Dengue Vaccine

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Biography

- Director of the National Drug Information Center (CIMED) at the Pharmaceutical Research Institute of the Pharmacy Faculty at the University of Costa Rica
- Professor of the Pharmaceutical Care and Clinical Pharmacy Department at the Pharmacy Faculty at the University of Costa Rica

Goals

- Recognize the **role of the pharmacist as part of the multidisciplinary health team** in the detection, prevention and care of dengue.
- Apply technical and scientific criteria in the **provision of pharmaceutical care services** for the treatment and prevention of dengue.

Contents

1. General aspects of the disease, its approach and treatment.
2. Hygienic measures and general prevention.
3. Dengue Vaccine
   - Vaccination schedule
   - Route of administration.
   - Conservation and storage.
   - Special population use.
   - Studies of efficacy and safety.

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Dengue, General aspects

- **Febrile illness** caused by the dengue virus
- Dengue is transmited by the bite of the ***Aedes aegypti*** **mosquito.**
- Symptoms occur after 4 to 7 days of being bitten by an infected mosquito:
  - Fever
  - Intense pain of muscles, joints, head and behind the eyes
  - Rash on trunk, arms and legs
  - Mild hemorrhagic manifestations such as bleeding gums and nose
  - Some cases may be asymptomatic
  - With or without the presentation of warning symptoms *

Dengue virus

4 serotypes of virus:

- DENV-1
- DENV-2
- DENV-3
- DENV-4

Evidence of another serotype with selvatic transmission cycle:

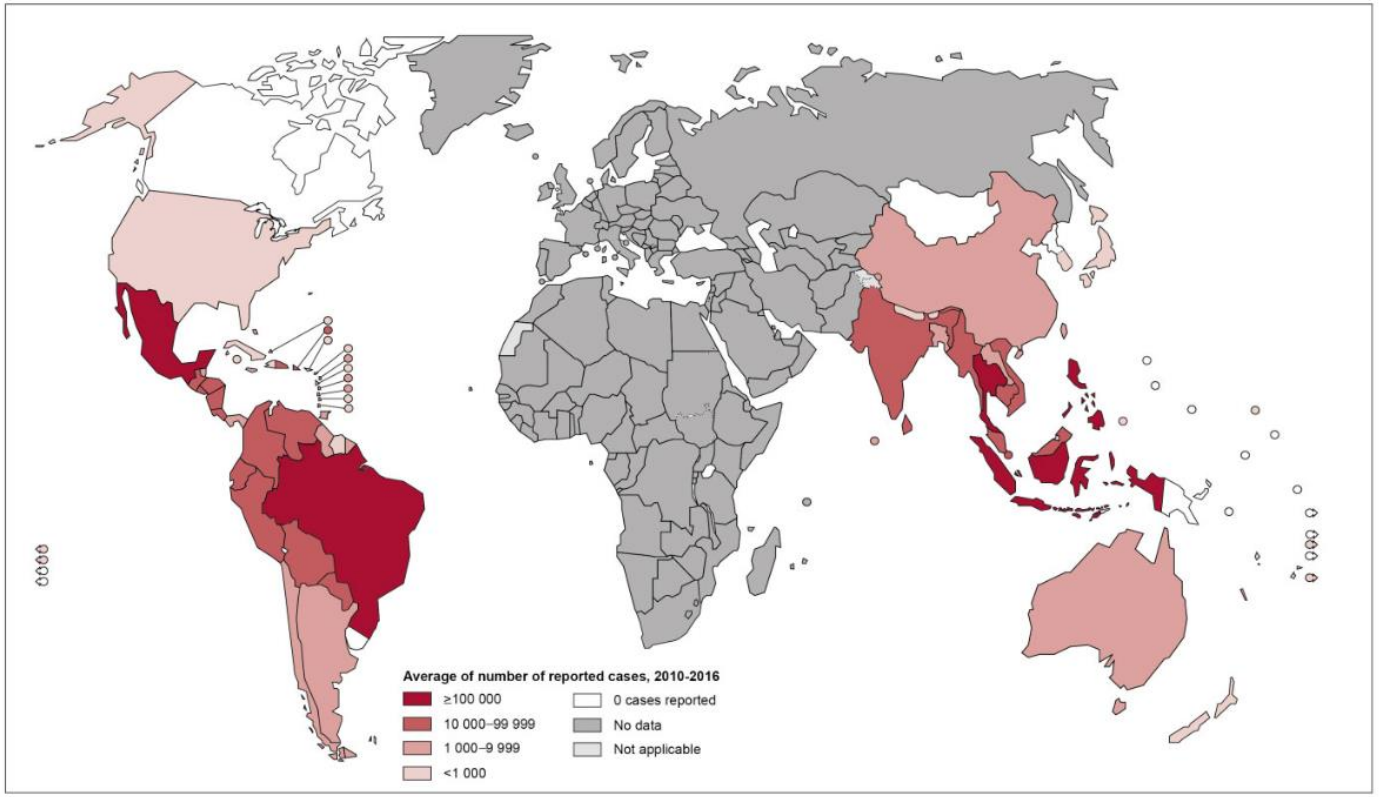
- DENV-5

Reyes J, Cardona-Arias A, López A et al. Seguridad e inmunogenicidad en ensayos clínicos de vacunas para Dengue. Revista Cubana de Investigaciones Biomédica 2016;35(1):78-90

Aedes aegypti mosquito

- The mosquito is known because it **has legs with white stripes**
- It has a **predilection for water retained** in empty cans, bottles, tires, drains, uncovered water tanks, pot dishes or other objects capable of retain water.
- Only the female mosquito sucks blood, usually itches in the exposed areas of the body in early morning hours **(from 7:00 a.m. to 10:00 a.m.)** or in the late afternoon (**from 4:00 p.m. to 7:00 p.m.)**.

