Proceedings of the

1ST ASIA DENGUE SUMMIT

Are we ready for the NEW VACCINE ERA?

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Proceedings of the
1st ASIA DENGUE SUMMIT
on evaluating the preparedness of countries for dengue vaccine introduction in the Asia-Pacific region

held on 13 – 14 January 2016, at Shangri-La Hotel, Bangkok, Thailand

Editors
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Proceedings of the

1st Asia Dengue Summit

Are We Ready For The New Vaccine Era?

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Preface

We are very pleased to introduce the proceedings of the first Asia Dengue Summit on evaluating the preparedness of countries for dengue vaccine introduction in the Asia-Pacific region.

Global temperatures are rising and the world is witnessing an urbanisation boom. Such climatic changes, coupled with closer proximity between mosquitos and humans in the urban settings have led to an epidemic rise in dengue. Despite keeping the mosquito population under control, the number of dengue cases continues to rise.

The trend highlights an immediate need for good urban planning and urges the use of dengue vaccine. There is good news; recently, the history of dengue control has reached a major milestone with the first dengue vaccine being introduced in Mexico, Philippines, Brazil and El Salvador. The vaccine was found to be safe and moderately effective, especially in reducing severe cases and hospitalisations due to dengue. It is now time that other dengue stricken countries gain traction in seeking approval for the use of dengue vaccine in their immunisation programme.

Introduction of dengue vaccine however is quite challenging as the disease shows considerable inter and intra-country variations within the Asia-Pacific region. In this context, the first Asia Dengue Summit, co-convened by four esteemed institutions – The Asia Dengue Vaccination Advocacy (ADVA), the Dengue Vaccine Initiative (DVI), Southeast Asian Ministers of Education Organisation (SEAMEO) and Fondation Merieux (FMx), came together to create an unique platform – The Asia Dengue Summit - where experts from different fields and participants from Asia-Pacific countries could interact fruitfully and benefit from each other's research and experience.

This proceeding contains written versions of the talks that were presented during the first Asia Dengue Summit. We hope that you find the proceedings as an enriching guide to help implement effective vaccine introduction strategies in your region.

Goh Yam Thiam Daniel, Usa Thisyakorn, Zulkifli Ismail, Sri Rezeki Hadinegoro, Rose Capeding, Sutee Yok, Terapong Tantawichien (Editors)

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Authors' Conflicts of Interest

Duane J Gubler has provided consultation and advice on dengue to: Globavir, GlaxoSmithKline, Hawaii Biotech, Inviragen, Janssen, Merck, National Institutes of Health, Novartis, Sanofi Pasteur, and Takeda; is a patent holder of a Takeda vaccine; and is an investor in Takeda Pharmaceuticals.

The other authors have no conflicts of interest.

WHO Perspective And Guidance On Burden Of Dengue, Prevention And Control, And Integrated Management

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Abstract

The threat of dengue is world wide, including in Africa and Europe. The World Health Organisation has developed the Global Strategy for Dengue Prevention and Control aiming to reduce dengue mortality by ≥50% and reduce dengue morbidity by ≥25% by 2020, and estimate the true burden of disease by 2015. The Global Strategy has five technical elements diagnosis and case management; integrated surveillance and outbreak preparedness; sustainable vector control; vaccine implementation; and basic operational and implementation research. Challenges to the implementation of the Global Strategy include dengue endemicity; human movement between urban and rural areas; potential for climate change and increases in temperature; and lack of an effective long-term vector control programme. Globally, as malaria declines, dengue continues to increase. This article outlines the Global Strategy for Dengue Prevention and Control.

Keywords: Dengue, Dengue prevention and control, Dengue virus, Global health, World Health Organisation

Introduction

The threat of dengue is world wide, including Africa and Europe. The World Health Organisation's (WHO's) Global Strategy for Dengue Prevention and Control(2012–2020) aims to reduce the burden of dengue through the following objectives: reduce dengue mortality by ≥50% and reduce dengue morbidity by ≥25% by 2020 and estimate the true burden of disease by 2015. [Global Strategy. WHO 2012.]

The Global Strategy is based on five technical elements of: diagnosis and case management; integrated surveillance and outbreak preparedness; sustainable vector control; vaccine implementation; and basic operational and implementation research. Five enabling factors support the technical elements: advocacy and resource mobilisation; partnership, coordination and collaboration; communication to achieve behavioural outcomes; capacity building; and monitoring and evaluation.

Burden Estimation

The burden estimation programme involves situational analysis in selected priority countries for greater access to dengue data and integration of data into the national health information system. A guideline is being developed to assess burden estimation at the national level, including real-time tracking of cases. Estimation of the economic burden of dengue on health systems during outbreaks or epidemics in selected countries is being targeted.

Criteria for the selection of countries are: dengue endemicity; existence of a national dengue programme and a health information system; availability of designated staff as a dengue focal point in WHO; and potential for introduction and evaluation of new tools. Burden studies have been completed Brazil, Mexico, Sri Lanka, Maldives, and Cambodia. Five more countries may be included within the next 2 years, but the focus for 2016 is to assess the burden in Africa. To estimate the real burden of dengue disease, data points for the different severity levels (including infection, fever, severe disease warranting medical attention, and death), cost factors, age- dependence, and probability of laboratory diagnosis need to be considered.

A Technical Working Group advising on the implementation of the Global Strategy has concluded that the WHO endorses and uses the burden estimates derived from the Oxford Group studies. The estimates and risk map [Simmons et al. N Engl J Med 2012.] will be updated using new data. Regular surveillance data continue to be collected and integrated. It is challenging that the gold standard for measuring dengue incidence is active detection through serology, but case detection from hospitalisation is more commonly used, and there is a need to refine the burden estimates for better prediction.

Case Management

For case management and diagnostics, there are tools available in the form of rapid diagnostic tests. Progress has been made on evaluating the performance and utility of

diagnostic tests, including immunoglobulin [Ig] M-based, dengue virus non-structural 1 [NS1] antigen-based, and combination IgM/NS1-based tests, and molecular diagnostics. Laboratory networks have been established in some regions,including the Western Pacific Region and the Americas, and the intention is to form a global network. However, the performance of the rapid diagnostic tests varies across populations, countries, and manufacturers, so need to be evaluated regularly.Resources are needed at the country level for diagnostic kits, and dengue laboratory networks need to be strengthened globally to maintain quality.

For clinical management and case classification, the 2009 classification has been refined and treatment algorithms have been developed aimed at reducing case mortality and helping clinicians with triage. Although opinion varies about redefining dengue case classifications, harmonisation is necessary. In a positive trend, mortality has declined in many countries, primarily due to better case management in hospitals.

Integrated Surveillance

Integrated surveillance is important for risk assessment and situation awareness, and can support outbreak preparedness and development of appropriate public communication. However, the focus must be on feasibility as resources are often limited at the national level. The combination of surveillance techniques employed at a national level must be prioritised while ensuring that surveillance can be sustained and dengue disease identified early for a locally appropriate response.

Outbreak Response

The primary purpose of outbreak response is to meet peak demand during epidemics. Theoretically, early outbreak detection and prediction provides an opportunity for interventions to moderate the size of the outbreak, especially if the response is fast and robust. Research into outbreak response and the variables that can be used to predict outbreak response (rainfall, relative humidity, and temperature) is ongoing. Some instances of outbreak control have been successful at curtailing dengue such as in Iquitos, Peru, and Cairns, Australia. Currently, identification of the key parameters for each epidemiological setting is ongoing to predict outbreaks, improve data quality at the national level, and evaluate the effectiveness of outbreak responses.

Sustainable Vector Management

One of the key elements of the Global Strategy is to highlight the term ‘sustainable’. As for malaria, tools and strategies for dengue are needed long term so must be able to be monitored for effectiveness. Multiple tools for sustainable vector management are available. Under the support of the WHO’s Vector Control Advisory Group, the scalability, coverage, sustainability, acceptability, quality of delivery, and effectiveness of these

tools need to be evaluated. Tools in development include genetically modified 'Release of Insects with Dominant Lethality' technology, Wolbachia-based Aedes aegypti, toxic sugar baits, and a matrix for long-term larval control. [Achee et al. PLoS Negl Trop Dis 2015.]

