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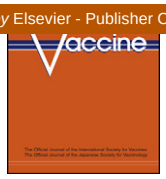

Review

Preparing for introduction of a dengue vaccine: Recommendations from the 1st Dengue v2V Asia-Pacific Meeting

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ABSTRACT

Infection with dengue virus is a major public health problem in the Asia-Pacific region and throughout tropical and sub-tropical regions of the world. Vaccination represents a major opportunity to control dengue and several candidate vaccines are in development. Experts in dengue and in vaccine introduction gathered for a two day meeting during which they examined the challenges inherent to the introduction of a dengue vaccine into the national immunisation programmes of countries of the Asia-Pacific. The aim was to develop a series of recommendations to reduce the delay between vaccine licensure and vaccine introduction. Major recommendations arising from the meeting included: ascertaining and publicising the full burden and cost of dengue; changing the perception of dengue in non-endemic countries to help generate global support for dengue vaccination; ensuring

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high quality active surveillance systems and diagnostics; and identifying sustainable sources of funding, both to support vaccine introduction and to maintain the vaccination programme. The attendees at the meeting were in agreement that with the introduction of an effective vaccine, dengue is a disease that could be controlled, and that in order to ensure a vaccine is introduced as rapidly as possible, there is a need to start preparing now.

Contents

1. Introduction

Dengue is a major public health concern throughout tropical and sub-tropical regions of the world. It is the most rapidly spreading mosquito-borne viral disease, with a 30-fold increase in worldwide incidence over the last 50 years [1]. It is estimated that there are more than 50 million dengue infections each year and almost half the world's population live in countries in which dengue is endemic [1,2]. While dengue is a global concern, with a steady increase in the number of countries reporting dengue, currently close to 75% of the global dengue burden is borne by the Asia-Pacific region [1].

Attempts to control dengue are focused on control of the mosquito vector [3]. Integrated vector management programmes have been shown to be effective in reducing total numbers of the vector [4]. However, many vector control programmes have little to no effect on dengue incidence [5] and those that are successful can have difficulties with sustainability [6]. The limitations of vector control include the cost of maintaining control programmes, the difficulty of destroying all mosquitoes in an area, and the movement of mosquitoes across borders.

Given the significant and increasing burden of dengue, the limitations of current control measures and the fact that disease treatment is limited to supportive care, it is not surprising that a dengue vaccine has been a priority of the World Health Organization (WHO) for a number of years [7]. Currently, there are a number of candidate dengue vaccines in development including recombinant, live attenuated, inactivated, DNA, and viral-vector vaccines, with several undergoing clinical evaluation [7,8]. The most advanced of these candidates has recently entered Phase III trials [9–11].

A dengue vaccine should be first introduced in countries where the disease burden is greatest. Many of these are developing countries, which pose unique challenges to the introduction of a new vaccine that in the past have led to significant delays, even for vaccines which had already been successfully introduced in developed countries [12]. Previous vaccine introductions have taught us that the key is to plan early [13]. This report presents a series of recommendations for the rapid introduction of a dengue vaccine into the national immunisation programmes (NIPs) of high disease burden countries of the Asia-Pacific.

2. Dengue v2V and the Asia-Pacific Meeting

The Dengue v2V initiative is a global scientific forum of experts in dengue and public health, established in 2009 to lay the groundwork for the rapid introduction of a dengue vaccine, focussing on candidate vaccines in advanced stages approaching licensure [14]. Its goals are to establish the human and economic costs of dengue, raise awareness of the benefits of vaccination, provide recommendations and guidance for vaccine introduction, and advocate funding for broad access to dengue vaccination [14]. At the 1st Dengue v2V Asia-Pacific Meeting, held in Singapore from 30 November to 1 December 2010, the challenges inherent to the introduction of a dengue vaccine into the NIPs of high disease burden countries of the Asia-Pacific were considered in light of the lessons learned from previous vaccine introductions. Participants at the meeting included experts in dengue, vaccine introduction and regional vaccination programmes (see acknowledgments for a full list of participants). The aim was to develop a series of recommendations to reduce the lag time from vaccine licensure to vaccine introduction.

3. Supporting vaccine adoption

Due to differences in climate, geography, urbanisation, socio-economic status and population movement, there are considerable intra- and inter-country variations in dengue epidemiology in the Asia-Pacific region. Variations include the affected age groups, case fatality rate, predominant serotype(s) and incidence rates. Furthermore, considerable differences in diagnosis and reporting systems

can limit the ability to make meaningful comparisons between countries. Southeast Asian national surveillance systems differ in the case definitions used, ages surveyed, reporting requirements, use of vector surveillance and the use of sentinel surveillance in addition to passive surveillance [15].