Dengue distribution worldwide, 2016

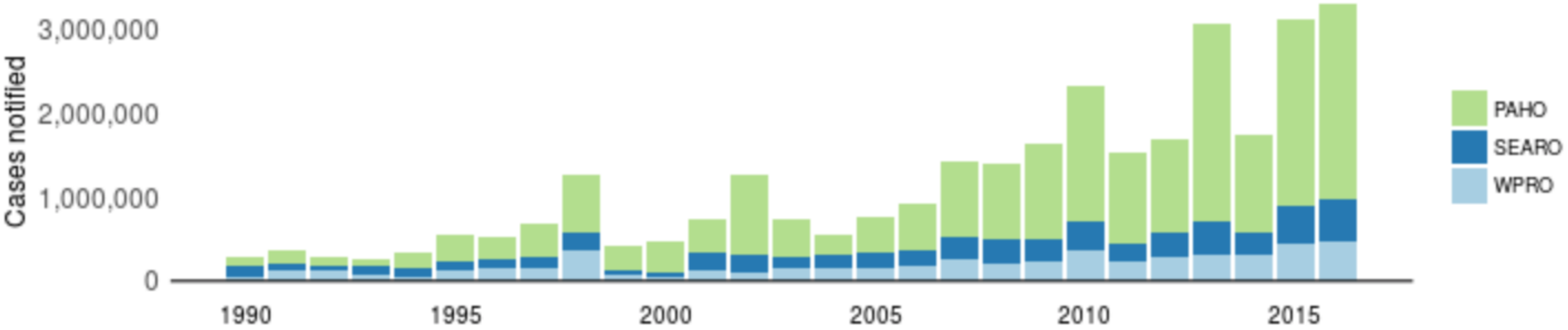


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2016. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

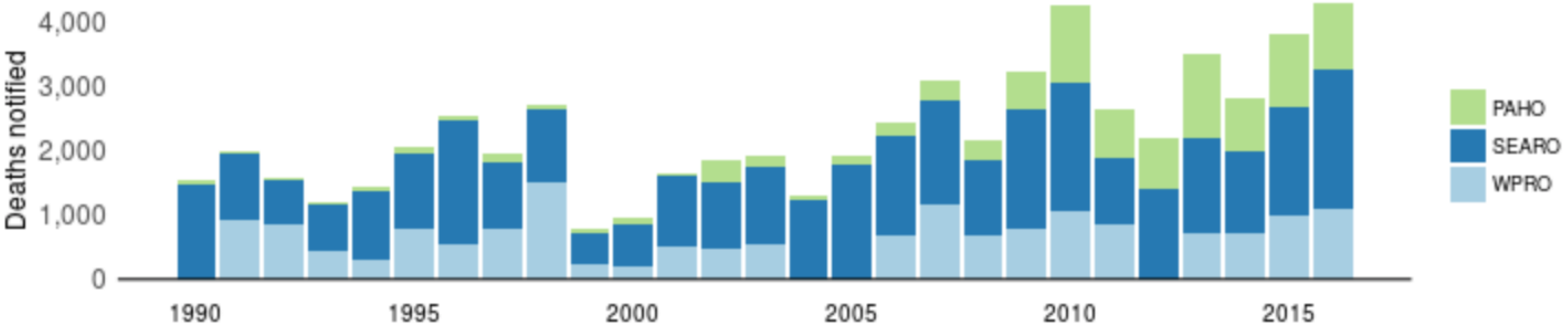
World Health Organization

Cases by Region



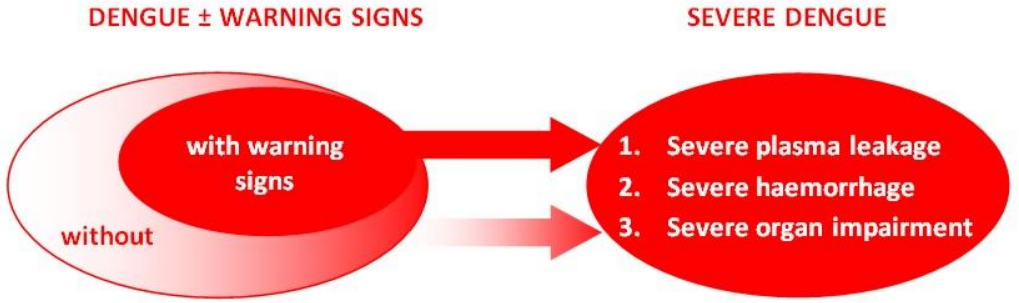
http://www.who.int/denguecontrol/epidemiology/dengue_data_application/en/

Mortality by Region



http://www.who.int/denguecontrol/epidemiology/dengue_data_application/en/

Classification of Dengue according to WHO



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

Live in / travel to dengue endemic area, fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue
(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT $\geq$ 1000
- CNC: Impaired consciousness
- Heart and other organs

Organización Mundial de la Salud. Dengue: Guías para el diagnóstico, tratamiento, prevención y control. 2009.

WHO Treatment by groups

- **Group A** - Patients who may be treated at **home**
- **Group B** - Patients who must be referred to **hospital management**
- **Group C** - Patients requiring **emergency treatment** and urgent referral when they have severe dengue

OMS/OPS. Dengue, Guías para la Atención de Enfermos en la Región de las Américas. 2015

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5.2.1 Group A: Patients who may be treated at home

These are patients who are able to tolerate adequate volumes of oral fluids, have passed urine at least once every six hours in the last 24 hours, and do not warning signs. They have no associated clinical disorders or social risk. Ambulatory patients should be evaluated on a daily basis and should have complete blood count at least every 48 hours, to observe the evolution of the disease 24 to 48 hours after defervescence without taking antipyretics. When fever subsides, check for clinical warning signs (Annex G). Advise patients and caregivers to return immediately to the nearest health care facility if any of the warning signs develops.

What should the patient do?

- bed rest, use of mosquito net during the febrile phase, especially during the day
- regular diet plus abundant fluids
- adults: abundant oral fluids, at least five glasses (250ml each) or more a day, for an average adult weighing 70 kg (119).
- children: abundant oral fluids (milk, natural fruit juice—caution with diabetics), oral rehydration solution (ORS), or recently prepared barley or rice water or coconut water. Plain water should be given with caution, since it may cause hydroelectrolytic imbalance.

- record the prescribed amount: liters in glasses (250 ml), ounces (8.45), or liters (0.25).

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

- paracetamol:
  - adults: 500 to 750 mg orally every four to six hours, maximum daily dose of 4 g
  - children: 10 mg/kg every six hours.
- tepid sponging of forehead
- recommendations: look for vector (*Aedes aegypti*) breeding sites in and around the home and eliminate them. This task should be monitored by an adult trained in vector control.

What should be avoided?

- Painkillers and anti-inflammatory medications, e.g., NSAIDs (aspirin, methimazole, diclofenac, others) steroids, antibiotics, and oral anticoagulants (16). If the patient is taking any of these medications, evaluate the advisability of continuing such treatment. Intramuscular or rectal administration of medications is contraindicated.

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

Recommend that if any of the following signs or symptoms appear, the patient should seek medical attention immediately:

- bleeding, petechiae, epistaxis, gingivorrhagia, hematemesis, melena, metrorrhagia, or polymenorrhea
- vomiting
- abdominal pain or tenderness
- drowsiness, mental confusion, fainting, seizures
- pale, cold or moist hands or feet
- respiratory distress

5.2.2 Group B1: Dengue without warning signs, but with associated disorder or social risk

Group criteria

- Patients in this group have associated diseases or conditions that may complicate dengue or its treatment such as pregnancy, age under 1 year or over 65 years, morbid obesity, hypertension, diabetes mellitus, asthma, renal failure, hemolytic diseases, chronic hepatopathy, peptic ulcer or gastritis of any etiology, use of anticoagulants, etc.
- Social risk: the patient lives alone or far from a health care facility, lacks transportation, or lives in extreme poverty.

