occurred in children aged nine or more years, while the Latin American study did not include children under nine. The age scheme to initiate vaccination with CYD-TDV has not yet been published. Neither is it known whether or not it will be determined by region. However, the results of the meta-analysis for both efficacy and safety suggest that it will be at least equal to or above nine years,[9] although there is not enough scientific evidence to support this criterion. If the general recommendation is to start vaccination at the age of nine, it must be taken with caution and evaluated at a local level, as, since we mentioned before, the age could be an indicator associated with a previous infection by dengue, and we do not have representative information at a national level over what should be the age limit which would allow greatest specificity in the selection of the population that has previously suffered from dengue and will be benefitted by the vaccine. Also, there is, so far, no rapid, low cost test to properly identify dengue seropositive and seronegative subjects at the time of vaccination to enable determination of who requires immunological reinforcement against DENV. This is not a feasible solution in the reality of vaccination programs. Likewise, the most appropriate age may vary by state or even by municipality – a fact that entails a substantial difficulty for the vaccination logistics.

The expected protection against infection by the dengue virus would increase with the seropositivity prevalence.[7-9] Assuming that the vaccine or other control and prevention interventions will bring about a progressive reduction of the dengue incidence, the likelihood of exposure to the virus will consequently decrease, and with it, the effectiveness of the vaccine.[16] The evidence that the vaccine has less efficacy in dengue seronegative individuals implies that, unlike all the vaccines currently in use within the national vaccination scheme, this is

not a preventive vaccine but an immunity "booster" associated with a previous natural infection.

Finally, we may conclude that the greatest virtue of the efficacy of the CYT-TDV vaccine is that it protects against infections by DENV 3 and 4, as well as against hospitalizations and serious cases in the age group of children above nine years who have previously had a dengue infection, and therefore it works mainly as a reinforcement vaccine.

Safety of the CYD-TDV vaccine

The three controlled clinical trials suggest that the frequency of adverse events ascribable to vaccination during the first 12 to 25 months of monitoring do not differ among those who were administered a vaccine and those who received a placebo. Therefore, it is considered to be safe within this monitoring period.[6-8] Notwithstanding, an important datum that should be considered for the licencing of this vaccine is described for the first time in the long-term monitoring study.[9] The global risk of hospitalization due to virologically confirmed dengue for all participants was 0.84 (95%CI 0.56- 1.24). However, when stratified by age at the onset of vaccination, the relative risk of hospitalizations among the group of children under nine years who received the vaccine is higher than in those who did not receive it, for it increases to 1.58 (95%CI 0.83-3.02). In contrast, for children aged nine or more years, the risk of hospitalization is lower among vaccinated children [0.50 (95%CI 0.29-0.86)]. A significant increase in hospitalization cases due to dengue by the group that received the vaccine —with an estimated relative risk of 7.5 (95%CI 1.15-313.80) among children aged 2 to 5 years and a protective effect in children over six years— accounts for the increase observed in children under nine years in the Asian study (CYD14). In the follow-up of another Asian Study —CYD23/57— an increase in the risk of hospitalization due to dengue was also observed among vaccinated children aged 4 to 5 years versus those who received a placebo (RR 2.44; 95%CI 0.27-115.34). Likewise, the protective effect was evident only for children over five years.[9] Finally, in the follow-up of the Latin American study,[8] all the individuals included were aged nine or more years, and no increase in the risk of hospitalization was observed at three years follow-up after the first vaccination dose.[9] This information is summarized in table II.

The long-term follow-up study also suggests that, despite the increased risk of hospitalization among children under nine years, no increase in serious (hemorrhagic or shock) cases of dengue due to vaccination has been reported.[9]

The first consideration on the increased hospitalization risk in children under nine years in the vaccinated group is the need to clarify whether this increase is related to age or whether, like the variation in global efficacy, it depends on the dengue immune status of the individual at the time of vaccination. This last consideration is very important from the point of view of the

Table II.
RELATIVE RISK OF HOSPITALIZATIONS DUE TO VIROLOGICALLY CONFIRMED DENGUE, BY STUDY AND BY AGE GROUP. MEXICO

Place	*Place*	*Age group*	*Relative Risk*	*(IC95%)*
Capeding MR, *et al.*[7,*]	Asia	2 to 5 years	7.45	(1.15-313.80)
		6 to 11 years	0.63	(0.22-1.83)
		12 to 14 years	0.25	(0.02-1.74)
		< 9 years	1.58	(0.83-3.02)
		≥ 9 years	0.50	(0.29-0.86)
Sabchareon A, *et al.*[6,*]	Thailand	4 to 5 years	2.44	(0.27-115.34)
		<9 years	0.54	(0.23-1.29)
		≥9 years	0.31	(0.05-1.58)
Villar L, *et al.*[8,‡]	Latin America	9 to 11 years	0.55	(0.20- 1.54)
		12 to 16 years	0.50	(0.13-1.87)

* During the third year of follow-up
‡ During the fourth year of follow-up

vaccine's safety, and it leaves an uncertainty whether or not dengue seronegative individuals of all ages might have a higher risk of suffering from a serious form of dengue due to exposure to a natural dengue infection after having received the vaccine.