Introduction Of Vaccines And Combined Interventions

Results of the first successful phase 3 trials of a dengue vaccine have been published recently. [Capeding et al. Lancet 2014. Villar et al. N Engl J Med. 2015.] Several other vaccines candidates are in development. The public health impact and cost effectiveness of the first available dengue vaccine remain to be determined.There are several challenges to vaccine implementation, including the target population, schedule, acceptability, affordability, and long-term effectiveness. Although dengue is challenging to model, several groups are modelling the impact of integrating the vaccine in conjunction with existing vector control tools, as well as new tools that will emerge in the future.

Partnerships

The Partnership for Dengue Control is a positive development for an integrated approach in dengue control as a concept. The three major objectives are to develop the research agenda, develop advocacy and communication, and ensure sustainability through fundraising. Intersectoral partnerships involve the health sector, environment sector, and community partnerships for dengue control, and several regional partnerships exist, such as UNITEDengue (www.unitedengue.org/). There is a need for integration and synergy among partners.

Challenges

Dengue is endemic in much of Africa, with several outbreaks occurring each year. [Amarasinghe et al. Emerg Infect Dis 2011.] Communication is needed to ensure that dengue is recognised as a priority disease in the continent.

Dengue is no longer a strictly urban disease, becoming semi-urban and even rural. One factor is human movement, which is a critical and understudied component of dengue transmission. [Stoddard et al. PLoS Negl Trop Dis 2009.] Identification of hot spots resulting in a prompt response is needed to suppress outbreaks. Integrated surveillance is the key to intervention and prevention, and points of entry need to be monitored for vectors under the International Health Regulation (2005).

There is debate around climate change, although increases in temperature favour the vector and virus multiplication. [Colón-González et al. PLoS Negl Trop Dis 2013.]Rainfall, relative humidity, and El Niño all play a role in dengue transmission and outbreaks, and a large outbreak is expected in 2016. Erratic access to piped water may aggravate

dengue incidence if it leads to increased domestic water storage.

A weak point in dengue vector control is lack of good studies and an effective monitored programme because dengue is usually treated as an outbreak disease. However, a cluster-randomised controlled trial has shown that vector control can reduce dengue by a non-chemical method with good community participation. [Andersson et al. BMJ 2015.] Each trial community in Nicaragua and Mexico selected their preferred vector control intervention and the programme was sustained over 3 to 4 years. The study showed that vector control is sustainable with community mobilisation and contributes to reduction in dengue transmission.

Globally, malaria is declining, with many countries on the verge of disease elimination, while dengue continues to increase (Table 1). Newer estimates are expected in 2016.

Table 1. Comparison of estimates of malaria and dengue

[WHO. World Malaria Report 2015. Brady et al. PLoS Negl Trop Dis. 2012. Bhattet.al. Nature 2013. WHO. Dengue and severe dengue. Factsheet N°117. Updated May 2015.]

Parameter	Malaria (2015)	Dengue	
		Old (2012–2013)	New (2015)
Population at risk	3.2 billion	2.5 billion	3.9 billion
Endemic countries	96 ↓	>100	128 ↑
Infections/year	214 million	50 million	70-500 million
Severe cases	3 million	2.1 million	?
Deaths/year	438,000	20,000	10,000

In Summary

Dengue is a disease of the future. There is uncertain distribution and burden. As malaria declines dengue increases; this is evident in Africa where the incidence of malaria has reduced, but febrile illness remains common due to dengue and other arbo-viral diseases. The impact of environmental changes needs further study. Additionally, there has been silent expansion of the vector (Aedes aegypti and Aedes albopictus). Aedes albopictus is present in 22 countries in Europe so the threat of dengue or chikungunya in Europe is increasing. The greatest challenge is the need for an effective strategy to improve urban health systems. A revised WHO guideline for diagnosis, treatment, prevention, and control of dengue is expected in 2017.

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The Dengue Vaccine Landscape

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Abstract

The global burden of dengue is increasing rapidly, driven by population growth,urbanisation, globalisation, and ecological changes. A dengue vaccine is needed as part of an integrated approach to dengue prevention and control. One vaccine, CYD-TDV (Dengvaxia® , Sanofi Pasteur), has recently completed phase 3 trials in Asia and Latin America and been licensed in Brazil, Mexico, and Philippines for use in 9- to 45-year- old individuals. Two other vaccines (TDV, Takeda, and TV003/TV005,National Institutes of Health) are at advanced stages of clinical development (phases 2 and 3). Several other vaccines are at varying stages of preclinical and clinical development. This article reviews the current status of dengue vaccine research.

Keywords: Asia, Dengue, Dengue vaccines, Dengue virus, Latin America

Introduction

Dengue is the most common global vector-borne viral infection. The global burden is increasing rapidly, driven by population growth, urbanisation, globalisation, and ecological changes. A dengue vaccine is needed as part of an integrated approach to dengue prevention and control, including vector management and improved surveillance.

Dengue Vaccine Development

The dengue virus is a positive-sense, single-stranded, 11 kb RNA flavivirus consisting of three structural proteins (premembrane/membrane [prM/M], envelope [E], and capsid [C]) and seven non-structural proteins. There are four antigenically distinct serotypes (DENV-1, 2, 3, and 4). There have been several different approaches to developing a dengue vaccine, all of which involve the E protein — the key part of the virus responsible for the antigenic distinction between serotypes.However, there are substantial challenges to the development of a dengue vaccine, primarily the presence of the four antigenic serotypes that interact with each other in significant, and often unpredictable, ways. This can result in protection, cross-protection, enhancement (immune enhancement is involved in severe disease), and interference (affecting development of a vaccine that is effective against all four serotypes). There are also technical challenges to vaccine development. Biological assays to measure immune response are imprecise and of unclear clinical relevance, and there is no laboratory measurement that is correlate of protection or risk. There are no valid animal models for preclinical research. Monkeys are frequently used in early trials, but they do not have clinical disease and have lower viraemia than humans, and immunodeficient mouse models have been developed, but they do not accurately reflect the disease in humans. However, there is a robust vaccine pipeline currently in clinical studies (Table 1). There are also several vaccines in preclinical development. [Vannice et al. Vaccine 2015.]

Table 1

Category	Sponsor	Vaccine designation	Approach	Phase
Live attenuated	Sanofi Pasteur	CYD-TDV	YF 17D backbone and YF-DENV chimera	Phase 3 completed Licensed in Mexico, Philippines, and Brazil in December 2015
	Takeda	TDV	DENV-2 PDK-53 backbone and DENV-DENV chimera	Phase 2;phase 3 planned
	US NIH licensed to: Butantan VaBiotech Panacea Serum Institute of India Merck	TV003/TV005	Direct mutagenesis and DENV-2/4 chimera	Preclinical to phase 2 and phase 3
Protein subunit	Merck	V180	DENV 80% E protein recombinant with adjuvant	Phase 1
Inactivated whole virus	GlaxoSmithKline/ Fiocruz/US Army	DPIV	Formalin inactivated with adjuvant	Preclinical to phase 1
DNA	US Navy	TVDV	Plasmid DNA with adjuvant	Phase 1
Heterologous prime-boost	US Army	TDENV-LAV + TDENV-PIV	Live attenuated/ina ctivated whole	Phase 1

DENV, dengue virus; E protein, envelope protein; NIH, National Institutes of Health; YF, yellow fever.

