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ORIGINAL ARTICLE

Dengue surveillance in children who received CYD tetravalent dengue vaccine during their second year of life while participating in a clinical trial in a southern state of Mexico

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ABSTRACT

Dengue is a systemic viral infection transmitted to humans by mosquitoes and is a public health challenge due to its rapid global expansion and lack of specific therapeutic agents. To date (January 2018), the CYD-TDV vaccine has been granted licensure in 19 countries. The World Health Organization global strategy for dengue prevention and control 2012-2020 has, as a global goal, the reduction of the burden of disease. One of the technical elements of this strategy is the implementation of a dengue vaccine. This is an epidemiological descriptive study of 248 subjects with retrospective and passive surveillance for 2 years; from this cohort, 162 subjects, ages 4 years 8 months to 5 years 9 months, underwent active surveillance. Eligible participants were children who participated in the previous randomized phase III trial conducted in Merida, Yucatan, Mexico. All the subjects who completed the previous trial were included for retrospective/passive surveillance; the subjects who underwent active surveillance (n = 162 subjects) were identified during a three-month enrollment period. Blood draws and phone calls (study procedures) were performed under the applicable local and international regulations. None of the 248 participants followed for passive surveillance had a reported confirmed dengue case. Forty-one cases of suspected vector-transmitted disease without virological or serological confirmation were detected. The result of this study provides support for the safety of the vaccine in this age group. Further follow-ups in similar populations should be done in order to obtain more information.

Key words: Dengue vaccines, child, surveillance, clinical trial, Mexico.

Vigilancia del dengue en niños que recibieron la vacuna tetravalente contra el dengue de CYD durante su segundo año de vida mientras participaban en un ensayo clínico en un estado del sur de México

RESUMEN

El dengue es una infección viral sistémica transmitida a los seres humanos por los mosquitos y es un problema de salud pública debido a su rápida expansión mundial y a la falta de agentes terapéuticos específicos. Hasta la fecha (enero de 2018), la vacuna CYD-TDV ha obtenido la licencia en 19 países. La estrategia mundial de la Organización Mundial de la Salud para la prevención y el control del dengue 2012-2020 tiene como objetivo mundial la reducción de la carga de morbilidad. Uno de los elementos técnicos de esta estrategia es la implementación de una vacuna contra el dengue. Se trata de un estudio epidemiológico descriptivo de 248 sujetos con vigilancia retrospectiva y pasiva durante dos años; de esta cohorte, 162 sujetos de cuatro años, de ocho meses a cinco años y nueve meses, fueron sometidos a vigilancia activa. Los participantes elegibles fueron niños que participaron en el ensayo aleatorio previo de fase III realizado en Mérida, Yucatán, México. Todos los sujetos que completaron el ensayo anterior fueron incluidos para la vigilancia retrospectiva/pasiva; los sujetos que se sometieron a vigilancia activa (n = 162 sujetos) fueron identificados durante un periodo de inscripción de tres meses. Los análisis de sangre y las llamadas telefónicas (procedimientos de estudio) se realizaron bajo las regulaciones locales e internacionales aplicables. Ninguno de los 248 participantes que siguieron la vigilancia pasiva tuvo un caso confirmado de dengue. Se detectaron 41 casos de sospecha de enfermedad transmitida por vectores sin confirmación virológica o serológica. El resultado de este estudio proporciona apoyo para la seguridad de la vacuna en este grupo de edad. Se deben hacer más seguimientos en poblaciones similares para obtener más información.

