Chris Nelson
Sanofi Pasteur

CYD-TDV – Dengvaxia® – clinical update

"Arboviruses: A Global Public Health Threat"
20-22 June 2018
Les Pensières Center for Global Health, Veyrier-du-Lac (France)

The Dengue Pandemic

1992

World Health Stat Q. 1992;45(2-3):292-8.

The XXth century dengue pandemic: need for surveillance and research.

Halstead SB[1].

Author information

Abstract

By the last decade of the XXth century Aedes aegypti and the 4 dengue viruses had spread to nearly all countries of the tropical world. Some 2 billion persons live in dengue-endemic areas with tens of millions infected annually. Dengue pandemics were also documented in the XVIIIth and XIXth centuries; they were contained by organized anti-Aedes aegypti campaigns and urban improvements. The XXth century dengue pandemic has brought with it the simultaneous circulation of multiple serotypes and in its aftermath, endemic dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). Nearly 3 million children have been hospitalized with this syndrome in the past 3 decades, mainly in South-East Asia. Recent outbreaks of DHF/DSS in the Pacific Islands, China, India, Sri Lanka, Cuba and Venezuela are indicators of the high intensity and rapid spread of dengue transmission. The magnitude of the XXth century dengue pandemic requires urgent improvements in early warning surveillance by WHO Member States and the development of the capacity to study underlying mechanisms of the disease. A key research question is why does DHF/DSS not occur with all second dengue infections? Two answers have been suggested: (1) a human resistance gene. Data from the 1981 DHF/DSS epidemic in Cuba have demonstrated the existence in blacks of a resistance gene. The effect of such a gene in reducing disease susceptibility of American and African blacks requires more study. (2) The existence of dengue "biotypes". Some, but not all biotypes may cause DHF/DSS during a second dengue infection.(ABSTRACT TRUNCATED AT 250 WORDS).

1998

CLINICAL MICROBIOLOGY REVIEWS, July 1998, p. 480–496 Vol. 11, No. 3
0893-8512/98/$04.00+0

Dengue and Dengue Hemorrhagic Fever

DUANE J. GUBLER*

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INTRODUCTION

Although first reports of major epidemics of an illness thought to possibly be dengue occurred on three continents (Asia, Africa, and North America) in 1779 and 1780 (73, 75, 109, 128), reports of illnesses clinically compatible with dengue fever occurred even earlier. The earliest record found to date is in a Chinese encyclopedia of disease symptoms and remedies, first published during the Chin Dynasty (265 to 420 A.D.) and formally edited in 610 A.D. (Tang Dynasty) and again in 992 A.D. (Northern Sung Dynasty) (108). The disease was called water poison by the Chinese and was thought to be somehow connected with flying insects associated with water. Outbreaks of illness in the French West Indies in 1635 and in Panama in 1699 could also have been dengue (73, 103). Thus, dengue or a very similar illness had a wide geographic distribution before the 18th century, when the first known pandemic of dengue-like illness began. It is uncertain whether the epidemics in Batavia (Jakarta), Indonesia, and Cairo, Egypt, in 1779 were dengue, but it is quite likely that the Philadelphia epidemic of 1780 was dengue (19). A more detailed discussion of the history of dengue viruses has recently been published (41).

EMERGENCE OF DENGUE AS A GLOBAL PUBLIC HEALTH PROBLEM

The disease pattern associated with dengue-like illness from 1780 to 1940 was characterized by relatively infrequent but often large epidemics. However, it is likely that dengue viruses became endemic in many tropical urban centers during this time because during interepidemic periods, when there was no apparent disease transmission, nonimmune visitors invariably contracted a dengue-like illness within months of their arrival.

The ecologic disruption in the Southeast Asia and Pacific theaters during and following World War II created ideal con-

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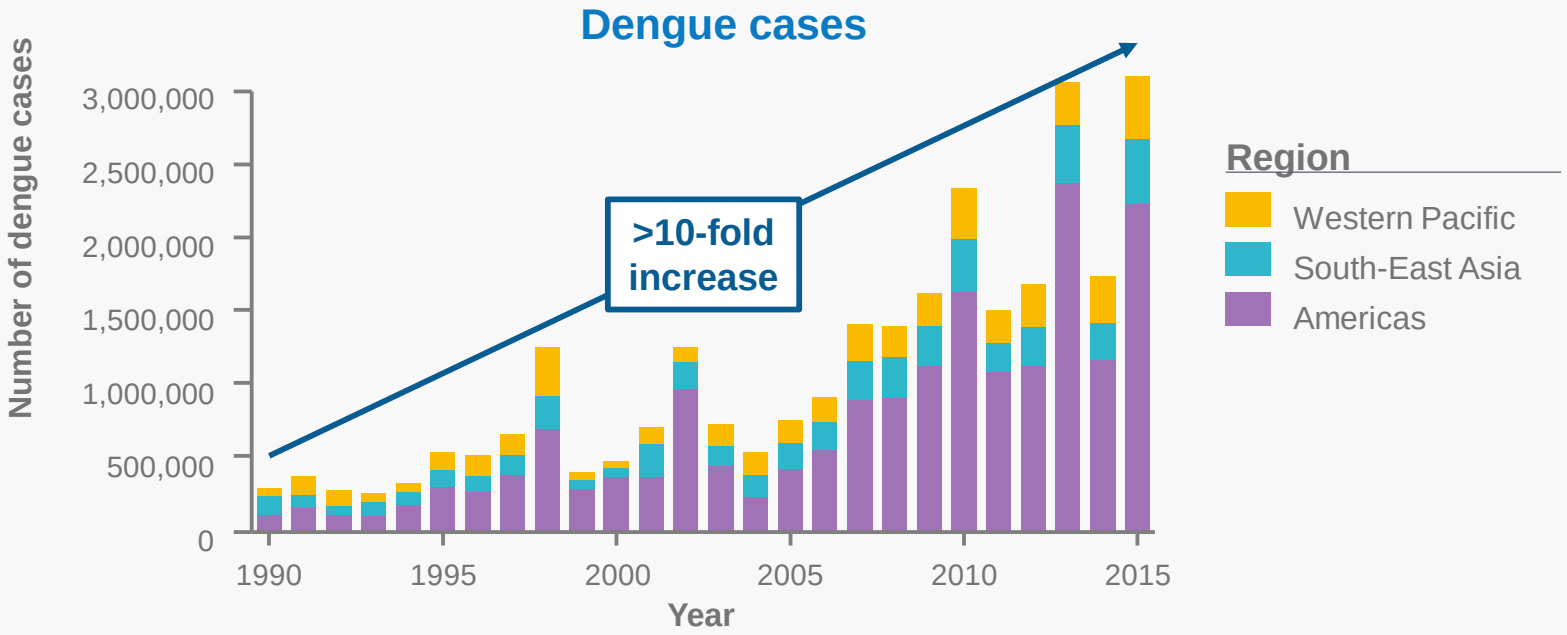
The burden of dengue is large and growing



Number of suspected or laboratory-confirmed dengue cases notified to WHO, 1990–2015. WHO, World Health Organization.

WHO, Dengue Control: Epidemiology, 2017.

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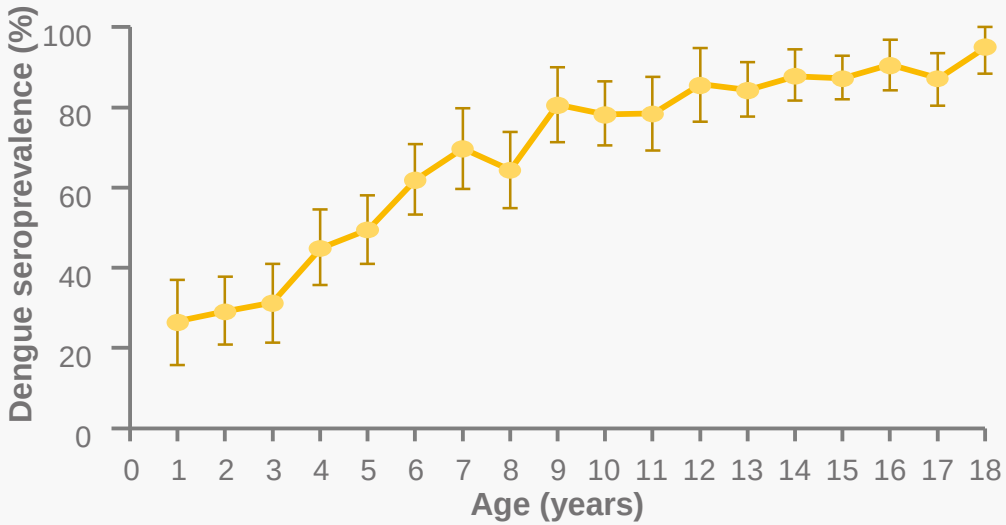
In endemic areas, most people will have had a dengue infection by the time of adolescence

Dengue seroprevalence among urban dwelling Indonesian children[1]



- The majority of children in endemic dengue areas in both Latin America and Asia-Pacific regions are seropositive by 9 years of age[1–3]
- Median age of seroconversion among urban dwelling children in Indonesia was 4.8 years[1]
- >80% seroprevalence among children aged 10 years or older[1]

3,210 children enrolled from 30 geographically dispersed clustered from October–November 2014.
Dengue seroprevalence assessed by testing for anti-dengue IgG antibodies by indirect ELISA. Error bars = 95% confidence interval.
ELISA, enzyme-linked immunosorbent assay.

1. Prayitno A, et al. PLoS Negl Trop Dis 2017;11:e0005621.
2. Dhar-Chowdhury P, et al. PLoS Negl Trop Dis 2017;11:e0005475.
3. L'Azou M, et al. Trans R Soc Trop Med Hyg 2018;112:158–68.

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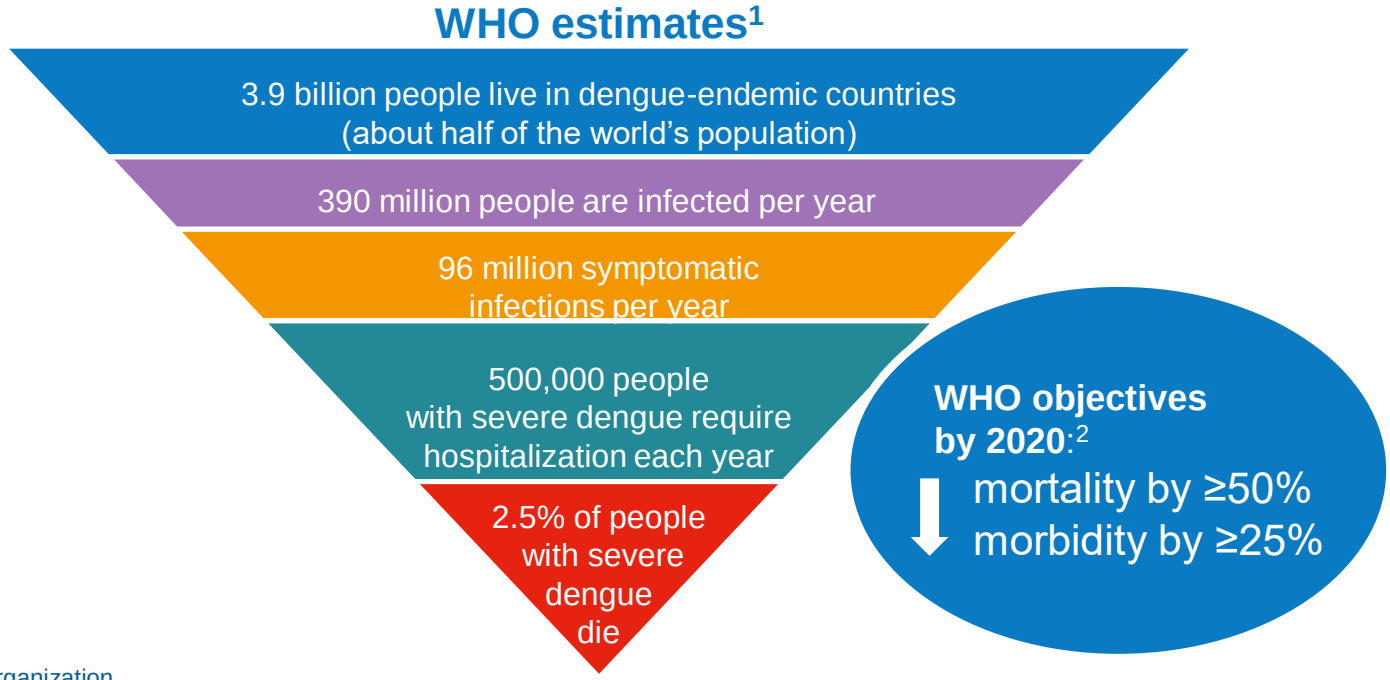
Measures for prevention and control of dengue are inadequate

Despite decades of research, no dengue-specific treatment is available[1]

- Prevention measures focus mainly on vector control – none of which have stopped the spread of dengue
  - Measures are largely reactive[2]
  - *Aedes aegypti* has developed widespread resistance to many common insecticides[2]
  - Community engagement is necessary to sustain effective vector control[2]
  - Even if low vector presence (eg, Singapore), dengue incidence is dramatically increased[3]

1. WHO, Dengue fact sheet, 2018. 2. WHO, Global Strategy for Dengue Prevention and Control, 2012.
3. Ooi EE, et al. Emerg Infect Dis 2006;12:887−93.

