Institution: University of Bristol		
Unit of Assessment: 2) Public Health, Health Services and Primary Care		
Title of case study: Bristol research critical to decision to introduce meningitis B vaccine for all UK infants, which led to a 75% reduction in cases		
Period when the underpinning research was undertaken: 2007 - 2015		
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:**
Hannah Christensen	Senior Lecturer in Infectious Disease Mathematical Modelling	10/2007 to present
Matt Hickman	Professor in Public Health and Epidemiology	09/2005 to present
Caroline L Trotter	Senior Research Fellow Honorary Senior Lecturer	12/2006 to 12/2012 01/2013 to 12/2015
Period when the claimed impact occurred: 1st August 2013 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

University of Bristol (UoB) research was critical to the Department of Health deciding, in 2015, to introduce the Bexsero vaccine against group B meningococcal (MenB) disease for babies. UoB led research to develop new models predicting which vaccine strategy could avert the most cases and the maximum vaccine cost for the NHS. The Joint Committee on Vaccination and Immunisation, who advise Government, recommended introducing the vaccine at a cost-effective price based on UoB's findings and MenB cases reduced by 75% by the third year of the programme. The research has also informed vaccination policy in Belgium and Germany.

2. Underpinning research

Mathematical models are now a critical tool for informing decisions on vaccine policy in the UK. This is because the Joint Committee on Vaccination and Immunisation (JCVI), who advise the Government on vaccine policy in the UK, can only recommend vaccine introduction if it is deemed cost-effective. When new vaccines are developed new mathematical models are required to assess potential effectiveness and cost-effectiveness when implemented in populations – UoB led research developed such models for novel vaccines against meningococcal B disease.

This body of research began in 2007 and has been undertaken by Hannah Christensen, in collaboration with Dr CL Trotter (Bristol, now at Cambridge), Prof M Hickman (Bristol) and Prof WJ Edmunds (Health Protection Agency (now Public Health England) and the London School of Hygiene & Tropical Medicine). Two types of mathematical model (cohort and transmission dynamic) were developed, incorporating epidemiological and economic data, to predict the potential impact of introducing a new meningococcal vaccine with the capacity to protect against capsular group B meningococcal (MenB) disease, in terms of case reduction and cost-effectiveness. The models were developed by Hannah Christensen, initially forming her PhD, with supervision by Profs Hickman, Edmunds and Dr Trotter. Subsequently these were further developed by Dr Christensen with ongoing advice from Dr Trotter and Profs Edmunds and Hickman.

These models were the first to comprehensively assess the potential impact of 'MenB' vaccines in late stage clinical trials, appropriately accounting for herd effects through vaccine disruption of transmission. The UoB-led research found that 27% of cases could be prevented over the lifetime of a birth cohort by vaccinating infants (with a vaccine preventing disease only) at 2, 3, 4 and 12 months of age [1]. At a willingness-to-pay of GBP 30,000 per Quality Adjusted Life Year, such a strategy could be cost-effective [1]. If the vaccine prevents transmission in addition to preventing disease, substantial disease reductions (71%) could be produced after 10 years by routinely vaccinating infants in combination with a large-scale catch-up campaign (1-17 years), due to the high levels of carriage in teenagers [4]. This could be cost-effective at GBP 17 per vaccine dose [1].

From 2011, the UoB-led team further developed the models in response to the availability of new data and requests by the JCVI. Model results considering several different 'MenB' vaccine scenarios, and the uncertainty in several of the model parameters, were produced, estimating the number of cases averted by vaccination and in what age groups over time. The cost-effectiveness of each programme was evaluated and the maximal vaccine price estimated for each scenario to be considered cost-effective in the UK [2]. Additionally, we were commissioned to tailor the models for Germany [3] and Belgium by the health authorities in these countries; Dr Christensen led the research team, which included UoB post-doctoral researchers Drs Tom Irving and Emily Nicoli.

3. References to the research

[1] **Christensen H**, **Hickman M**, Edmunds WJ, **Trotter CL**. Introducing vaccination against serogroup B meningococcal disease: An economic and mathematical modelling study of potential impact. Vaccine. 2013; 31(23): 2638-46. DOI:10.1016/j.vaccine.2013.03.034

[2] **Christensen H**, **Trotter CL, Hickman M**, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. BMJ. 2014; 349:g5725. DOI:10.1136/bmj.g5725

[3] **Christensen H**, Irving T, Koch J, **Trotter CL**, Ultsch B, Weidemann F, Wichmann O, Hellenbrand W. Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero® to reduce meningococcal group B disease in Germany. Vaccine. 2016; 34(29): 3412-9. DOI:10.1016/j.vaccine.2016.04.004

[4] **Christensen H**, May M, Bowen L, **Hickman M**, **Trotter CL.** Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infectious Diseases. 2010; 10(12): 853-861. DOI:10.1016/S1473-3099(10)70251-6