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

- Manage associated conditions and treat dengue according to the protocol; also treat related compensated illnesses (e.g., hypertension, diabetes mellitus, asthma, renal damage, hemolytic diseases, chronic hepatopathy, peptic ulcer, or gastritis), according to the protocols of each country, in dengue units.
- Oral intake should be encouraged. If the patient is not drinking, drinks little, or is dehydrated, intravenous fluids should be started to rehydrate them or keep them hydrated (based on Holliday-Segar formula) with Ringer's lactate or 0.9% normal saline solution at a maintenance dose (2 to 3 ml/kg/hour). Oral treatment should be resumed as soon as possible.

Vital signs will need to be recorded and evaluated (pulse, heart rate, respiration rate, temperature, blood pressure) in addition to evaluating:

- laboratory, according to the type of associated disorder (hematocrit, platelets, leukocytes, glucose, electrolytes, others)
- thermic curve (to detect defervescence)
- volume of fluids ingested or infused, and losses
- urine output (volume, frequency, and time of last voiding)
- warning signs

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

5.2.3 Group B2: Dengue with warning signs

The main objective is to prevent shock.

Group criteria

This group includes patients who, close to defervescence and ideally at defervescence or in the following hours, present one or more of the following signs (beginning of the critical phase):

- intense and continuous abdominal pain or tenderness
- persistent vomiting
- fluid accumulation in serous cavities (pleural effusion, ascites, pericardial effusion) diagnosed clinically or by imaging
- mucosal bleeding
- hepatomegaly >2 cm
- lethargy, restlessness
- postural hypotension (lipothymia)
- progressively rising hematocrit

Action Plan

Response to dengue with warning signs

- Obtain a complete blood count (hematocrit, platelets and leukocytes) before hydrating the patient. The lack of a hematocrit should not delay initiation of hydration.
- Immediately administer crystalloid solution at 10 ml/kg of bodyweight in the first hour; preferably give balanced electrolyte solutions, such as Ringer's acetate or lactate or 0.9% normal saline solution.
- Strictly monitor vital signs, particularly blood pressure, pulse pressure, MAP, and heart rate.
- Re-evaluate the patient. If clinical improvement is observed and urine output is ≥1 ml/kg/h, the drip will be reduced to 5-7 ml/kg/h, and this dose will be maintained for the following 2 to 4 hours; continue tapering the drip at a rate of 3-5 ml/kg/h for 2 to 4 more hours. If improvement continues, reduce the dose to 2 to 4 ml/kg/h.
- Re-evaluate the patient's clinical and hemodynamic status and repeat hematocrit. Home care may be considered, as long as the patient has been evaluated and improvement is observed along with tolerance to oral intake for 24 hours. In cases where the patient faces some social risk or difficulty in access to health services, it is recommended that the patient remains in the hospital or a dengue unit. If vital signs deteriorate or hematocrit increases rapidly after three loads of 10 ml/kg/h, the case will be managed as if it were severe dengue with shock.

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

Improvement is indicated by:

- progressive disappearance of warning signs
- progressive remission of general symptoms
- stable vital signs
- normal or increased urine output
- reduction of hematocrit below baseline value in a stable patient
- good tolerance to oral intake
- improved appetite

Follow-up or monitoring by health care workers (nurses/physicians)

Patients with warning signs should be monitored until the risk has passed (48 hours after defervescence). Maintain an appropriate fluid and electrolyte balance.

Evaluate the following parameters

- vital signs (pulse, heart rate, respiration rate, temperature, blood pressure) and peripheral perfusion every hour, until the patient is out of the critical phase (for the first four hours if evolution is satisfactory, then every four hours)
- urine output every hour (for the following four to six hours) and then every four hours

Clinical assessment is critical (vital signs and urine output) as indicated. The following laboratory tests contribute to patient evaluation and monitoring; however, they should never replace clinical monitoring of the patient:

- hematocrit (before and after fluid replacement, then every 12 to 24 hours)
- glucose (before fluid replacement, then every 12 to 24 hours as needed)
- other studies, depending on the organ affected and associated disease

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

5.2.4 Group C: Severe dengue

In all countries with dengue, medical practice and the most recent medical literature recognize that intravenous rehydration is the most effective treatment for preventing death from plasma leakage during severe dengue (120). There is also consensus that fluid replacement should be initiated as soon as possible in these cases (9, 121).

Results of a systematic analysis of studies on this topic, published between 1999 and 2009 were compatible and consistent with the recommendations of the World Health Organization (1) and the Pan American Health Organization (56) on care of patients with severe dengue with regard to the initiation of treatment with isotonic solutions (e.g., Ringer's lactate or normal saline solution) and using colloid solutions (e.g., dextran or starch) only as a supplement to crystalloid solutions, if necessary (25, 121-130). It is also important to not over-hydrate patients (120).

Studies in this field only refer to the pediatric population and all except one were carried out in Asia. Nor was intravenous fluid therapy studied in patients with co-existing conditions, such as obesity, asthma, diabetes, heart disease, nephropathies, or others, in which the regimen might require different algorithms. More cases of adults with and without co-existing conditions need to be studied, particularly in the countries of Latin America and the Caribbean. The adverse effects of different types of solutions have also not been sufficiently studied, particularly in adults (120).

Appropriate training of medical and paramedic staff in fluid administration is possibly the key to obtaining good results. There is evidence that suggests that reorganization of services to *guarantee immediate rehydration* of patients who need it during epidemic dengue outbreaks can be decisive (131, 132).

WHO. Dengue: Guiidelines for paatient care in the Rgion of the Americas. 2 ed. 2016

With respect to the use of corticoids in the treatment of dengue shock syndrome, a meta-analysis was published in 2014 on eight clinical trials also done in pediatric populations (18, 133-139). It did not find a reduction in mortality (relative risk [RR] = 0.68; 95% confidence interval [CI] = 0.42–1.11), need for transfusions (RR = 1.08; 95% CI = 0.52–2.24 risk of pulmonary hemorrhage (RR = 0.97; 95% CI = 0.06–14.82), or risk of seizures (RR 6.79; CI = 95% 0.36–126.24) in patients treated with corticoids compared to those who received placebo. However, the intervention group had an average of 1.1 more inpatient days (12).

To date, no antiviral medication of demonstrated efficacy exists against dengue, although several research projects are currently underway that address this issue (16, 140).

