Institution: London School of Hygiene & Tropical Medicine (LSHTM)		
Unit of Assessment: 2		
Title of case study: Using mathematical modelling to inform policy decisions on vaccination		
Period when the underpinning research was undertaken: 2013-2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed:**
Mark Jit	Associate Professor; Professor	01/10/2011-present
John Edmunds	Professor	23/06/2008-present
Marc Baguelin	Assistant Professor; Associate Professor	0107/2010-present
Stefan Flasche	Assistant Professor; Associate Professor	19/04/2012-present
Albert van Hoek	Assistant Professor	03/11/2014-31/03/2020
& associated research teams		
Period when the claimed impact occurred: 2013-2020		
Is this case study continued from a case study submitted in 2014? No		

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

Evidence from LSHTM research has influenced many high-profile decisions about new vaccines, and how and when people in England are immunised against a range of diseases. Health and economic modelling specialists regularly presented analysis of the impact of potential changes to the UK vaccination schedule to the Joint Committee on Vaccination and Immunisation (JCVI). This directly informed recommendations to introduce new vaccines or change the way existing vaccines were used to improve coverage and efficiency throughout 2013 to 2020. LSHTM research underpinned key changes, such as introducing meningitis B vaccination, influenza vaccination in children, and HPV schedule changes, saving lives, reducing morbidity, and saving millions of pounds of NHS resources.

2. Underpinning research (indicative maximum 500 words)

Vaccines prevent disease and save lives. But vaccinations introduced to a population also have wider benefits, including preventing healthcare costs and loss of productivity for those vaccinated who would otherwise have suffered from a disease.

Research teams at LSHTM led by Jit and Edmunds used mathematical modelling to predict the impact of different potential UK vaccine strategies. The results were then used in economic models that projected the implications of different strategies for NHS resources and UK population health, to determine if a strategy was cost-effective. These models translated the special characteristics of infectious diseases into outcomes satisfying the gold standard methods set by the National Institute for Health and Care Excellence (NICE) for evaluating all health interventions.

The models drew on data and expert knowledge from electronic health database experts at LSHTM as well as from long-standing collaboration with scientists at Public Health England (PHE). LSHTM's methodological excellence and the strength of its collaborative ties with PHE were recognised in 2014 when LSHTM was awarded an NIHR Health Protection Research Unit in Immunisation, to continue this work on evidence for vaccine decisions. The teams at LSHTM applied mathematical models of transmission to virological, clinical, epidemiological and behavioural data to make predictions on the health and economic implications of vaccines against influenza (seasonal and pandemic), human papillomavirus (HPV), meningococcus, pneumococcus, and many other diseases that can be prevented by a vaccine.

Influenza vaccination

In 2013, the team estimated the reduction in infections and deaths achieved by England and Wales' flu vaccination programme, compared with no vaccination, and found that children were key spreaders (3.1). Targeting the people who transmitted flu by extending the vaccination programme to 5- to 16-year-old children was found to increase the efficiency of the whole programme, resulting in an overall reduction of 0.7 infections per dose and 1.95 deaths per 1,000 doses. Extending the programme was also found to be highly cost-effective (3.2).

Meningococcus B vaccination
Similarly, in 2014, the researchers found that routine infant immunisation for group B meningococcal disease was the most effective vaccination strategy, preventing 27% of meningococcal disease cases over the lifetime of an English birth cohort by vaccinating infants at 2, 3, 4 and 12 months of age. They also estimated that 71% of meningococcal B cases could be prevented after 10 years by routine vaccination of infants in combination with a large-scale catch-up campaign (3.3). Routine infant immunisation was also found to be cost-effective at GBP3 a vaccine dose, and could result in long-term reductions in cases (3.4).

HPV vaccination
The HPV vaccine protects against cancers caused by HPV, including cervical cancer, and some mouth, throat, anal and genital cancers, and against genital warts. In the UK, HPV vaccination was offered to girls aged 12 to 13 through a 3-dose schedule. Following clinical trials suggesting that 2 doses may offer sufficient protection against HPV, Jit and colleagues investigated whether offering the vaccination as a 2-dose schedule would be a cost-effective approach.

They compared 2-dose and 3-dose HPV vaccine schedules in the UK among males and females aged 12 to 74 years. This cost-effectiveness study was based on a dynamic model of HPV vaccination. The 2-dose schedule was found to be the most cost-effective option if 2 doses provided more than 20 years' protection against HPV-related cancers (3.5).

Conjugate pneumococcal vaccination
The pneumococcal conjugate vaccine (PCV) protects against serious pneumonia caused by *Streptococcus pneumoniae* and is given on the NHS to those at a higher risk of illness, including babies, older adults, and those with underlying health conditions. Van Hoek assessed the cost-effectiveness of this programme in older adults aged 65 years and over, in a static cohort cost-effectiveness model of adults with normal immune responses, who were due to be vaccinated in the autumn of 2016 with a PCV (3.6). The analysis demonstrated that whilst the programme was effective in preventing pneumococcus diseases, the wider benefits of the vaccination programme in children significantly reducing incidence of the disease in adults meant that the programme targeting the elderly was not cost-effective given the cost of vaccine administration.