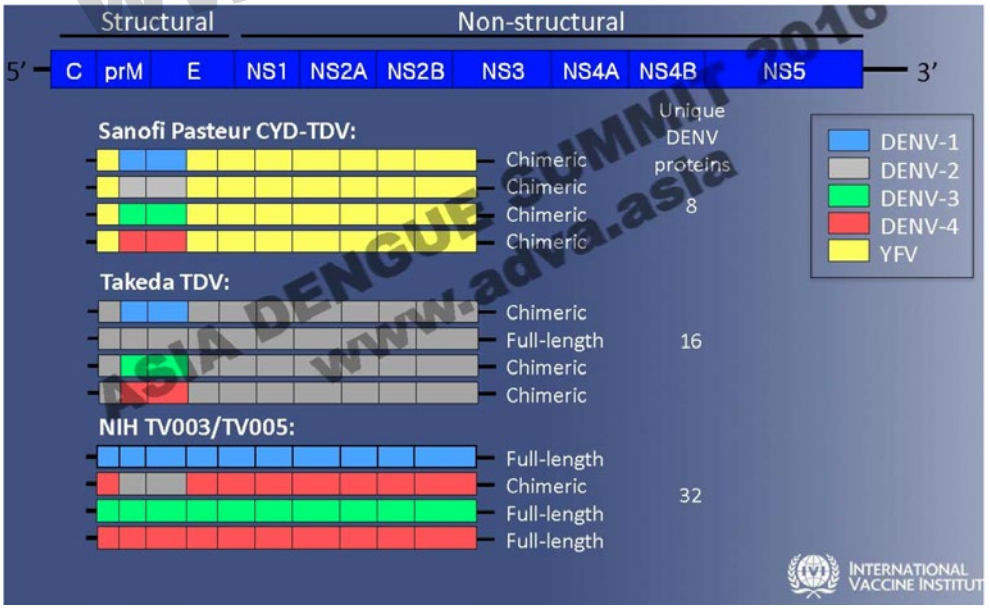
Licensed Dengue Vaccine

CYD-TDV (Dengvaxia® , Sanofi Pasteur, Lyon, France) has completed phase 2b and 3 trials, [Sabchareon et al. Lancet 2012. Capeding et al. Lancet 2014. Villar et al. N Engl J Med 2015. Hadinegoro et al. N Engl J Med 2015.] and is the first vaccine to be licensed. CYD-TDV has serotype-specific efficacy, with poor efficacy against DENV-2, moderate efficacy against DENV-1, and good efficacy against DENV-3 and 4. Immunogenicity

by plaque reduction neutralisation test is of unclear clinical relevance, although further investigation is ongoing. CYD-TDV has better efficacy against severe dengue and in older children and dengue-primed individuals; older children are more likely to be primed. Efficacy is apparent after the first dose in primed individuals. There was increased risk in very young children during the third year after vaccination in the Asian trial. [Capeding et al. Lancet 2014.] Given the efficacy profile and the lack of observed safety signals in post hoc analysis in older children in these trials, Sanofi Pasteur submitted the dossier for licensure in multiple dengue endemic countries in Asia and Latin America. In December 2015, CYD-TDV was licensed in Brazil, Mexico, and Philippines for use in 9- to 45-year-old individuals in endemic areas.

Dengue Vaccines In The Pipeline

Two vaccine candidates at advanced stages of clinical development are TDV(Takeda, Osaka, Japan) and TV003/TV005 (National Institutes of Health [NIH],Bethesda, MD, USA). CYD-TDV, TDV, and TV003/TV005 are all live-attenuated vaccines and all have one or more chimeric serotype component: CYD-TDV has a yellow fever backbone and all four serotype components are chimeric (DENV prM and E proteins); TDV has one component that is attenuated but not chimeric (DENV-2) and three chimeric serotype components (DENV prM and E proteins); and TV003/TV005 have three attenuated components and one chimeric component (DENV-4 backbone with DENV-2 prM and E proteins).



There are also three vaccines at the phase 1 trial stage. GlaxoSmithKline (Brentford, UK), Fiocruz (Rio de Janeiro, Brazil), and the US Army (Walter Reed Army Institute of Research, Silver Spring, MD, USA) have collaborated on a tetravalent purified formalin-inactivated whole virus vaccine. The vaccine is used with an adjuvant, either alum or a GlaxoSmithKline proprietary adjuvant system used in previous vaccines (endemic influenza, malaria). The vaccine is given in a two-dose schedule intramuscularly (IM) at 0 and 21 days, although this may be modified depending on the clinical development plan. The US Army has developed a tetravalent dengue virus purified inactivated vaccine (TDENV-PIV), used with an adjuvant, that has undergone phase I trials in dengue naïve and non-naïve adults.There have been good tetravalent neutralising antibody responses. GlaxoSmithKline has manufactured an inactivated whole virus vaccine (DPIV), used with an adjuvant, which is currently in preclinical studies in monkeys. The collaboration is therefore between two vaccines of similar design that may be expected to act in a similar way.

The potential advantages of DPIV are that it is a non-live vaccine so could be co-administered with other vaccines or to immunocompromised individuals. There should be no or minimal viral interference and there is potential for an accelerated schedule for travellers or for outbreak control. However, there are no non-structural proteins, so there may be immunity issues. As the vaccine is formalin inactivated, it is unclear how much of the native conformation is maintained, which may be important for immunity against wild-type infection, and the relevance of neutralising antibodies is unclear. The vaccine is at a relatively early stage of clinical development.

The V180 vaccine (Merck & Co, Kenilworth, NJ, USA) is a tetravalent recombinant protein subunit vaccine based on a truncated E protein (DENV-80E) and is expressed in the Drosophila S2 expression system. The vaccine requires an adjuvant to elicity sufficient immunogenicity; either alhydrogel or a proprietary adjuvant (e.g., ISCOMATRIX® , CSL Behring, King of Prussia, PA, USA). The vaccine is given in a three-dose schedule IM over 2 months, although this schedule may be modified depending on the clinical development plan. A phase 1 dose-escalation trial in adults is ongoing and a prime-boost phase 1 trial in combination with the NIH dengue vaccine candidate is planned.

The potential advantages are similar to those for an inactivated virus vaccine in that it could be co-administered with other vaccines, administered to immunocompromised individuals, has none or minimal viral interference, and has potential for an accelerated schedule for travellers or for outbreak control. The potential challenges of no non-structural proteins, unclear maintenance of native conformations, unclear relevance of neutralising antibodies, and early clinical development stage are also similar.

The TVDV vaccine (Naval Medical Research Center, Silver Spring, MD, USA) is a tetravalent DNA plasmid vaccine with genes encoding prM and E proteins. The vaccine requires an adjuvant to elicit sufficient immunogenicity (e.g., the proprietary adjuvant, Vaxfectin® [Vical, San Diego, CA, USA]); a trial of the monovalent DENV-1 vaccine without the adjuvant had a poor neutralising antibody response. The vaccine is administered in a three-dose schedule IM over 3 months, although this may be further modified. A phase I dose-escalation trial in adults in the US is ongoing.

The potential advantages of this vaccine are that it could be co-administered with

other vaccines, could be administered to immunocompromised individuals, has none or minimal viral interference, and is stable and relatively easy to produce. The challenges are that it has no non-structural proteins, unclear maintenance of native conformations, and poor neutralising antibody response in humans when used without an adjuvant.

In Summary

Sanofi Pasteur's vaccine, Dengvaxia, has now been licensed in three dengue endemic countries (Brazil, Mexico, and Philippines), and is likely to be licensed in other countries in the future. Butantan's TV003 vaccine (developed by the NIH) has been approved for a phase 3 trial in Brazil. Takeda's TDV vaccine is due to enter a phase 3 trial. Three other candidates (TDENV-PIV, V180, TVDV) are in phase 1 trials. Future clinical development of vaccine candidates will need to consider the fact that Dengvaxia is likely to be introduced into many endemic countries.

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Dengue Control: Is It Possible?

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Abstract

Efforts to prevent the spread of dengue virus and control dengue disease in the past 40 years have been unsuccessful despite the many methods of mosquito control. However, there are some promising new approaches to dengue control, including novel insecticides, genetic control methods, biological controls, spatial repellents, lethal ovitraps, and insecticide-treated materials. The first dengue vaccine (CYD-TDV; Dengvaxia® , Sanofi Pasteur, Lyon, France) has been recently licensed, and others are being developed. New vector control measures are being investigated. None of these new tools are likely to be effective if used alone. Combining vector control with vaccination and integrating these technologies with clinical management, therapeutics, and community engagement will form a targeted control program. An integrated and synergistic control strategy will reduce dengue transmission and help the World Health Organisation to reach the 2020 dengue objectives.