Passive surveillance is based on the reporting of confirmed or suspected cases encountered by health care workers. However, as most dengue cases are ambulatory, and not always seen by health care workers, this system results in significant under-reporting. Under-reporting also results from the lack of a universally applicable or uniformly applied case definition [16]. Improving the availability and reliability of diagnostics for dengue is a major priority. Recent recommendations from the Asia-Pacific and Americas Dengue Prevention Boards (organised by the Dengue Vaccine Initiative Consortium) include: making the reporting of dengue mandatory, use of electronic reporting systems, application of minimum reporting requirements and sharing of expertise and data [15].

3.1. Health economics

To obtain support from governments and global decision-makers, a dengue vaccine must be shown to be cost-effective. This requires accurate data on the economic costs of dengue. Dengue is responsible for an annual estimated global burden of 750,000 disability-adjusted life years (DALY) [6,17,18]. A study across eight countries in Asia and Latin America estimated that the mean cost per hospitalised case of dengue is US$571, of which 76% was direct costs and 24% indirect costs [19]. For ambulatory cases the mean cost per case was US$248, of which 28% was direct costs and 72% indirect costs [19]. Another study estimated the total cost of dengue illness across the Americas (based on data from 2000 to 2007) at US$2149.8 million per year, with a total of 72,772 DALY lost [17]. Ambulatory cases accounted for 73% of the costs, hospitalised cases 24%, and deaths 3% [17]. A comprehensive review of health economic studies of dengue burden has recently been published [20].

Such cost studies face two main challenges: (i) it is difficult to incorporate all of the costs of a case of dengue, and (ii) incidence of dengue is considerably under-estimated. Expansion factors are used to adjust for the under-reporting of cases and provide estimates of the true extent of the dengue burden [21]. Expansion factors of 10–27 in Puerto Rico [22], 6 in Panama [23] and 21.3 in Nicaragua [24] have been reported. While different expansion factors for different countries might be expected given differences in surveillance systems, the wide variation observed calls for a systematic and comprehensive analysis of dengue under-reporting. Indeed, reliable expansion factors will be essential to calculate the full cost of dengue.

The threshold for vaccine cost-effectiveness recommended by the WHO is a cost per DALY saved of three times the annual per capita gross domestic product (GDP) [25]. For dengue-endemic countries in the Asia-Pacific region this threshold is approximately US$3000. The cost-effectiveness of a dengue vaccine in Southeast Asia was calculated assuming a two-dose schedule and different potential prices per dose [26,27]. At US$10 per dose, and an assumed dengue haemorrhagic fever (DHF) incidence of 72 cases per 100,000 population per year, the cost-effectiveness ratio was estimated at US$1212 per DALY saved, which is significantly below the US$3000 threshold.

It may be beneficial to select a discrete dengue outbreak, such as the recent outbreak in Martinique, and examine all the associated costs. This could then be more broadly applied to better understand the total costs of dengue. The indirect costs that are typically unaccounted for include the cost of disruption to health care services (caused by the influx of dengue cases), and the cost of decreased tourism, shipping, transport, and commerce due to fears of the disease spreading.

3.2. The human burden of dengue

The impact of dengue on patients and their families is significant, both economically and in terms of quality of life. The economic cost disproportionately falls on the poor, particularly in countries where most costs are covered by the patient. A study in Cambodia showed that patients with dengue cover, on average, 78% of the total cost and 63% of the direct medical cost [28]. In a study in Thailand, 47% of patients with dengue could not afford to visit a reputable medical provider, 14% could not afford treatment, and 17% had to borrow money to cover the cost of illness [29]. Other studies in Cambodia show how these costs are a continuing burden to the poor [30], with the majority (62%) still unable to repay their debts up to one year later [31]. There is also a significant drop (>50%) in the quality of life of both children and adults with dengue, which does not return to baseline until 12–16 days after onset of illness which is almost twice the duration of fever [32].

To raise the profile of dengue among governments and global decision-makers, which will be essential to secure funding for vaccine introduction, it will be necessary to publicise the full extent of the human burden of dengue. The morbidity caused by dengue should be highlighted and attempts made to move the global focus away from simply considering mortality statistics. While the mortality statistics for dengue are lower than for some other diseases considered a global health priority, the human impact of dengue morbidity is profound and, if better conveyed, persuasive. In particular, the impact of dengue on communities and its psychological impact on patients and families are often ignored.