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General prevention measures

- Clean batteries, canoes, cannons, buckets, animal troughs or **other useful containers that can accumulate water.**
- **Cover all containers** where water is stored.
- Fill hollows of trees, vases of cemeteries, **blocks, walls, among others.**
- Eliminate in the garbage **any waste material capable of accumulate water.**
- **Fumigate** dark places in your home such as cabinets and closets.
- **Get organize with other neighbors** to reduce the possibility of mosquito reproduction in your neighborhood

General prevention measures

- **Recycle** all plastic, aluminum or glass materials that can accumulate water.
- **Reuse** in a creative and friendly way with the environment, all plastic containers, aluminum, glass and tires.
- **Bury pipes**, coconuts, shells or any other organic waste.
- **Put under the roof** any object that accumulates water and can not get rid of it.
- Protect yourself if you live or visit a place where there is active transmission of dengue, **use repellent**, especially at dawn and evening and in the most exposed areas of your body.

Caja Costarricense del Seguro Social. Con estos 13 mandamientos luchamos contra el dengue.

General prevention measures

- **Use of repellents**
- The most effective repellents are those that contain N, N-diethylmethaltoluamide (DEET).
- Content of DEET 15%-25%: use not indicated in children under 12 years.
- Commercial product with DEET 5% or 7.5%. Do not use in children under 6 months.
- **CDC recommends DEET in concentrations of 30-50%** that gives protection for several hours.
- Under 2 years old: **mosquito net**

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Dengue Vaccine

Vaccine authorized in several countries: Dengvaxia (CYD-TDV): **tetravalent vaccine with attenuated live virus (recombinant).**

The vaccine has been evaluated in 2 parallel phase 3 studies.

- **CYD14 in Asia**: Indonesia, Malaysia, Philippines, Thailand and Vietnam.
- **CYD 15 in Latin America**: Brazil, Colombia, Honduras, Mexico and Puerto Rico.
- More than 35,000 participants.
- Ages 2-16 years: 2-14 years in CYD14 and 9-16 years in CYD15.
- Vaccination Schedule: 3 doses at 0,6 and 12 months.

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengue Vaccine

	CYD14	CYD15
Trial size	10,275	20,869
Randomization CYD:Placebo	2:1	2:1
Ages included	2-14 years	9-16 years
Countries participating	Indonesia, Malaysia, Philippines, Thailand, and Vietnam	Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)
Primary endpoint (per protocol)	Vaccine efficacy after 3 vaccinations at 0, 6, and 12 months (VE measured from 28 days after the 3rd dose) in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes up to 13 months pose-dose 3.	Vaccine efficacy after 3 vaccinations at 0, 6, and 12 months (VE measured from 28 days after the 3rd dose) in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes up to 13 months pose-dose 3.
Study start date	June 2011	June 2011
End of Active Phase for primary endpoint	December 2013	April 2014
Estimated completion date	November 2017	April 2018

Background paper noc dengue vaccines.
http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf?ua=1

Dengue Vaccine

Vaccination schedule

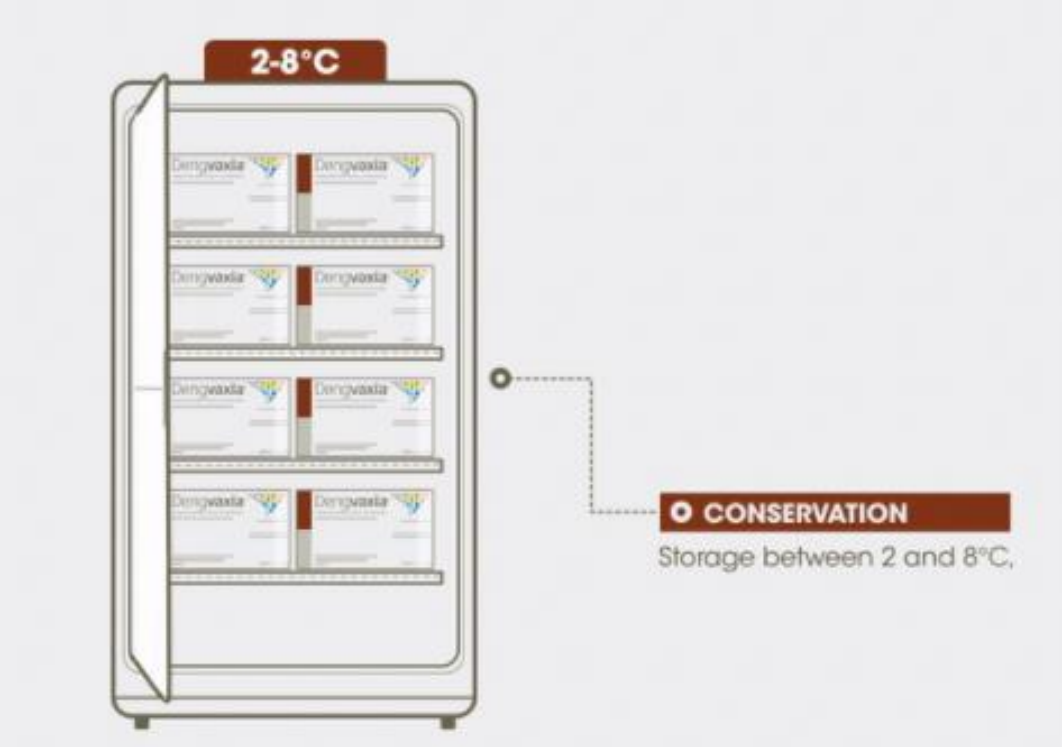
- **3 doses of 0.5ml** administered at 6-month intervals (0,6,12 months).
- If the administration of a **dose is delayed**, the **6-month interval should be maintained**, but should NOT be restarted.
- Subcutaneous administration

First licence was for:

- Prevent dengue by any of the 4 serotypes.
- People living in endemic areas.
- 9-45 years or 9-60 years (according to licence).
- **Not used in children under 9 years.**

