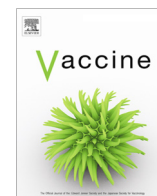


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Assessing dengue vaccination impact: Model challenges and future directions

Mario Recker^a, Kirsten Vannice^b, Joachim Hombach^b, Mark Jit^{c,d}, Cameron P. Simmons^{e,f,g,*}

^a Centre for Mathematics and the Environment, University of Exeter, Penryn Campus, Penryn, UK

^b Initiative for Vaccine Research, Department of Immunizations, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland

^c Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

^d Modelling and Economics Unit, Public Health England, 61 Colindale Avenue, London NW9 6BT, UK

^e Oxford University Clinical Research Unit, Hospital for Tropical Diseases, 764 Vo Van Kiet Street, District 5, Ho Chi Minh City, Viet Nam

^f Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

^g Department of Microbiology and Immunology, Peter Doherty Institute, University of Melbourne, Parkville, Victoria 3010, Australia

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ABSTRACT

In response to the sharp rise in the global burden caused by dengue virus (DENV) over the last few decades, the WHO has set out three specific key objectives in its disease control strategy: (i) to estimate the true burden of dengue by 2015; (ii) a reduction in dengue mortality by at least 50% by 2020 (used as a baseline); and (iii) a reduction in dengue morbidity by at least 25% by 2020. Although various elements will all play crucial parts in achieving this goal, from diagnosis and case management to integrated surveillance and outbreak response, sustainable vector control, vaccine implementation and finally operational and implementation research, it seems clear that new tools (e.g. a safe and effective vaccine and/or effective vector control) are key to success. The first dengue vaccine was licensed in December 2015, Dengvaxia[®] (CYD-TDV) developed by Sanofi Pasteur. The WHO has provided guidance on the use of CYD-TDV in endemic countries, for which there are a variety of considerations beyond the risk–benefit evaluation done by regulatory authorities, including public health impact and cost-effectiveness. Population-level vaccine impact and economic and financial aspects are two issues that can potentially be considered by means of mathematical modelling, especially for new products for which empirical data are still lacking. In December 2014 a meeting was convened by the WHO in order to revisit the current status of dengue transmission models and their utility for public health decision-making. Here, we report on the main points of discussion and the conclusions of this meeting, as well as next steps for maximising the use of mathematical models for vaccine decision-making.

1. Background

Over the last few decades dengue has become the most important and wide-spread, vector-borne viral infection affecting humans [1,2]. The geographic expansion of dengue's two mosquito vectors, *Aedes aegypti* and *Ae. albopictus*, together with ongoing globalisation and urbanisation have resulted in more frequent and bigger epidemic outbreaks as well as endemic establishment of dengue in previously unaffected areas.

Infection with one of dengue's four antigenically related serotypes (DENV1–4) can result in a systemic viral illness, with symptoms lasting for around 2–7 days. Infection with one serotype is assumed to provide life-long, homotypic immunity but might leave the individual more vulnerable to develop clinically severe out-

comes upon secondary, heterotypic infection [3–5]. The commonest severe outcome is hypovolemic shock, called (Dengue Shock Syndrome (DSS)) and is precipitated by a vascular leakage syndrome that manifests between days 4–7 of illness. Treatment of dengue is limited to supportive care and when done carefully can decrease mortality to <0.5% of hospitalised cases.

In the absence of effective vaccines, current control efforts against DENV transmission are targeted against the mosquito vectors, either through direct measures (e.g. application of insecticides) or through the limitation of vector breeding habitat (e.g. environmental management). Although vector control efforts can show reductions in entomological indicators, there is a limited evidence base to demonstrate effectiveness against dengue disease of any of these public health interventions [6]. There is clear consensus that new tools are needed to prevent and control dengue, including the development of a safe and efficacious vaccine to control dengue. The most advanced vaccine candidate to date is Sanofi Pasteur's recombinant live attenuated tetravalent

* Corresponding author at: Department of Microbiology and Immunology, Peter Doherty Institute, University of Melbourne, Parkville, Victoria 3010, Australia.