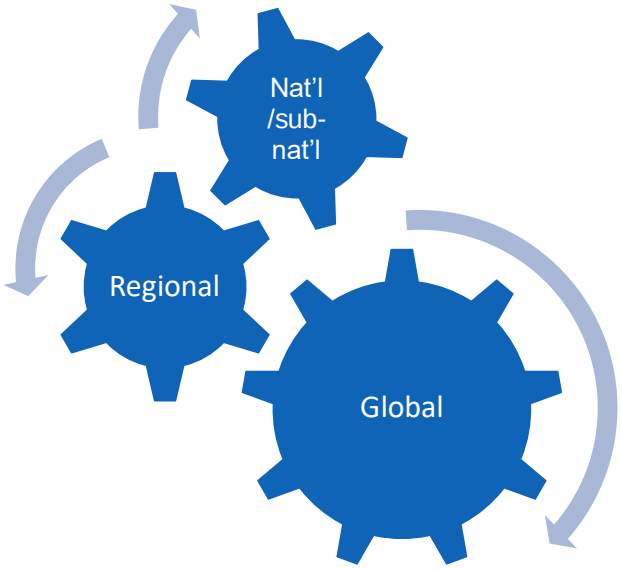
With the expectation of a new vaccine …
Dengue is a public health priority

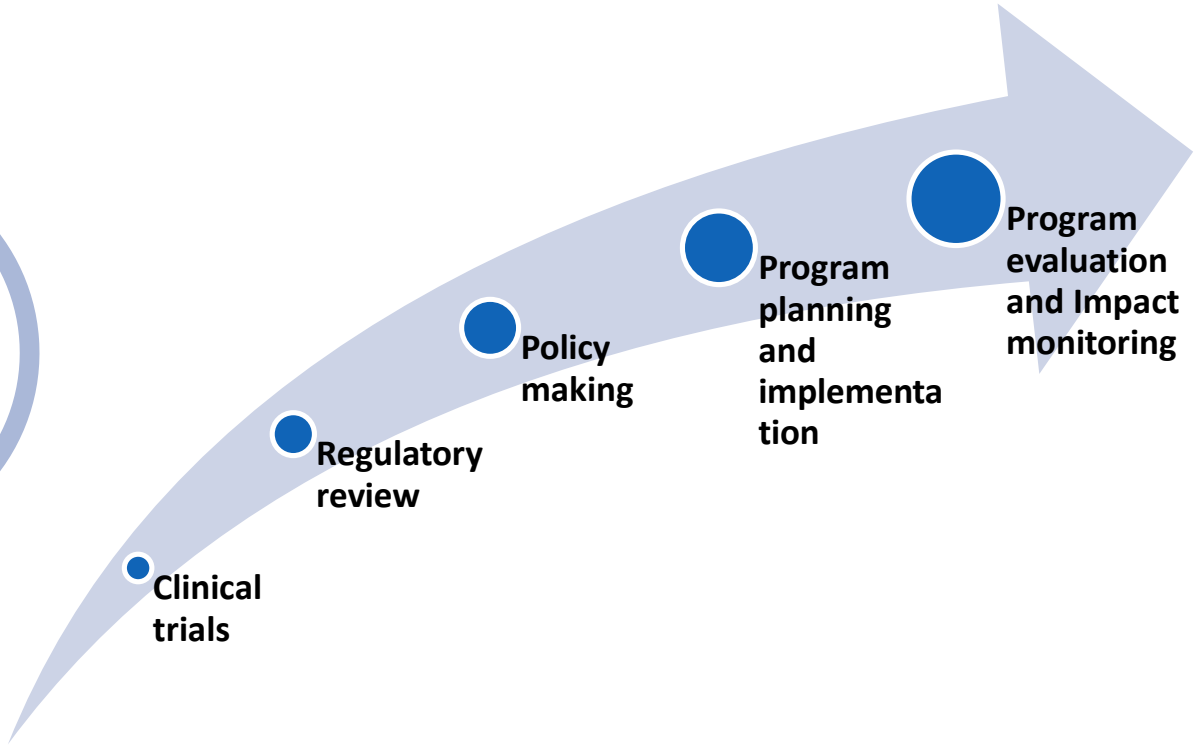


WHO, World Health Organization.

1. WHO, Dengue Fact Sheet, 2018. 2. WHO, Global Strategy for Dengue Prevention and Control, 2012.

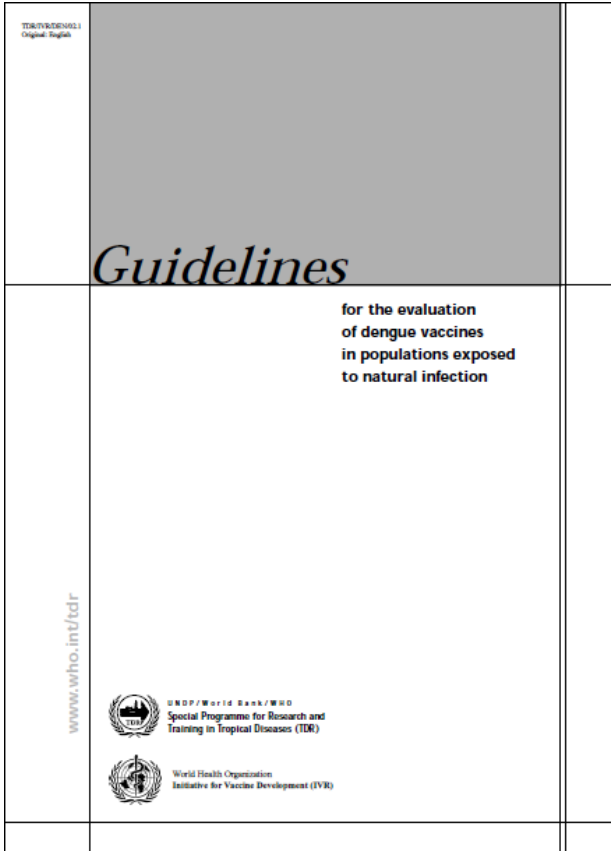
From (candidate) Vaccines to Vaccination



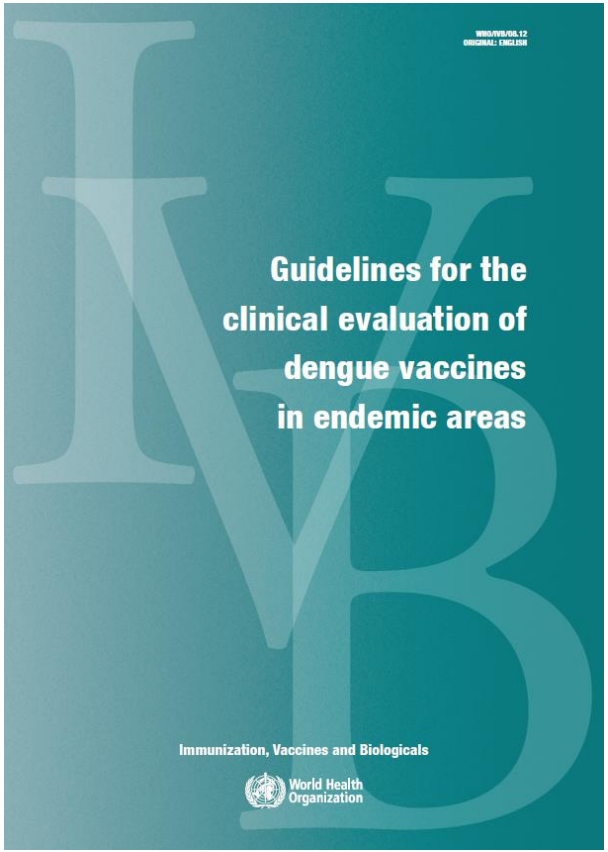


Guidance for the Clinical Evaluation of Dengue Vaccine Candidates

2002



2008



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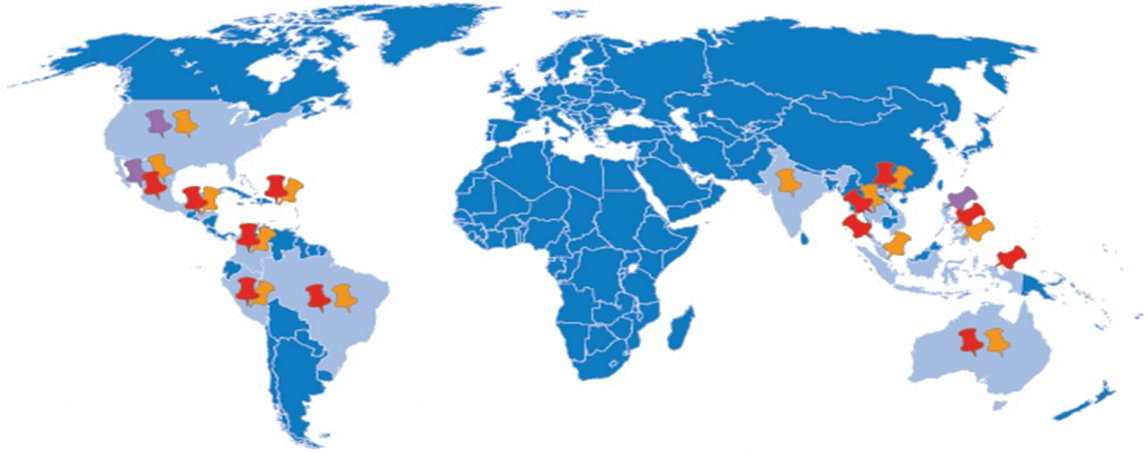
http://www.who.int/iris/handle/10665/67783

http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.12_eng.pdf?ua=1

Overview of the CYD-TDV Clinical Program*

- **25 clinical studies** supporting the dossier, **in 15 countries**.
- More than **40,000 subjects** included in clinical studies.
- Nearly **29,000** children, adolescent and adults **received the vaccine**.*



5 phase I trials
in 3 countries
(USA, Mexico, Philippines)
N=400 CYD vaccinees
Ages: 2–45 years

14 phase II trials
in 13 countries
(USA, Australia, Latin America, Asia)
N=5400 CYD vaccinees
Ages: 12 months–45 years

6 phase III trials
in 12 countries
(Australia, Latin America, Asia)
N=23,000 CYD vaccinees
Ages: 9 months–60 years

Phase I | *Non endemic* **Phase II** *Endemic* | **Phase III**

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*As of August 2015
SP=Sanofi Pasteur

Clinical Trial Results

Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial

Arunee Sabchareon, Derek Wallace, Chukiat Sirivichayakul, Kriengsak Limkittikul, Pornthep Chanthavanich, Saravudh Suvannadabba, Vithaya Jiwariyavej, Wut Dulyachai, Krisana Pengsaa, T Anh Wartel, Annick Moureau, Melanie Saville, Alain Bouckenooghe, Simonetta Viviani, Nadia G Tornieporth, Jean Lang

Sabchareon et al. LANCET 2012. Epub 2012 Sep. doi: 10.1016/S0140-6736(12)61428-7

Clinical Trial Results

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 8, 2015 VOL. 372 NO. 2

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., asquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., do Noriega, M.D., for the CYD15 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2015 VOL. 373 NO. 13

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

Capeding et al. LANCET 2014. Epub 2014/07/16 doi: 10.1016/s0140-6736(14)61060-6
Villar et al. NEJM 2015 Epub 2014/11/05 doi: 10.1056/NEJMoa1411037
Hadinegoro et al NEJM 2015 Epub 2015/07/28 doi : 10.1056/NEJMoa1506223

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Scientific Discussion

PERSPECTIVES

VECTOR-BORNE DISEASES

OPINION

Dengue vaccine: hypotheses to understand CYD-TDV-induced protection

Bruno Guy and Nicholas Jackson

Abstract | Dengue virus (DENV) is a human pathogen with a large impact on public health. Although no vaccine against DENV is currently licensed, a recombinant vaccine — chimeric yellow fever virus–DENV tetravalent dengue vaccine (CYD-TDV) — has shown efficacy against symptomatic dengue disease in two recent Phase III clinical trials. Safety observations were also recently reported for these trials. In this Opinion article, we review the data from recent vaccine clinical trials and discuss the putative mechanisms behind the observed efficacy of the vaccine against different forms of the disease, focusing on the interactions between the infecting virus, pre-existing host immunity and vaccine-induced immune responses.

Asia[12] and the other in children 9–16 years of age in Latin America[13] (BOX 1). The active phase of these two trials (the 25 months following the initial vaccination) has now been completed, and both trials reached their primary endpoint by demonstrating vaccine efficacy against virologically confirmed dengue (VCD), when overall efficacy was measured (that is, irrespective of disease severity and infecting DENV serotype) (BOX 1). An acceptable safety profile, consistent with prior trials, was also demonstrated in both trials during the active surveillance period. All four serotypes contributed to the overall efficacy in both studies, and both trials also showed greater efficacy against severe disease and against disease leading to hospitalization, in comparison with the overall efficacy (BOX 1). Newly published longer-term safety data have now been obtained for the first year of follow-up during the surveillance phase for the safety of participants requiring hospitalization (referred to as the hospital

Guy & Jackson. Nature reviews Microbiology. 2015 Epub 2015/12/07 doi:10.1038/nrmicro.2015.2

Scientific Discussion

PLOS | MEDICINE

RESEARCH ARTICLE

The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study

Stefan Flasche[1☯], Mark Jit[1☯*], Isabel Rodríguez-Barraquer[2☯], Laurent Coudeville[3☯], Mario Recker[4☯], Katia Koelle[5☯], George Milne[6☯], Thomas J. Hladish[7☯], T. Alex Perkins[8☯], Derek A. T. Cummings[2,7], Ilaria Dorigatti[9], Daniel J. Laydon[9], Guido España[8], Joel Kelso[6], Ira Longini[7], Jose Lourenco[10], Carl A. B. Pearson[7], Robert C. Reiner[11], Luis Mier-y-Terán-Romero[2], Kirsten Vannice[12], Neil Ferguson[9☯]

1 London School of Hygiene and Tropical Medicine, London, United Kingdom, **2** Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **3** Sanofi Pasteur, Lyon, France, **4** University of Exeter, Exeter, United Kingdom, **5** Duke University, Durham, North Carolina, United States of America, **6** University of Western Australia, Crawley, Australia, **7** University of Florida, Gainesville, Gainesville, Florida, United States of America, **8** University of Notre Dame, Notre Dame, Indiana, United States, **9** Imperial College London, London, United Kingdom, **10** University of Oxford, Oxford, United Kingdom, **11** Indiana University, Bloomington, Indiana, United States of America, **12** World Health Organization, Geneva, Switzerland