Palabras clave: *Vacunas contra el dengue, niño, vigilancia, ensayo clínico, México.*

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INTRODUCTION

Dengue is described as a self-limited, systemic viral infection transmitted to humans by mosquitoes and is a public health challenge due to its rapid global expansion and the lack of specific therapeutic agents or licensed vaccines.[1] According to the World Health Organization (WHO), 50-100 million new infections occur annually in more than 100 endemic countries, with a documented further spread to previously unaffected areas. Although the WHO does not receive dengue case notifications from all affected countries, Mexico has been identified as one of the countries with a high average of reported cases between 2010 and 2016.[2] In fact, Mexico is one of the countries where infection with dengue has an important public health impact. At a global level, hundreds of thousands of severe cases arise every year and often affect very poor populations; 20,000 deaths and 264 disability-adjusted life years per million population per year are lost at an estimated cost for ambulatory and hospitalized cases of US$514-1394.[3,4]

The WHO global strategy for dengue prevention and control 2012–2020 has as a global goal of reducing the burden of disease; this goal includes a reduction in mortality by at least 50% and morbidity by 25% by 2020 (baseline year 2010).[3] One of the technical elements of this strategy is the implementation of dengue vaccination. Several trials have been conducted in order to evaluate the safety and immunogenicity of the vaccine in children receiving the already recommended immunizations. One of these studies, Study CYD33, was recently published and was a randomized, observer-blind, multicenter, phase III trial conducted in 732 healthy toddlers aged 9-12 months in Mexico (Guerrero, Yucatan and Nuevo Leon) between July 18, 2011, and February 4, 2014; this study demonstrated the noninferiority of immunologic responses to the DTaP-IPV/Hib booster vaccine when coadministered with tetravalent dengue vaccine (CYD-TDV) compared with those associated with coadministration with placebo. One hundred percent of the participants in both treatment groups were seropositive for all 4 dengue serotypes after the third CYD-TDV dose; notably, there were no safety concerns.[5]

Two phase III CYD vaccine efficacy trials are being conducted in Asia-Pacific (CYD14)[6] and Latin American (CYD15)[7] countries; a total of 30,964 children from 2 to 16 years received either 3 doses of vaccine or placebo on a 2 vaccine: 1 placebo ratio at 0, 6, and 12 months. During the first 25 months (primary objective), the CYD dengue vaccine prevented 56.5% to 60.8% of dengue cases.

In Asia-Pacific countries (CYD14), the baseline two groups were similar in age and sex ratio. In the immunogenicity subset, 1340 (68%) of 1983 children tested positive for neutralizing antibodies to dengue by PRNT50; this number increased with age from 348 (51%) of 678 children aged 2-5 years, 507 (72%) of 706 children aged 6-11 years, and 485 (81%) of 599 children aged 12-14 years. In the CYD14 trial, prespecified age-specific analyses showed a clear trend toward a higher relative risk for hospitalization for virologically confirmed dengue among younger children, although the number of cases was low; the relative risks were 7.45 among children between the ages of 2 and 5 years, 0.63 among those between the ages of 6 and 11 years, and 0.25 among those between the ages of 12 and 14 years. Until now, the above mentioned observations were not seen within the observed time period in any of the 5 Latin American countries participating in the phase III efficacy trial; the subjects participating in this study were all ≥ 9 years of age.[8]

All the ethics committees (EC) affiliated with the sites that conducted the vaccine trials in dengue endemic regions were informed of these results by the sponsor through the respective investigators. Based on the mentioned report of a higher incidence of dengue hospitalizations in vaccinated children ≤5 years of age, the EC for the study site in Merida, Yucatan, Mexico, which is a state located within the first 5 areas with more dengue confirmed cases than other areas in the country, recommended an extension of surveillance for those who participated in Study CYD33. For a total of 4 years after the last vaccine dose was administered, a retrospective surveillance for dengue events was performed and followed up with active surveillance to detect any clinically diagnosed dengue case and to determine its severity.

The primary objective of this study was to determine the number of virologically confirmed dengue (VCD) cases in children who received tetravalent dengue vaccine during the previous randomized, observer-blind (for the second dose of CYD-TDV), open-label (for the first and third doses of CYD-TDV), multicenter, phase III trial at the clinical site in Merida, Yucatan, Mexico; the study was conducted for four years after the last vaccination.

MATERIAL AND METHODS

Study design and participants

Epidemiological surveillance longitudinal retrospective-prospective study, at a clinical site in Merida, Yucatan, Mexico.

