Institution: University of Exeter		
Unit of Assessment: UoA 10 Mathematical Sciences		
Title of case study: Shaping WHO vaccine policy recommendations with mathematical modelling		
Period when the underpinning research was undertaken: 2010-2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Dr Mario Recker	Associate Professor in Applied Mathematics	2013- present
Period when the claimed impact occurred: 2016 – 31 July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Exeter research played a vital role in shaping World Health Organisation vaccine policy recommendations for the effective and safe use of the first ever dengue vaccine, Dengvaxia®. As part of a WHO-led model inter-comparison study, Dr Recker's work was used to define the scenarios under which the vaccine would be beneficial and where its use would not be advised. These findings have:

1) Shaped WHO global vaccination policy recommendations;
2) Informed policy decisions in the Philippines with regards to the use of Dengvaxia® in a national immunisation programme;
3) Influenced the conditions attached to the licensing of Dengvaxia® from the FDA and European drug agency.

2. Underpinning research

Dengue is one of the most widespread viral diseases transmitted by mosquito vectors. It causes an estimated 390 million infections and 25,000 deaths worldwide each year. With no anti-viral treatment available, an effective vaccine against dengue has been urgently needed. However, the first dengue vaccine to be licensed, Dengvaxia®, showed varying levels of protection and risk of adverse outcomes in different groups of the population, making the development of policy recommendations regarding its use extremely difficult. In view of the potential for mathematical modelling to help to define the scenarios where use of the vaccine could be beneficial, the World Health Organisation convened a series of meetings with experts, including Dr Recker. These were designed to discuss model requirements and best practices by which models should be used to evaluate dengue vaccination strategies and to inform public health policies **[3.1]**.

In view of the high level of complexity and significant uncertainties associated with dengue infection, the WHO concluded that a single model approach would be insufficiently robust; instead, they opted for a multi-model exercise to investigate the long-term impact and safety of Dengvaxia®. These multi-model comparison studies are increasingly used in various fields of research where the underlying system is highly complex and model predictions inherently uncertain. By comparing the predicted outcomes across a range of different models it is possible to derive a more comprehensive picture and gain better insights into the overall levels of uncertainty. In the case of dengue modelling, significant uncertainty revolves around the effect that an infection can have on the susceptibility, infectiousness and likelihood of severe disease following a subsequent infection with a different viral subtype, or serotype. As Dengvaxia® showed different efficacies in individuals who had or had not been infected with dengue before, these uncertainties could potentially lead to differing model predictions of the vaccine's long-term impact, which model comparisons are designed to capture.

In June 2015, Dr Recker was invited by the WHO to lead one of the eight modelling groups involved in the international study; his was one of two groups from the UK, the other was from Imperial College London. Each group had developed their own model based on their own assumptions regarding dengue immunity and immune interactions. Model harmonisation was deliberately minimised in order to capture some of the uncertainties underlying dengue's complex epidemiology; however, all models assumed the same mode of vaccine action, including waning immunity and differential protection in seropositive and seronegative individuals. Dr Recker's model was a spatially-explicit, agent-based framework, developed over many years of research. Its unique feature amongst the models included in the study was the way it captured spatial aspects of disease transmission in the population as well as the way it considered the altered risk of disease and transmission following a primary dengue infection, both of which are important determinants of dengue epidemiology. His research has shown that stochasticities underlying disease transmission together with the fact that most individuals are spatially segregated from each other are sufficient to explain dengue's characteristic multi-annual cycles in disease incidence **[3.2]**. Furthermore, he demonstrated how our ability to make model predictions about the impact of a vaccine is significantly affected by the model's assumptions regarding not only spatial mixing but crucially the effect of a primary exposure to the disease on the course of a subsequent infection **[3.3]**.

In order to facilitate comparability across the models, Dr Recker's previously developed framework was extended and modified to enable vaccination and monitoring of specific age cohorts within the population. The model was calibrated using Markov Chain Monte Carlo to infer transition rates and infection outcome probabilities from simulated timeseries. The fitted model was then used to simulate different vaccination schedules in terms of vaccine coverage and target age groups under different transmission intensities. Due to its stochastic nature, the model was simulated multiple times and summary statistics put forward for model comparisons. The projected number of averted severe and hospitalised infections over a pre-determined time window was taken as one of the outcome measures and later used for cost-benefit analyses.