In clinical-epidemiological studies, the increase in the risk of suffering from a serious form of dengue has been associated with subsequent infections. One of the main hypotheses regarding the physiopathogenesis of the increased seriousness within the clinical spectrum of dengue is the so-called antibody-dependent amplification, a phenomenon accounted for by the fact that a primary dengue infection induces neutralizing antibodies and produces potentially lasting protection against homotypic DENV serotypes, but only temporarily, during a period ranging between three months and two years[12] against heterotypic DENV. In second infections by other serotypes, a response of weakly neutralizing antibodies which is nonetheless capable of facilitating the entry of the virus into the monocytes is induced; this results in an amplification of the infection by the virus, as well as of the inflammatory response.[2,12,18-20]

Ideally, a dengue vaccination must include a balanced immunity against all four serotypes.[2] The inefficacy of the vaccine against DENV 2 and the limited efficacy against DENV 1 may have implications beyond not conferring protection against infection by that serotype, since there is at least a theoretical possibility that the antibodies induced by the vaccine against the same or another serotype may potentiate symptomatic infection by DENV 2.

Various epidemiological studies suggest that, the longer the time interval between the primary and the secondary infections, the larger the risk of symptomatic infection and hospitalization.[21-24] In the face of the increased risk of hospitalization due to cases of virologically confirmed dengue within the group of vaccinated children aged nine years or less, the follow-up periods after vaccination must be extended.

In the face of uncertainty as to whether or not the increased risk of hospitalization detected among children under nine years is a problem associated with the negative baseline dengue immune status, we cannot dismiss the fact that any population with this characteristic might be in risk of developing symptomatic or serious dengue with time, regardless of age, in the event of a subsequent dengue infection. As stated by a recent report of the Advisory Committee on Vaccine Safety of the World Health Organization (WHO),[24] it is imperative to have more evidence regarding the role of serology in association with this risk, for this vaccine or for any other potential candidate.

In Mexico here are local studies on dengue seroprevalence, with limited information, based on at convenience samplings that are not representative of the national or regional reality.[25-33] The information available in clinical trials in various parts of the world[6,7] and particularly in Latin America[8] has the limiting condition of corresponding to a small, non-random sub-sample (electronic supplement) and that all the studied individuals were over nine years of age in the Latin American study. The data show a wide variation in baseline dengue seroprevalence between the various studied regions. The significant variation in the efficacy of the vaccine, according to the proportion of the population that had been previously infected with dengue and with the predominant dengue subtype makes it very difficult to directly extrapolate the results of the trial to all the dengue endemic areas and calls for further studies in order to clarify these differences and to make recommendations based on a more complete scientific evidence.

It is certainly difficult to assess the increased risk associated with the CYT-TDV vaccine under conditions of a baseline dengue non-immune status for any age group from the studies that have already been implemented. However, in the face of the current evidence, this risk cannot be perceived as a tendency or a signal but must be approached as an evidence to be seriously considered. The risk of reinfection is proportional to the duration of the exposure to dengue; it is therefore improbable that a second infection will follow shortly after the first. Consequently, the initial 12- or 24-month follow-up period contemplated by the protocol of the cited clinical trials[7,8] appears to be too short to detect serious dengue events potentially associated with the vaccine as previously recommended by WHO.[34-36] This is best documented in the long-term follow-up study,[9] where the increased risk of hospitalizations in the group of smaller children begins to become evident. Likewise, the manufacturer is required to make a change in the originally approved experimental design so as to allow incorporation of active surveillance of any virologically confirmed dengue case in order to have better elements of evidence of a foreseeable risk not yet adequately ruled out.