Keywords: Dengue, Dengue vaccines, Dengue virus, Insect vectors, Mosquito control, World Health Organisation

Introduction

Efforts to prevent the spread of dengue virus and control dengue disease in the past 40 years have been unsuccessful despite the many methods of mosquito control,which include space spraying, perifocal control, targeted source reduction, integrated vector management, community participation, bio-control, and genetic control. However, there are some promising new approaches to dengue control.

Vector Control

New mosquito control tools include novel insecticides, genetic control methods,biological controls, spatial repellents, lethal ovitraps, and insecticide-treated materials. Residual insecticides of new non-resistant compounds could be effective replacements for dichlorodiphenyltrichloroethane that are suitable for indoor spraying and for treating oviposition sites and cryptic larval habitats. Lethal ovitraps have a place in an integrated prevention and control programme, but may have a limited impact on the mosquito population. Vapour-active spatial repellents are designed to emit a chemical to prevent mosquitoes from entering an enclosed area, so are effective for personal protection. Insecticide-treated materials (curtains, screens) prevent human-mosquito contact, thus reducing dengue transmission. [Manrique-Saide et al. Emerge Infect Dis 2015.]

Genetic control has not been successful in the past. However, a new repressible dominant lethal gene has been developed. Once the gene is in a mosquito population, all the male mosquitoes are born sterile. When the sterile male mosquitoes mate with wild female mosquitoes, the eggs are sterile so there are no progeny. This technique has been highly successful in eliminating the screwworm population in the southern USA and Mexico, and reducing the cotton boll weevil population in the southern USA. Although this method will rapidly reduce a mosquito population, it is self-limiting so needs to be used repeatedly. Trials conducted in the Cayman Islands and Brazil have been promising. [Harris et al. Nat Biotechnol 2011.Carvalho et al. PLoS Negl Trop Dis 2015.]

Another development is Wolbachia pipientis, a bacterium that is a natural insect parasite. Approximately 75% of the global insect population is infected with W pipientis, but Aedes aegypti is not a natural W pipientis host. A modified W pipientis strain has been developed that infects A aegypti and reduces transmission of the dengue virus by reducing the fecundity and survival age of the mosquitoes, reducing replication of the virus, and making it hard for older mosquitoes to feed by producing a 'bendy' proboscis. Trials have been successful in several countries. [Nguyen et al.Parasit Vectors 2015. Hoffmann et al. PLoS Negl Trop Dis 2014.]

The challenges associated with these new mosquito controls are that they must be used correctly by trained personnel and monitored for resistance. It is unlikely that any of these methods will control dengue if used alone. However, if these control methods are successful at reducing the mosquito population, they will not only control dengue, but also yellow fever, chikungunya, Zika, and other mosquito-borne diseases.

Vaccine Introduction

Currently, there are three lead candidate vaccines, and several others in development. The three main vaccines have been developed by Sanofi Pasteur, Takeda, and National Institutes of Health/Merck (Table 1). CYD-TDV (Dengvaxia® ; Sanofi Pasteur, Lyon, France) was licensed in December 2015 and the other two vaccines are expected to become available within 2 to 3 years.

Table 1. Live Attenuated Dengue Vaccines

	Sanofi-Pasteur	Takeda	NIH/Merck
Doses	3	2	1
Potency	5, 5, 5, 5	4, 4, 4, 5	3, 4, 3, 3
% Tetravalent response (naïve participants and subcutaneous dosing)	78% [Villar et al. Ped Infect Dis 2013.]	100% [Takeda Data on file.]	90%
T-cell epitopes	YFV	DENV-2	DENV-1, -3, -4
Clinical phase	3[a]	2-3	2-3
Overall efficacy	56–61%	?	?

[a] Licensed in Brazil, Mexico, and Philippines in December 2015.

NIH, National Institutes of Health; YFV, yellow fever vaccine.

2015 was a milestone year in dengue vaccine development — CYD-TDV was licensed in Brazil, Mexico, and Philippines in December 2015. CYD-TDV has variable efficacy against the four DENV serotypes, with moderate overall efficacy of 56–61%. There is increased efficacy in people who have had prior exposure to dengue infection. The vaccine has high efficacy in protecting against severe disease, especially dengue haemorrhagic fever, and good efficacy in reducing hospitalisation. In trials involving more than 40,000 people, CYD-TDV has not shown any safety signals, indicating a safe vaccine.

Based on knowledge of dengue infection and immunity, and depending on the required endpoint, a tetravalent vaccine may not be necessary. There is high seroprevalence in endemic countries as most people have had dengue disease at some point in their lives. Most, if not all, cases of severe dengue disease occur during the first or second dengue infections, [Gibbons et al. Am J Trop Med Hyg 2007.] and the third and fourth dengue infections tend to be mild or asymptomatic.[Olkowski et al. J Infect Dis 2013.] Therefore, protection is most needed against the first two infections (bivalent protection).

In endemic countries, the risk of antibody-dependent enhancement is relatively low and can be mitigated with good surveillance and case management. Additionally, effective risk management and clinical diagnosis can reduce the risk of severe dengue disease.

It is uncertain whether any of the three lead live attenuated candidate vaccines will provide balanced tetravalent protection, and they may provide variable protection against the different serotypes. The public health rationale for use of moderately effective dengue vaccines in endemic countries is the priming effect of previous dengue infection on immunity. Most people in hyperendemic areas have already had at least one dengue infection, so vaccinees will be protected against two or more dengue serotypes and against severe disease. However, the public health benefits and challenges of moderately effective dengue vaccines go beyond direct efficacy. The advantages include decreased dengue transmission, reduced magnitude and frequency of epidemics, and reduced risk of health care overload resulting in better management of severe disease and decreased case fatality rate, severe disease and hospitalisation, which has great economic benefits for endemic countries.

Uncertainties related to use of moderately effective vaccines include a paucity of research on third and fourth infections, inadequate surveillance systems to distinguish infection sequence, and reservations about whether the attenuated vaccine viruses will perform as wild type viruses, the role of the virus strain (possible mutation), the role of patient age (possible surrogate for prior infection), temporal distribution of infections with different serotypes (effect on disease severity), and the role of cellular immunity (impact of yellow fever versus dengue backbone on sustainable immunity). Long-term phase 4 studies could be done, but would delay introduction of a vaccine. Alternatively, the vaccines could be introduced under controlled conditions. Vaccine safety and impact need careful evaluation, therefore, rather than deploying the vaccines in widespread national programs, step-wise introduction with strong evaluation and quality control could be considered. Uncertainties and safety issues can only be resolved by introducing the vaccine in endemic countries with careful monitoring. Any safety issues can be mitigated by an effective risk management program, active surveillance for infection and severe disease with high-quality laboratory support, and clinical management training. Similar to the situation for mosquito control, it is unlikely that vaccines alone will be effective in controlling dengue as a public health problem.

Dengue Prevention And Control

There are major challenges for dengue prevention and control. Expanding urbanisation in tropical countries is problematic for effective sustainable strategies for mosquito control in areas of up to 20 million people. Increasing globalisation leads to greater movement of viruses and vectors; it has been estimated that 3 billion people will travel by airplane in 2016, many of whom will be carrying pathogens, including urban pathogens such as dengue. Hidden larval habitats often exist in overcrowded old cities. Resources are needed to build capacity, in terms of laboratory, epidemiology, entomology, virology, training, surveillance, and response. Political will is needed for economic support, public health leadership, and regional dengue control.