☯ These authors contributed equally to this work.
* Mark.Jit@lshtm.ac.uk

OPEN ACCESS

Citation: Flasche S, Jit M, Rodríguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. (2016) The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Med 13(11): e1002181. doi:10.1371/journal.pmed.1002181

Abstract

Scientific Discussion

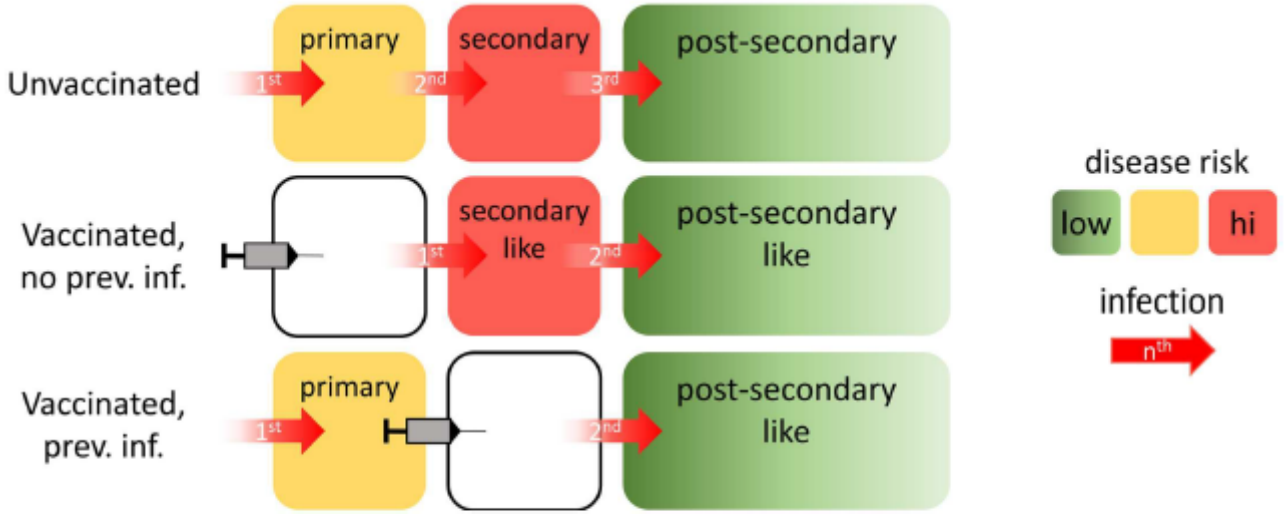


Fig 1. Illustration of the assumed vaccine mode of action. Without vaccination (top row), an individual will (by definition) experience a primary infection first, followed by a secondary infection, and then postsecondary infections. For vaccinees seronegative at the time of vaccination (middle row), their first natural infection behaves immunologically as a second natural infection would. Subsequent infections would immunologically behave as postsecondary infections. For vaccinees seropositive at the time of vaccination, any subsequent infection would immunologically behave as a postsecondary infection. The bottom row depicts such a case, in which the vaccinated individual has previously experienced only a single dengue infection. Because all postsecondary infections are assumed to have the same risk of disease, vaccination of individuals who have already had two infections would not modulate the risk of disease for subsequent infections. Boxes are color-coded according to the level of disease risk thought to be associated with primary, secondary, and postsecondary infections. The specific risks of developing dengue disease differ by modelling group (S1 Appendix Tables B and C).

doi:10.1371/journal.pmed.1002181.g001

Flasche et al. PLoS Med. 2016 Nov. doi: 10.1371/journal.pmed.1002181

Scientific Discussion

DENGUE VACCINE

Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment

Neil M. Ferguson,[1]*† Isabel Rodríguez-Barraquer,[2]* Ilaria Dorigatti,[1] Luis Mier-y-Teran-Romero,[2] Daniel J. Laydon, Derek A. T. Cummings[2,3]

The first approved dengue vaccine has now been licensed in six countries. We propose that this live attenuated vaccine acts like a silent natural infection in priming or boosting host immunity. A transmission dynamic model incorporating this hypothesis fits recent clinical trial data well and predicts that vaccine effectiveness depends strongly on the age group vaccinated and local transmission intensity. Vaccination in low-transmission settings may increase the incidence of more severe "secondary-like" infection and, thus, the numbers hospitalized for dengue. In moderate transmission settings, we predict positive impacts overall but increased risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative. However, in high-transmission settings, vaccination benefits both the whole population and seronegative recipients. Our analysis can help inform policy-makers evaluating this and other candidate dengue vaccines.

dynamics—make it far from simple to extrapolate from the trial results to predict the potential impact of wide-scale use of this vaccine.

We therefore developed mathematical models of DENV transmission (*10*) to explore hypotheses about vaccine action and to examine the potential consequences for the impact of routine use of this vaccine. Given the trial results (see table S1), any model needs to incorporate waning of efficacy over time. Hence, we fitted a "simple" model to the publicly available trial data (*6*–*8*), where efficacy was allowed to decay from an initial high value to some lower long-term value, with these efficacy values assumed to be different for seropositive and seronegative vaccine recipients. The resulting parameter estimates and poor overall fit (table S5 and fig. S5) led us to propose a more biologically motivated model, in which the immunological effect of vaccination is comparable to a silent natural infection (fig. S1). Seronegative recipients gain transient protective cross-reactive immunity akin to that observed for natural infection (*21*–*23*). After this protection decays, lower concentrations of heterotypic antibodies increase the risk of severe disease upon a breakthrough

Ferguson et al. Science 2016 Sep doi: 10.1126/science.aaf9590

Joint Regulatory Review

Technical consultation with seven NRAs on the dengue vaccine dossier
28–30 July 2015, at WH

Vaccine 35 (2017) 5731–5733

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

The value of multi-country joint regulatory reviews: The experience of a WHO joint technical consultation on the CYD-TDV (Dengvaxia®) dossier

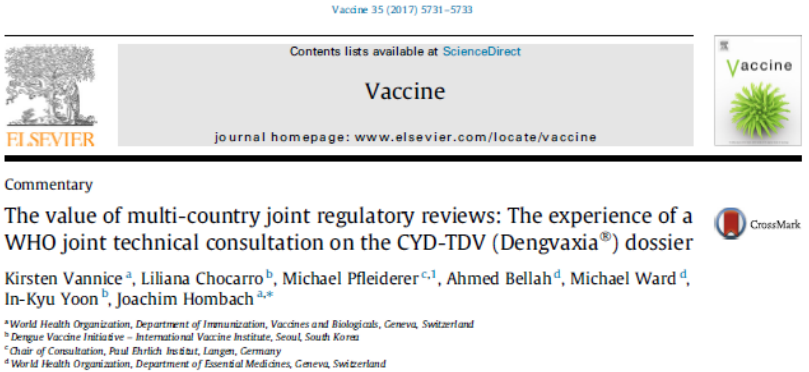
Kirsten Vannice [a], Liliana Chocarro [b], Michael Pfleiderer [c,1], Ahmed Bellah [d], Michael Ward [d], In-Kyu Yoon [b], Joachim Hombach [a,*]

[a] World Health Organization, Department of Immunization, Vaccines and Biologicals, Geneva, Switzerland
[b] Dengue Vaccine Initiative – International Vaccine Institute, Seoul, South Korea
[c] Chair of Consultation, Paul Ehrlich Institut, Langen, Germany
[d] World Health Organization, Department of Essential Medicines, Geneva, Switzerland

http://dx.doi.org/10.1016/j.vaccine.2017.07.044

Joint Regulatory Review

- **Technical consultation with seven NRAs on the dengue vaccine dossier 28–30 July 2015, at WHO**
  1. Agência Nacional de Vigilância Sanitária (ANVISA), **Brazil**;
  2. Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), **Colombia**;
  3. National Agency of Drug and Food Control (NA-DFC), **Indonesia**;
  4. National Pharmaceutical Control Bureau, Ministry of Health, Selangor, **Malaysia**;
  5. Federal Commission for the Protection from Sanitary Risks (COFEPRIS), **Mexico**;
  6. Center for Drug Regulation and Research, Department of Health, **Philippines**;
  7. Department of Medical Sciences, Ministry of Public Health, **Thailand**.
- **MXC and BRA are WHO approved functional NRA's**
- **US FDA and EMA participate**



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Kirsten Vannice [a], Liliana Chocarro [b], Michael Pfleiderer [c,1], Ahmed Bellah [d], Michael Ward [d], In-Kyu Yoon [b], Joachim Hombach [a,*]

[a] World Health Organization, Department of Immunization, Vaccines and Biologicals, Geneva, Switzerland
[b] Dengue Vaccine Initiative – International Vaccine Institute, Seoul, South Korea
[c] Chair of Consultation, Paul Ehrlich Institut, Langen, Germany
[d] World Health Organization, Department of Essential Medicines, Geneva, Switzerland

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

http://dx.doi.org/10.1016/j.vaccine.2017.07.044

Safety Review - WHO GACVS

2013, 88, 65–72 No. 6

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

8 FEBRUARY 2013, 88th YEAR / 8 FÉVRIER 2013, 88e ANNÉE
No. 6, 2013, 88, 65–72
http://www.who.int/wer

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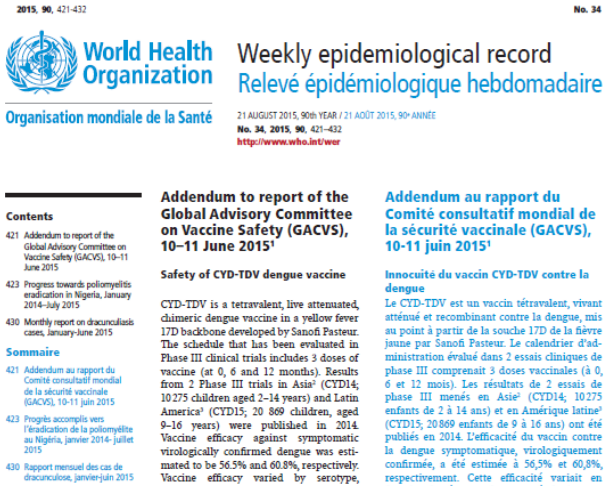
71 Rectificatif

Global Advisory Committee on Vaccine Safety, December 2012

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body lished by WHO to provide scientifically rigorous advice safety issues of potential gl tance.[1] GACVS held its 27th Geneva, Switzerland, on 5–2012.[2] The committee reviewe profile of varicella vaccines; narcolepsy related to use of and that of Guillain-Barré syn with multiple influenza A(vaccine use; and safety aspect ment of dengue vaccines. reviewed progress with imple the Global Vaccine Safet through the Global Vaccine tive.

Comité consultatif mondial de la Sécurité vaccinale, décembre 2012

Le Comité consultatif mondial de la Sécurité vaccinale (GACVS), un organe consultatif



2015, 90, 421-432

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

21 AUGUST 2015, 90th YEAR / 21 AOÛT 2015, 90e ANNÉE
No. 34, 2015, 90, 421–432
http://www.who.int/wer

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423 Progrès accomplis vers l'éradication de la poliomyélite au Nigéria, janvier 2014- juillet 2015
430 Rapport mensuel des cas de dracunculose, janvier-juin 2015

Addendum to report of the Global Advisory Committee on Vaccine Safety (GACVS), 10–11 June 2015[1]

Safety of CYD-TDV dengue vaccine

CYD-TDV is a tetravalent, live attenuated, chimeric dengue vaccine in a yellow fever 17D backbone developed by Sanofi Pasteur. The schedule that has been evaluated in Phase III clinical trials includes 3 doses of vaccine (at 0, 6 and 12 months). Results from 2 Phase III trials in Asia[2] (CYD14; 10 275 children aged 2–14 years) and Latin America[3] (CYD15; 20 869 children, aged 9–16 years) were published in 2014. Vaccine efficacy against symptomatic virologically confirmed dengue was estimated to be 56.5% and 60.8%, respectively. Vaccine efficacy varied by serotype, serostatus at the time of receiving the first dose (measured by presence of neutraliz-

Addendum au rapport du Comité consultatif mondial de la sécurité vaccinale (GACVS), 10-11 juin 2015[1]

Innocuité du vaccin CYD-TDV contre la dengue

Le CYD-TDV est un vaccin tétravalent, vivant atténué et recombinant contre la dengue, mis au point à partir de la souche 17D de la fièvre jaune par Sanofi Pasteur. Le calendrier d'administration évalué dans 2 essais cliniques de phase III comprenait 3 doses vaccinales (à 0, 6 et 12 mois). Les résultats de 2 essais de phase III menés en Asie[2] (CYD14; 10 275 enfants de 2 à 14 ans) et en Amérique latine[3] (CYD15; 20 869 enfants de 9 à 16 ans) ont été publiés en 2014. L'efficacité du vaccin contre la dengue symptomatique, virologiquement confirmée, a été estimée à 56,5% et 60,8%, respectivement. Cette efficacité variait en fonction du sérotype, du statut sérologique au moment de la réception de la première dose

2015, 90, 17–24 No. 4

World Health Organization
Organisation mondiale de la Santé

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17 Global Advisory Committee on Vaccine Safety, 3–4 December 2014

Sommaire

No. 34 ...nsultatif mondial ...rité vaccinale, ...mbre 2014

Global Advisory Committee on Vaccine Safety, 3–4 December 2014

The Global Advisory Committee on Vaccine Safety (GACVS), an international expert clinical and scientific advisory body, was established by WHO to provide independent, scientifica on vaccine safety issues importance.[1] GACVS he in Geneva, Switzerland, 2014.[2] The Committe concerning monitorin novel vaccines agains and Ebola virus. It als dological issues relate mance of vaccine safet tems, the assessment for inclusion in the Vac enhancing the standard safety surveillance f during pregnancy.