The results from this study, which were published in 2016 **[3.4]**, demonstrated that although Dengvaxia® has the potential to reduce the burden of dengue disease in areas of moderate to high levels of dengue transmission, there is a potential risk of administering the vaccine in low endemic regions, where individuals without prior exposure could be put at an increased risk of severe disease following a post-vaccination infection. These results were presented to the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization in April 2016, where they helped to form the evidence base upon which WHO policy recommendations were subsequently made.

3. References to the research

1. **M. Recker**, K. Vannice, J. Hombach, M. Jit, and C. P. Simmons. Assessing dengue vaccination impact: Model challenges and future directions. *Vaccine*, 34(38):4461-5 (2016). doi: 10.1016/j.vaccine.2016.06.082
2. J. Lourenço and **M. Recker**. Natural, persistent oscillations in a spatial multi-strain disease system with application to dengue. *PLoS Comp Biol*, 9(10):e1003308 (2013). doi: 10.1371/journal.pcbi.1003308
3. J. Lourenço and **M. Recker**. Dengue serotype immune-interactions and their consequences for vaccine impact predictions. *Epidemics*, 16:40-8 (2016). doi: 10.1016/j.epidem.2016.05.003
4. S. Flasche, M. Jit, I. Rodriguez-Barraquer, L. Coudeville, **M. Recker**, K. Koelle, G. Milne, T. J. Hladish, T. A. Perkins, D. A. Cummings, et al. The long-term safety, public health impact, and cost-effectiveness of routine vaccination with a recombinant, live-attenuated dengue vaccine (Dengvaxia): a model comparison study. *PLoS Medicine*, 13(11):e1002181 (2016). doi: 10.1371/journal.pmed.1002181

4. Details of the impact (indicative maximum 750 words)

Dr Recker led one of the international modelling teams that took part in a mathematical model comparison study to assess the long-term safety and public health impact of the first licensed dengue vaccine, Dengvaxia® under the guidance from the World Health Organization (WHO). The findings of the study have:

1) Shaped WHO global vaccination policy recommendations;
2) Informed policy decisions in the Philippines with regards to the use of Dengvaxia® in a national immunisation programme;
3) Influenced the conditions attached to the licensing of Dengvaxia® from the FDA and European drug agency.

(1) Shaping WHO global policy recommendations

The results of the model comparison study were presented to the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization in April 2016 **[5.1, 5.2]**. SAGE reviewed the overall findings, together with the evidence generated from two large Phase 3 clinical trials, and recommended that countries should consider the introduction of Dengvaxia® only in geographic areas with high endemicity (as indicated by an average of >70% of 9 year-olds having previously been infected by the virus). The vaccine was not recommended for countries / regions with lower transmission intensities due to the highlighted potential negative effect of vaccination in dengue-naïve individuals, i.e. those who have not previously been infected with dengue. The recommendations align directly with the outcome of the model comparison study; the agreement in findings across the different models strongly supported this process and were "*instrumental in defining the areas and ages highlighted by SAGE*" (WHO scientist) **[5.3]**.

The above recommendations by SAGE were subsequently adopted by the WHO as their official dengue vaccination policy recommendation as noted in their WHO position paper published in July 2016 **[5.4]**. The key role played by the Exeter group is reflected in the following comment by WHO Senior Health Adviser and SAGE Executive Secretary: "*Dr Recker's contribution to the modelling consortium therefore had, by defining the areas and vaccine target ages highlighted by SAGE, a real impact on shaping global vaccine policy*" **[5.5]**.

The WHO revised their policy recommendation in December 2017 **[5.6]** based on further data being released by multinational pharmaceutical company Sanofi-Pasteur from the long-term follow-up study, which confirmed that the vaccine should only be given to individuals with prior dengue infection in order to minimise the potential adverse effects; this risk had also been highlighted by the model comparison study.

Finally, following implementation of the WHO policy recommendations, Dengvaxia®, which so far is the only licensed dengue vaccine, has been included on the WHO's list of essential medicines **[5.7]**. The WHO list of essential medicines suggests which drugs should be available at a reasonable price as they satisfy priority health needs of certain populations.