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengvaxia®

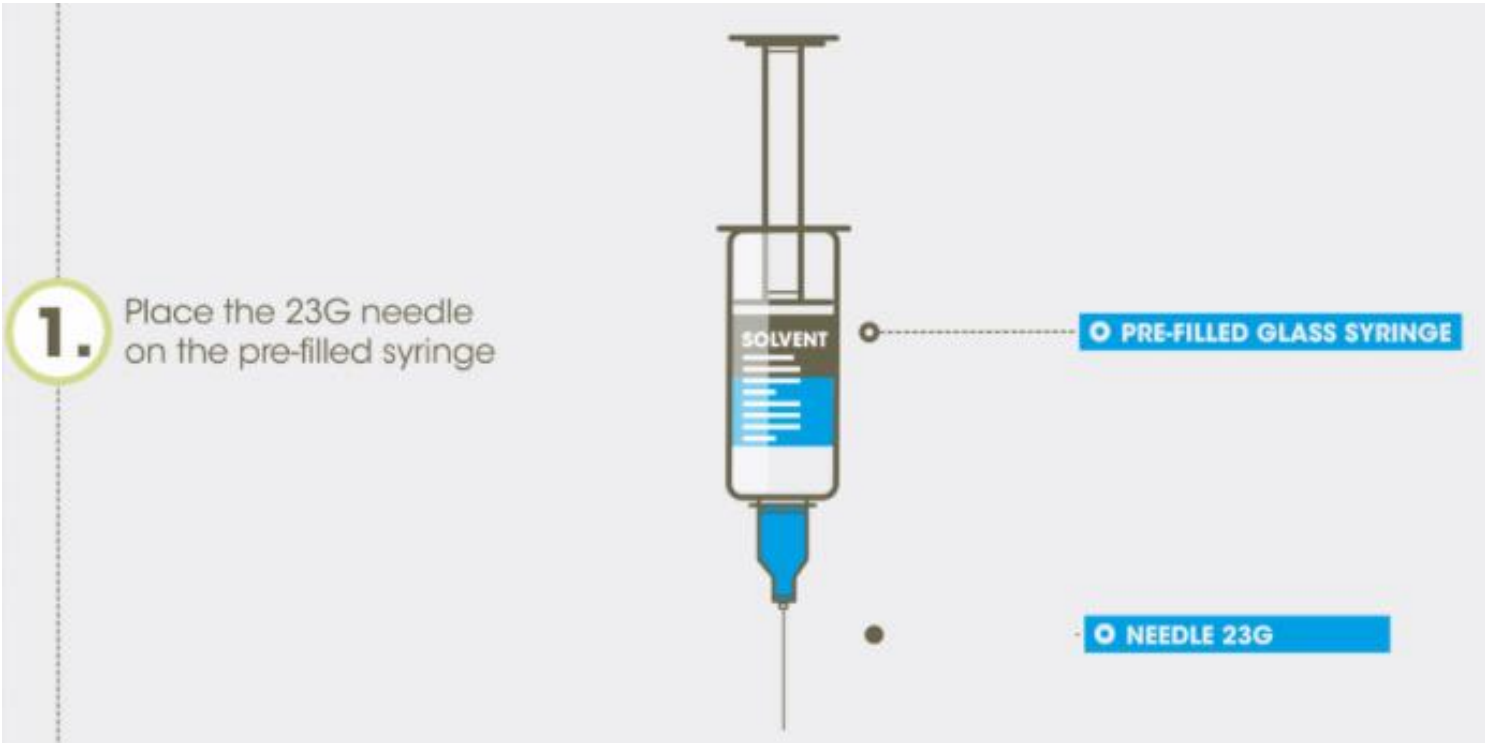


http://www.bupla.com/motion-design/dengvxia

Dengvaxia®

http://www.bupla.com/motion-design/dengvxia

Dengvaxia®



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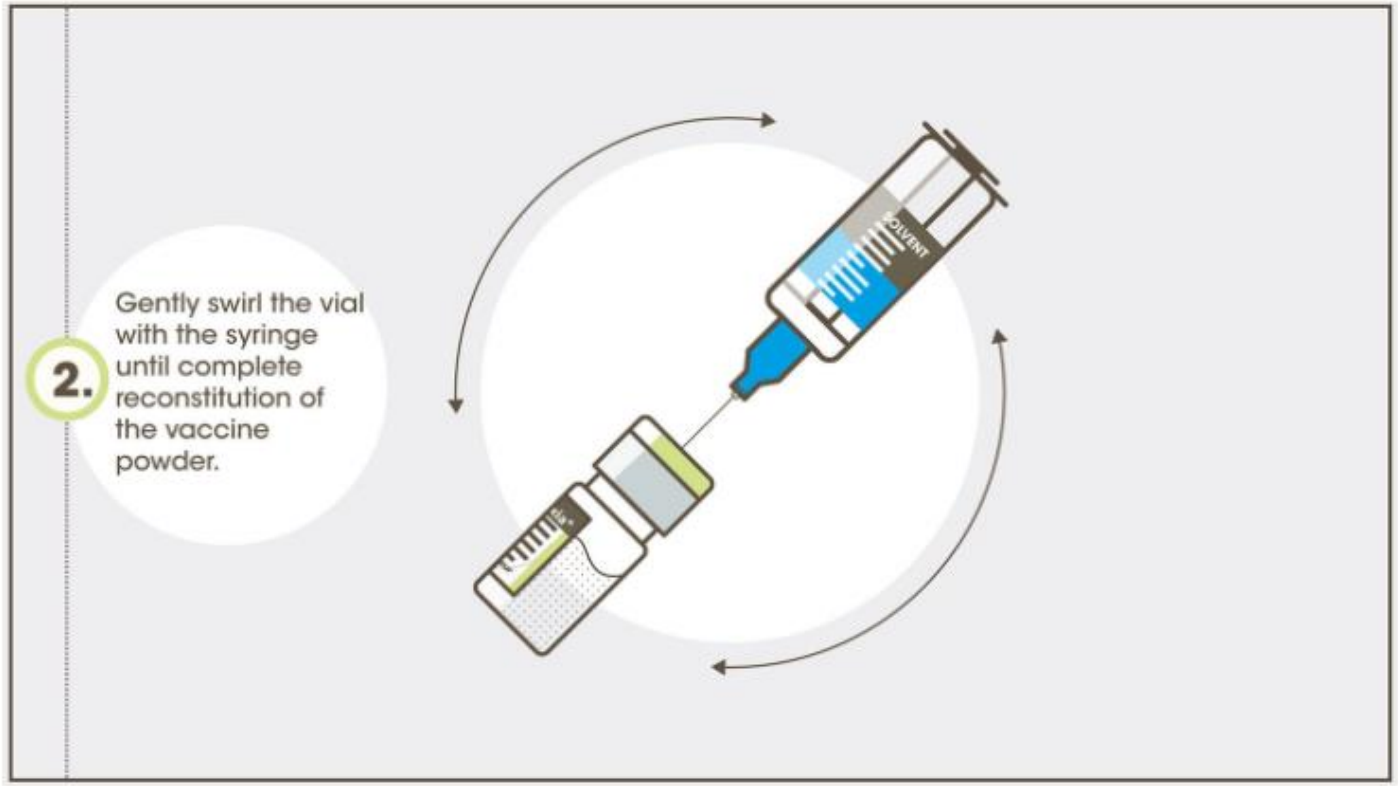