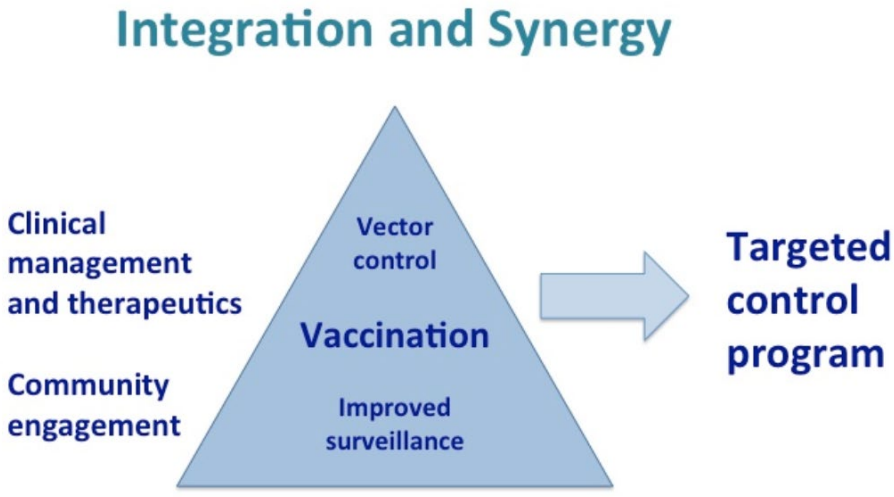
To support regional control of dengue, the Partnership for Dengue Control (PDC) at Fondation Mérieux is in discussion with the Dengue Vaccine Initiative to form the Global Dengue and Aedes-transmitted diseases Consortium to avoid duplication of efforts and resource use. The goals are to:

- eliminate dengue as a public health problem
- promote development and implementation of innovative and synergistic approaches for dengue pevention and control
- support the World Health Organisation (WHO) global strategy for dengue control
- strengthen advocacy, capacity building, and networking
- work closely with vaccine early adopter countries
- promote integration and innovation.

Integration And Synergy

Integration is an old concept, but synergy has been introduced to correspond with the new technologies in development. Vector control continues to be needed to reduce the mosquito population and vaccination will increase herd immunity; combining these technologies with clinical management, therapeutics, and community engagement forms a targeted control programme (Figure 1). Targeted control programmes can research the epidemiology, ecology, culture, and economics of individual countries, and develop a programme of integrated vaccination, vector control, and other tools that will be best suited to that ecological environment. For this approach to work, international mobilisation of resources is needed.

Figure 1 Global Dengue And Aedes-Transmitted Diseases Consortium Paradigm Using New Tools To Control Dengue.



In Conclusion

This may be the dawn of a new era in the fight against dengue. The first dengue vaccine has been licensed and others are in development. Moderately effective vaccines have a role in dengue control, and new vector control measures and antiviral drugs are being investigated. However, none of the new tools are likely to be effective if used alone, and effective dengue prevention and control will require integration of vaccines with mosquito control and enhanced surveillance. An integrated and synergistic control strategy will reduce dengue transmission and help the WHO reach the 2020 dengue objectives. International mobilisation of resource is needed to implement this strategy. Research is still needed to better understand the disease, its pathogenesis, transmission dynamics, and immunology. The tools to prevent and control dengue are available or will be soon. Control of dengue will also help to control other Aedes-transmitted diseases such as chikungunya, Zika, and yellow fever.

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Value And Interpretation Of Modelling As A Public Health Tool

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Abstract

Computer modelling is an underutilised research method with many useful applications. Models can test the empirically untestable with no ethical constraints, and questions can be investigated that would not be possible in real-world research such as forecasting future disease burden or cost-effectiveness of an intervention, or studying the immune dynamics of an entire population. Use of detailed modelling in the field of public health is a relatively new concept. However, as more information about the natural history of dengue infection has become available, more appropriate models can be constructed, and newer computers and statistics enable more sophisticated modelling. Models need to be developed with extensive communication between modellers, clinicians, and public health officials. Ideally, models are extensively tested, but when that is not possible, comparative modelling efforts between independent groups is the best alternative. Bridges between modellers, clinicians, and public health communities are critical for creating well-informed models that are useful and well understood.

Keywords: Dengue, Models, Forecasting, Public health, Public health informatics

Introduction

Computer modelling is an underutilised research method with many useful applications. Models can test the empirically untestable with no ethical constraints, and questions can be answered that would not be possible in real-world research such as future disease level, population immunity, and cost-effectiveness of an intervention.

There are many reasons for underutilisation of computer models. Use of detailed modelling in the field of public health is a relatively new concept. However, as more information about the natural history of dengue infection has become available, more appropriate models can be constructed. Newer computers and statistics enable more sophisticated modelling. Complicated models require time and resources. Understanding of models by non-modellers requires a new literacy.

In an intuitive, everyday type of model such as 'Will it rain today?' predictors of previous weather and the presence of dark clouds can be thought of as input, where the output is whether you need an umbrella. We often have questions where our intuition is not sufficient, however. More sophisticated, quantitative models can be used to answer specific questions, or questions that have more serious consequences. For example, intuition is not sufficient for the following questions, but they could be addressed by an appropriate quantitative model:

- Will it rain >0.5 cm in the next 12 hours?
- Will water reservoirs be re-filled this summer?
- Will mosquito populations increase with climate change?
- How will dengue incidence change over time?

Model Types

A model is an approximation of reality. There are two basic types of model: statistical models describe patterns (for example, perhaps we know the timing of how dengue follows the start of the rainy season, but not exactly why), while mechanistic models (potentially) can predict and explain patterns (Aedes mosquitoes reproduce in standing water and distribute virus via biting). A mechanistic model is more sophisticated and more complicated to set up than a statistical model, but is also more powerful. For example, if dengue disease is expected when it rains then dengue would be found in northern European countries, but factors such as mosquito distribution and temperature also come into play, and these can be accounted for in a mechanistic model.

Extrapolation from models can be unreliable in that predictions will be less dependable the further ahead they are from the available data. Purely descriptive statistical models are particularly vulnerable to this effect.

All quantitative models have a similar structure of inputs (parameters), interactions between variables, and outputs. Parameters include the information that is input and could be the speed of an event, or duration of the infectious period. The interaction between variables could be the transmission of disease by mosquitoes biting people, perhaps on a seasonal basis. The outputs are the information that comes from the model that can be compared to the real world, such as projected epidemic size. In order to be

useful, models need to relate to empirical data.

There are a few different kinds of approaches used to model the spread of diseases. Compartmental (e.g. people are represented as counts in susceptible, infectious, and recovered groups) models are the simplest type, while network models represent explicit population structure, and agent-based models are the most realistic, but also the most complicated to construct and interpret (Table 1). The issues in the complexity of a model include interpretability, analytical and computational tractability, availability of real-world information and parameters, explanatory power and applications, maintainability and re-use. Detailed models can be more accurate than simple models, but greater complexity does not necessarily mean a better model.

Table 1. Model Types By Complexity

Compartmental models	Network models	Agent-based models
Long history	Structured population	Most detailed and flexible
Most mathematically tractable	Sometimes mathematically tractable	Arbitrarily realistic
Everyone in a compartment is the same	Population structure is important and 'known'	Computationally intensive
Deterministic/stochastic	Deterministic/stochastic	Stochastic

Independent Comparative Modelling

A good model makes sense (remember, extraordinary claims demand extraordinary evidence), fits well to the data, is applied in ways that stay close to the fitted data, and is predictive. However, when we construct dengue models we are often trying to predict events decades into the future. We rarely have the data we would like to have to test these ambitious forecasts. Independent, comparative modelling is the best option when validating models is difficult. Comparative modelling involves different groups who are working independently, using different methods and different assumptions, but collaborating and comparing their results. If the results between groups are similar they are more likely to be predictive of a situation. Examples of this include the National Aeronautics and Space Administration's work on climate change from which consensus maps from different models have been prepared. An example for epidemiology is that of the World Health Organisation (WHO), in which four different groups compared their malaria models.1 While the results of each group were not always in agreement the trends were consistent enabling conclusions to be reached. On-going dengue modelling work includes comparative modelling of dengue vaccine impact, supported by the WHO.

Epidemiology modellers working in isolation from clinicians, virologists, entomologists, and public health officials may produce models that are academically interesting, but are frequently not useful. Modellers working in isolation tend to construct poorly informed, unrealistic models that cannot produce reliable predictions. Modellers need to be kept

informed of the important questions and provided with available data to produce reliable results. Equally, modellers must specify their data needs to provide accurate answers and interpretations for public health decision-making.

In Conclusion

Bridges between modellers and clinical and public health communities are needed. Clinical and public health professionals can be critical consumers of models as well as supporting cooperative modelling efforts.