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice as well as with all local and/or national regulations and directives. In addition, the study protocol was approved by the study site's Institutional Review Board and the independent EC.

The children selected for participation in the study (n = 248) were from site 002, Merida, Yucatan, Mexico, at the request of the Committee of Ethics and Research of the State of Yucatan, who participated in the previous randomized, observer-blind (for the second dose of CYD-TDV), open-label (for the first and third doses of CYD-TDV), multicenter, phase III trial conducted in 732 healthy toddlers in 3 Mexican states (Guerrero, Yucatan and Nuevo Leon) between July 18, 2011, and February 4, 2014.

The study group of 248 healthy children, ages 4 years and 8 months to 5 years and 9 months, were surveilled retrospectively and passively for 2 years; of this population, only 162 subjects were identified in a period of 3 months and included in a new cohort to perform active surveillance for 10 and half months.

Exclusion criteria included children who were not included in the previous trial for at site 002 Merida, Yucatan, Mexico, and children who were withdrawn from the previous trial due to loss to follow-up.

Retrospective/passive surveillance

The retrospective/passive surveillance was done with the review of the Epidemiological Dengue Platform of the Ministry of Health in Yucatan through the active search of dengue cases during the entire trial; the platform was also reviewed for the years 2012 to 2017 *(Figure 1)*.[9]

In addition, the number of hospitalizations due to dengue (International Classification of Diseases 10th Revision codes A90 and A91) with residence in the Municipality of Merida, Yucatan, disaggregated by age and year of discharge was consulted for the population without social security.[10]

Parents or legal guardians of the 246 subjects signed an informed consent form before the participation in the study and were asked to report any spontaneous case of fever among the population under study.

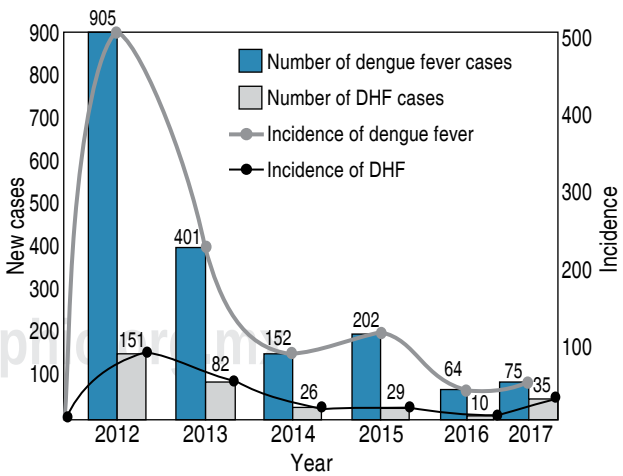
For performing the retrospective/passive surveillance, a collaborative network was established between the parents or legal guardians, health local services and the investigator site in order to follow up the positive dengue cases confirmed by laboratory serological tests.

Active surveillance

For the active surveillance, the parents/guardians of the 162 subjects signed an informed consent form. During the first patient visit, the parents or legal guardians were provided with a thermometer and a memory aid guide, with the description of the fever and the WHO clinical criteria for dengue and were asked to report any temperature rise in the child. Researchers telephoned the patients and their parents with a frequency of one call every two weeks. In the case of a febrile period suggestive of dengue, the parents were advised to visit the research center. Researchers made a domiciliary visit to the patients who were unable to go to the research center and took blood samples to confirm the possible dengue diagnosis according to international guidelines.

Dengue case assessment

In accordance with the established criteria, if a 48-hour episode of fever occurred in any of the subjects (two episodes per year of surveillance), whether by spontaneous report, telephone call, or spontaneous visit of the subject to the clinical site, medical personnel at the clinical site conducted the following procedure: clinical assessment of the subject to confirm acute febrile illness (i.e., temperature ≥ 38 °C on at least 2 consecutive



These data were obtained from the monthly report of each of the states of the Mexican Republic and concentrated in the general direction of epidemiology of the Ministry of Health of Mexico.