(2) Policy decisions informed by research evidence

The Philippines was the first country to roll out a large-scale dengue vaccination programme with Dengvaxia®, which started in April 2016 vaccinating a total of around 830,000 individuals through school programmes. In the areas where the vaccine was rolled out, the proportion of the population previously infected with dengue was estimated to be at least 85%, although this was based on a population average and not age-specific as specified by the WHO. The programme was halted in November 2017 due to the findings that the vaccine could put previously uninfected individuals at a higher risk of a severe case of dengue fever.

However, new research has shown that over five years following vaccination, there will have been a 70% reduction in the number of severe dengue cases within the vaccinated population **[5.8].** This equates to the avoidance of between 5,800 and 29,000 severe dengue cases (based on a recorded 1% - 5% annual incidence of symptomatic dengue in children, e.g.

Alera *et al*. (2016) *PloS Negl Trop Dis*). The research also indicates that this number significantly outweighs the number of cases likely in seronegative vaccinees (around 623 – 3,113 individuals, based on the numbers above), findings which are consistent with the predictions from the WHO multi-model study. Informed by this, the Philippines government is currently considering restarting the vaccination programme, following the protocol set by the World Health Organization (informed by the modelling) for all individuals to be screened before receiving the vaccine, to determine if they have ever been exposed to the infection previously **[5.9]**, thus minimising the risks to seronegative individuals.

(3) Influence on legislation and licencing of new drugs

The WHO dengue vaccine policy recommendations **[5.4]**, as informed by the results of the model-comparison study, was further used to support Sanofi's application for approval of Dengvaxia® by the Food & Drug Administration (FDA) **[5.10]**. The vaccine was approved for use in the US in 2019 **[5.11]** and by the European Commission in 2018 with the condition that Dengvaxia® only be given to people who are known to have had a previous infection, in line with WHO policy.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. World Health Organisation (2016) "Meeting of the Strategic Advisory Group of Experts on immunization, April 2016– conclusions and recommendations" *Weekly epidemiological record* No 21, 91, 265–284 (see pp. 282-3 specifically).
2. The SAGE decision making process – Evidence to Recommendations Table
3. Email from a Scientist at WHO's Initiative for Vaccine Research in 2016, saying that the contributions of the modelling consortium have been "*instrumental in defining the areas and ages highlighted by SAGE*" and that our "*efforts have had a real impact on global vaccine policy*"
4. World Health Organisation (2016) "Dengue vaccine: WHO position paper – July 2016" *Weekly epidemiological report* No 30, 91, 349–364 (see pp.360-361 specifically)
5. Letter of Testimony from Senior Health Adviser, SAGE Executive Secretary, WHO
6. World Health Organisation (December 2017) "WHO advises Dengvaxia be used only in people previously infected with dengue" https://bit.ly/31jtHSF
7. World Health Organisation (2019) "Model List of Essential Medicines – 2nd List" https://bit.ly/39ewhOc
8. Overall positive effect of dengvaxia® in the Philippines:
   (i) Flasche, S., Wilder-Smith, A., Hombach, J., Smith, P.G (2019) "Estimating the proportion of vaccine-induced hospitalized dengue cases among Dengvaxia vaccinees in the Philippines" *Wellcome Open Research;* 4:165. https://bit.ly/2PwcKSE

   (ii) Wilder-Smith, A., Flasche, S., Smith, P.G. (2019) "Vaccine attributable severe dengue in the Philippines" *The Lancet* 394:10215 https://bit.ly/3slFWKD
9. Reuters (2nd August 2019) "Philippines weighs re-use of controversial dengue vaccine". https://bit.ly/2QE9jd5
10. Sanofi Pasteur (7th March 2019) "Dengvaxia. Tetravalent, Live-Attenuated Viral Vaccine against Dengue Serotypes 1, 2, 3 and 4. Briefing Document for the Vaccines and Related Biological Products Advisory Committee" (pp. 57-58 refer to WHO SAGE guidance) https://bit.ly/3cilJyw
11. FDA approval
    (i) STAT (2019) "FDA approves the first vaccine for dengue fever, but with major restrictions" https://bit.ly/3snE9o2
    (ii) FDA (2019) "First FDA-approved vaccine for the prevention of dengue disease in endemic regions" https://bit.ly/3u6jZQf