Comité consultatif mondial de la sécurité vaccinale, 3-4 décembre 2014

Le Comité consultatif mondial de la sécurité vaccinale (GACVS), organisme international composé d'experts cliniques et scientifiques, a été créé par l'OMS pour la conseiller en toute

2016, 91, 341-348 No 28/29

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
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341 Global Advisory Committee on Vaccine Safety, 15–16 June 2016

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341 Comité consultatif mondial de la sécurité des vaccins, 15–16 juin 2016

Global Advisory Committee on Vaccine Safety, 15–16 June 2016

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 34th meeting in Geneva, Switzerland, on 15–16 June 2016.[2] The Committee examined 3 generic issues: (i) a new initiative to promote health product vigilance in low- and middle-income countries (LMICs); (ii) the harmonization of the definition of health events for pharmacovigilance studies in pregnancy and early childhood; and (iii) a proof-of-concept study to assess rare events through multi-country collaboration. The Committee also reviewed vaccine-specific safety issues on routine infant vaccination in India and initial post-licensure data related to dengue vaccine.

Comité consultatif mondial de la sécurité des vaccins, 15–16 juin 2016

Le Comité consultatif mondial de la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.[1] Le GACVS a tenu sa 34e réunion à Genève (Suisse) les 15 et 16 juin 2016.[2] Il a examiné 3 questions génériques: i) une nouvelle initiative pour promouvoir la vigilance à l'égard des produits sanitaires dans les pays à revenu faible ou intermédiaire; ii) l'harmonisation de la définition des manifestations indésirables dans les études de pharmacovigilance durant la grossesse et la petite enfance; et iii) une étude de preuve de concept pour évaluer les manifestations rares au travers d'une collaboration multi-pays. Le GACVS a également examiné une étude de l'innocuité des vaccins dans le cadre de la vaccination systématique des nourrissons en Inde, ainsi que les premières données post-homologation du vaccin contre la dengue.

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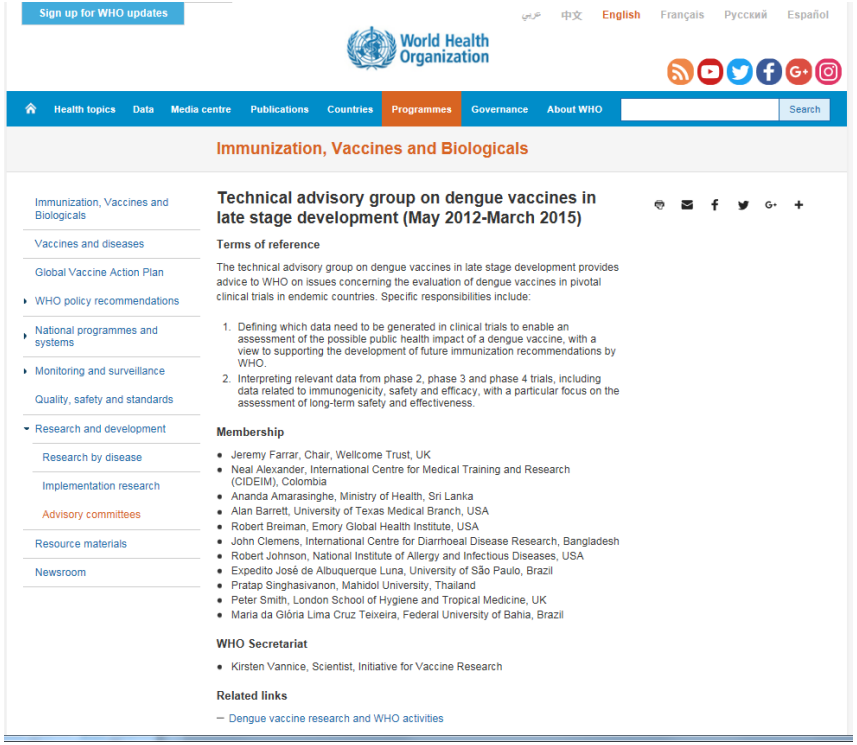
WER 88, 2013, pp. 68-69; WER 90, 2015, pp. 17-18; WER 90, 2015, pp. 421-423; WER 91, 2016, pp. 346-347

Immunization Policy



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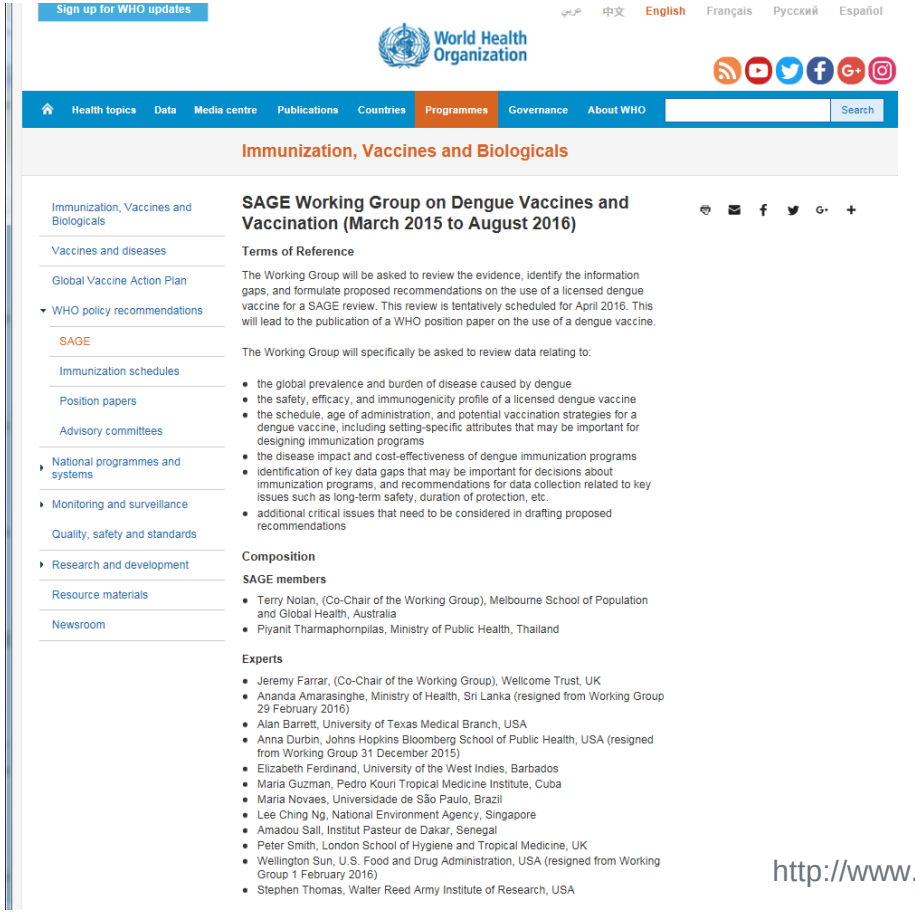
http://www.who.int/immunization/research/committees/dengue_tag/en/

Immunization Policy



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Immunization, Vaccines and Biologicals

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SAGE Working Group on Dengue Vaccines and Vaccination (March 2015 to August 2016)

Terms of Reference

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of a licensed dengue vaccine for a SAGE review. This review is tentatively scheduled for April 2016. This will lead to the publication of a WHO position paper on the use of a dengue vaccine.

The Working Group will specifically be asked to review data relating to:

- the global prevalence and burden of disease caused by dengue
- the safety, efficacy, and immunogenicity profile of a licensed dengue vaccine
- the schedule, age of administration, and potential vaccination strategies for a dengue vaccine, including setting-specific attributes that may be important for designing immunization programs
- the disease impact and cost-effectiveness of dengue immunization programs
- identification of key data gaps that may be important for decisions about immunization programs, and recommendations for data collection related to key issues such as long-term safety, duration of protection, etc.
- additional critical issues that need to be considered in drafting proposed recommendations

Composition

SAGE members

- Terry Nolan, (Co-Chair of the Working Group), Melbourne School of Population and Global Health, Australia
- Piyanit Tharmaphornpilas, Ministry of Public Health, Thailand

Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK
- Ananda Amarasinghe, Ministry of Health, Sri Lanka (resigned from Working Group 29 February 2016)
- Alan Barrett, University of Texas Medical Branch, USA
- Anna Durbin, Johns Hopkins Bloomberg School of Public Health, USA (resigned from Working Group 31 December 2015)
- Elizabeth Ferdinand, University of the West Indies, Barbados
- Maria Guzman, Pedro Kouri Tropical Medicine Institute, Cuba
- Maria Novaes, Universidade de São Paulo, Brazil
- Lee Ching Ng, National Environment Agency, Singapore
- Amadou Sall, Institut Pasteur de Dakar, Senegal
- Peter Smith, London School of Hygiene and Tropical Medicine, UK
- Wellington Sun, U.S. Food and Drug Administration, USA (resigned from Working Group 1 February 2016)
- Stephen Thomas, Walter Reed Army Institute of Research, USA

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http://www.who.int/immunization/policy/sage/sage_wg_dengue_mar2015/en/

Regulatory Approvals

First regulatory approvals in December 2015

Mexico*
Brazil*
The Philippines

✶ Private implementation / ✶ Public program
* WHO approved functional NRA

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Immunization Policy

SAGE - APRIL 2016

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http://www.who.int/immunization/policy/sage/en/

Immunization Policy

2016, 91, 265-284 No 21

World Health Organization
Organisation mondiale de la Santé

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Relevé épidémiologique hebdomadaire

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Dengue vaccine

Worldwide, dengue is the most extensively spread mosquito-borne viral infection. It is caused by 4 related viruses (DENV 1-4). In the last 60 years, the incidence of clinical dengue cases reported to WHO has increased 30-fold, with a much increased geographic range and expansion from urban to rural settings. The objectives of the WHO Global Strategy for dengue prevention and control (2012–2020) are to reduce mortality and morbidity from dengue by 2020 by at least 50% and 25% respectively.[7] The first dengue vaccine, CYD-TDV (Dengvaxia®), has now been licensed by several dengue-endemic countries in Asia and Latin America for use in persons aged 9–45 or 9–60 years, and is under regulatory review in several others.

Vaccin contre la dengue

La dengue est la maladie virale transmise par les moustiques dont la propagation est la plus forte dans le monde. Elle est provoquée par 4 virus apparentés (DENV 1-4). Au cours des 60 dernières années, l'incidence des cas cliniques de dengue notifiés à l'OMS a augmenté d'un facteur 30, la zone géographique touchée est devenue beaucoup plus vaste et la maladie s'est propagée des zones urbaines aux zones rurales. La Stratégie mondiale de lutte contre la dengue (2012-2020) de l'OMS vise à réduire la morbidité et la mortalité imputables à cette maladie d'au moins 50% et 25% respectivement d'ici 2020.[7] Le premier vaccin contre la dengue, CYD-TDV (Dengvaxia®), est désormais homologué dans plusieurs pays d'endémie d'Asie et d'Amérique latine pour la tranche d'âge de 9-45 ans ou de 9-60 ans, et est actuellement examiné par les autorités réglementaires de plusieurs autres pays.

2016, 91, 349-364 No 30

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Sommaire

Dengue vaccine: WHO position paper – July 2016

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are generally concerned with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with the current WHO position on the use of vaccines worldwide.

Note de synthèse de l'OMS sur le vaccin contre la dengue – juillet 2016

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies qui ont une incidence sur la santé publique internationale. Ces notes, qui traitent généralement de l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations essentielles sur les maladies et les vaccins concernés et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins à l'échelle mondiale.

http://www.who.int/wer/2016/wer9121.pdf?ua=1

http://www.who.int/wer/2016/wer9130.pdf?ua=1

Regulatory Approvals

License obtained in 20 countries

First licenses granted in December 2015

Mexico*
Brazil*
The Philippines

Implementation

- 2 public programs
- 11 private markets

✶ Licenses granted but no private market launched nor public program implemented
✶ Private implementation / ✶ Public program
* WHO approved functional NRA

Knowledge gap

Research Priorities

Table 12 Research priorities related to CYD-TDV identified by the SAGE Working Group on Dengue Vaccines.

CYD Research Question	Priority	Addressed in RMP?	Notes
Risk of severe/hospitalized dengue over time in vaccinated seronegatives	**Critical**	Post-licensure studies in RMP will not test serostatus at the time of vaccination, although serostatus from yearly surveys will be known.	This is a critical research question that needs to be addressed with carefully considered research protocols. Dedicated studies are needed.

- The scientific and public health community, as well as several regulatory agencies expressed high interest in obtaining more clarity on the safety and efficacy of the CYD dengue vaccine according to presence or absence of previous dengue exposure (refer commonly as “baseline sero-status”)
- However, baseline samples were not obtained in the majority of study participants in CYD14 and CYD15 studies (80% and 90%, respectively)
  - Baseline Dengue sero-status (as a surrogate of pre-vaccination dengue exposure) is unknown for the majority of subjects in these studies

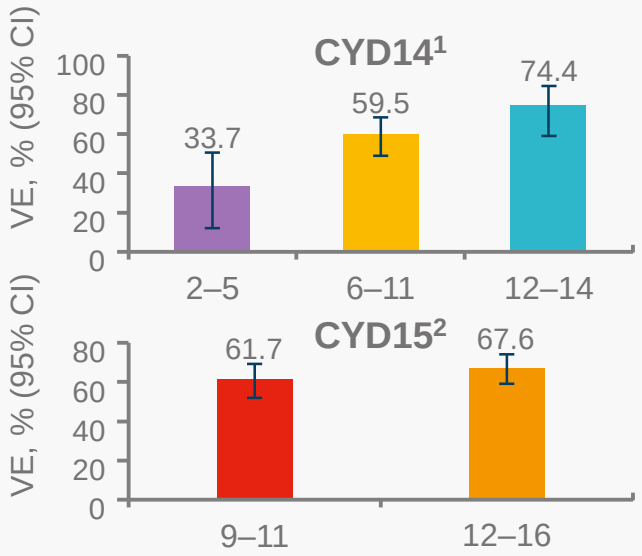
WHO, SAGE Background paper on dengue vaccines, March 2016. Available at: http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf?ua=

Efficacy and safety of CYD-TDV dengue vaccination in seropositive individuals aged 9 years or older

Impact of dengue serostatus on dengue vaccine safety and efficacy.
Sridhar S, et al. N Engl J Med 2018: In press.