E-mail address: csimmons@unimelb.edu.au (C.P. Simmons).

dengue vaccine (CYD-TDV), which has been evaluated in Phase III clinical efficacy trials across various endemic countries in Asia and Latin America [7,8]. The vaccine has recently obtained licensure in Mexico, the Philippines, Brazil, El Salvador and Paraguay, with applications submitted in several other endemic countries.

Overall vaccine efficacy of CYD-TDV was estimated to be around 60% against virological confirmed dengue (VCD), with high levels of protection offered against hospitalisation and severe disease [7,8]. However, marked variations were observed between endemic settings and between individual serotypes, with efficacies ranging from 35% (in the case of DENV2) to well over 70% (for DENV3 and DENV4). A significant difference in vaccine efficacy was also observed between naïve individuals and individuals with pre-existing antibodies to one or more dengue serotypes, where naïve individuals were on average twice as likely to experience a symptomatic break-through infection. Recent pooled analyses of the first 2–3 years of long-term follow-up provided further supportive evidence of efficacy against hospitalised dengue in children 9 years of age or older [9]. There was however a concerning signal for increased hospitalised dengue illness amongst participants 2–5 years of age (RR = 7.45, 95%CI 1.15, 313.80). There are multiple hypotheses that could explain this increased risk [10], including age-specific susceptibility to severe disease, suboptimal vaccine immunogenicity and/or waning immunity in vaccine recipients who were seronegative for dengue viruses at baseline, and temporal clustering of cases in the CYD group [11]. As a result, Sanofi Pasteur has limited the age indication to individuals 9+ years of age.

As the vaccine is licensed, countries are faced with decisions about whether and how to introduce a dengue vaccine, and what the public health impact might be, both in terms of the reduction in disease burden and potential risks. Depending on disease epidemiology, vaccine price, and other factors, these decisions may not be straightforward. Mathematical models can provide policy makers with additional potential considerations to inform their decisions on optimal vaccine use in the context of the broader dengue control program. To this end, a meeting was held at the WHO in 2014 in order to revisit the current status of dengue intervention models and to discuss their utility for public health decision-making. Here we summarise the meeting with regards to the challenges faced by modellers and health policy makers identified during this meeting.

2. Role for modelling in shaping national and international recommendations on dengue vaccination

Mathematical models have long been recognised as useful tools for addressing public health questions. Their ability to both simplify and elucidate complex relationships have contributed greatly to our understanding of epidemiological concepts, including the basic reproductive number (R_0), herd immunity and vaccine escape. Consequently, models of vaccination are used at both national and global levels to inform decision making. Often, several models exist which examine the same vaccine-related decision question using different input data sources, modelling methods and levels of complexity. Comparative modelling exercises can be used to understand the similarities and differences between different models in order to draw overall conclusions about the likely impact of vaccination strategies [12]. Such exercises are useful to inform countries, which rely on the results of models but do not have the technical capacity to appraise an entire suite of models.

Mathematical models can also be used to inform global recommendations and policies about vaccines, which need to take into account a variety of settings and potential strategies. For instance, WHO is advised by the Strategic Advisory Group of Experts (SAGE)

on Immunization to make global vaccine-related recommendations, with input from models that have been appraised by its advisory committee, the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC). Recently, the outputs of a coordinated mathematical model comparison of the potential impact of the RTS, S malaria vaccine were used in the decision-making process for WHO recommendations on the use of this vaccine [13,14]. The modelling revealed that despite the overall low efficacy, the vaccine could have a substantial additional public health impact across a broad range of settings representative of malaria parasite prevalence in Africa in the presence of other ongoing interventions. It also provided indication on cost-effectiveness and performance in various transmission settings. WHO has also used comparative modelling to inform country decision-makers on the use of cost-effectiveness tools for other vaccines, including pneumococcal vaccines, rotavirus and human papillomavirus vaccines [15–18].