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

3.1 Baguelin M, **Flasche S**, **Camacho A**, Demiris N, Miller E, **Edmunds WJ**. 2013. Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLoS Medicine.* 10(10):e1001527. doi: 10.1371/journal.pmed.1001527.

3.2 Baguelin M, **Camacho A**, Flasche S, **Edmunds WJ**. 2015. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. *BMC Medicine.* 13:236. doi: 10.1186/s12916-015-0452-y.

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

3.4 Christensen H, Hickman M, **Edmunds WJ,** Trotter C. 2013. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine.* 2638-2646. doi: 10.1016/j.vaccine.2013.03.034

3.5 Jit M, Brisson M, Laprise JF, Choi YH. 2015. Comparing two-dose and three-dose human papillomavirus vaccine schedules: cost-effectiveness analysis based on transmission model. *BMJ*. 350:g7584. doi: 10.1136/bmj.g7584.

3.6 van Hoek AJ, Miller E. 2016. Cost-effectiveness vaccinating immunocompetent ≥65 year olds with the 13-valient pneumococcal conjugate vaccine in England. *Plos One.* doi: 10.1371/journal.pone.0149540

We believe this body of research meets the 'at least 2*' definition given its reach, significance and rigour.

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

The Joint Committee on Vaccination and Immunisation (JCVI) advises UK health departments about vaccines that should be introduced. Under the Health Protection (Vaccination) Regulations 2009, the Health Secretary is obliged to adopt these recommendations if certain conditions are met, the most important of which is that they are based on an assessment that demonstrates cost-effectiveness. LSHTM has been the main provider of the first opinion for the health and economic modelling evidence required to assess this, in collaboration with PHE. LSHTM researchers regularly attended JCVI meetings to present evidence before publication, and advised JCVI members prior to their final recommendation. Economic evaluations from LSHTM were also used in the tendering process by the Department of Health and Social Care when selecting manufacturers to supply vaccines to the UK.

As a result of JCVI recommendations underpinned by LSHTM research, changes to vaccine schedules have directly benefited thousands of vaccine recipients since 2013. They have also provided indirect protection to the UK public by reducing the spread of infection and averting cases in other individuals, reduced the burden of several diseases, and saved on NHS resources. There are also the wider benefits of averting costs to society and the individual, and of the quality of life improved by disease prevention.

Evidence of impact on specific vaccines:

Influenza

In 2012, Edmunds and Baguelin presented work to the JCVI on the cost-effectiveness of changes to flu vaccination; the JCVI recommended extending the flu campaign to include school-aged children (age 5 to 17) and children aged 2 to 5 (5.1). This supported the gradual roll-out of seasonal influenza vaccination to children, beginning with a pilot in 2013 where all 2- to 3-year-olds were offered vaccination through GPs in England, and a pilot in English schools. This pilot was extended every year to include all children up to school year 6 (age 10 to 11) in 2019 and 2020 (5.2). It eventually became the largest change ever made to the UK's vaccination programmes in terms of numbers of people vaccinated. Projections suggested that around 5 million extra people would be vaccinated every year, and around 2.5 million fewer would get influenza, when the programme covered all primary school children, compared to before the programme was implemented. The flu vaccine is now offered to all children aged 2 to 10 years old, meaning all primary school age children are now eligible for vaccination and direct protection from flu, and those aged up to 18 years old in clinical risk groups. Data from the 2019/2020 winter season provided by all local authorities showed that over 2.8 million children from reception to school year 6 were vaccinated, representing 60.4% of the eligible pool of primary school age children (5.3).

With the risk of COVID-19 and flu both circulating at the same time over the winter of 2020, the Scientific Advisory Group for Emergencies (SAGE) (of which Edmunds was a member) advised the UK government that seasonal flu vaccination should be more widely deployed to protect vulnerable individuals (5.4). In autumn 2020, flu vaccination was additionally offered to household contacts of those on the NHS Shielded Patient List, children in year 7 (age 11 to 12) in secondary schools, and health and social care workers employed through Direct Payment and/or Personal Health Budgets (5.4).

HPV

Since 2013, Jit has presented several pieces of work to the JCVI which underpinned successive changes to the HPV vaccination programme, offering direct protection to the public and reducing the burden of HPV-related cancers. These included:

i) Changing the schedule from 3 to 2 doses in 2014 (5.5), saving up to 800,000 doses annually (reflecting the size of the 12-13 age cohort) of a quadrivalent vaccine that costs the NHS up to GBP86.50 per dose to procure and distribute (3.1, 3.2), with the added benefit of reduced

logistical complexity. This work also informed international stakeholders, for example, the World Health Organization's recommendation of a 2-dose HPV vaccination in 2014 (5.6).

ii) Rolling out, in 2017, the world's first programme to vaccinate men who have sex with men (MSM), who are at exceptionally high risk of acquiring HPV-related cancers (5.7).

iii) Vaccinating all boys in England aged 12 to 13 from 2019 onwards (5.8).

