Institution: University of Cambridge		
Unit of Assessment: 5		
Title of case study: Shaping WHO meningitis vaccine guidelines		
Period when the underpinning research was undertaken: 2010-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Caroline Trotter	**Role(s) (e.g. job title):** Principal Research Associate	**Period(s) employed by submitting HEI:** Jane 2013 – to date
Period when the claimed impact occurred: 2015-2019		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

The World Health Organisation engaged Dr Caroline Trotter as a trusted advisor to help tackle the challenge of meningitis on the African continent. Epidemiological modelling of vaccine strategies using MenAfriVac® to control bacterial meningitis group A, widely found in sub-Saharan Africa, was undertaken at the University of Cambridge. This led to the successful introduction of the vaccine into routine immunisation schedules, supported by a 'catch up' campaign. Between 2016 and 2020, 11 countries included MenAfriVac® in their routine vaccination programme, and overall more than 340 million people at risk between the ages of 0 and 29 years have now been vaccinated in 24 countries. This has led to group A meningitis now being controlled effectively in the affected regions. Alongside recommended vaccination programmes, further modelling work led the WHO to formally reduce the threshold value for the number of cases needed to declare an epidemic, to allow countries more time to prepare should the situation develop into an epidemic, and thereby prevent the spread of emergent bacterial variants.

2. Underpinning research (indicative maximum 500 words)

The challenge of meningitis in the African belt

Meningitis is a serious infection that causes swelling of the meninges, the membranes surrounding the brain and spinal cord. Around 10% of cases are fatal and survivors may experience brain damage and deafness. The African meningitis belt is an area stretching from Senegal to Ethiopia, which, during the past 120 years has suffered epidemics that have devastated communities. In 1996-97 an epidemic of meningitis caused by the bacterium *Neisseria meningitidis* group A (NmA), resulted in 250,000 cases and took over 25,000 lives.

A new model for immunisation strategies

Dr Trotter has extensive experience working on meningitis and has pioneered the use of models to predict the impact of alternative meningococcal immunisation strategies. She is an honorary epidemiologist at Public Health England and contributes to national discussions on immunisation policy. Her previous work on the impact of meningococcal group C conjugate vaccines in the UK was highly relevant to the Meningitis Vaccine Project (MVP), a partnership between the World Health Organisation (WHO) and the global health organisation PATH, which aimed to develop and introduce a meningococcal group A conjugate vaccine for Africa. As a result, she was invited to work closely with the WHO meningitis team. In 2013/14 Dr Trotter and her team were asked to provide evidence to the WHO, based on her established expertise and reputation.

The vaccine created by MVP, known as MenAfriVac®, was introduced in mass campaigns, starting in 2010, targeting individuals aged 0-29 years in affected regions. However, at the time

of introduction, there was no long-term plan to sustain the protection afforded by MenAfriVac®. Dr Trotter and her group created a new mathematical model to simulate various immunisation strategies and estimate their impact on disease burden and transmission [R1]. This approach allowed for a much wider range of options to be considered *in silico* than could ever be tested in real life. Modelling showed that without a long-term vaccination programme, meningitis group A epidemics would return to the region within 15 years [R1], meaning that a long-term vaccine strategy was essential to ensure that the gains made from mass campaigns were not lost. Based on these models, Dr Trotter's group predicted that the best approach, i.e. resulting in the smallest number of future meningitis cases, would be to introduce MenAfriVac® into the routine childhood immunisation schedule in combination with a mini-catch-up campaign targeting children born since vaccine introduction. An economic analysis of vaccination scenarios further emphasised the benefits of long-term vaccination [R2].