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Global Dengue Vaccine Recommendations And Considerations For Vaccine Decision-Making

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Abstract

There is a rich clinical dengue vaccine development pipeline with one recently registered vaccine, CYD-TVD (Dengvaxia®, Sanofi Pasteur, Lyon, France), and two other promising vaccines in phase 2 or 3 trials. The World Health Organisation supports the process of dengue vaccine development, and has provided guidance and scientific consensus during this period. The World Health Organisation Vaccine Position Papers include global recommendations for use of a specific vaccine (or vaccine class). Position papers are endorsed by the Strategic Advisory Group of Experts on immunisation and published in The Weekly Epidemiological Record. The information includes review of the evidence for key policy questions and review of the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation process. The process is rigorously evidence based, transparent, and inclusive. In April 2016, a Strategic Advisory Group of Experts session on recommendations for dengue vaccines is anticipated, and the first World Health Organisation Vaccine Position Paper on dengue vaccines is expected in mid-2016.

Keywords: Consensus, Dengue vaccines, Public health, World Health Organisation

Introduction

There is a rich clinical dengue vaccine development pipeline. As well as the recently registered vaccine, CYD-TVD (Dengvaxia®, Sanofi Pasteur, Lyon, France), TV003/TV005 from the US National Institutes of Health/Butantan is in phase 2 and 3 trials and DENVax2 from Takeda is in phase 2 trials. It is likely that many of the considerations for vaccine introduction that apply to CYD-TVD will also apply to TV003/TV005 and DENVax2.

The World Health Organisation (WHO) has been supporting the process of dengue vaccine development, and has provided guidance and scientific consensus. During the pre-product registration period, the WHO engaged in activities to support global vaccine guidance and introduction, for example developing regulatory standards. More recently, a dedicated technical advisory group consulted on the pivotal clinical trial results on behalf of the WHO to better understand the complex data from the trials and to ascertain the data needs from a public health/policy recommendation perspective; this information was shared with the vaccine developers. Post-product registration, the most important activity is guidance and recommendations for vaccine introduction and use, but guidance for monitoring vaccine effectiveness and safety post-registration is needed among other support activities.

Guidance On New Vaccine Introduction And Use

The WHO Vaccine Position Papers include global recommendations for use of a specific vaccine (or vaccine class). [WHO. Vaccine position papers.] Development of a position paper starts in anticipation of the registration of a vaccine by national regulatory authorities and is issued after a vaccine is licensed. Position papers are endorsed by the Strategic Advisory Group of Experts (SAGE) on immunisation and published in The Weekly Epidemiological Record [http://www.who.int/wer/en/]. The information includes review of the evidence for key policy questions and review of the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation process. The position papers are upgraded regularly as new knowledge becomes available. The nature of the recommendations can be distinct, and SAGE can identify areas where further research is needed.

Much of the recommendation development is done by a dedicated SAGE working group, with input from other WHO advisory groups on specific issues. A background paper is produced and discussed by SAGE at an open meeting. The recommendations are then reviewed by the WHO Director General, and tendered for broad stakeholder consultation before a position paper is developed. The process is rigorously evidence based, transparent, and inclusive. All the information that is critical for decision-making by SAGE is in the public domain or will be made public at the time of the SAGE meeting.

The current SAGE Working Group on Dengue Vaccines was established in March 2015. The group was established through an open call for nomination with the process resulting in a diverse group with different backgrounds to address the various aspects of the vaccine from biologic, through clinical, to implementation.

Key Considerations For Policy

Key considerations for dengue vaccine policy include vaccine safety, vaccine efficacy, and programmatic aspects (Table 1). As the dengue vaccine is new, there may not be sufficient data to answer all the considerations, hence a need for mathematical modelling to inform and underpin policy recommendations.

Table 1. Key Considerations For Dengue Vaccine Policy

Parameter	Consideration
Vaccine safety	Reactogenicity and serious adverse events, AESI Long-term safety and risk of hospitalisation/severe dengue
Vaccine efficacy	Overall, by age, by serostatus, by serotype Efficacy against laboratory-confirmed dengue, severe disease Duration of protection
Programmatic aspects	Dose scheduling Co-administration Vaccine introduction strategies, including outbreak response Vaccine impact and cost-effectiveness Criteria for country decision-making

AESI, adverse events of special interest

Comparative Modelling

Comparative modelling of dengue vaccine public health impact will provide additional information for SAGE recommendations on the use of dengue vaccine by assessing various scenarios and their impact on public health. A secondary objective is to understand the key features of dengue vaccine models that influence results in order to improve the standard of modelling and help country-level decision makers interpret the results of modelling evidence. The final objective is to identify circumstances for potential long-term safety concerns for CYD-TVD.

The WHO has used comparative modelling since 2008 for cost-effectiveness analysis for pneumococcal conjugate vaccine, rotavirus, human papillomavirus (HPV), and malaria (Table 2). There are many tools to investigate cost-effectiveness, so the WHO advises on the use of models on a community or country basis.

Table 2. Who Use Of Comparative Modelling For Cost-Effectiveness Analysis							
Antigen	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Pneumococcal conjugate vaccine [Chaiyakunapruk 2011.]							
Rotavirus [Postma 2011.]							
Human papillomavirus [Jit 2011. Jit 2013.]							
Malaria [Penny 2016.]							

Comparative modelling of dengue vaccine impact evaluated the following parameters: routine introduction at 9 years; catch-up vaccination at 10–17 years; Asian and Latin-American reference country scenarios and different transmission intensities; and vaccine impact on infection, clinical cases, severe cases, and death. The vaccine impact was modelled overall, by age group, and by 10- and 30-year time horizons. An exploratory economic evaluation was also done, although this will be done more accurately by each country to suit their specific circumstances. The economic evaluation included traditional cost-effectiveness analysis (costs per clinical case and costs per disability-adjusted life year averted); delivery costs adapted from HPV vaccine delivery experience; and literature appraisal of the broader economic impact (no modelling).

An example of comparative public health impact modelling comes from the research by Penny et al, which compared the cumulative impact of a vaccine over 15 years among four malaria transmission models. [Lancet 2016.] The model was designed to predict clinical cases and deaths averted per 100,000 children fully vaccinated with a three- or four-dose schedule across various transmission intensities (in the presence of existing malaria control interventions). There was good overall agreement between the four models, and the results suggested greater vaccine impact in moderate-high transmission settings.

Timelines For Who Global Policy On Dengue Vaccine

In April 2016, a SAGE session on recommendations for dengue vaccines is anticipated. SAGE will issue recommendations, which should be available publically during the week following the SAGE meeting. The first WHO Vaccine Position Paper on dengue vaccines is expected in mid-2016.

Development of vaccine policy is done at the global, regional, and national levels. The global recommendations from the WHO are intended to inform country decision makers and provide general orientation. Decisions are ultimately made by the National Immunisation Technical Advisory Groups in an evidence-based transparent manner at the country level.

Considerations For Vaccine Introduction

Considerations for vaccine introduction include disease factors (high morbidity with low mortality, outbreaks and burden on health system, school or work absenteeism, and alternative or additional preventive methods, i.e. vector control) and vaccine factors (availability, price, programmatic costs, economic impact, national budget and vaccine affordability, and funding gaps and sustainability). [WHO 2014.] The strength of the immunisation programme and the health system in the country also need to be considered. Important programmatic considerations include overall readiness for a new vaccine, school readiness, and implementation readiness, [WHO 2013.] as well as tracking of vaccination status.

Vaccination will not replace vector control. Mathematical modelling will help to show how vaccination and vector control interact, but there could be additive or synergistic effects to reduce transmission. The use of both vector and vaccination strategies is essential, and communication, community mobilisation, and advocacy remains important for both vector control and vaccination.

In Summary

The WHO official recommendations related to dengue vaccination are forthcoming following vaccine registration. There are multiple considerations for vaccine decision-making at the global, regional, and national levels, including vaccine characteristics/ profile, disease burden, health systems and programmatic considerations, and complexity of vaccine performance and heterogeneity of dengue epidemiology. Mathematical modelling is increasingly important for informing vaccine recommendations and policy choices at the global and country levels. Programmatically, lessons can be learned from other vaccination efforts in this age group such as the experience with HPV. A new vaccine is an opportunity to strengthen immunisation infrastructure, such as immunisation registries.