Figure 1. Epidemiological panorama of dengue virus infection in Yucatan State, Mexico, from 2012 to 2017.[9]

days) without an obvious clinical etiology. If this occurred, then a blood sample was drawn to perform a confirmatory ELISA test for dengue NS1 antigen; also, the subject was referred to the local health services in order to comply with the local Ministry of Health protocol, including laboratory confirmation, for the study of dengue. If the diagnosis of dengue was confirmed, a clinical follow-up of the patient was conducted by the clinical site personnel *(Figure 2)*.

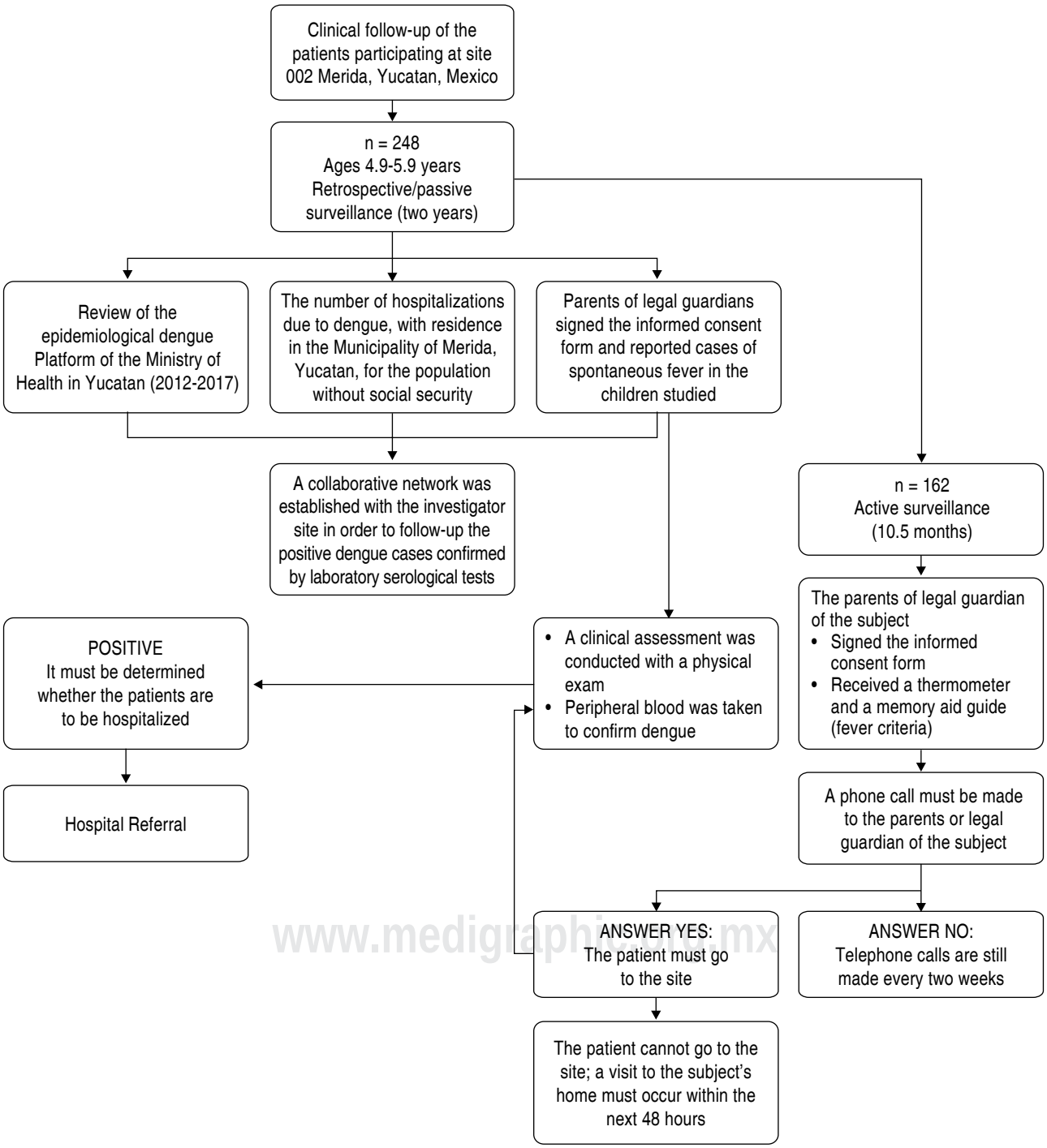


Figure 2. Clinical follow-up algorithm for the patients enrolled in this study.

Pharmacovigilance assessment

The VCD cases and the adverse events, including the severe adverse events related to the procedures, were reported in a pdf format to the PV outsourcing platform at the following email address: pv.outsourcing@sanofipasteur.com; this method of transmission included password protection.

Statistical analysis

There was no estimation of sample size, as the population participating in the study was limited to subjects who had participated in the previous CYD33 at the Merida study site (248 subjects), as requested by the ethical and research committees from the province of Yucatan.

The demographic characteristics of the subjects and the descriptive variables were analyzed with descriptive statistics (frequencies for nominal variables; means and standard deviations for numerical variables with a normal distribution; or medians, minimums and maximums when the variables did not have a normal distribution).

RESULTS

Symptomatic VCD, hospitalized VCD cases and dengue hemorrhagic fever (DHF)

A total of 162 children were actively surveilled. The characteristics of this population were as follows: 78 females aged 5.4 ± 0.2 years with a body mass index (BMI) of 16.5 ± 2.6 kg/m^2 and height of 109.7 ± 4.6 cm and 84 males aged 5.3 ± 0.3 years with a BMI of 16.6 ± 2.5 kg/m2 and height of 110.2 ± 5.1 cm. The nutritional status indexes for short height, low weight, and overweight were as follows: 5.1%, 2.6% and 10.3%, respectively, for females; and 4.3%, 5.6% and 12.3%, respectively, for males. No differences were found in the nutritional status of the subjects who received the vaccine and those who received the placebo.