Reviewing epidemic thresholds

The success of MenAfriVac® has changed the makeup of the meningitis threat in Africa. Given the residual threat of outbreaks due to other strains not covered by the vaccine, Dr Trotter was asked to investigate whether the weekly incidence thresholds used by WHO and meningitis belt countries to guide epidemic response were still appropriate. Dr Trotter joined an international team reviewing the complete meningitis guidelines and took the lead in addressing the issue of epidemic response thresholds. Dr Trotter reviewed relevant primary surveillance data, conducted a literature review and developed a statistical simulation model of the predicted impact of a range of operational thresholds [R3]. This work showed that earlier initiation of vaccination programmes would prevent more cases of meningitis than would lowering the threshold of cases for an epidemic; the lowest alert threshold modelled of three per 100,000 per week resulted in substantially more cases being potentially preventable as this resulted in the longest time between the threshold being reached and the epidemic peak, allowing a more effective response.

3. References to the research (indicative maximum of six references)

R1. Karachaliou A, Conlan AJK, Preziosi M-P, **Trotter CL**. Modelling long-term vaccination strategies with MenAfriVac® in the African meningitis belt. Clin Infect Dis. 2015 ;61:S594-S600. DOI:10.1093/cid/civ508

R2. Colombini A, **Trotter CL**, Madrid Y, Karachaliou A, Preziosi MP. Costs of Neisseria meningitidis group A disease and economic impact of vaccination in Burkina Faso. Cli Infect Dis. 2015; 61:S473-S82. DOI: 10.1093/cid/civ600

R3. **Trotter CL**, Cibrelus L, Fernandez K, Lingani C, Ronveaux O, Stuart J. Response thresholds for epidemic meningitis in sub-Saharan Africa following the introduction of MenAfriVac®. Vaccine.2015; 33:6212–6217. DOI: 10.1016/j.vaccine.2015.09.107

All publications have been peer reviewed.

Competitive funding received:

- July 2013 - Oct 2014. Using mathematical models to investigate the impact of different immunisation strategies using a meningococcal group A conjugate vaccine in the African meningitis belt. PATH GBP45,218, [RG 72559]
- Jan 2015 - Dec 2017. Mathematical modelling consultant for Meningococcal A conjugate vaccine impact evaluation. WHO USD233,172 / GBP147,577 [RG 78696]

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

Impact on World Health Organisation (WHO) policy

The research described above was used to directly inform WHO's policies. The results from the modelling of long-term vaccination strategies were presented by Dr Trotter to the WHO Strategic Advisory Group of Experts (SAGE) committee in October 2014. The committee considered the

modelling evidence alongside results from clinical trials of immunisation in children under two years of age. They subsequently recommended that MenAfriVac® should be given according to the 'best' strategy defined by the modelling, i.e. that the vaccine be introduced into the routine immunisation schedule (EPI), with a single dose given between the ages of 9 and 18 months, and at the same time a catch-up campaign should be conducted to target children born since the original mass campaigns [E1]. This decision was explained by an article in The Economist [E2], which featured the modelling work and emphasised that: *"To keep a proper lid on meningitis A, though, the next step should be to make vaccination routine for infants and remain vigilant for outbreaks".* Dr Trotter presented her work at the Meningitis Vaccine Project meeting in Ethiopia in 2016 to an audience including representatives from African Ministries of Health. At this meeting, affected countries were persuaded to co-invest with Gavi, the Vaccine Alliance, in the vaccine [E3].

Medical Officer and Meningitis lead in the Department of Immunization, Vaccines and Biologicals at the WHO has said that "the quality of [Dr Trotter's] contributions over the years has largely contributed to the success of the Meningitis Vaccine Project for sub-Saharan Africa's meningitis belt, which has been repeatedly identified as a public health achievement of the decade" [E3].