With a similar exercise now under way with regards to a dengue vaccine, it is important to note that the level of certainty we can have in model conclusions ultimately depends on the availability of suitable data as well as our understanding of the biological and epidemiological mechanisms driving disease dynamics. Given currently available data dengue disease dynamics and performance of dengue prevention tools (i.e. vaccine and vector control effectiveness), there are several policy questions that can be well-informed by mathematical modelling, such as: what is the impact of different vaccination strategies on disease, taking into consideration different target age groups, variable vaccine efficacies and/or vaccine coverage levels? Or what is the cost-effectiveness of different strategies for a dengue vaccination program? There is also substantial programmatic interest in extensions of mathematical modelling to other aspects, such as the impact of integrated vaccination/vector control programs or the change in disease dynamics and dengue epidemiology following vaccine introduction. However, due to the current limitations in empiric data on vaccine performance and mechanism of action, many of these should be considered as exploratory at this stage and with great uncertainties attached to their outputs.

3. Model and other uncertainties

There is an appreciable degree of freedom, by which biological and ecological phenomena can be described mathematically. Consequently, models of dengue transmission and/or intervention can be found in various shapes and sizes, ranging from differential equation models to spatially explicit agent-based approaches that include most of the known ecological and immunological determinants influencing the transmission cycle of dengue; for an overview of recent models investigating dengue epidemiology and control see e.g. [19–21]. Regardless of the wide range of modelling taken to investigate the potential impact of individual or integrated control strategies on reducing the burden of disease, an important issue that was highlighted during the meeting was that of uncertainties, not only those relating to underlying model assumptions but also those relating to vaccine action and the (long-term) effectiveness of vector control. That is, ambiguities still exist relating to the various factors affecting dengue virus transmission and immunity, which mostly revolve around the short and long-term effects of a primary dengue virus infection on the immuno-epidemiology and pathology of subsequent infections. For example, it is commonly assumed that following an infection the host remains fully protected against reinfection by all other serotypes for a certain length of time (between 6 months and 2 years) [22–24] and that due to the phenomenon of antibody-dependent enhancement, severe infection outcomes

are not only much more likely during secondary, heterologous infections but also much more transmissible. This view has recently been challenged, however [25]; and with the majority of dengue infections going unreported and much of the available epidemiological data based on clinical cases only, robust empirical evidence that conclusively relate age, prior exposure, infection pathology and viral transmission is still lacking.

Similar uncertainties also apply to vaccine induced protection, such that data from the recent trials do not allow us to discriminate whether the vaccine offers any protection against infection or against clinical disease only, or what effect breakthrough infections have on the immune status of the vaccinees. The vaccine trials further highlighted significant uncertainties associated with a partially efficacious vaccine. That is, the observed differences in vaccine efficacy between individuals that were seropositive or seronegative at baseline indicate that serostatus is an important consideration and possibly relevant for other live attenuated dengue vaccine candidates, too. For CYD-TDV in particular it will therefore be important to investigate vaccine efficacy under different levels of transmission intensity and target age groups for vaccination to maximise impact whilst preventing adverse outcomes, given the reported elevated risk of hospitalisation with dengue amongst the 2–5 yr old CYD-TDV vaccine recipients in the 3rd year post-vaccine initiation. More generally, though, while the transmission models themselves can be applied across all dengue vaccine candidates, the mode of action of the different vaccines may need to be considered differently, based on the available immunogenicity and efficacy data.

Given these uncertainties it is imperative that thorough model sensitivity analyses are to be carried out [26], not only to gain a better understanding of the full range in qualitative and quantitative model behaviour under parameter changes, but also to highlight the most important knowledge gaps. In that respect, sensitivity analyses need to go beyond finding and reporting on the most influential parameters but crucially have to incorporate uncertainties in parameter values as well as in the underlying model structure and assumptions [27].