Grants:

[i] **Christensen H.** Investigating the potential benefit of enhanced or alternative interventions for infectious disease control: a focus on adolescent vaccination and contact tracing, *National Institute of Health Research*, *Post-Doctoral Fellowship*, 1 January 2013 to 31 December 2015 GBP240,296 (peer-reviewed grant for post-doctoral fellowship)

[ii] **Christensen H.** Modelling the impact of vaccination targeted against serogroup B meningococcal disease, *National Institute of Health Research, Researcher Development Award*, 1 October 2007 to 30 September 2010, GBP 184,596 (peer-reviewed grant for doctoral fellowship)

4. Details of the impact

Meningococcal disease is a leading infectious cause of death in young children in the UK. The disease progresses rapidly even with appropriate treatment and can leave survivors with severe disabling after-effects, including amputation, skin scarring and neurological damage. At the time of initial model development for this work, a broadly effective vaccine against group B meningococcal disease was not available, though several candidate 'MenB' vaccines were in late stage clinical trials.

Impact on vaccination policy in the UK

In January 2013, once the first broadly effective vaccine against MenB disease (Bexsero) was granted an EU license, policy makers needed to urgently consider if and how to utilise it. In the UK, the requirement for the JCVI to only recommend vaccines that are cost-effective means that mathematical models are used as a key tool to inform policy making, as they can explore multiple different scenarios.

The underpinning research by UoB had indicated which introductory vaccine strategy would have the greatest impact in terms of meningococcal case reduction and estimated the cost-effectiveness of the programme [1]. As a result of submitting evidence on UoB's research results to a JCVI call for evidence on issues relating to meningococcal vaccination in 2011, Dr Christensen was invited to present the findings of the ongoing model development at closed JCVI meetings in February, April, June 2013, and February 2014 [A].

In March 2014, the JCVI recommended the introduction of Bexsero in the UK with a schedule from UoB's model that offered the greatest direct protection at reduced cost [2], subject to a cost-effective vaccine price [B]. JCVI's position statement on the use of Bexsero explained that a "key component" in JCVI's assessment of the drug was *"a study on the impact and cost-effectiveness of different vaccination strategies using Bexsero® conducted by the University of Bristol and London School of Hygiene and Tropical Medicine"* [Bi p.2]. UoB's research is discussed at length (pp.2-3) and cited on five occasions in the statement [Bi]. The vaccine has been offered free on the NHS to babies at 2, 4 and 12 months of age since September 2015 and forms part of the ongoing national programme [B].

Public Health impact in the UK

Bexsero vaccine uptake has been high. In 2019/20, 92.5% of 12 month olds had been vaccinated [C]. The programme has been effective at reducing cases of meningococcal disease [D] and the associated morbidity and mortality. Cases in vaccine-eligible infants halved in the first 10 months of the programme, irrespective of the infants' vaccination status, and subsequent data have shown a sustained reduction in MenB cases compared with pre-vaccine levels in those targeted for vaccination (Figure 1). By the third year of the programme there was a 75% reduction in MenB cases in children who were fully eligible for vaccination [E]. Due to the vaccine's composition, it also offers some protection against other capsular groups and, whilst case numbers are small, there is evidence that the vaccine has also reduced MenW disease in infants [D].

Economic impacts for the NHS

UoB's models suggested vaccination would only be cost-effective at a low vaccine price [2]. The JCVI can only recommend introducing a vaccine if it is deemed cost-effective, thus UoB's models were critical to their decision to recommend the vaccine and at what price.

These were the only independent models considered by JCVI [B]. The list price for the Bexsero vaccine in the UK was GBP 75 per vaccine dose; however, UoB's final model results suggesting ≤GBP 7 per dose [2] were used to inform the procurement process, thus leveraging a considerable saving to the NHS. As for all vaccines procured for the NHS, the final price paid for the vaccine is confidential. Notwithstanding, if the negotiated price of the vaccine was close to that suggested by UoB's final model, it can be assumed that the research could currently save the Department of Health approximately GBP 136 million annually on delivering the programme (difference between GBP 75 and GBP 7 for a 3-dose vaccine given to a birth cohort annually of 722,881 UK infants with 92.5% uptake).

Impact on international vaccination policy

The models developed for the UK have been adapted by the UoB-led group in collaboration with international researchers to inform Bexsero policy decisions in Belgium (2014) [G] and Germany (December 2013) [H]. Our group was approached by researchers at the Robert Koch Institute and the Belgian Healthcare Knowledge Centre and commissioned to undertake the work. Models for these countries [3] indicated that whilst vaccination could reduce case numbers, immunisation would be beyond that normally considered cost-effective; consequently, these countries have not recommended widespread introduction of the vaccine [G, H].