None of the 248 participants who underwent retrospective/passive surveillance were reported as a dengue case in the Official Epidemiological Platform of Yucatán; no spontaneous cases were reported either.

There were no spontaneous cases of fever during the planned phone calls in the 162 children under active surveillance. None of these children went to the site with suggestive clinical features of dengue.

Suspected dengue without confirmation

Of the 248 subjects, forty-one cases of febrile episodes without confirmation were detected during this trial (16.5%). Of these, 25 were clinically diagnosed as Chikungunya disease (61%), 10 were diagnosed as Zika disease (24.5%), 4 were unspecific (9.7%), and only 2 were considered suspected dengue (4.8%). None of these cases were classified as severe, and none of these subjects were hospitalized.

Safety evaluations

There were no adverse events related to the procedures of the trial.

The expected number of hospitalizations due to dengue in the studied group from 2011 to the end of follow-up in 2017, assuming the incidence of the uninsured population in the Municipality of Merida at comparable ages, was 0.4311 cases (out of 248 subjects). In the two-tailed contrast, the observed number of hospitalizations due to dengue (x = 0, 95% CI: 0.000-3.689) was not significantly different from the expected value of 0.4311 (p = 1.00).

DISCUSSION

The aim of this study was to generate descriptive long-term safety data for CYD-TDV thus helping to refine the safety information on this vaccine in view of reports of a higher incidence of hospitalizations due to dengue in <5-year-old vaccinated subjects participating in the efficacy study CYD14.[8,11,12] This surveillance study was performed following the recommendations of a study site's EC to capture all cases of clinical (febrile) dengue in subjects who participated in the previous study, CYD33, at the Merida study site. A retrospective/passive surveillance enhanced with an active/prospective surveillance were important tools to detect the presence of dengue cases in this population. Notably, during the review of the official platforms from the Ministry of Health, no confirmed dengue cases were reported in the study participants at this site since 2010 until the completion of this trial at the end of 2017.