When introducing a new vaccine or a new drug, we must consider the ever present possibility that adverse events, which are not frequent, may only be detected in the post-surveillance studies, after millions of doses of the vaccine have been applied, as has been the case with other vaccines, e.g. the Rotashield vaccine, against the rotavirus, which was withdrawn from the market after it had been registered and implemented in 1999, due to the detection of an increase in the number of cases of intussusception as an adverse event associated to the vaccine that was not detected in the clinical trials.[37] Unlike in the case of the rotavirus vaccine, there is evidence that indicates the possibility of an increased risk of hos-

pitalization in those who have received the CYD-TDV vaccine, within an age group in which the vaccine has proven to have the lowest efficacy and in which dengue antibodies are absent at the time of vaccination. The risk of transferring the surveillance of adverse effects to the post-commercialization period must be taken with caution, particularly the risk of increased hospitalizations associated to this vaccine, for, in the case of the development of serious cases of dengue associated to subsequent infections, it may persist throughout the life of the vaccinated subjects until they meet a new DENV infection.

Likewise, in the face of the eventual licensing of this vaccine in Mexico by Cofepris, it is indispensable to establish beforehand what the expected risk may be, compared to the benefit that it provides, in order to determine its potential use within the national vaccination program and, consequently, adequately determine all the elements of the risk management plan to be established by the regulating agency. On the other hand, post-commercialization studies required great solidity in the surveillance programs of adverse events associated with the vaccine. In the case of Mexico, these are managed as events supposedly attributable to the vaccination (ESAVI) and they are regulated by the numeral 13 (13.1, 13.2, 13.3) of the norm NOM.-036-SSA2-2012, and operated according to the recently updated manual of technical procedures (Manual de Eventos Supuestamente Atribuibles a la Vacunación [Manual of events supposedly attributable to vaccination], SSA/CENSIA/2014). In general, the ESAVIs must be detected by the medical and paramedical staff at the local levels of health care and reported to all levels of the system. I.e., it is a passive process with certain components of active research, depending on the capacity of the work teams at all levels. The situation of the dengue vaccine differs from that of any other vaccines currently applied in Mexico. The subsequent natural infection may occur months or years after vaccination, and therefore, both appraisal of the increased risk of serious form of the disease associated with vaccination and identification of case clusters, as described in the ESAVI manual, will be a new, complex challenge for the Mexican Universal Vaccination Program. The document on the International Evaluation of the Mexican Universal Vaccination Program issued by the Panamerican Health Organization in 201438 describes ESAVI surveillance as an opportunity area and recommends its reinforcement at all levels of the system. The consideration of licensing and implementation of the dengue vaccine in Mexican population groups alone demands a nominal registry of the vaccinated patients, as well as the reinforcement of training at all levels of the ESAVI system, particularly for serious cases and for hospitalizations due to dengue.

The data described above suggest that it is important to have a dengue seroprevalence analysis available in Mexico in order to direct the efficacy and safety of this vaccine. These data are very relevant, in the face not only of the results obtained for the CYD-TDV vaccine but also of any other candidate vaccine in the future. However, this type of seroprevalence survey must be appropriately designed to demonstrate representativity by state, municipality, socioeconomic stratum, age groups, potential comorbidity, etc. Furthermore, this can change from one year to the next, depending on the outbreaks and the impact of the control measures. The risk management plan after the licensing of this vaccine faces complex challenges which include, among other aspects, keeping all the required information updated through time and having qualified human resources as well as access to the diagnosis infrastructure at all levels. This will represent a major socioeconomic burden that must be added to the costs of acquisition and application of this vaccine.

General considerations

There is no doubt that the morbidity burden due to disease produced by the dengue virus is large, and the possibility of prevention using a safe, effective and affordable vaccine would represent a substantial advance for global public health.[2,39,40] Therefore, the regulating agencies and the public health decision makers in charge of the dengue control and prevention policies have the enormous responsibility of determining the best possible scientific evidence in regard to safety and efficacy before registering and introducing the only currently available dengue vaccine, CYD-TDV, within a universal immunization program.

For their approval, vaccines are subjected to a rigorous sequence of tests in order to determine the safety and efficacy that will prove to afford individuals greater benefits than the risk of serious health effects. Assuming that the risk signal associated with the CYD-TDV vaccine described above were inexistent and that only the efficacy of the vaccine were to be taken into account, the cost-effectiveness balance must prevail over the decision-making process.

So far we have found no public evidence regarding the cost of this vaccine in Mexico or elsewhere in the world; therefore, it is important to know the elements for considering that this vaccine, which has an acceptable efficacy only in subjects previously infected with dengue, is a priority for Mexico, as an urgent dengue

prevention strategy, at this epidemiological moment. As we have previously mentioned, the cost-effectiveness studies for this vaccine are complex and must be specific for the region and for the epidemiological moment, with models that include a variable efficacy according to the serotypes circulating at a specific time and to the baseline dengue immune status of the vaccinated individuals.