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Current School-Based Vaccination Programs And Plans In Asia

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Abstract

When the World Health Organisation endorsed the human papillomavirus vaccine, Malaysia made it available to all girls aged 13 years old via a School Health Program. Reasons for using school-based immunisation programs include the relative ease of providing vaccinations and booster doses at a specific age to a captive population with high compliance rates. This article discusses the current status of school-based immunisation programs in four Asian countries, Malaysia, Philippines, Thailand, and Indonesia, and describes the introduction of the human papillomavirus vaccine into the school-based immunisation program in Malaysia.

Keywords: Asia, Human papillomavirus, Immunisation programs, School health services, Vaccination

Building The School-Based Human Papillomavirus Vaccination Program In Malaysia

Human Papillomavirus Vaccination In Malaysia

Malaysia has low uptake of cervical cancer screening with the Papanicolaou smear test at approximately 50% of women in the reproductive age group, and Malaysian women delay seeking treatment with 76% of women with cervical cancer seeking treatment at stage 2 or above. Thus, there is a need for cervical cancer prevention measures. When the World Health Organisation (WHO) endorsed the human papillomavirus (HPV) vaccine, Malaysia made it available to all girls aged 13 years.[1]

Cost-effectiveness analysis showed that HPV vaccine introduction would reduce the incidence of cervical cancer from 19.7/100,000 population to 8/1,000,000 (0.8/100,000) population. The vaccine was made available privately in 2006, and was approved for public healthcare in 2009 and implemented in 2010.

The goal of the vaccine was to reduce the incidence of cervical cancer related to HPV types 16 and 18 among immunised girls over next 20 years. The strategy was to deliver the vaccine as part of the Cervical Cancer Prevention and Control Program and integrate it into the Expended Program of Immunisation (EPI). The operational policy was for voluntary free school-based HPV vaccination delivery to Malaysian girls in form 1 (age 12–13 years) because Malaysia has good school attendance. Owing to the availability of a structured comprehensive school health program the HPV vaccine was delivered as an additional vaccination to the existing EPI. There was strong commitment and support from the Ministry of Education (MoE).

Owing to the association of HPV with sexual promiscuity, the vaccine was promoted as a cervical cancer vaccine. A health belief model was used in the campaign (Table 1), which was built on public access to interactive information. An important component was rumour surveillance and program monitoring, and the religious and cultural aspects were addressed by the Ministry of Health (MoH) and religious authorities.

Table 1. Promoting Hpv Vaccine As A Cervical Cancer Vaccine.

Media campaign based on health belief model	Public access to interactive information	Rumours surveillance and program monitoring
Cervical cancer is preventable	Social media HPV Facebook	Response to media and public queries
Parental awareness on voluntary vaccination Persuade girls to complete 3 doses of vaccination as scheduled	HPV Twitter Phone hot line Email Print and electronic advertisement	Provide guideline to implementers Monitor potential program threat and proposed counter measures

HPV, human papillomavirus.

The program target of completion of three doses for 95% of form 1 girls was surpassed at 98% completion. Malaysia has the highest uptake (97.9% in 2012–2013) when compared with Australia (71.0%), England (86.1%), and Scotland (91.4%). The adverse event (AE) rate has been approximately 1% up to 2014, and AEs are primarily

due to local reaction at the injection site; there have been no serious AEs following immunisation.

Factors contributing to the success of the HPV immunisation programme include:

- political will and commitment
- public trust in the Malaysian EPI
- availability of school health services infrastructure
- existing strong relationship with the MoE
- effective risk communication strategy
- addressing religious issues
- competitive procurement mechanism.

Integration Of New Programs Into School Health Activities

Integrating the HPV vaccine into the School Health Program (SHP) made it part of the immunisation package rather than a new program. The SHP was established in 1967 in partnership with the MoE. The School Health Service is part of the SHP, and is a life course perspective wellness program under the Family Health Program. Services in schools are delivered by School Health Teams, which usually comprise a doctor, public health nurses or assistant medical officer, community nurses, and medical aid. The School Health Teams provide mobile health services to 10,159 primary and secondary schools. The role and function of each team member is defined by the School Health Service Standard Operating Procedure. Performance targets are monitored and discussed at district, state, and national meetings on regular basis. The SHP has increased dramatically in recent years, and now delivers a wide variety of packages, including screening, health education, and immunisation, with the latest addition being thalassaemia carrier screening.

The guiding principles of adding a new program into the School Health Service are:

- additional new service introduction must not affect existing services performance
- implementation must be approved by the MoE
- implementation must not interfere with the school schedule
- participation must be voluntary, with parental approval.

There are several factors to consider before integrating a new program into school health activities, as shown in Table 2. Preparation and planning is key to the success of a school-based immunisation program.

Table 2. Factors To Consider Before Integrating A New Program Into School Health Activities	
Factor	**Requirements**
School health infrastructure and resources	Initial budget to include implementation, e.g. cold-chain, transportation Resource mobilisation
New program objectives and expected impact	Long-term/short-term impact Coverage (>95% for HPV)
Capacity building	Training and introduction phase Updates (e.g. policy changes)
Monitoring and evaluation	Track implementation and impact
Dealing with public expectation	Health promotion campaign budget Crisis management Demand for service
Parental acceptance	Confidence in new program Vaccine safety and efficacy Vaccine combination (e.g. HPV and tetanus toxoid)
Will the new program effect students' performance	Which cohort to choose from (consideration of examinations, prophylaxis status of HPV vaccine)
Compliance to schedule/follow-up	Completion within one schooling period (timing of doses)
HPV, human papillomavirus.	

School-Based Immunisation Program And Plans In Philippines

There are many reasons for school-based immunisation programs. Protection produced by many vaccines will decline over time, and booster doses may be needed to ensure that high levels of protection are maintained. New vaccines are more effective if delivered at a specific age. Compliance rates are assumed to be better in school-based programs as a school has a 'captive' population. The current vaccinations delivered to Philippines schoolchildren are measles-rubella and tetanus-diphtheria vaccine in grades 1 and 7 and HPV vaccine in grade 4. A school deworming program has recently been introduced.

Guidelines for the implementation of school-based immunisation were introduced in 2015. The guidelines comprise both general and specific guidelines on the use of the vaccine, vaccine storage and transport, immunisation safety, recording and reporting accomplishment reports, and AEs following immunisation. The Department of Health (DoH) provides the necessary vaccines and other immunisation logistics for routine distribution of the vaccine, training, and pharmacovigilance reporting support. All school-based vaccines are provided free of charge by the DoH. The Department of Education assists and facilitates the implementation of the immunisation in schools,

issues memoranda about the activity, informs students, parents, teachers, and school clinic staff, screens students at school entry, and submits reports to the local health units. Parental consent is necessary for vaccine delivery to the students. The Department of Interior and Local Government issues a memorandum to all local chief executives for their participation in the activity, including organisation of the vaccination team for deployment to schools and completion of the activity, and ensures high immunisation coverage per grade level. Local Government Units are responsible for providing healthcare personnel to lead the vaccination in collaboration with schools, hospitals, and other partners within the catchment areas. Local Government Units also run awareness and information campaigns at a local level. The Parents–Teachers Association plays an important role by raising awareness according to the guidelines for school-based immunisation.

Dengue Prevention And Control Program

There are several components to the dengue prevention and control program, including surveillance, integrated vector management, case management, social mobilisation and communication, outbreak response, and research. For dengue surveillance, the existing standard dengue case definition adopted and case fatality rate standardised is based on the recommendations of the WHO. Laboratory surveillance is being upgraded to enable monitoring of the different serotypes circulating in different areas as an indicator of an impending outbreak. Mechanisms for sharing timely and accurate data are in place (UNITEDengue; https://www.unitedengue.org/index.html). Dengue surveillance (case, vector, and seroprevalence) is incorporated into an integrated and strengthened disease surveillance system.

Dengue vectors have been fully described and vector indicators are regularly monitored. An integrated vector management strategy has been implemented, including recruitment and training of entomologists, and evidence-based strategies to control vector populations have been adopted. Community involvement for vector control is facilitated. For rational use of insecticide for vector control, the WHO Pesticide Evaluation Scheme guidelines on pesticide management are being adopted. Vector resistance is monitored regularly.