4. Model comparisons

To develop global policy recommendations, SAGE constituted a Working Group on Dengue Vaccines, for which a key input for decision-making is the predicted disease impact and cost-effectiveness of a dengue immunization program based on mathematical modelling. SAGE reviewed CYD-TDV as well as model-based predictions of public health and economic impact in April 2016. SAGE recommended countries consider introduction of the vaccine only in geographic settings (national or subnational) with high endemicity, with seroprevalence thresholds informed by the mathematical modelling analyses (see http://www.who.int/immunization/sage/meetings/2016/april/SAGE_April_2016_Meeting_Web_summary.pdf?ua=1&ua=1). A WHO vaccine position paper outlining WHO recommendations is expected to be published in July 2016.

The above mentioned uncertainties underlying the immunology of dengue and vaccine action will undoubtedly have significant effects on the models' ability to make quantitative and robust predictions about the impact of integrated control measures. In light of these findings, the WHO initiated a model comparison exercise in April 2015 [28,29] with the aim of quantifying the health and economic impact of a dengue vaccination campaign based on our current understanding of the action of the CYD-TDV candidate. Such a model comparison exercise adds significant value towards an evidence-based decision making process. Not only does it yield a much better understanding of

the features, similarities and differences between models, it also crucially enhances communication between the modelling groups, and between modellers and other scientists, stakeholders and policy-makers. The results from this exercise, based on eight models using standardised input datasets representing a variety of dengue-endemic settings, have now been appraised by both IVIR-AC and SAGE's Dengue Working Group, with the detailed results expected to be published later this year.

At this stage, however, emphasis is predominantly placed on vaccination impact without explicitly taking vector control measures into consideration, due to the added complexities and uncertainties underlying the large-scale application and effectiveness of vector control. Nevertheless, more data, especially from the CYD-TDV long-term follow-up studies will become available in the near future. It is thus expected that some of these uncertainties will get resolved before too long, which will greatly facilitate model harmonisation and a shift in focus towards integrated intervention programmes.

5. Endemic country perspectives

Mathematical models may also inform country-specific decisions about vaccine introduction, although interpretation of the results must always be put in the context of local data quality and uncertainty in model predictions. There are a number of efforts to model dengue and vaccine impact locally to inform decision-making. In these efforts, local priorities and questions for dengue vaccine programs can best be taken into account.

To date, there has been no published systematic survey of what dengue endemic countries most desire as outcomes from a dengue vaccine program. Feedback from endemic country clinical and public health professionals suggests a desire for a vaccine-mediated reduction in the number of fatal cases and those requiring hospitalisation. This priority is driven by multiple realities. First, hospitalised case incidence can be measured by existing surveillance systems and hence endemic countries have an available tool to measure and communicate to their internal stakeholders the impact of vaccination, i.e. a vaccine interrupted time series. Second, the public perception of dengue as a public health problem is driven partly by media reports and images of large caseloads in hospital settings; these make for strong visual messages that undermine community confidence in the competence of government to manage public health. Third, hospitalised cases account for much of the economic cost of dengue to health care systems. Against this backdrop it is reasonable to assume that endemic countries require, at a minimum, that a dengue vaccine will deliver reductions in fatal and hospitalised cases. These priorities should be reflected in vaccine modelling efforts, which can allow policy makers to consider the potential impact of various interventions utilised as a component of their overall dengue control programme. Given the competing demands for financing, modelling efforts could ultimately help countries design the optimal dengue control program package, considering local dengue epidemiology and resource constraints. This, however, crucially relies on more effort being put into improving communication between the modellers and policy makers as well as the development of more user-friendly models for countries to use in decision-making.

6. Enhancing input from mathematical models into vaccine decision making

Different models make different, and often untested or unvalidated assumptions about the key drivers of dengue epidemiology and vaccine performance due to underlying uncertainties. In order

for policy makers to understand the assumptions, allowing their own evaluation of the integrity of the results and confidence in the model predictions, it is important that sufficient detail is provided on the model assumptions and parameters. These include assumptions for infection states, disease states, serotype or strain differences, transmission, vaccine response, vector, seasonality, and spatial aspects (Box 1). A possible strategy for reporting based on supporting of an archive of vector-borne disease models and

Box 1 Reporting requirements for dengue transmission models of vaccine impact to improve transparency.