3.3. Computational modelling

Computational modelling is an additional tool to support the decision-making process. It has proven to be highly advantageous in dengue research, for example in mapping the movement of the dengue virus from urban centres [33] and identifying the causes of the upwards shift in the average age of patients with dengue in some countries [34]. Each dengue-endemic country should have the opportunity to run its own modelling programs, however both human (skilled technicians/programmers) and material (sufficient computational power) resources are currently lacking. This limitation may be overcome by establishing broadly applicable protocols and sharing data, expertise and equipment. The use of common protocols will additionally facilitate comparisons and meta-analyses. Finally, it is important that policymakers and their advisors be educated in the interpretation of computational models so that they may fully understand the information and use it as part of their decision-making process.

A series of workshops to train suitably skilled people in running computational models could be an effective way to establish new modelling groups based in dengue-endemic countries. Interested groups from dengue-endemic countries, including a decision-maker, a dengue expert and a professional computational analyst, could approach groups such as the Vaccine Modeling Initiative (VMI) [35] to obtain open source software, advice and expertise, and perhaps most importantly, access to the computational power required. Regional workshops, where this information is shared, could accelerate this process and also ensure collaboration between all parties and the use of consistent protocols across groups. In return, these groups would provide local data and parameters for the models, validation of the modelling results against local historical data, a link between data generation and decision making, and country ownership of the endeavour.

4. Implementing dengue vaccination

Vaccine introduction strategies should be tailored to national requirements, taking into account existing NIPs, dengue epidemiology, and regulatory restrictions. NIPs are well established in the Asia-Pacific region and have proved successful in reducing the burden of many infectious diseases. The best approach for incorporating a dengue vaccine into the NIPs of Vietnam, Indonesia, the Philippines, Malaysia, and Thailand, was considered, assuming (based on the most advanced vaccine candidate) a three-dose vaccination regimen (baseline, 6 months and 12 months) for children from the age of 9 months. At the current time the proposed vaccination schedule does not perfectly correspond to any of the NIPs in the region. After the introduction of a dengue vaccine, as more is learnt about the vaccine's characteristics, it may become possible to alter the vaccination schedule to better fit existing programmes and capabilities. The initial introduction, however, will most likely be based on the schedule specified in the vaccine's product profile. Possible approaches to facilitate this include: national vaccination days, school-based vaccination, and opportunistic vaccination (taking advantage of individuals receiving medical care to vaccinate at the same time).

4.1. Logistics and infrastructure

Lessons can be learnt from the introduction of other vaccines in developing countries. During the introduction of rotavirus vaccine in Latin America for example, lessons were learnt in relation to programmatic feasibility, cold chain systems, information systems for coverage monitoring, training and supervision, monitoring of adverse events following immunisation (AEFI), vaccine supply and financial sustainability [36]. These illustrated the importance of having precise national plans to ensure, in particular, the technical, programmatic and financial feasibility of vaccination [36]. With respect to dengue vaccine introduction, countries should develop detailed logistical plans considering: catch-up immunisation, forecasting of supply needs, information systems requirements (record keeping) and requirements for safe disposal of consumables. These plans need to be specific for a dengue vaccine and its unique challenges.

It has been estimated that 2.4–3.5 billion dengue vaccine doses could be needed in the first five years after global introduction [37]. It will be crucial to ensure and demonstrate that vaccine supply needs can be met, particularly as a new vaccine will, at least initially, likely have a single manufacturer. Ultimately, decentralised production of the vaccine could help to address these concerns.

5. Establishing long-term effectiveness and safety

5.1. Vaccine effectiveness

As dengue vaccines become available, it will be essential to measure the impact of their introduction. This will be achieved using established surveillance systems or by implementing post-licensing effectiveness studies. If existing surveillance systems are used, many will need to be reorganised for this purpose, with improved reporting, adequate case investigation, and strengthened infrastructure. The implementation of specific surveillance activities such as sentinel networks and the expanded use of data from hospitals, emergency rooms and laboratories could also serve to improve current systems.