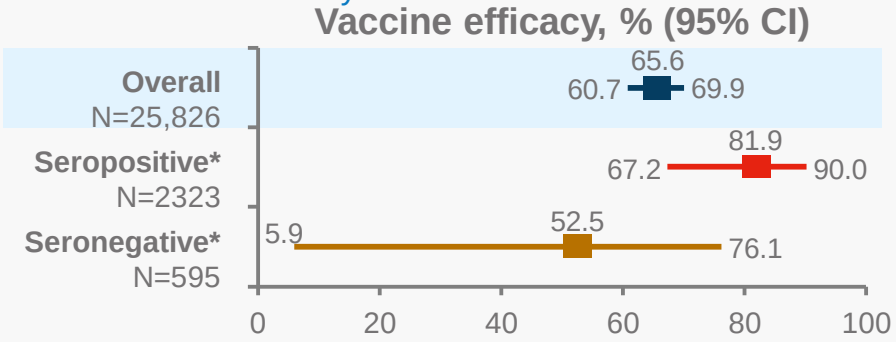
Summary of phase III efficacy results

Vaccine efficacy by age (years)



Vaccine efficacy in 9−16-year-olds[3]

Pooled analysis of CYD14 and CYD15



- Vaccine efficacy is impacted by age and baseline serostatus[3]
- An increased risk of hospitalization and severe dengue with vaccination was seen in <9-year-olds, mainly driven by data in 2−5-year-olds in the CYD14 study[3]
- Supplemental analyses conducted to investigate the effects of age and previous dengue infection on vaccine efficacy[4]

*Serostatus assessed at baseline with the plaque reduction neutralisation test ($PRNT_{50}$) in immunogenicity subset.
CI, confidence interval; N, number of subjects included in the analysis; VE, vaccine efficacy.

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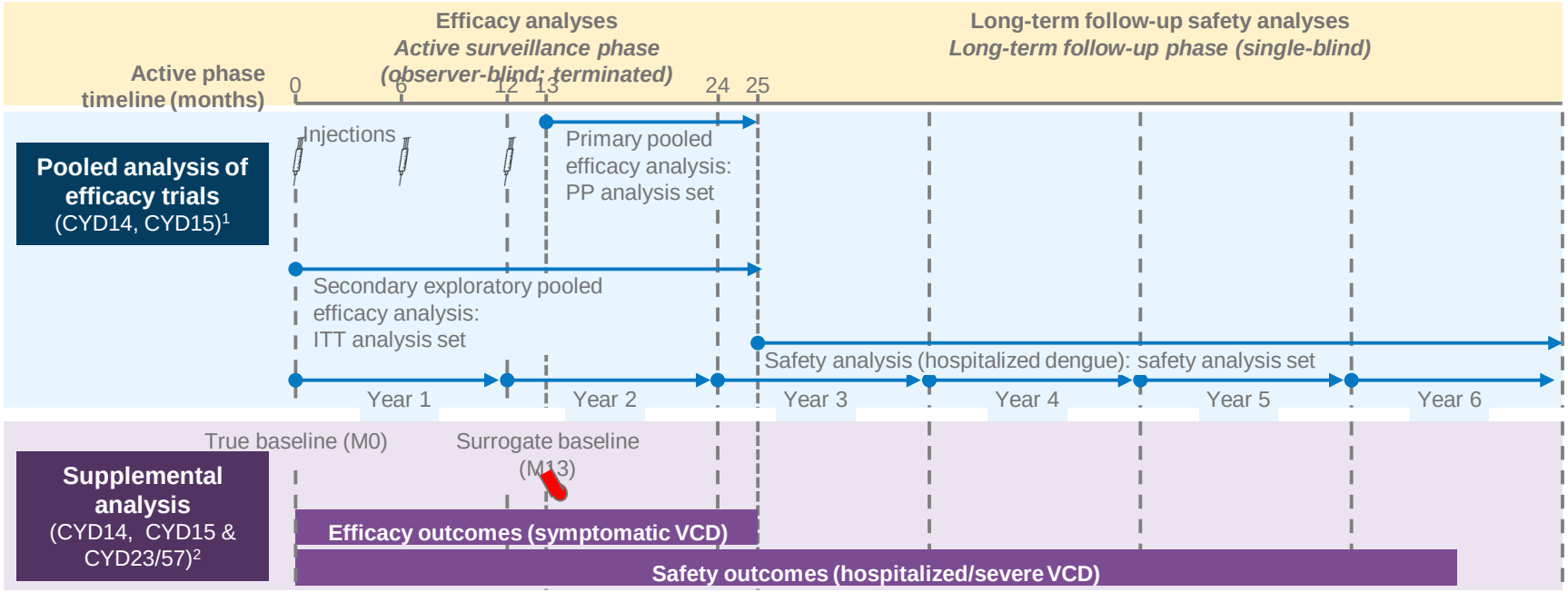
1. Capeding MR, et al, Lancet 2014;384:1358−65 & Supplementary appendix. 2. Villar L, et al. N Engl J Med 2015;372:113−23 & Supplementary appendix. 3. Hadinegoro SR, et al. N Engl J Med 2015;373:1195−206. 4. Sridhar S, et al. N Engl J Med 2018: In press & Supplementary appendix.

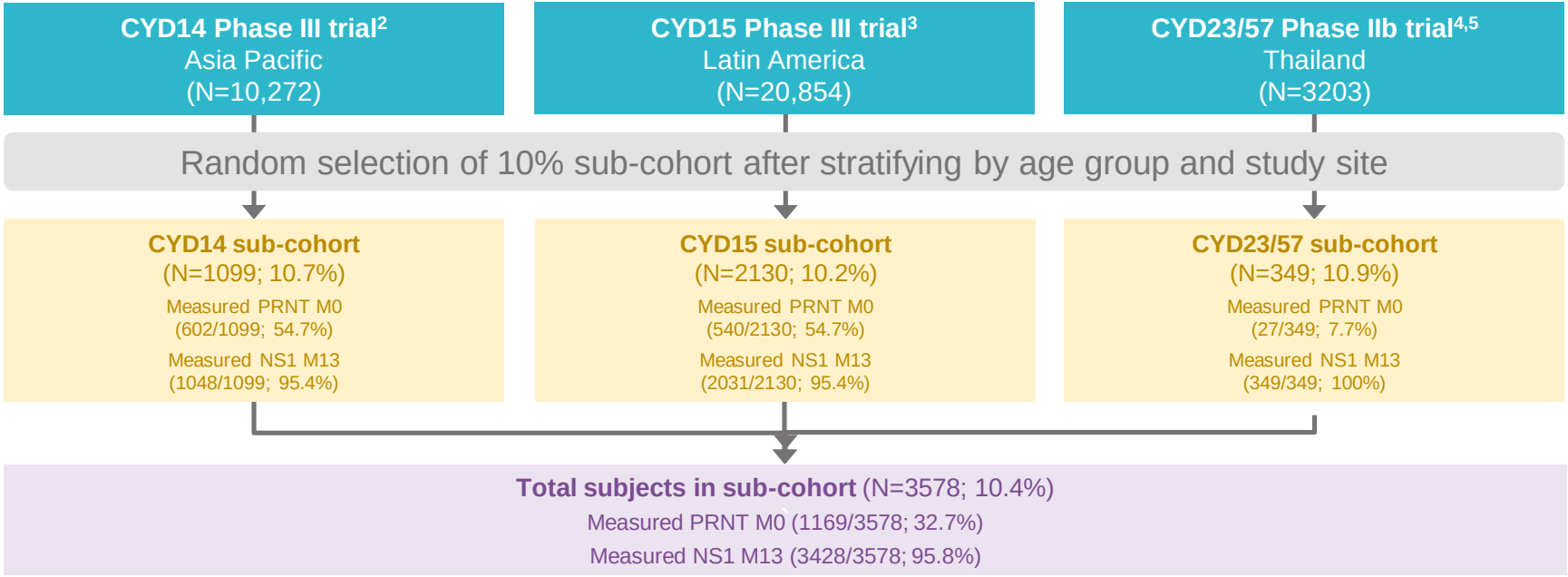
Supplemental analysis and pooled analysis of efficacy trials



ITT, intention-to-treat; PP, per-protocol; VCD, virologically confirmed dengue.

1. Hadinegoro SR, et al. N Engl J Med 2015;373:1195−206. 2. Sridhar S, et al. N Engl J Med 2018: In press & Supplementary appendix.

Supplemental analysis design



PRNT M0, plaque reduction neutralization test at Month 0;
NS1 M13, anti-non-structural protein 1 (NS1) immunoglobulin G enzyme-linked immunosorbent assay at Month 13.

1. Sridhar S, et al. N Engl J Med 2018: In press & Supplementary appendix. 2. Capeding MR, et al. Lancet 2014;384:1358−65.
3. Villar L, et al. N Engl J Med 2015;372:113−23. 4. Sabchareon A, et al. Lancet 2012;380:1559−67. 5. Hadinegoro SR, et al. N Engl J Med 2015;373:1195−206.

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Assessment methods

- Cumulative incidences, hazard ratios or relative risks of hospitalized dengue, severe dengue and vaccine efficacy in the case-cohort were analyzed using three methodologies:

1 NS1-Th9-M13

- Analysis based on serostatus based on anti-NS1 titers from Month 13 onwards
- As the CYD-TDV vaccine encodes the NS1 protein from yellow fever virus, it is not expected to induce meaningful antibodies to the dengue NS1 protein
- Therefore, presence of dengue NS1 antibodies may differentiate previous exposure to natural dengue infection from previous exposure to CYD vaccination

2 MI-M0

- Multiple Imputation method applied on entire dataset to impute missing baseline $PRNT_{50}$ serostatus based on variables including M13 anti-NS1 titers, vaccination status, age, country and indicators of symptomatic VCD
- Regression modelling used to estimate hazard ratio or vaccine efficacy from M0 onwards

3 TMLE-M0

- Machine learning used to predict baseline serostatus based on M13 anti-NS1 titers, M13 $PRNT_{50}$ titers (if available), vaccination status, age and country.
- Risk of dengue hospitalization and severe dengue and vaccine efficacy from M0 onwards estimated by Targeted Minimum Loss-based Estimator

M0, Month 0; M13, Month 13; MI-M0, Multiple Imputation, Month 0; NS1, non-structural protein 1; $PRNT_{50}$, 50% plaque reduction neutralization test; TMLE, Targeted Minimum Loss-based Estimator; VCD, virologically confirmed dengue.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

Assessment methods

- Cumulative incidences, hazard ratios or relative risks of hospitalized dengue, severe dengue and vaccine efficacy in the case-cohort were analyzed using three methodologies:

1 NS1-Th9-M13

- Analysis based on serostatus based on anti-NS1 titers from Month 13 onwards
- antibodies to the dengue NS1 protein
- Therefore, presence of dengue NS1 antibodies may

Data will be presented for the Multiple Imputation (MI-M0) assessment

2 MI-M0

- Multiple Imputation method applied on entire dataset to impute missing baseline $PRNT_{50}$ serostatus based on variables including M13 anti-NS1 titers, vaccination status, age, country and indicators of symptomatic VCD
- Regression modelling used to estimate hazard ratio or vaccine efficacy from M0 onwards

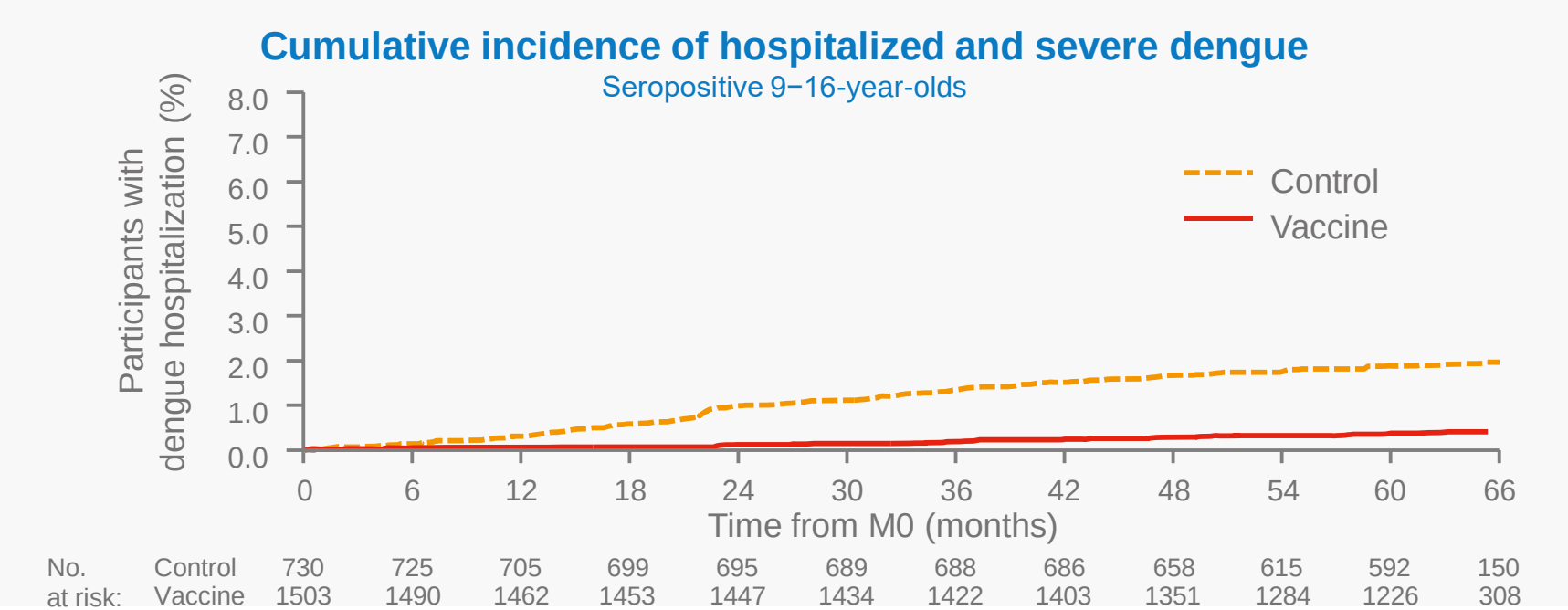
3 TMLE-M0

- Machine learning used to predict baseline serostatus based on M13 anti-NS1 titers, M13 $PRNT_{50}$ titers (if available), vaccination status, age and country.
- Risk of dengue hospitalization and severe dengue and vaccine efficacy from M0 onwards estimated by Targeted Minimum Loss-based Estimator

M0, Month 0; M13, Month 13; MI-M0, Multiple Imputation, Month 0; NS1, non-structural protein 1; $PRNT_{50}$, 50% plaque reduction neutralization test; TMLE, Targeted Minimum Loss-based Estimator; VCD, virologically confirmed dengue.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

Vaccination reduces the risk of hospitalized and severe dengue in seropositive 9−16-year-olds up to 5 years after first injection



Cumulative incidence of dengue hospitalization in seropositive participants aged 9–16 years old. MI-M0 estimate.
M0, Month 0; MI-M0, Multiple Imputation, Month 0.