- **Infection states**
How many serotypes are considered in the model and how many possible infections are assumed? Following an infection, what are the assumptions about the infectiousness and susceptibility of every subsequent infection? Details about the infection state should also extend to the vector (if explicitly modelled) and their interactions with the host should be detailed. Finally, what are the assumptions regarding cross-protection and/or cross-enhancement?
- **Disease states**
Details should be provided about the modelled outcome of an infection (e.g. in terms of clinically apparent disease or hospitalisation). Related to this, what is the link between infection outcome and infectiousness? Furthermore, does the probability of disease change with subsequent infections and/or is it a function of other model states, such as age or immunisation?
- **Serotype or strain differences**
Does the model assume heterogeneities in the transmissibility and/or pathogenicity between serotypes or (if considered) between different strains? Are there heterogeneities in terms of cross-protection and/or cross-enhancement? Equally, are vaccine efficacies assumed to be symmetric or different for different serotypes?
- **Transmission**
What are the assumptions underlying the transmission coefficients (e.g. biting rate, transmission probabilities, etc.)? What is the assumed basic reproductive number and what data is that based on? Are vectors explicitly modelled in the model, which would warrant a description of human → vector and vector → human transmission probabilities? And for more detailed models, temporal and spatial contact structures should be described if assumptions are made regarding age- or location-dependent probabilities of infection.
- **Vaccine response**
What assumptions are made regarding the action of a vaccine, e.g. 'all-or-nothing' (i.e. the vaccine offers complete protections to some part of the population but not the other) or 'leaky' (i.e. vaccine offers partial protection to every vaccinated individual)? Does vaccination have an effect on infection, disease or both? Are there serotype/strain- or age-dependent differences? How does the immune status prior to immunization affect the vaccine response? Finally, does the response vary with time, e.g. during a multi-dose regime or because of waning immunity?

- **Vector**
If vectors are explicitly modelled, what is their relative population size? What mosquito life-stages are considered and what states are considered in terms of their infection status? How their natural histories are realised and are there temporal variabilities in demography? How should heterogeneous, focal transmission, which arises from the biology and landscape on which mosquito biting and pathogen transmission unfold, be modelled? Attention should focus on the ecological and social context of mosquito biting behaviour.
- **Seasonality**
How is seasonality incorporated in the model, e.g. temporal variation in biting rates, temporal variability in population densities and/or temporal variability in incubation rates and how are these parameterised?
- **Parameterisation**
The data used for parameterising the model should be described in sufficient details and, where possible, either with references to published literature or better included. Details about inference/algorithm used to parameterise the data should also be supplied.
- **Spatial aspects**
Where applicable, details about spatial processes should be described in sufficient details, including host and vector movement and contact patterns, ecological heterogeneities.
- **Uncertainties and model sensitivity**
How do the results depend on any of the above assumptions? What are the major uncertainties underlying the model and the reported results? Has a sensitivity analysis been carried out, and does it cover model structure and/or model parameter uncertainties?

using an online questionnaire for researchers to fill in their model specifications and key features. As mentioned earlier, reproducibility of model results is imperative to improve transparency and enable comparisons between different approaches. Models should therefore be described in sufficient details, including initial conditions and the data used to inform and/or justify their choice of parameter values.

7. Concluding remarks

The availability of epidemiological and clinical data from the Phase III efficacy trials of Sanofi Pasteur's tetravalent dengue vaccine has provided a great opportunity for mathematical models to make semi-quantitative predictions about expected outcomes, including short-term reduction in disease burden as well as potential unintended effects. Point estimates for vaccine efficacy, particularly those that are variable by serotype, age, host immune status, and severity, only provide one kind of information to policy-makers considering vaccination in their specific setting. Mathematical models are valuable tools to translate these data into country- or region-specific impact estimates as an additional input into the policy-making process. However, data sharing and communication with policy-makers, especially regarding the extent and nature of uncertainties are critical for the success of mathematical models to provide the best possible predictions and to maximise their use health policy recommendations.

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