5.2. Herd immunity

There is a risk that vaccination against dengue will simply lead to an increase in the age of peak incidence rather than broad herd immunity. For example, in Singapore it is thought that a vector-control-driven reduction in herd immunity in older people ultimately led to increased dengue incidence in this population who were more susceptible to clinically significant disease [38]. Requirements to determine herd immunity are likely to differ from one country to the next, and perhaps even within different areas or communities within countries. Ultimately, strategies to determine herd immunity will need to be tailored to each country, and in this respect it will be critical to share data, and establish best practices and consistency of reporting.

5.3. Antibody dependent enhancement

Antibody dependent enhancement (ADE) is an *in vitro* observation that has been proposed to explain the increased risk of severe disease both in the case of secondary infection and in infants infected at the age of 6–9 months. In the first case the enhancing antibodies would be non-neutralizing cross reactive antibodies, while in the second case the enhancing antibodies would be maternal antibodies that have waned to sub-neutralizing levels [39–41]. In the context of vaccination, two questions must be raised with respect to the ADE theory; (i) will infection be enhanced if it occurs in an individual before the completion of the full vaccination regimen, and (ii) will an infection be enhanced in an individual some time after vaccination due to waning immunity.

Clinical trials of the lead dengue vaccine candidate which are closely monitored for the appearance of any ADE, of which there has been no sign to date [11], will be the key to answering the first of these questions, but monitoring should continue well beyond vaccine introduction. Principally this will be to ensure that an increased incidence of severe dengue does not emerge in the vaccinated population, but it could also serve to ensure accurate data are available to address concerns or refute any claims about vaccine-related ADE should cases arise.

5.4. Pharmacovigilance

Establishing effective pharmacovigilance systems will be essential to accurately monitor the safety of a dengue vaccination programme; this will be particularly important in countries that are among the first to adopt the vaccine. Certain conditions can potentially be mistaken for AEFI. For example, leptospirosis or infection with *Rickettsia* may be mistaken for viscerotropic or neurotropic disease, which is an extremely rare adverse event with the TFV 17D yellow fever vaccine (which forms the backbone of the current lead candidate dengue vaccine [9]) [42]. There is therefore a need for good differential diagnostic capacity at the country level, with training of physicians in the recognition and diagnosis of these illnesses. There is also a need for comprehensive background data on potential adverse events such as viscerotropic or neurotropic disease to respond to any perceived increase in incidence.

6. Demonstration projects

Demonstration projects are studies conducted in some countries after registration to support vaccine introduction activities a step beyond licensure (but short of full scale introduction) and help convince local authorities of the effectiveness of a vaccine and the feasibility of vaccination [43]. The ongoing introduction of the human papillomavirus (HPV) vaccine provides an example of the usefulness of demonstration projects [44]. In Vietnam, formative research identified the suitability of established delivery systems and the receptiveness of policymakers to an HPV vaccine [45]. At the same time it identified gaps in the cold chain system and public concerns about vaccination which needed to be addressed.

There are a number of complex issues surrounding dengue vaccination which highlight the importance of demonstration projects [43]. Specific sites which could be considered for demonstration projects include sentinel sites, urban centres, high-risk regions, regions with well established NIPs, schools, and island communities. Any specific project should examine programme feasibility with respect to training and logistics together with vaccine effectiveness and issues related to AEFI and catch-up vaccination. While national programmes should consider the need for, and feasibility of, demonstration projects, it should not be necessary for every country to run separate projects. Projects in one country could be applicable to other countries in the region.

7. Education

During the introduction of the rotavirus vaccine in Latin America some countries did not allow sufficient time to train all health care workers in vaccine administration, leading to uncertainty regarding possible contraindications and AEFI, reconstitution and administration, the interval between doses and minimum/maximum ages for administration [36]. For the successful introduction of a dengue vaccine, comprehensive education programmes will need to be in place and enough time must be taken to ensure that they are completed. Programmes for NIP managers, vaccine providers, paediatricians, other clinicians and nurses, and the general public will be required. In addition, it will be important to educate policymakers on the extent of the dengue burden, the increasing spread of dengue and the cost-effectiveness of a dengue vaccine. It will also help to train decision-makers, and those that advise them, in the understanding of computational models and demonstration projects so that they might fully understand the data generated.

Given the potential controversies that surround every vaccine, together with those unique to a dengue vaccine, expert advisory bodies with the ability to offer second opinions and advice should be established. These advisory bodies will be able to support health care workers and programme managers at the time of vaccine introduction by providing informed responses to issues and concerns based on up-to-date information. Such a body would be able to coordinate responses to ensure that only the most accurate information is shared. A proactive communication strategy targeting vaccine providers, authorities, clinicians and the public will also be essential to manage potential myths and controversies. These may include concerns about a genetically modified vaccine, the risk of ADE, other potential severe AEFIs (both real and misattributed), media misinformation, public rumour and coincidental events during vaccine introduction (including dengue outbreaks).