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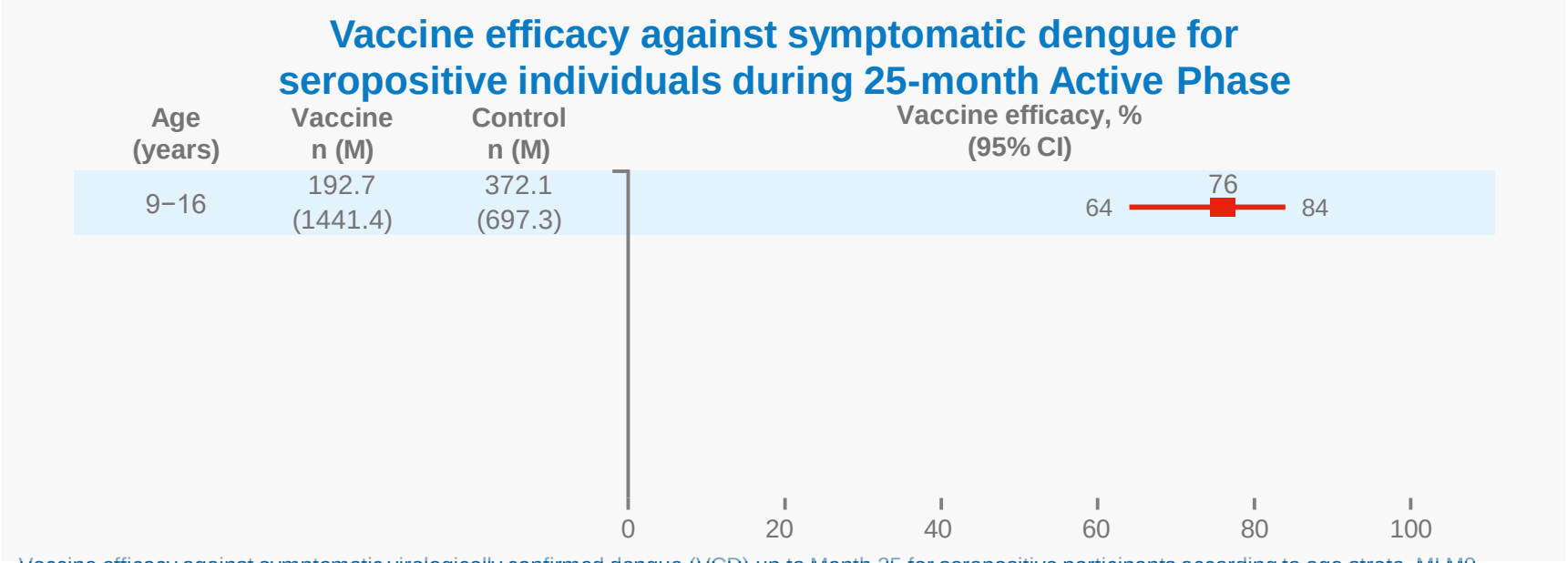
Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

High vaccine efficacy against symptomatic dengue (VCD) for seropositive 9−16-year-olds during 25-month Active Phase

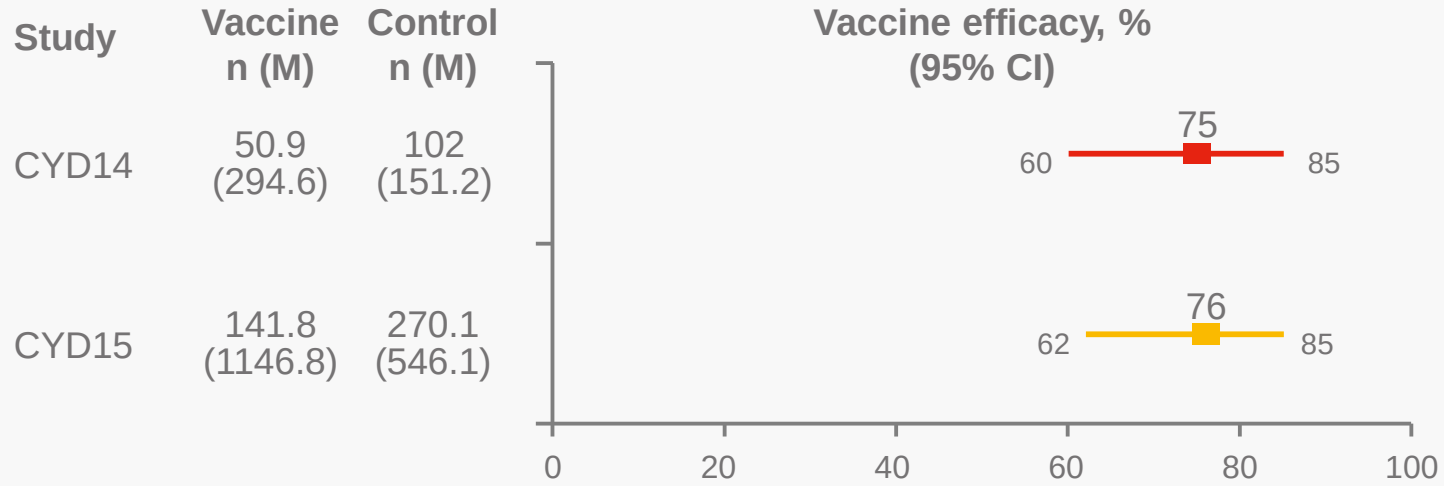


Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) up to Month 25 for seropositive participants according to age strata. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort; estimates are from M0–M25. CI, confidence interval; MI-M0, Multiple Imputation, Month 0.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

Comparable vaccine efficacy across the individual efficacy trials in seropositive 9−16-year-olds up to 25 months after first injection

Vaccine efficacy against symptomatic dengue (VCD) for seropositive individuals during 25-month Active Phase



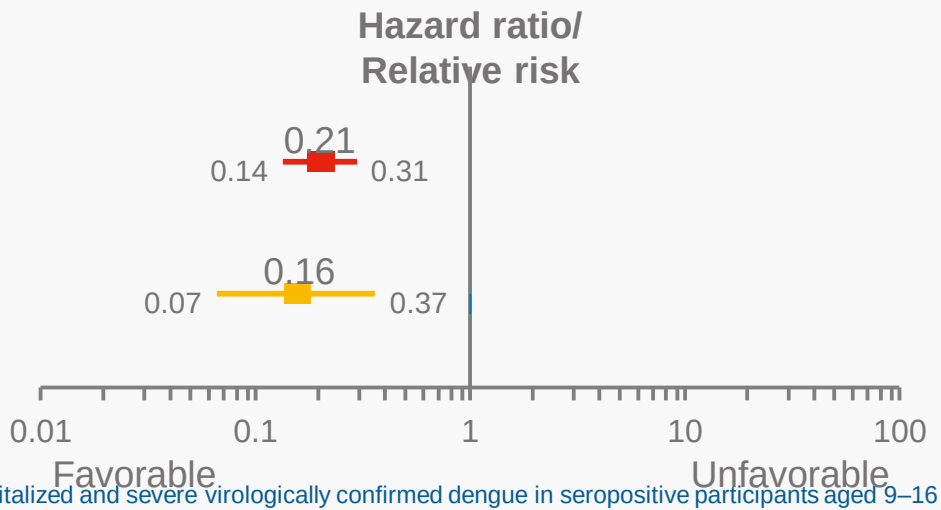
Vaccine efficacy against symptomatic virologically confirmed dengue up to Month 25 according for seropositive 9−16-year-old participants. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort; estimates are from M0–M25. CI, confidence interval; MI-M0, Multiple Imputation, Month 0.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

Consistent reduction in the risk of hospitalized and severe dengue in seropositive 9−16-year-olds up to 5 years after first injection

Hazard ratio/Relative risk of hospitalized and severe dengue

	Vaccine n (M)	Control n (M)
Hospitalized	58.8 (1502.9)	137.7 (729.8)
Severe*	11.2 (1502.9)	33.4 (729.8)



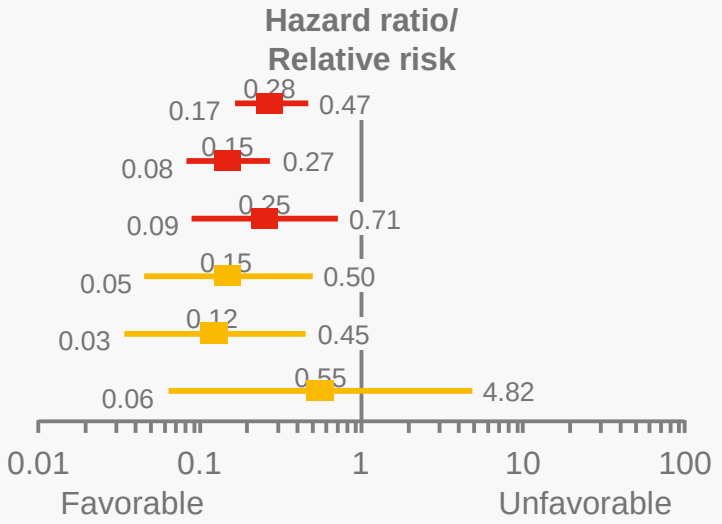
*As per IDMC assessment. Hazard ratio/Relative risk of hospitalized and severe virologically confirmed dengue in seropositive participants aged 9–16 years old. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort. Error bars: 95% confidence intervals.
IDMC, Independent Data Monitoring Committee; MI-M0, Multiple Imputation, Month 0.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

Consistent reduction in the risk of hospitalized or severe dengue in seropositive 9−16-year-olds up to 5 years after first injection

Hazard ratio/Relative risk of hospitalized and severe dengue

	Study	Vaccine n (N)	Control n (N)
Hospitalized dengue	CYD14	28.2 (294.6)	52.5 (151.2)
	CYD15	20.3 (1146.9)	63.6 (546)
	CYD23/57	10.3 (61.4)	21.6 (32.6)
Severe dengue	CYD14	5 (294.6)	16.7 (151.2)
	CYD15	4 (1146.9)	14.7 (546)
	CYD23/57	2.2 (61.4)	2 (32.6)



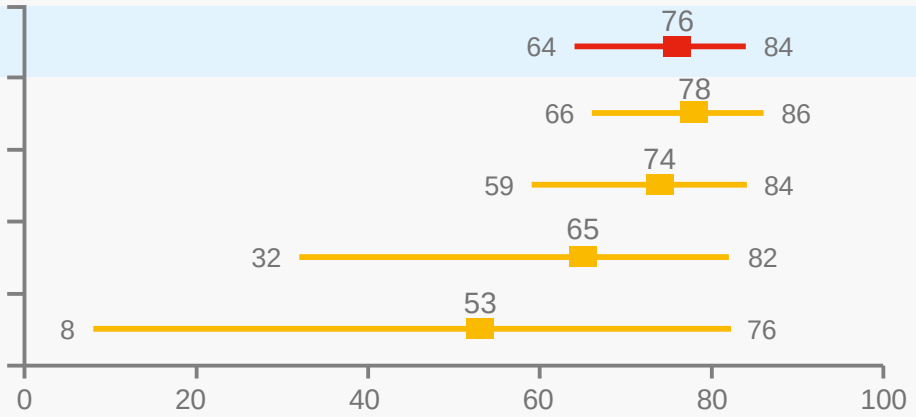
Relative risk of hospitalized and severe virologically confirmed dengue (VCD) in seropositive participants aged 9–16 years old. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort. Error bars: 95% confidence intervals. MI-M0, Multiple Imputation, Month 0.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

High vaccine efficacy in seropositive individuals

Vaccine efficacy against symptomatic dengue for seropositive individuals during 25-month Active Phase

Age (years)	Vaccine n (M)	Control n (M)	Vaccine efficacy, % (95% CI)
9–16	192.7 (1441.4)	372.1 (697.3)	76 (64, 84)
12–16	85 (802.9)	181 (386.1)	78 (66, 86)
9–11	107.7 (638.5)	191.1 (311.2)	74 (59, 84)
6–8	39.3 (97.9)	56.2 (51.3)	65 (32, 82)
2–5	49.2 (119.4)	48.1 (58.2)	53 (8, 76)



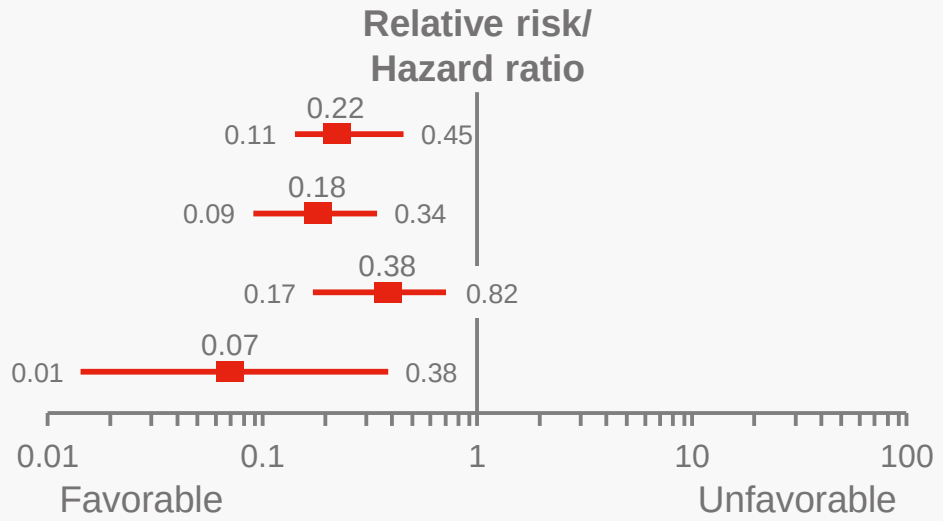
Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) up to Month 25 for seropositive participants according to age strata. MI-M0 estimate. n and M are averages from 10 iterations of multiple imputations with n representing the number of participants that were cases of symptomatic VCD and M the total number of participants selected in the subcohort; estimates are from M0–M25. CI, confidence interval; MI-M0, Multiple Imputation, Month 0.