According to the WHO position, countries should consider introducing the dengue vaccine CYD-TDV in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease;[2] in this case, the evaluated subjects came from a high endemic area in Mexico, between the 10 states with the highest dengue rates. Also, according

to the WHO, for defining the target population for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the over 9 years of age group.

On April 19, 2018, the Strategic Advisory Group of Experts (SAGE) on Immunization made a recommendation for the Dengvaxia® vaccine against dengue to the WHO and confirmed the value that Dengvaxia® has for public health and its importance in reducing outbreaks of dengue in endemic populations.[13]

The results of this trial support the safety of the vaccine in an age group in which the vaccine is not indicated due to safety and efficacy considerations.[12] Hospitalizations due to dengue are rare events with a frequency that shows wide variances across time; thus, it is possible that the lack of observed cases in this case is due to chance. However, it is important to make visible the cumulative safety experience with this vaccine even when the sample size does not allow us to make definitive conclusions. In this case, what we can say is that these subjects have not experienced dengue cases, of any severity, that might be attributable to the vaccine.

Ethical approval and consent to participate. Epidemiological surveillance longitudinal retrospective-prospective study, at a clinical site in Merida, Yucatan, Mexico. This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice as well as with all local and/or national regulations and directives. In addition, the study protocol was approved by the study site's Institutional Review Board and the independent Ethics Committee.

Consent for publication. Parents or legal guardians of the subjects signed an informed consent form before the participation in the study.

REFERENCES

1. Simmons CP, Farrar JJ, Nguyen VV, Wills B. Dengue. N Engl J Med. 2012; 366: 1423-1432.
2. World Health Organization. Dengue control. Epidemiology, Geneva, Switzerland. [Accessed July 31, 2017] Available at: http://www.who.int/denguecontrol/epidemiology/en/.
3. World Health Organization. Global strategy for dengue prevention and control, 2012-2020. Geneva: Publications of the World Health Organization; 2012. Available at: http://apps.who.int/iris/bitstream/10665/75303/1/9789241504034_eng.pdf?ua=1. Accessed May 25, 2014.
4. La Ruche G, Souarès Y, Armengaud A, Peloux-Petiot F, Delaunay P, Desprès P et al. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill. 2010; 15 (39): 19676.
5. Melo FIR, Morales JJR, De Los Santos AHM, Rivas E, Vigne C, Noriega F. Immunogenicity and safety of a booster injection of DTap-IPV//Hib (Pentaxim) administered concomitantly with tetravalent dengue vaccine in healthy toddlers 15-18 months of age in Mexico: a randomized trial. Pediatr Infect Dis J. 2017; 36 (6): 602-608.
6. Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, Chua MN et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014; 384 (9951): 1358-1365.
7. Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015; 372: 113-123.
8. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med. 2015; 373 (13): 1195-1206.
9. Secretaría de Salud. Panorama epidemiológico de dengue, 2017, México. 2017. [Accessed 1 Jan 2018] Available at: https://www.gob.mx/cms/uploads/attachment/file/285237/Pano_dengue_sem_52_201 7.pdf.
10. Secretaría de Salud. Dirección General de Información en Salud. Cubos Dinámicos Egresos Hospitalarios. SAEH 2017. [Accessed 18 Sept 2017] Available at: http://www.dgis.salud.gob.mx/contenidos/basesdedatos/bdc_egresoshosp_gobmx.html
11. Aguiar M, Stollenwerk N, Halstead SB. The risks behind Dengvaxia recommendation. Lancet Infect Dis. 2016; 16: 882-883.
12. Pang T. SAGE committee advice on dengue vaccine. Lancet Infect Dis. 2016; 16: 880-882.
13. World Health Organization. Revised SAGE recommendation on use of dengue vaccine, Geneva. Geneva: WHO; 2018. [Accessed 5 June 2018] Available at: http://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/:

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