8. Funding

Adequate funding will be essential to support the effective introduction of a dengue vaccine. There are two key funding issues to be addressed: (i) obtaining initial funding for vaccine introduction, and (ii) establishing sustainable funding to support an ongoing vaccination programme. Initial funding will need to cover all associated costs of vaccine introduction outlined above, including logistics, vaccine supply, education, and surveillance costs. Funding for an ongoing vaccination programme will need to cover ongoing maintenance of these requirements and, potentially, the expansion of the programme, including catch-up vaccination.

To secure funding it will be critical to demonstrate the cost-effectiveness of dengue vaccination. Convincing data showing that a hepatitis B vaccine was cost-effective were required before it was introduced into the NIPs of developing countries [46]. Preliminary analyses strongly suggest that dengue vaccination would be cost-effective [26,27]; however, there is a need to generate country-specific data and share it with decision-makers.

Box 1: Recommendations to prepare for dengue vaccine introduction.

- Document and publicise the true human and economic costs of dengue.
- Ensure high quality surveillance systems and diagnostics so that reliable background data can be generated.
- Generate and share applications and protocols in diagnostics, surveillance, efficacy studies and computational modelling.
- Identify countries or regions for initial vaccine implementation based on existing capabilities and data.
- Individual countries should start developing detailed logistical plans for dengue vaccine introduction.
- Implement educational programmes for health care workers, decision-makers and the public.
- Identify sustainable sources of funding.
- Dengue-endemic countries need to take ownership of the disease and redefine how dengue is viewed globally.

Given the wide-ranging costs and the immediate need for some of the projects recommended in this report to either start or accelerate, governments of dengue-endemic countries should consider assigning and securing funding now. Funding from a range of public and private organisations should be considered including both traditional and innovative funding sources. At the same time, funding from the global community will be essential. Unfortunately, while dengue is a high priority in endemic countries, it is a low priority among decision-makers in the global health community, whose priority is typically those diseases with the highest mortality. It is critical that the global public health community starts to view dengue as the major public health concern that it is.

9. Summary of recommendations

The collected meeting recommendations highlight the importance of preparing for dengue vaccine introduction now (see Box 1 for a summary of recommendations). It will be necessary to document and publicise the true human and economic costs of dengue. Under-reporting of dengue remains a significant problem so comprehensive analyses in different regions need to be performed to quantify expansion factors. To support these efforts and to prepare for requirements during and after vaccine introduction, there is a need to ensure that high quality active surveillance systems and diagnostics are introduced so as to gather more detailed and representative background data. To facilitate comparisons and meta-analyses, toolkit applications and protocols in diagnostics, surveillance and computational modelling that can be easily shared and applied in different countries/regions should be developed and disseminated.

Initial introduction of a dengue vaccine should be in a country or region with effective surveillance capabilities, where reliable data are already available, and where there is the ability to conduct high quality pharmacovigilance studies. Regardless, each dengue-endemic country should develop detailed logistical plans for dengue vaccine introduction, including how to incorporate a dengue vaccine into existing vaccination schedules and other requirements unique to a dengue vaccine.

A series of educational programmes for health care workers, decision-makers and the public should be planned and implemented where required. These would include continuing, and enhanced, training of physicians in the diagnosis of dengue, training health care workers in logistical aspects of vaccine implementation,

and preparation for potential issues in order to be ready to address public concerns as they arise.

It will be critical to identify sustainable sources of funding, both to support vaccine introduction and to maintain the vaccination programme. To achieve this, ownership and advocacy of dengue disease and dengue control measures by individual countries will be critical. Dengue-endemic countries have an increasingly strong voice on the world stage; they should use it to redefine how dengue is viewed by the rest of the world.

10. Conclusions

The consensus at the meeting was that while dengue is currently a major global public health problem, with the introduction of an effective vaccine it is a disease that can be controlled. It will be crucial to change the perception of dengue in non-endemic countries, where much of the funding may need to originate, and publicise the full burden and cost of dengue. The prospect of a vaccine for dengue being available in the near future is encouraging, but in order to ensure that it is introduced successfully, and as rapidly as possible, there is a need to start preparing now.

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