Sridhar S, et al. N Engl J Med 2018 & Supplementary appendix.

Consistent reduction in the risk of hospitalized or severe dengue in seropositive 9−16-year-olds up to 5 years after first injection, by serotype

Relative risk of hospitalized or severe dengue

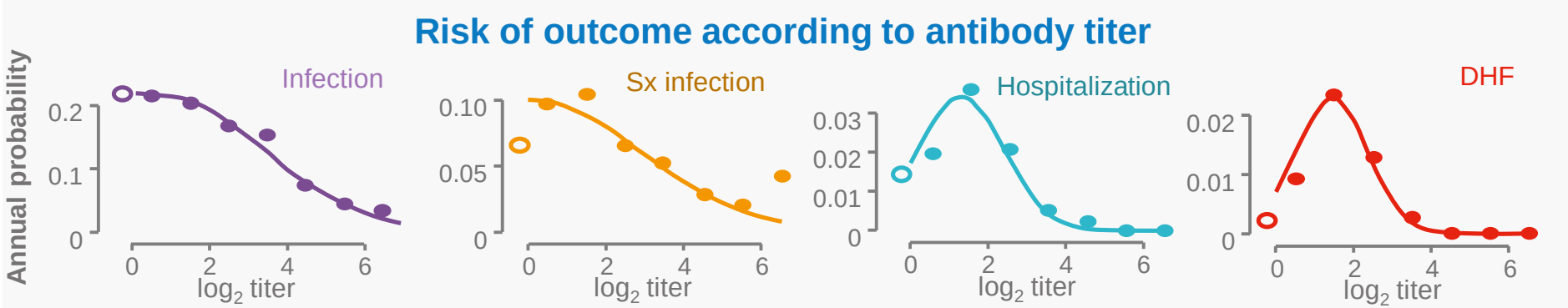
Serotype	Vaccine n (N)	Control n (N)
Serotype 1	15.4 (1495.6)	32.9 (708.1)
Serotype 2	15.8 (1495.6)	42.1 (708.1)
Serotype 3	14.9 (1495.6)	18.6 (708.1)
Serotype 4	3.6 (1495.6)	21.1 (708.1)



Relative risk of hospitalized and severe virologically confirmed dengue in seropositive participants aged 9–16 years old. MI-M0 estimate. Error bars: 95% confidence intervals.
MI-M0, Multiple Imputation, Month 0; n/N, number of symptomatic cases/total number of participants in cohort.

Sridhar S, et al. N Engl J Med 2018: In press & Supplementary appendix.

Subsequent infection increases the risk of severe dengue



Open circles represent primary infections (i.e. with no detectable titer before exposure). Antibody titers measured by hemagglutination inhibition testing.
DHF, dengue hemorrhagic fever.

LETTER

RESEARCH

LETTER

https://doi.org/10.1038/s41586-018-0157-4

Reconstruction of antibody dynamics and infection histories to evaluate dengue risk

Henrik Salje[1,2,3,4]*, Derek A. T. Cummings[4,5,6], Isabel Rodriguez-Barraquer[7], Leah C. Katzelnick[5], Justin Lessler[4], Chonticha Klungthong[8], Butsaya Thaisomboonsuk[8], Ananda Nisalak[8], Alden Weg[8], Damon Ellison[8], Louis Macareo[8], In-Kyu Yoon[9], Richard Jarman[10], Stephen Thomas[11], Alan L. Rothman[12], Timothy Endy[11,13] & Simon Cauchemez[1,2,3,13]

NATURE | www.nature.com/nature

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Salje H, et al. Nature 018;557:719–23.

WHO–SAGE recommendations on use of dengue vaccine 2018

- The SAGE working group has acknowledged the public health role of the CYD-TDV vaccine and the strong protective benefit in seropositive individuals for the subsequent dengue infection
- In order to maximize the public health impact and minimize harm with dengue vaccination, SAGE has recommended two main approaches:

Preferred approach

Pre-vaccination screening

- Serological screening prior to vaccination
- Dengue IgG ELISA could potentially be used for screening
- Currently available Rapid Diagnostic Tests could be considered in high transmission settings
- Only confirmed dengue-seropositive persons vaccinated

Alternative approach

Population seroprevalence

- Subnational or national mass vaccination strategy in areas of high seroprevalence
- Population surveys to identify areas with high seroprevalence where public impact is maximized and harm minimized
- Mass vaccination in identified high seroprevalence areas without serological screening

CYD-TDV, chimeric yellow fever 17D-tetravalent dengue vaccine; ELISA, enzyme-linked immunosorbent assay; SAGE, Strategic Advisory Group of Experts; WHO, World Health Organization.

SAGE Working Group & WHO. Revision to the Background paper on dengue vaccines, 2018.

Summary and conclusions

1. Findings from the case-cohort study confirm the substantial benefit of CYD-TDV vaccination in those aged 9 years or older and who are dengue seropositive[1]
2. Vaccination confers protection against hospitalized and severe dengue with subsequent infection for more than 5 years[1]
3. Risk of hospitalized dengue and of severe dengue is reduced by ~80% in the vaccine-indicated group of seropositive individuals aged 9 years or older[1]
4. The role of CYD-TDV in public health and the strong protective benefit in seropositive individuals is acknowledged by WHO-SAGE[2]
5. Based on the evidence, SAGE has recommended two main dengue vaccination approaches in endemic settings in order to maximize the public health impact and minimize harm[2]

CYD-TDV, chimeric yellow fever 17D-tetravalent dengue vaccine; SAGE, Strategic Advisory Group of Experts; WHO, World Health Organization.

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1. Sridhar S, et al. N Engl J Med 2018: In press & Supplementary appendix.
2. WHO, Revised SAGE recommendation on use of dengue vaccine, 2018.

Clinical Trial Results

SANOFI

Press Release

Source: Sanofi (EURONEXT: SAN) (NYSE: SNY)

Sanofi updates information on dengue vaccine

- New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection
- Company will ask regulators to update product label to reflect new information

PARIS, FRANCE – November 29, 2017 – Sanofi will ask health authorities to update information provided to physicians and patients on its dengue vaccine Dengvaxia® in countries where it is approved. The request is based on a new analysis of long-term clinical trial data, which found differences in vaccine performance based on prior dengue infection.

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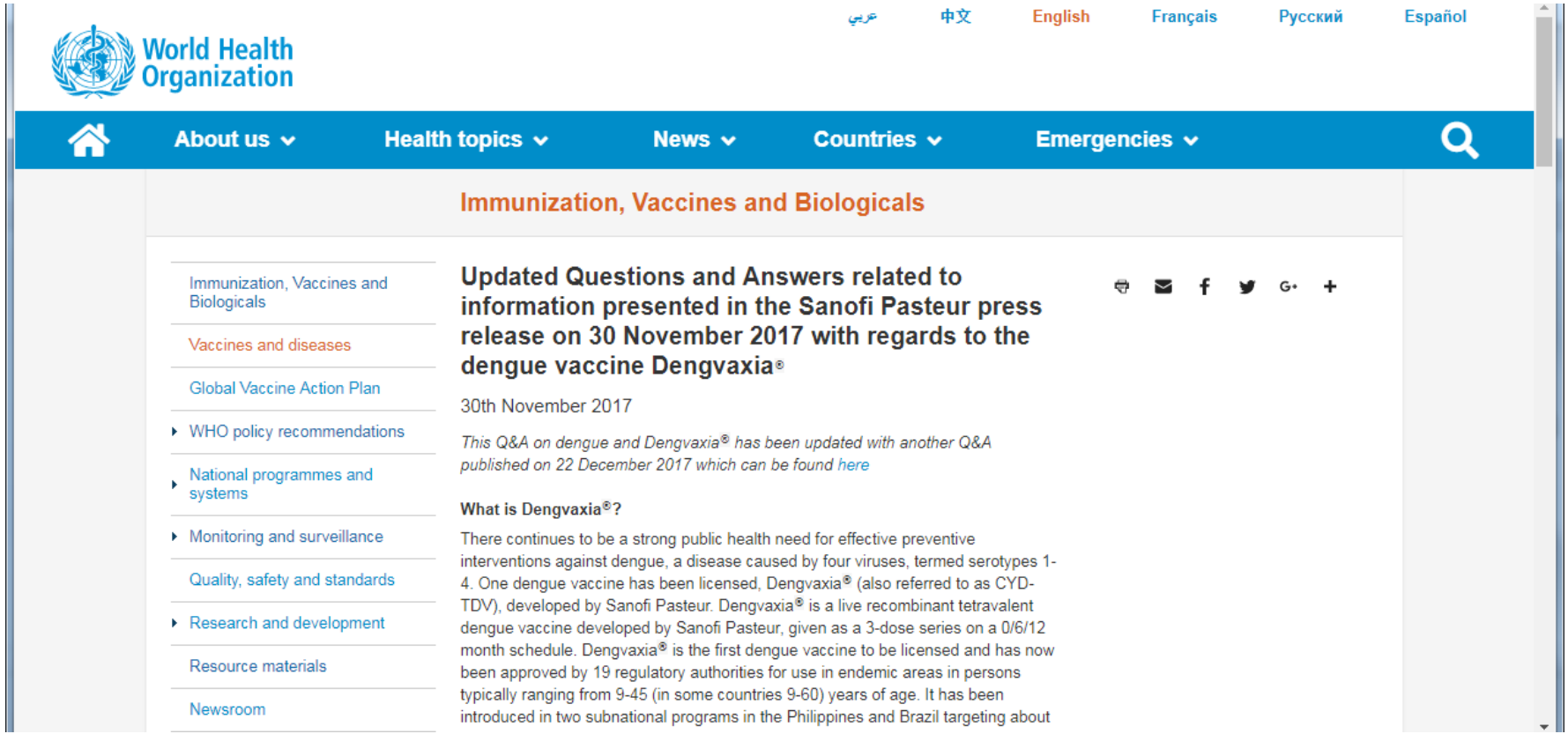
http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine/

Immunization Policy



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Updated Questions and Answers related to information presented in the Sanofi Pasteur press release on 30 November 2017 with regards to the dengue vaccine Dengvaxia®

30th November 2017

This Q&A on dengue and Dengvaxia® has been updated with another Q&A published on 22 December 2017 which can be found here

What is Dengvaxia®?

There continues to be a strong public health need for effective preventive interventions against dengue, a disease caused by four viruses, termed serotypes 1-4. One dengue vaccine has been licensed, Dengvaxia® (also referred to as CYD-TDV), developed by Sanofi Pasteur. Dengvaxia® is a live recombinant tetravalent dengue vaccine developed by Sanofi Pasteur, given as a 3-dose series on a 0/6/12 month schedule. Dengvaxia® is the first dengue vaccine to be licensed and has now been approved by 19 regulatory authorities for use in endemic areas in persons typically ranging from 9-45 (in some countries 9-60) years of age. It has been introduced in two subnational programs in the Philippines and Brazil targeting about

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

WHO GACVS – Safety Review

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Global Vaccine Safety

- Global Vaccine Safety
- Global Vaccine Safety Initiative
- Global Advisory Committee on Vaccine Safety
  - Topics
  - Committee reports
- Reference documents and publications

GACVS Statement on Dengvaxia ® (CYD-TDV)

December 7, 2017

The WHO Global Advisory Committee on Vaccine Safety has been following the development of a tetravalent recombinant live dengue virus vaccine for the past 5 years [1,2,3,4]. The most advanced product, CYD-TDV by Sanofi-Pasteur (Dengvaxia®) is a yellow fever vaccine virus backbone vector that expresses envelope proteins of dengue viruses type 1 to 4 yellow fever vaccine virus genetic backbones. During early clinical trials no serious vaccine-related events had been documented among the recipients, and no excess cases of dengue fever or severe dengue attributable to the vaccine had been observed. Subsequent large scale phase 3 trials, CYD14 in Asia (among subjects aged 2 to 14 years) and CYD15 in Latin America (among subjects aged 9 to 16 years) were conducted in over 20,000 vaccine recipients and 10,000 control subjects and demonstrated partial efficacy of the vaccine.

Related links

Media statement

Dengvaxia has received its first marketing authorizations in late 2015 and is currently available in several Asian and Latin American countries. This statement briefly reviews the experience presented to GACVS during clinical trial development (with now over 5 years of follow up), and discusses new evidence presented to WHO during the December 2017 GACVS meeting. This new data is based on re-analysis of clinical trial data using a new test that retrospectively distinguished subjects with and without prior exposure to wild dengue virus.