For dengue case management, training has been done to capacitate health professionals to diagnose, treat, or refer cases. There is laboratory support for case management and a referral network system in both the public and private sectors. The public are made aware of the warning signs and actions to be taken. Currently, the case fatality rate in Philippines is 0.3%, but the number of dengue cases is increasing.

For social mobilisation and communication for dengue, communication for behavioural impact (COMBI) training has been implemented and the COMBI approach disseminated and promoted. Development and implementation of the COMBI plan is supported and partnerships with the private healthcare sector and other stakeholders have been established.

For dengue outbreak response, there is a dengue outbreak standard operating system and national early warning system/dengue surveillance system. Coordination

mechanisms are within the DoH and with other programs and sectors. Health workers have the ability to respond to the dengue outbreak and there is a risk communication plan.

Research into disease burden has been done, but will be updated with the latest profile. There will be evaluation of tools and strategies for dengue control and case management, and operational research.

Dengue Vaccine

Philippines is the first country in the Asia-Pacific region to register the dengue vaccine, on 22 December 2015. The vaccine will be delivered under the school-based immunisation program to children aged 9 years, in accordance with the results of the phase 3 trials,[2,3] in selected public schools. The vaccine will be implemented slowly in three highly endemic regions with a high-risk population.

Training of healthcare providers, active surveillance for AEs following immunisation, and a recording and reporting system will be needed. Good communication will be needed to explain why only certain regions and only public schools have the vaccine. The DoH will provide all logistical items such as vaccine, syringes, and reporting forms before vaccination starts. The dengue program will continue the various prevention strategies in conjunction with the vaccine implementation initiative.

Operational research will include a post-authorisation phase 4 study, collection of data on access to care, cost-effectiveness research, and policy studies to support expansion of the vaccine to other parts of country.

Potential problems for the DoH include low coverage and unmet health objectives. Teachers may be uncertain about implementing the program and parents may lose trust in DoH programs resulting in children being lost to the DoH programs. However, all these efforts are being made to reduce the number of dengue cases in the country.

School-Based Immunisation Program And Plans In Bangkok Metropolitan Administration, Thailand

The Bangkok Metropolitan Administration (BMA) covers an area of 1568 km2. The registered population is 5,674,843 in 2.4 million households. The organisation of the BMA is headed by the Governor, and the DoH is responsible for vaccination. The BMA healthcare providers run 68 public health centres, which are responsible for school-based vaccination, and eight hospitals. The Ministry of Public Health has 36 hospitals and 135 health units, and there are 95 hospitals and 466 clinics run by private healthcare providers.

Thailand has a very full EPI, as shown in Table 3. The only routine vaccinations given in school are diphtheria and tetanus at the age of 12 years, but catch-up vaccines are given at age 7 years to children who have not completed the immunisation program. Coverage for the school-based diphtheria and tetanus vaccination is 86%.

Table 3. Expanded Program Of Immunisation In Thailand.	
Age	**Antigen**
Birth	BCG, HB1
2 months	OPV1, DTP-HB1
4 months	OPV1, OPV2, DTP-HB2
6 months	OPV3, DTP-HB3
9 months	MMR1
1 year	JE1-2
18 months	OPV4, DTP4
30 months	MMR2, JE3
4 years	OPV5, DTP5
7 years	BCG, dT, OPV, MR
12 years	dT
Pregnant women	dT
Healthcare personnel and risk groups	Influenza
BCG, Bacillus Calmette–Guérin; dT, diphtheria and tetanus; DTP, diphtheria, tetanus, and pertussis; HB, hepatitis B; JE, Japanese encephalitis; MMR, measles, mumps, and rubella; MR, measles and rubella; OPV, oral polio vaccine.	

There are several optional vaccines recommended by the Infectious Disease Society of Thailand, including whooping cough (pertussis), Haemophilus influenzae type b, and HPV (two doses at the age of 11–12 years). Cervical cancer is a public health problem, and Thailand has approximately 10,000 new cases each year, with a 50% case fatality rate. In 2015, a campaign for optional HPV vaccine was launched in the BMA, and coverage was 98% for the first dose.

School-based vaccination coverage in the BMA is well accepted with high coverage. Strengthening of capacity building is an important step for a successful school-based vaccination program.

School-based immunisation program and plans in Bangkok Metropolitan Administration, Thailand

The ultimate goal of a public health program is maximal control of disease and improvement of health. The Indonesian constitution states that health is the right of all Indonesian people. The goals of the EPI are to reduce morbidity, mortality, and disability caused by the EPI target diseases by reduction, elimination, or eradication of these diseases.

The mandatory immunisation services include routine immunisation for infants, children younger than 5 years, schoolchildren, and women of childbearing age. Additional immunisation is done for backlog fighting, catch-up programs and campaigns, national

immunisation days, and outbreak response immunisation. Specific case immunisation may be done for meningitis, yellow fever, and rabies. Optional immunisation includes those vaccines not provided by the government.

The policy and operational strategy is to achieve high immunisation coverage, that is equally distributed via a static and accessible EPI service and EPI services in hard-to-reach areas; continuous quality improvement through skilled personnel, quality vaccine and cold chain system, and correct vaccination procedure; and community mobilisation and participation. The target for the EPI is shown in Table 4.

Table 4. Expanded Program Of Immunisation In Indonesia.

Age	Antigen
Birth	HB
1 month	BCG, OPV1
2 months	DPT-HB-Hib 1, OPV1
3 months	DPT-HB-Hib 1, OPV2
4 months	DPT-HB-Hib 1, OPV3, IPVa
9 months	Measles
18 months	Measles, DPT-HB-Hib

[a] IPV will be introduced in July 2016.
BCG, Bacillus Calmette–Guérin; DTP, diphtheria, tetanus, and pertussis; HB, hepatitis B; Hib, Haemophilus influenzae type b; IPV, inactivated polio vaccine; OPV, oral polio vaccine.

The SHP began in 1956 in collaboration with the Ministries of Health, Education, Internal Affairs, and Religious Affairs. The programs under the Usaha Kesehatan Sekolah (SHP) are health education, health service delivery through schools, and healthy school environment, and the Bulan Imunisasi Anak Sekolah (School Immunisation Month Program; BIAS). The reason for a school immunisation program was the low coverage of tetanus toxoid immunisation among pregnant women, women of childbearing age, and grade 6 elementary schoolchildren and the high level of neonatal tetanus. The universal child immunisation level was achieved in 1990, and this cohort reached grade 1 elementary school level in 1997, and the school enrolment ratio was >95% at elementary school.

The objective of a school immunisation program is to provide long-term protection to children against EPI target diseases of measles, diphtheria, and tetanus, including neonatal tetanus. Specific objectives are to provide life-long protection against measles, 10 years protection against diphtheria, and 25 years protection against tetanus. The BIAS is well designed with elements for a successful program of official policy, operational guidelines for health workers and teachers, roles and responsibilities of each Ministry, budget at health centres and districts, and vaccine and supplies provided by central

government. There is high coverage in all schools where the program is conducted and local ownership of operational costs, it is not a heavy burden on health staff, operational costs per student vaccinated are low (<US$1.00), and there are consistent data from schools upwards to the provincial health office. There are cost and financing issues of limited operational costs, limited resources for monitoring and evaluation, and lack of advocacy to local government. However, coverage is >90%. Guidance and information, education, and communication materials are supplied to the local authority.

The role of the MoH is development of policy and guidelines for technical matters, preparation and implementation of immunisation services at schools, and monitoring and evaluation. The role of the MoE is socialisation and mobilisation of teachers in both public and private schools to support the program, and coordination with schools to approach the parents. The role of the Ministry of Religion is socialisation and mobilisation of teachers in faith-based public and private schools, including Islamic boarding schools, which are common in most of areas of Indonesia. The role of the Ministry of Home Affairs is socialisation and advocacy to local governments for logistics and supplies budget allocation (not including vaccines) and operational costs for program implementation.

The challenges include how to institutionalise the BIAS, improve parents' awareness, and integrate new vaccines such as HPV and dengue into the program. Global disease elimination and eradication is a public health strategy.

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