Impact on health

In 2016, Ghana and Sudan became the first countries to implement the recommendation for routine immunisation with MenAfriVac®. This was followed by Burkina Faso, Central African Republic, Chad, Mali and Niger in 2017, Cote d'Ivoire in 2018, Gambia and Nigeria in 2019, Eritrea in 2020 and four other countries plan to do so in 2020 – 2021 [E3]. In 2019, an estimated 14.3 million babies and toddlers received MenAfriVac® in the EPI schedule. By 2025, cumulatively, 155 million children are projected to have received MenAfriVac® in the EPI [E11]. As well as routine vaccination, more than 340 million people at risk between the ages of 1 and 29 years have now been vaccinated through mass and catch-up campaigns in 24 countries, which has led to Group A meningitis now being controlled effectively in the affected regions [E3]. The vaccine strategies adopted for MenAfriVac are highly effective. To date, only a handful of NmA cases have been reported in vaccinated countries and there have been no NmA epidemics. A quantitative analysis of vaccine impact commissioned by the WHO suggests that NmA cases have been reduced by 98%, and the burden of both suspected meningitis cases and meningitis outbreaks are 60% lower in immunised populations [E4]. The effectiveness of routine immunisation in sustaining protection will become apparent over the longer term.

Impact on WHO guidelines and emergency response

Although MenAfriVac® has been a resounding success, there is still a threat from other causes of meningitis. The epidemic meningitis guideline was updated by WHO in 2014 [E5] to reflect the changing nature of the meningitis threat. This guideline used evidence from Dr Trotter's work on operational thresholds for other serogroups of meningitis. The previous guideline used an upper incidence limit of 15 per 100,000 per week to define the 'epidemic threshold', the point at which reactive immunisation may be recommended, although in practice a lower limit of 10 per 100,000 was usually used. The research by Trotter *et al* provided justification for WHO to formally adopt the lower epidemic threshold of 10 per 100,000 per week. In addition, given the emphasis of the modelling work on the importance of timeliness in response, WHO decided to adopt a lower 'alert threshold' of three per 100,000 per week, rather than keep the status quo of five per 100,000 per week. This would allow countries more time to prepare should the situation develop into an epidemic.

Since 2016, the International Coordinating Group on Vaccine Provision has provided reactive meningitis vaccination in response to epidemics in 11 countries, with approximately 5.5 million vaccine doses delivered [E6]. The meningitis guideline has been particularly important in the context of the emergence of serogroup C meningitis as a new threat. Dr Trotter has also been involved in ongoing WHO discussions about this threat [E7] and has been commissioned by the WHO to conduct further work to estimate the appropriate size of the meningitis vaccine stockpile [E8]. She is a member of the WHO-led global Technical Taskforce to Defeat Meningitis by 2030 [E3], which published its first draft roadmap in April 2020, as a call to action to continue progress

in tackling this serious disease [E9]. On 12 November 2020, at the 73rd World Health Assembly, WHO Committee A decided to recommend the adoption of the first-ever resolution on meningitis, approving this roadmap and setting in motion a path to eradicate meningitis [E10].

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

E1. WHO weekly epidemiological record including decision on routine vaccinations
E2. Article in The Economist explaining the routine vaccination decision
E3. Testimonial from the Initiative for Vaccine Research (IVR) at WHO
E4. Trotter CL, Lingani C, Fernandez K, Cooper LV, Bita A, Tevi-Benissan C, Ronveaux O, Preziosi MP, Stuart JM. The impact of MenAfriVac in nine countries of the African meningitis belt, 2010-2015: an analysis of surveillance data. Lancet Infect Dis 2017, pii: S1473-3099(17)30301-8. Study funded and supported by the WHO
E5. WHO meningitis guidelines incorporating advice from Caroline Trotter's research
E6. International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control, collated reports 2016-2019. Vaccine doses on: page 8 (2016 = 1,217,560), page 34 (2017 = 2,877,490), page 52 (2018 = 412,830) and page 76 (2019 = 977,460)
E7. Serogroup C in the meningitis belt WHO expert group meeting report
E8. Trotter, C. 2017 Stockpile needs for epidemic meningitis response 2018-2022 WHO website
E9. WHO Defeat Meningitis roadmap
E10. WHO endorsement of resolution on meningitis control
E11. Li et al., Estimating the health impact of vaccination against 10 pathogens in 98 low and middle income countries from 2000 to 2030, medRxiv 19004358; doi: 10.1101/19004358