WHO

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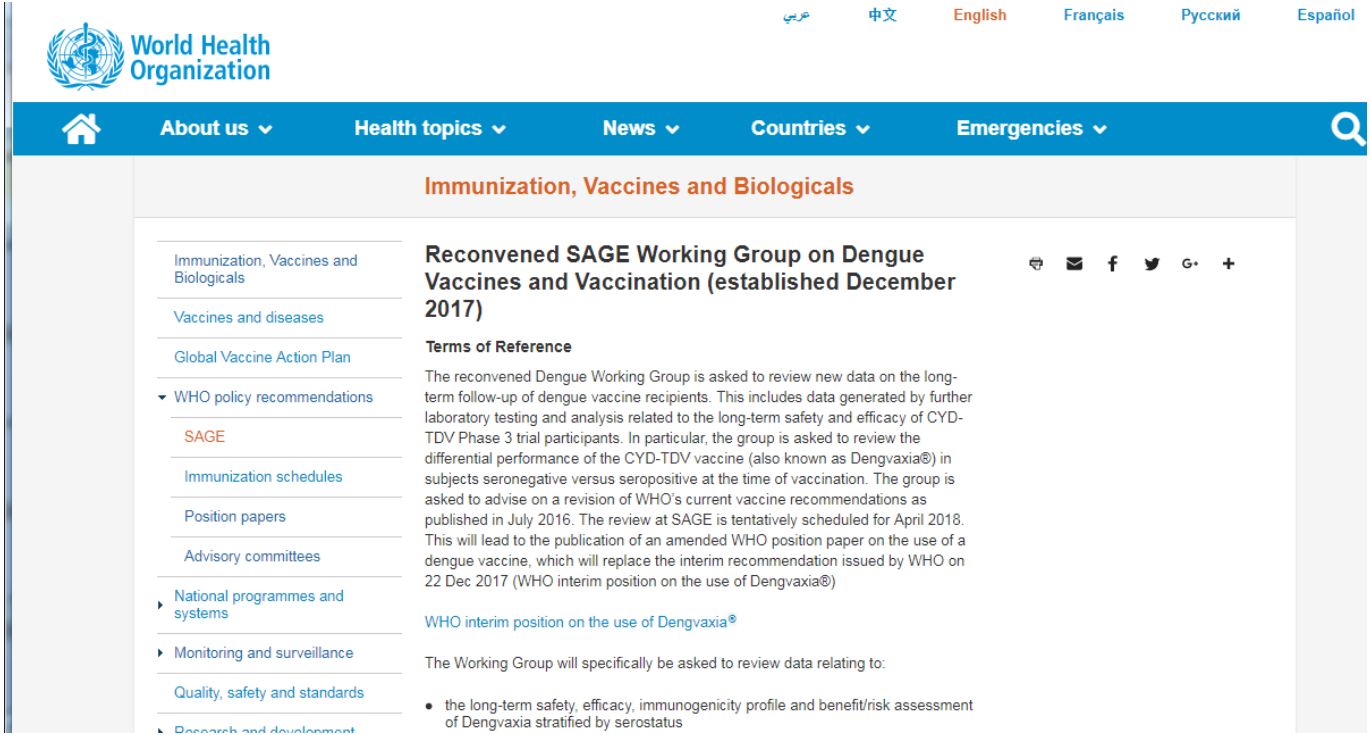
http://www.who.int/vaccine_safety/committee/GACVS-StatementonDengvaxia-CYD-TDV/en/

Immunization Policy



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  - Position papers
  - Advisory committees
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Reconvened SAGE Working Group on Dengue Vaccines and Vaccination (established December 2017)

Terms of Reference

The reconvened Dengue Working Group is asked to review new data on the long-term follow-up of dengue vaccine recipients. This includes data generated by further laboratory testing and analysis related to the long-term safety and efficacy of CYD-TDV Phase 3 trial participants. In particular, the group is asked to review the differential performance of the CYD-TDV vaccine (also known as Dengvaxia®) in subjects seronegative versus seropositive at the time of vaccination. The group is asked to advise on a revision of WHO's current vaccine recommendations as published in July 2016. The review at SAGE is tentatively scheduled for April 2018. This will lead to the publication of an amended WHO position paper on the use of a dengue vaccine, which will replace the interim recommendation issued by WHO on 22 Dec 2017 (WHO interim position on the use of Dengvaxia®)

WHO interim position on the use of Dengvaxia®

The Working Group will specifically be asked to review data relating to:

- the long-term safety, efficacy, immunogenicity profile and benefit/risk assessment of Dengvaxia stratified by serostatus

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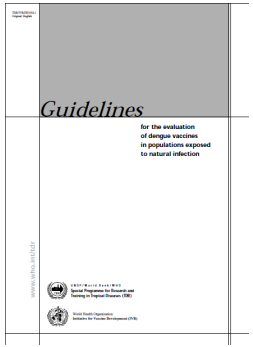
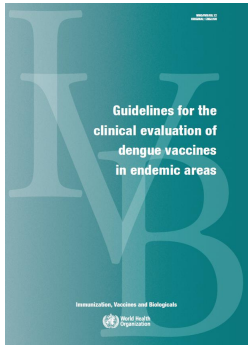
http://www.who.int/immunization/policy/sage/sage_wg_dengue_reconvened_dec2017/en/

Guidance for the clinical evaluation of dengue vaccines candidates 2002 / 2008 / 2018





ARTICLE IN PRESS

Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO Report

Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines

Kirsten S. Vannice [a,1], Annelies Wilder-Smith [a,b,1], Alan D.T. Barrett [c,1], Kalinka Carrijo [d,1], Marco Cavaleri [e,1], Aravinda de Silva [f,1], Anna P. Durbin [g,1], Tim Endy [h,1], Eva Harris [i,1], Bruce L. Innis [j,1], Leah C. Katzelnick [i,1], Peter G. Smith [k,1], Wellington Sun [l,1], Stephen J. Thomas [h,1], Joachim Hombach [a,1,*]

https://doi.org/10.1016/j.vaccine.2018.02.062

Comment on the clinical evaluation of dengue vaccines candidates

Personal View

The dynamic role of dengue cross-reactive immunity: changing the approach to defining vaccine safety and efficacy

Kathryn B Anderson, Timothy P Endy, Stephen J Thomas

Dengue virus infections cause a substantial public health burden in tropical and subtropical regions. A single dengue vaccine has been approved by regulatory authorities in 19 countries, but concerns regarding vaccine safety in people who are dengue naive at the time of immunisation has introduced uncertainty into the vaccine's future. As other dengue vaccines complete or enter large-scale efficacy trials, we argue that foundational work by Sabin, historic epidemiological observations of dengue outbreaks, and prospective cohort studies in Asia and the Americas indicate that modifications must be made to the methods of assessing dengue vaccines. In this Personal View, we review and relate previous data that supports a dynamic role of cross-protective dengue immunity to the goals and challenges of measuring and interpreting dengue vaccine immunogenicity, efficacy, and safety in clinical trials. We suggest that for partly protective vaccines, temporary cross-protective immunity could lead to overestimation of vaccine safety and efficacy in the early years following vaccination. We recommend that assessment of dengue vaccines should span several years, involve active surveillance to clinically characterise incident infections and regular blood draws to define kinetic changes in immunological profiles, and include sample sizes that are large enough to support detailed analyses of vaccine trial subgroups, such as individuals who are dengue naive.

Lancet Infect Dis 2018

Published Online
May 18, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30126-9

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thomstep@upstate.edu

Introduction

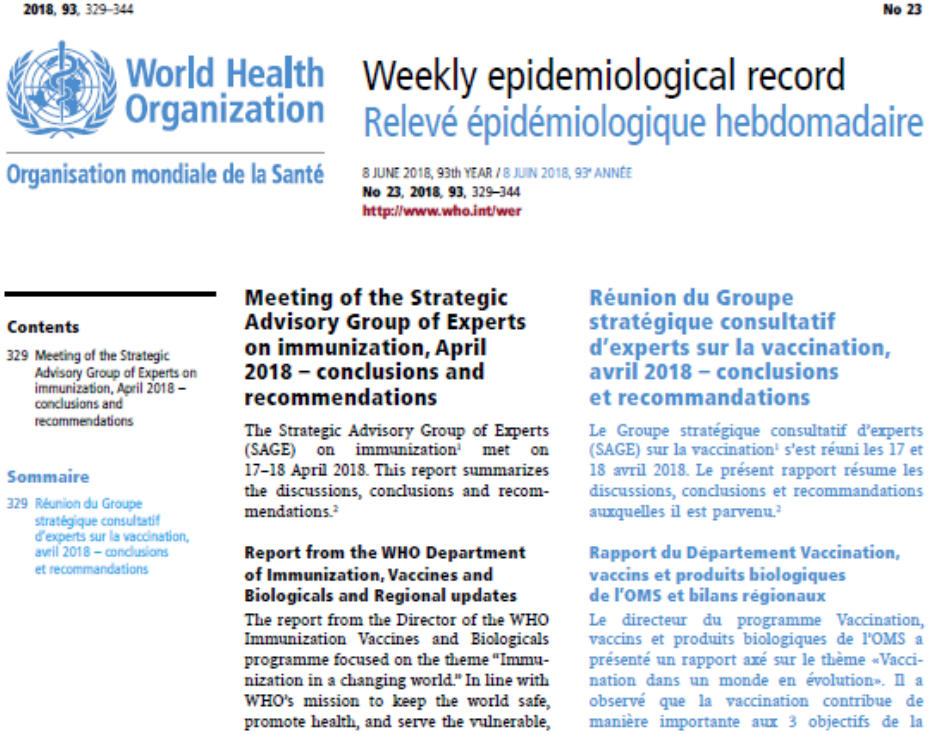
Dengue causes a substantial global public health burden, with endemic transmission across tropical and subtropical regions.[1] Dengue virus infections are also a virus type. The primary efficacy endpoint was determined 13 months after administration of a third dose of vaccine.[8,9] A subsequent multiyear analysis identified a potential safety issue in a subgroup of 2–5-year-old

www.thelancet.com/infection **Published online May 18, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30126-9**

Immunization Policy - SAGE APRIL 2018

http://www.who.int/immunization/policy/sage/en/

Immunization Policy – Updated SAGE reco and WHOPP



2018, 93, 329–344 No 23

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

8 JUNE 2018, 93th YEAR / 8 JUIN 2018, 93e ANNÉE

No 23, 2018, 93, 329–344

http://www.who.int/wer

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Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 17–18 April 2018. This report summarizes the discussions, conclusions and recommendations.[2]

Report from the WHO Department of Immunization, Vaccines and Biologicals and Regional updates

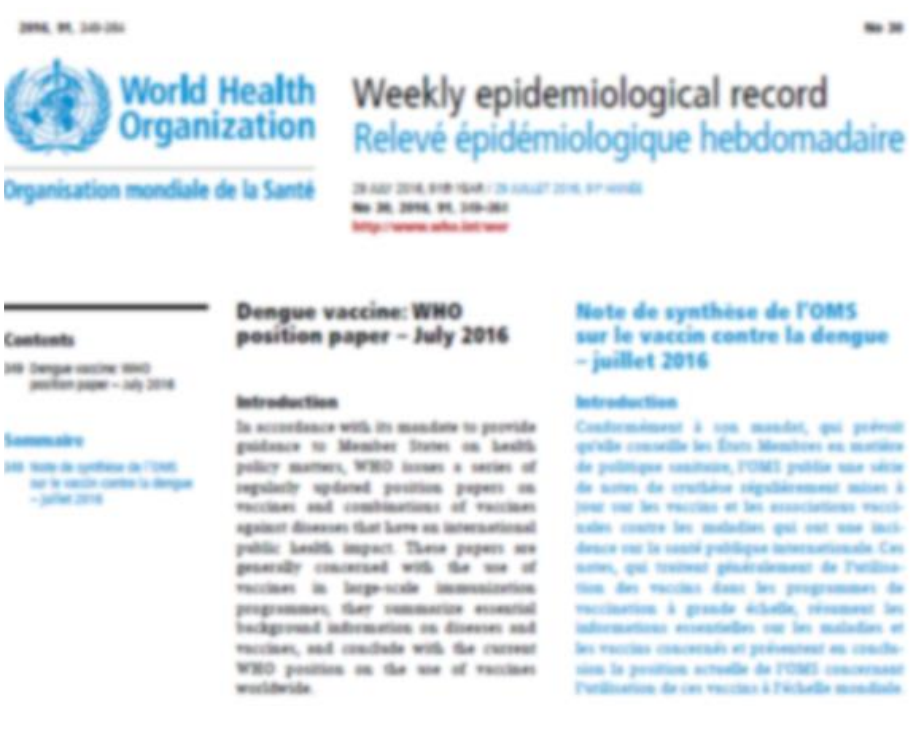
The report from the Director of the WHO Immunization Vaccines and Biologicals programme focused on the theme "Immunization in a changing world." In line with WHO's mission to keep the world safe, promote health, and serve the vulnerable,

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, avril 2018 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni les 17 et 18 avril 2018. Le présent rapport résume les discussions, conclusions et recommandations auxquelles il est parvenu.[2]

Rapport du Département Vaccination, vaccins et produits biologiques de l'OMS et bilans régionaux

Le directeur du programme Vaccination, vaccins et produits biologiques de l'OMS a présenté un rapport axé sur le thème «Vaccination dans un monde en évolution». Il a observé que la vaccination contribue de manière importante aux 3 objectifs de la



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http://www.who.int/wer/2018/wer9323/en/

http://www.who.int/wer/2018/wer9341/en/

Summary

- The development of a vaccine candidate is carried out within an established ecosystem to assure a safe and effective vaccine of assured quality is licensed and appropriately implemented.
    - The ecosystem includes: Clinical Trial Evaluation, Regulatory Review, Programmatic Policy Making, Program Planning and Implementation, and Program and Impact Monitoring and Evaluation
    - The process includes scientific, clinical, regulatory, policy and program expert consultations at the global, regional, and national/sub-national levels.
- The challenge that remains is to assure that populations which can benefit have access to the licensed vaccine, while minimizing individual risk.

Thank you / Obrigado / Merci