In a costing exercise at a set price of 15 US dollars, countries like Colombia and Brazil were estimated to require investing a 2 400 million USD budget from the public sector in five years.[41] In Mexico, as in most countries with a medium income, decision makers must carry out budget prioritization exercises for several public health issues. One example is the improvement of the conditions for a safe water supply; this would reduce water storage, which favors the emergence of breeding grounds for mosquitoes. This, in turn, would have an impact on many other public health issues.

According to a disease burden study on dengue in Mexico, almost 50% of the cost of the disease burden due to dengue may be attributed to the financial resources invested in epidemiological surveillance programs and in vector control.[39] It will not be possible to reduce this component of the cost in the short or medium term, since the efficacy of the CYD-TDV vaccine depends on the circulating DENV serotypes and on previous natural dengue infection —two factors whose control is extremely complex. In addition, neither the critical coverage threshold that needs to be attained with the CYD-TDV vaccine among the population nor the necessary time required to reduce the burden of the virus —which may have an impact on dengue transmission— are known. Likewise, in the face of the introduction and rapid dissemination of infection by the Chikunkunya virus in Mexico,[42-45] and of the presence of the Zika virus in the American continent,46 and given that all these viruses share the same vector, the battle control the Aedes mosquito must be reinforced.

Other factors must be taken into account before making the decision to introduce a new vaccine into the immunization program of a country.[47-49] The direct and indirect costs and, in particular, the pressure generated within the national vaccination program itself, the human resources and the infrastructure must be considered from an integral perspective in order to prevent overburden and jeopardizing of the attained achievements. To the present moment, the CYD-TDV vaccine requires an initial scheme in three doses with six-month intervals within a potential age group that is difficult to capture and a scheme that is hard to complete; this will require investment in a specific recruitment and monitoring program that is unusual in the vaccination schemes in Mexico.

It is necessary to acknowledge and plan the manner in which the epidemiological surveillance systems must be adjusted in the post-commercialization stages. A critical analysis of the current dengue surveillance system is required in order to obtain a better estimate of the incidence, since reports that include only confirmed cases result in underestimation of the real incidence, while informing only on potential cases leads to overestimation; therefore, an estimation model based on data with an adequate quality is required.

The need to amplify the algorithms for laboratory confirmation within a good surveillance system (primary care, notification, confirmation, etc.) must be considered in order to be able to differentiate between DENV, chikungunya and Zika infections, among others. All of this adds costs and complexities to the vaccination program.

Since one of the relevant benefits of this vaccine is protection against hospitalizations and serious forms of dengue, it is essential to have evidence of the risk factors identified in Mexico for these events, such as comorbidity or care quality.

This will allow more adequate definition of the target groups for vaccination, as well as provide elements for the comparison of the costs involved with those of other prevention strategies.

It will be relevant to ensure programs and budgets in order to introduce and to sustain the new vaccination schemes in the long term, as well as to reinforce the existing schemes. The 2012 National Nutrition and Health Survey[50] reports a global vaccination coverage of less than 70% for three vaccines and less than 50% for five vaccines in children aged one year in Mexico, with heterogeneity between states. In the International Evaluation of the Universal Vaccination Program document,[38] the rapid monitoring of the vaccination coverage carried out in 32 municipalities in nine states of the country reports an incomplete vaccination scheme in 29% of the children aged 1 to 5 years, with variations ranging from 11 to 48% between states. This evaluation identifies various weaknesses in the universal vaccination system of Mexico, which require prompt reinforcement in order to maintain and enhance the attained achievements. The complexity of implementing vaccination with CYD-TDV would add onto the universal vaccination in Mexico a significant and complex burden which must be considered prior to its implementation for purposes of investment in reinforcement programs.

Doubtless, the highest ethics that must prevail over any decision in matters of public health is, first of all, not to cause harm, i.e. the vaccine must provide a direct benefit to those who receive it; care must be taken to avoid any harm that might be derived from the vaccine (when