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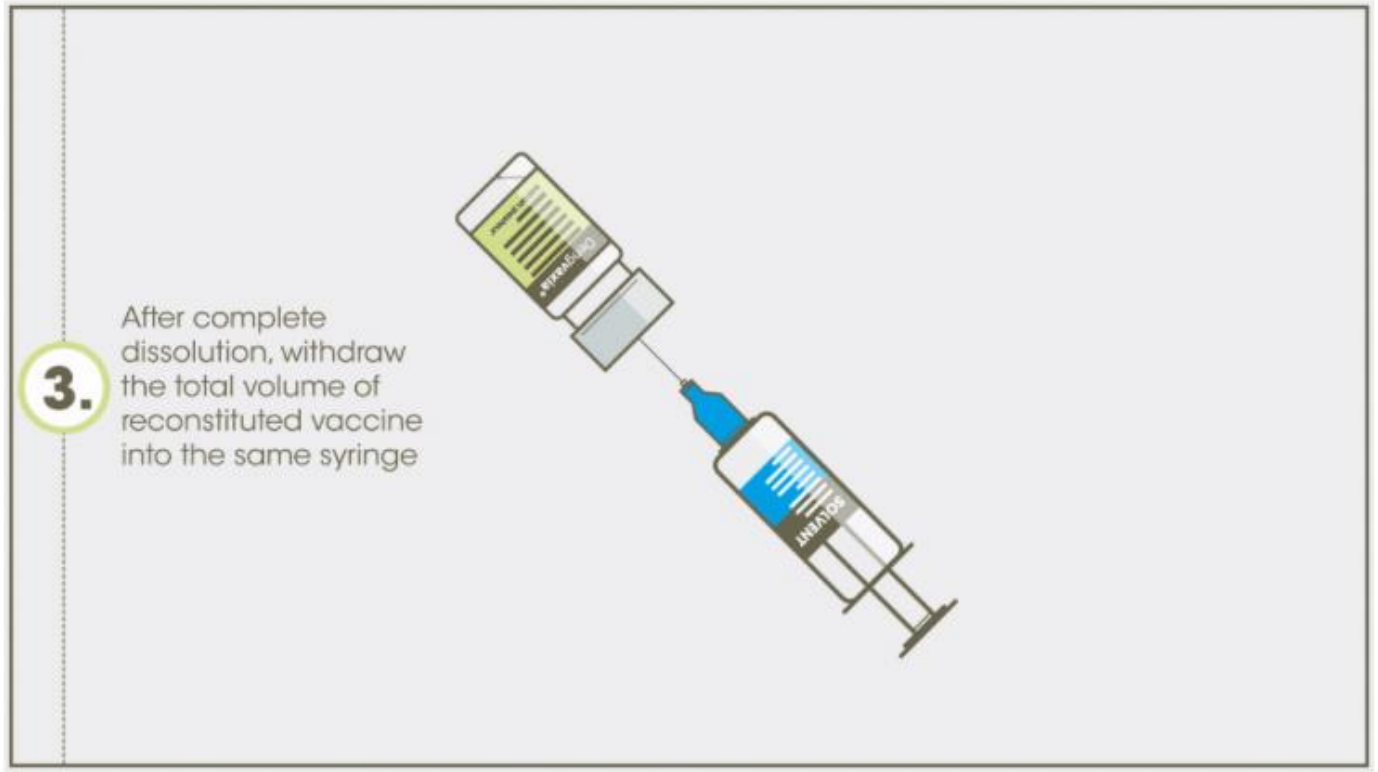


http://www.bupla.com/motion-design/dengvxia

Dengue Vaccine

Contraindications

- People with a history of severe **allergic reactions** to the vaccine.
- People with **immunodeficiency**.
- People with **symptomatic or asymptomatic HIV** with evidence of impaired immune function.
- During **pregnancy and lactation.**

Vaccination should be postponed in people with acute illness or moderate-severe fever.

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengue Vaccine

Efficacy

- CYD 14: **56.5%** (95% CI 43.8%-66.4%)
- CYD 15: **60.8%** (95% CI 52.0%-68.0%) measurement made 12 months after the third dose.

Taking the data from both trials:

- People older than 9 years: efficacy of 65.6% .
- Children under 9 years: efficacy 44%.
- **Efficacy from lowest to highest**: DENV-2, DENV-1, DENV-3 and DENV-4.

_ WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1
_http://www.who.int/immunization/research/development/dengue_q_and_a/es/

Dengue Vaccine

Efficacy

- **Variations by country:**
  - Mexico 31.3%
  - Malaysia 79%
  - Depending on types of circulating virus and seropositivity at the beginning of the study.

- Vaccine efficacy was **higher in individuals who were seropositive** at baseline vs those who were not:
  - With pooled vaccine efficacies of 78.2% (95% CI 65.4–86.3) and 38.1% (95% CI -3.4–62.9), respectively.

- Taking the data from both trials, the efficacy **preventing hospitalization for dengue:**
  - 72.7% (95% CI 62.3%–80.3%) among participants of all ages.
  - 80.8% (95% CI 70.1%–87.7%) among participant ≥ 9 years old.

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengue Vaccine

Efficacy

- During the active phase of the disease, both trials showed greater efficacy **preventing dengue and hospitalization**
- CYD14:
  - 56.5% - dengue
  - 67.2% - hospitalization
- CYD15
  - 60.8% - dengue
  - 80.3% - hospitalization

Labasi-Sammartino C, Sauer J, Fanous J et al. Dengavia: The world`s firt dengue vaccine. The Prognosis. 2017; 6(1): 30-42.

Dengue Vaccine

Efficacy

- The efficacy of the vaccine was **59.2% for the year following the primary series.**
- At **25 months**, the efficacy of the vaccine is 65.6% (95% CI 60.7% -69.9%)
- Active surveillance is currently being initiated, so that the efficacy of the **vaccine 5-6 years after fist dose, can be evaluated.**

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1
Background paper noc dengue vaccines.
http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf?ua=1

Dengue Vaccine

Safety

- Local and systemic adverse drug reactions (ADRs) are similar to the ADRs of other attenuated live virus vaccines.
- **Most frequent ADRs**
  - Headache (more than 50%)
  - Malaise (more than 40%)
  - Myalgia (more than 40%)
  - Fever in 5% and 16% in people aged 18-60 years and 9-17 years respectively.
- **ADRs in the application site:**
  - 49.6% vs. 385% with placebo.
  - Pain in 45.2% and 49.2% in people aged 18-60 years and 9-17 years respectively

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengvaxia® Adverse Drug Reactions in VigiAccess

dengvaxia contains the active ingredient(s): **Dengue fever vaccine**.
Result is presented for the active ingredient(s).
Total number of records retrieved: **1864**.