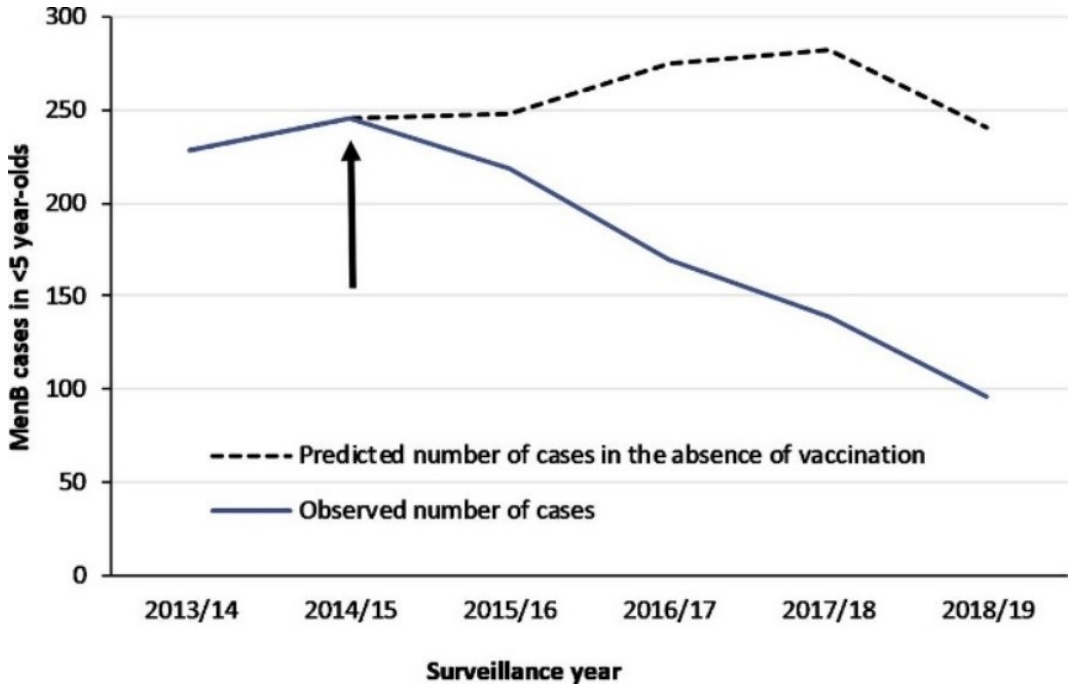

Figure 1: *MenB cases in children under 5 years of age during 2013/2014–2018/2019 surveillance years (September–August following year) in England (solid line) compared with MenB cases predicted by trends among unvaccinated childhood cohorts (dashed line) over the same period. The arrow indicates the start of the MenB infant immunisation programme. Only around half of the birth cohorts in children under 5 in this figure were eligible for the Bexsero vaccine, thus underestimating the true impact of the vaccine in those who actually received it [F]. In children who were fully eligible for vaccination there was a 75% reduction in MenB cases by the third year of the programme [E].*

5. Sources to corroborate the impact

[A] JVCI (2014). Minutes of the meeting on Tuesday 11 and Wednesday 12 February 2014, Department of Health

[B] i) JVCI (2014). JVCI position statement on use of Bexsero® meningococcal B vaccine in the UK
ii) JCVI (2020). Supporting statement – JCVI Chair

[C] NHS Digital (2020). Childhood Vaccination Coverage Statistics - England 2019-20

[D] i) PHE (2018). Invasive meningococcal disease in England: annual laboratory confirmed reports for epidemiological year 2017 to 2018
ii) PHE (2018). Recent epidemiology of meningococcal disease and impact of immunisation programmes in the UK

[E] i) Parikh *et al.* (2016) Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *Lancet,* 388 (10061). 2775-2782. DOI:10.1016/S0140-6736(16)31921-3
ii) Ladhani *et al.* (2020). Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England. *N Engl J Med,* 382(4):309-317. DOI:10.1056/NEJMoa1901229

[F] Isitt *et al.* (2020). Success of 4CMenB in preventing meningococcal disease: evidence from real-world experience. *Archives of Disease in Childhood,* 105:784-790. DOI:10.1136/archdischild-2019-318047

[G] i) Belgian Health Care Knowledge Centre (KCE) (2014). KCE Report 231. A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study
ii) Belgian Health Care Knowledge Centre (KCE) (2020). Supporting statement – Medical epidemiologist

[H] i) Robert Koch Institute (Dec 2013). Statement of the Standing Vaccination Commission (STIKO) at the Robert Koch Institute (RKI) on the status of the evaluation of new meningococcal B vaccine Bexsero®, Epidemiologisches Bulletin 49. (translation available).
ii) Robert Koch-Institute (2020) Supporting statement – Infectious Disease Epidemiologist, on behalf of the MenB working group at the Robert Koch-Institute