Table III.
CONSENSUS ON THE CONSIDERATIONS FOR THE LICENSING OF THE CYD-TDV DENGUE VACCINE IN MEXICO

Approval criteria	*What evidence indicates*	*Comments*
Vaccine safety	Adequate safety at 25 months follow-up. The results of the clinical trials three years after the administration of the vaccine indicate a higher hospitalization rate due to dengue among the youngest participants.	The vaccine is safe according to the evaluation at 25 months after the initial vaccination. These data suggest that vaccinated patients may be more predisposed to suffer from a form of dengue that will require hospitalization when exposed to the virus after immunization. If the increased risk of suffering from a serious form of dengue in vaccinated patients is confirmed, the uncertainty arises as to the time limit of this risk.
Vaccine efficacy	The available evidence indicates that there is a larger efficacy in the vaccine to protect against infections by DENV 3 and 4, a lower efficacy for DENV 1 and no protection against infections by DENV 2. The efficacy is higher in subjects with previous antibodies.	The vaccine has a variable efficacy, depending on the circulating serotypes, and acts as a reinforcement of the immunity resulting from a previously existing natural infection. If the vaccine is approved, its greatest efficacy may be for populations with a high dengue seroprevalence.
	Good efficacy to prevent serious forms of dengue and hospitalizations in the follow-up, up to two years. Analysis of the results of the three trials during the third year shows that this protection is maintained throughout the follow-up of children aged nine or more years and diminishes in children under nine years.	The vaccine reduced the risk of hospitalization and of serious forms of dengue in children aged 9 to 16 years.
Characteristics of the control and prevention program		If the vaccine is approved, it will be necessary to integrate vaccination to the rest of the interventions of the dengue prevention and control program.
Impact of the introduction of the dengue vaccine into the UVP of Mexico	The 2012 National Nutrition and Health Survey reports global vaccination coverages of less than 70% for three vaccines and less than 50% for five vaccines in children aged one year in Mexico, with heterogeneity between states.	If the vaccine is approved, it will be necessary to guarantee its administration to target populations without affecting the Mexican UVP.
Cost-effectiveness	The cost of the vaccine is unknown.	According to certain studies carried out in Latin America, it will be necessary to spend 2 4000 million US dollars in five years of use, at the fixed cost of 15 USD per vaccine.
Epidemiological surveillance		If the vaccine is approved, it will be necessary to assess the impact of the vaccination on the disease burden, as well as to reinforce the sensitivity and specificity of the dengue surveillance systems.
Adverse effect surveillance	There is a possibility of more frequent hospitalization due to dengue several years after vaccination.	If the vaccine is approved, it will be necessary to increase the sensitivity and specificity of the adverse effect surveillance program and adapt this to the particular characteristics of this vaccine. In addition, it will be necessary to include a nominal registry of vaccinated patients and match it to the surveillance of hospitalizations, serious cases and deaths due to dengue. Likewise, it will be necessary to have a documented vaccination history for serious cases of dengue, in order to be able to differentiate dengue cases associated with vaccination in the future.

UVP= universal vaccination program

comparing this strategy to other procedures that have been alternatively used to address the same situation). Finally, vaccination must afford the best opportunity to successfully prevent the disease, compared to the likelihood of its causing harm.[51] It is relevant to consider the so-called caution principle, propounded by Gostin and his collaborators, in the public health response to infectious diseases in emergency situations.[52] However, in the scenario of the dengue vaccine, we should consider whether or not provision of the vaccine even under certain conditions of uncertainty, and taking into account the cost of not providing it, would warrant its implementation.[52]

Finally, the risk management after the licensing and potential implementation of this vaccine would have to be based on a clear determination of the expected risk; this should also be the basis for defining a detailed risk management plan that will guarantee the timely and

adequate identification of any risk associated to vaccination and will include an estimate of the related costs.

Conclusion

The development of the CYD-TDV vaccine by the Sanofi-Pasteur company entails great effort and is an example of quality basic, epidemiological and clinical research. The results are encouraging as to the first evidences regarding the introduction of protective immunity to dengue, which is a complex disease, given its physiopathogenics, its clinical repercussions and its transmission dynamics. Table III summarizes the considerations stated in this document. Despite this significant contribution to the development of a dengue vaccine –a priority public health issue–, the results which show a variable efficacy of this vaccine and suggest the possibility of an increase in the hospitalization risk associated with vaccination in children under nine years who have not been previously exposed to dengue generate enough concern to insist on the suggestion to postpone sanitary authorization for the vaccine and, consequently, its implementation within the national immunization program, until more robust evidence is available to define the target groups for vaccination and the vaccine's medium-term safety. In addition, we must take into account that seronegative subjects will not be protected against dengue and may present a higher risk of suffering from a serious form of dengue in the future; we must then be certain that this risk is truly small and similar to risks that are often regarded as acceptable.

The opportunity to obtain this evidence may emerge from the complete follow-up according to the protocol proposed by the applicant's own studies, in keeping with the recommendation of the World Health Organization.[35,36]

Declaration of conflict of interest. Celia Alpuche Aranda participates as a member of the International Independent Monitoring Committee on the Safety of the CYD-TDV vaccine. The opinion expressed by her in this document regarding the published information is personal.

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