http://www.vigiaccess.org al 04 de marzo del 2018

Dengvaxia® Adverse Drug Reactions in VigiAccess

ADR reports per year

Year	Count	Percentage
2018	911	49
2017	129	7
2016	824	44

http://www.vigiaccess.org al 04 de marzo del 2018

Dengvaxia® Adverse Drug Reactions in VigiAccess

Geographical distribution

Continent	Count	Percentage
Americas	769	41
Asia	1095	59

http://www.vigiaccess.org al 04 de marzo del 2018

Dengvaxia® Adverse Drug Reactions in VigiAccess

Patient sex distribution

Sex	Count	Percentage
Female	1095	59
Male	745	40
Unknown	24	1

http://www.vigiaccess.org al 04 de marzo del 2018

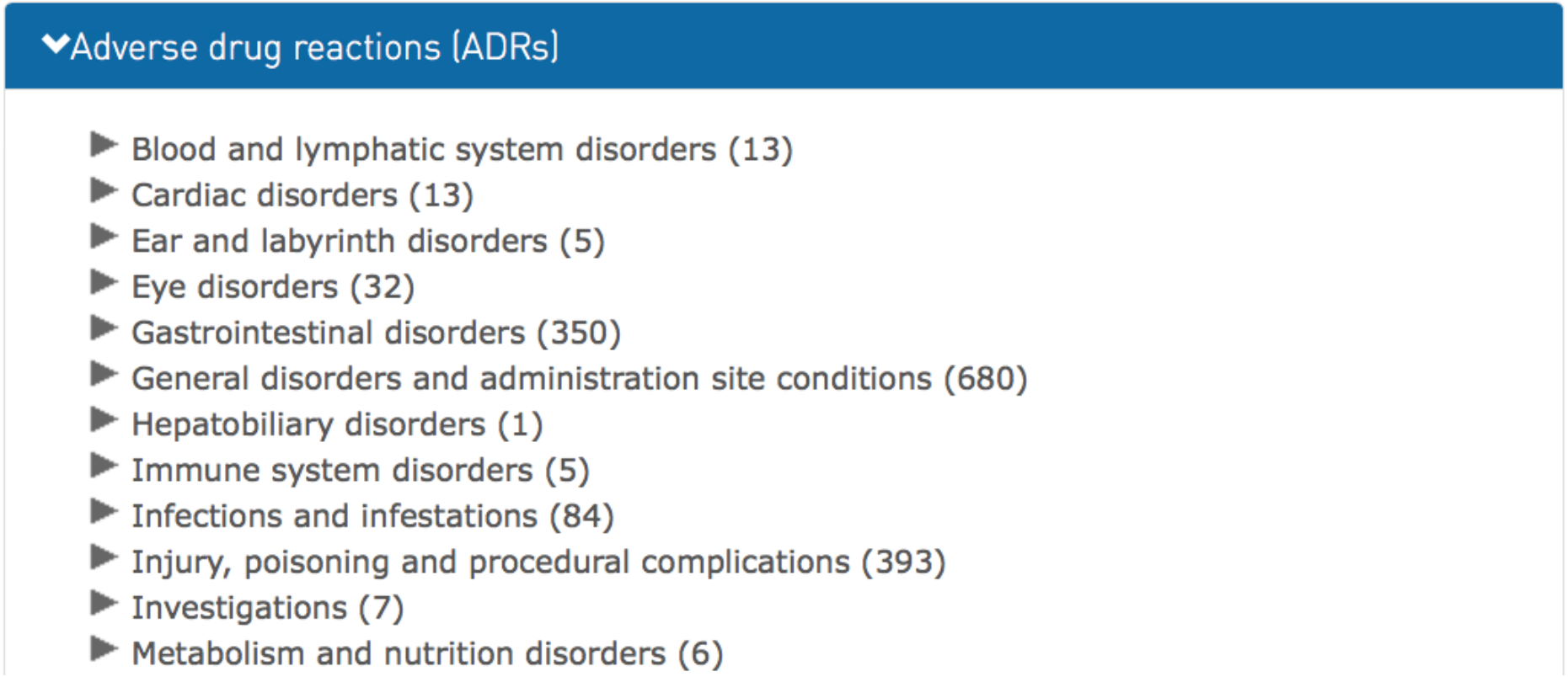
Dengvaxia® Adverse Drug Reactions in VigiAccess

Age group distribution

Age group	Count	Percentage
0 - 27 days	5	0
28 days to 23 months	6	0
2 - 11 years	973	52
12 - 17 years	225	12
18 - 44 years	617	33
45 - 64 years	5	0
65 - 74 years	1	0
Unknown	32	2

http://www.vigiaccess.org al 04 de marzo del 2018

Dengvaxia® Adverse Drug Reactions in VigiAccess



http://www.vigiaccess.org al 04 de marzo del 2018

Dengvaxia® Adverse Drug Reactions in VigiAccess

- Musculoskeletal and connective tissue disorders (182)
- Neoplasms benign, malignant and unspecified (incl cysts and polyps) (2)
- Nervous system disorders (806)
- Pregnancy, puerperium and perinatal conditions (12)
- Psychiatric disorders (4)
- Renal and urinary disorders (4)
- Reproductive system and breast disorders (1)
- Respiratory, thoracic and mediastinal disorders (165)
- Skin and subcutaneous tissue disorders (219)
- Social circumstances (1)
- Vascular disorders (63)

http://www.vigiaccess.org al 04 de marzo del 2018

Dengue Vaccine

Safety

- The vaccine may be ineffective or **could theoretically increase the risk of severe dengue in seronegative patients after the first** application**, in children under 9 years.**

- No similar data was found for children over 9 years.

- There was an **increase in the risk of being** hospitalized for dengue in children 2-5 years after 3 years of the first dose.

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengue Vaccine

Interactions with other vaccines

No changes in safety or efficacy have been found when administering the vaccine in children at the same time that:

- Yellow fever vaccine
- Diphtheria, tetanus and pertussis vaccine
- Measles, rubella and mumps vaccines
- Vaccine against *Haemophilus influenzae type b*
- In adults, a lower response to DENG-4 has been found in people who have been co-administered with the yellow fever vaccine.

Another source indicates that it should not be administered with other vaccines, due to lack of information

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1
Background paper noc dengue vaccines.
http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf?ua=1

Dengue Vaccine

Use in special populations

- **During pregnancy and lactation:** Lack of information.
- If during the vaccination scheme, the woman becomes pregnant, the remaining doses will be applied once the lactation is concluded.
- **Immunocompromised**: use contraindicated.
- **Travelers**: the use in this case is not formally established, but in people who have previously dengue and who traveled to the area with high transmission, vaccination could be beneficial.
- **Healthcare professionals**: there are no specific recommendations.

Background paper noc dengue vaccines.
http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf?ua=1

Dengue Vaccine

WHO Position 2016

- Countries should consider the introduction of the vaccine, in geographical areas where **epidemiological data** justify it.
- In people with a **previous dengue infection**, with any serotype, should reach a 70% vaccination of the target population.
- Vaccination in conjunction with other **vector control strategies.**

WHO. Weekly epidemiological record. No 30, 2016, 91, 349–364 .
http://www.who.int/wer/2016/wer9130.pdf?ua=1

Dengue Vaccine

WHO Position November 30th, 2017

http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia/en/#

Dengue Vaccine

WHO Position November 30th, 2017

What are the preliminary results from the recent analysis of vaccine safety in persons seronegative to dengue prior to vaccination?

While vaccinated trial participants overall had a reduced risk of virologically-confirmed severe dengue and hospitalizations due to dengue, the subset of trial participants who had not been exposed to dengue virus infection prior to vaccination had a higher risk of more severe dengue and hospitalizations due to dengue compared to unvaccinated participants, regardless of age. This increased risk was observed after an initial protective period and persisted over the observation period of up to 66 months post primary vaccination.

http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia/en/#

Dengue Vaccine

WHO Position November 30th, 2017

What is WHO's interim interpretation of the data?

WHO's interim interpretation of data is that:

- The vaccine significantly protects against hospitalized and severe dengue in individuals seropositive for dengue at time of first vaccination in all age groups studied;
- The risk of hospitalized and severe dengue is significantly increased among vaccinated individuals who were seronegative for dengue at the time of first vaccination in all age groups studied;

WHO will conduct a full review of the data through the Global Advisory Committee on Vaccine Safety and SAGE, for revised guidance of the use of Dengvaxia®.

Pending the full review of the data, *as a precautionary and interim measure*, WHO recommends that Dengvaxia® is only administered to individuals that are known to have been infected with dengue prior to vaccination.

http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia/en/#

Dengue Vaccine

WHO Pharmaceutical Newsletter - 2018

Dengvaxia®

Risk in individuals with no prior experience of dengue infection

Singapore. The Health Sciences Authority (HSA) has strengthened warnings and recommendations in the prescribing information for Dengvaxia® about the increased risk of developing clinically severe dengue in individuals not previously infected by dengue.

WHO Pharmaceutical Newsletter. 2018; (1): 5.
http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No1-2018.pdf?ua=1

The package insert provides advice on assessing individuals for a history of previous dengue infection before vaccination, and states that vaccination is not recommended for individuals who have not been previously infected with dengue.

Dengvaxia® is used for the prevention of dengue infection caused by dengue virus (serotypes 1, 2, 3 and 4) in individuals aged between 12 and 45 years. Currently in Singapore, dengue vaccination is not part of the national immunisation programme.

Results from clinical and long-term safety studies by the manufacturer confirmed that there is a postulated risk of a higher incidence of severe dengue following vaccination in individuals who have not been previously infected by dengue.

All health-care professionals have been issued advice on these findings and were informed of the recommendation not to vaccinate individuals who have no history of a previous dengue infection. The HSA will monitor the vaccine closely to ensure continued safety and efficacy.

Reference:

HSA Updates, HSA,
1 and 8 December 2017
(*http://www.hsa.gov.sg/*)

Dengue Vaccine

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journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America

J.L. Arredondo-García [1], S.R. Hadinegoro [2], H. Reynales [3], M.N. Chua [4], D.M. Rivera Medina [5], T. Chotpitayasunondh [6], N.H. Tran [7], C.C. Deseda [8], D.N. Wirawan [9], M. Cortés Supelano [10], C. Frago [11], E. Langevin [12], D. Coronel [13], T. Laot [14], A.P. Perroud [15], L. Sanchez [14], M. Bonaparte [16], K. Limkittikul [17], D. Chansinghakul [18], S. Gailhardou [19], F. Noriega [16], T.A. Wartel [12], A. Bouckenooghe [11], B. Zambrano [20,*], for the CYD-TDV Dengue Vaccine Study Group[†]

Dengue Vaccine

Results: Overall, from Year 1 to Year 4, 233 and 228 participants had at least one episode of hospitalized VCD in the vaccinated ($n = 22\,603$) and placebo ($n = 11\,301$) groups, respectively (RR = 0.511, 95% CI 0.42–0.62). Among these, 48 and 47 cases, respectively, were classified as clinically severe. In children aged ≥9 years, 88 and 136 participants had at least one episode of hospitalized VCD in the vaccinated ($n = 17\,629$) and placebo ($n = 8821$) groups, respectively (RR = 0.324; 95% CI 0.24–0.43). In vaccinated participants aged <9 years, particularly in those aged 2–5 years, there were more hospitalized VCD cases compared with the control participants in Year 3 but not in Year 4. The overall RR in those aged <9 years for Year 1 to Year 4 was 0.786 (95% CI 0.60–1.03), with a higher protective effect in the 6–8 year olds than in the 2–5 year olds.

Conclusions: The overall benefit-risk remained positive in those aged ≥9 years up to year 4, although the protective effect was lower in years 3 and 4 than in years 1 and 2. **J.L. Arredondo-García, Clin Microbiol Infect 2018;▪:1**

Arredondo-García JL, et al., Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America, Clinical Microbiology and Infection (2018), https://doi.org/10.1016/j.cmi.2018.01.018

Dengue Vaccine

- ***Countries where Dengvaxia is available:***
  - Mexico
  - Philippines*
  - Brazil*
  - Costa Rica
  - El Salvador
  - Paraguay
  - Guatemala
  - Peru
  - Indonesia
  - Thailand
  - Singapore
- ***Research and development***
  - 6 vaccines

Labasi-Sammartino C, Sauer J, Fanous J et al. Dengavia: The world`s firt dengue vaccine. The Prognosis. 2017; 6(1): 30-42.
WHO. Weekly epidemiological record. No 3, 2018. 17-32 - http://apps.who.int/iris/bitstream/10665/259874/1/WER9303.pdf

Role of the pharmacist in the management of dengue as part of the health team

- ***Development of Pharmaceutical Care activities***
  - **Dispensation**
  - **Information on Medicines and Health Education**
    - Work in communities with the health team, local governments and community actors
  - **Health promotion and disease prevention - Vector control**
  - **Pharmacovigilance**
    - Report of events supposedly attributable to vaccination or immunization (ESAVIs)
    - Risk minimization plans
    - Monitoring in clinical trials
- ***Development of complete economic evaluations - Pharmacoeconomics***

Thanks

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Dengue Vaccine

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