Meningococcal B

In 2013 and 2014, Edmunds presented impact and cost-effectiveness analyses to the JCVI which led to babies being given the infant meningococcal B vaccination, making the UK the first country in the world to do so (5.9). This was a complex decision, involving a vaccine with an innovative but relatively untried mechanism of action, a rare but devastating disease, and interest from a large number of civil society groups (such as meningitis charities). The vaccine was introduced in 2015 to children at 2, 4 and 12 months, preventing hundreds of meningitis cases per year. Public Health England data in 2020 showed that since the vaccine's introduction, cases of meningitis B disease in England fell by 62% in children who received at least two doses (5.10).

Conjugate pneumococcal

In 2015, van Hoek presented work to the JCVI showing that vaccinating older adults with a conjugate pneumococcal vaccine would have little impact and not be cost-effective (5.11). Based on this research, the JCVI did not introduce this vaccination. An independent report by RAND Europe stated that this decision saved the NHS up to GBP25 million pounds per year, and the NIHR recognised this work as 1 of 100 examples of positive change arising from its support of research in its first 10 years (5.12).

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

5.1 Joint Committee on Vaccination & Immunisation statement on the annual influenza vaccination programme – extension of the programme to children. 25 July 2012. (pg1-3). Accessed at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf

5.2 Public Health England. The National Childhood Flu Immunisation Programme 2019/20. July 2019. Information for healthcare practitioners.

5.3 Public Health England. Seasonal influenza uptake in children of primary school age: winter season 2019 to 2020. Final data for 1 September 2019 to 31 January 2020. June 2020.

5.4 Thirtieth SAGE meeting on COVID-19, 30 April 2020. SAGE recommendation to scale up flu vaccination, Edmunds and Medley in attendance. Accessed at: https://www.gov.uk/government/publications/sage-minutes-coronavirus-covid-19-response-30-april-2020

Department of Health & Social Care, Public Health England. National flu immunisation programme 2020 to 2021 – update. Wednesday 5 August 2020. Professor Chris Whitty (Chief Medical Officer for Engand), Professor Yvonne Doyle (Public Health England Medical Director & Director for Health Protection), Professor Stephen Powis (NHS England & NHS Improvement, National Medical Director).
Accessed at: https://www.england.nhs.uk/wp-content/uploads/2020/05/Letter_AnnualFlu_2020-21_20200805.pdf

5.5 Joint Committee on Vaccination and Immunisation. 11/12 February 2014: meeting minutes and agenda. Agenda item 10. Accessed at: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes

5.6 World Health Organization. Evidence based recommendations on human papilloma virus (HPV) vaccines schedules: background papers for SAGE discussion. March 11 2014.

- Background evidence on 2-dose schedule rather than 3-doses, also includes suggested recommendation that 2 doses are non-inferior to 3 for SAGE consideration

World Health Organization. Weekly epidemiological record. 23 May 2014. No 21, 2013, 89, 221-236. Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 – conclusions and recommendations. Accessed at: https://www.who.int/wer/2014/wer8921.pdf?ua=1 pg no. 229

5.7 JCVI subcommittee minutes. Accessed at: https://app.box.com/s/600veu6zr6s3qjvx8mkt#/s/600veu6zr6s3qjvx8mkt/1/2678951279/27417239964/1?&_suid=144681145000103725482991649253
HPV Subcommittee of the Joint Committee on Vaccination and Immunisation. Minute of the meeting held on Monday September 22 2014.

- VI;18, Vaccination of men who have sex with men (Jit presentation). VII;29-34 Conclusion of the Subcommittee.

HPV Subcommittee of the Joint Committee on Vaccination and Immunisation. Minute of the teleconference held on Friday 2 June 2017.

- Jit presented, and details of pilot MSM included

5.8 JCVI interim statement on extending HPV vaccination to adolescent boys. July 2017. Accessed at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/630125/Extending_HPV_Vaccination.pdf

- Jit modelling referenced pg 9, LSHTM findings referenced pg 18.

5.9 JCVI position statement on use of Bexsero meningococcal B vaccine in the UK. March 2014. Accessed at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/294245/JCVI_Statement_on_MenB.pdf

- Studies referenced pg 2 and reference 8

5.10 The impact of the MenB vaccine. Public Health England. January 23 2020. Accessed at: https://publichealthengland.exposure.co/the-impact-of-the-menb-vaccine
Study: Ladhani SN, Andrews N, Parikh SR, Campbell H, White J, Edelstein M, Bai X, Lucidarne J, Borrow R, Ramsay M. Vaccination of infants with Meningococcal Group B Vaccine (4CMenB) in England. 2020. N Engl J Med 2020; 382:309-317. doi: 10.1056/NEJMoa1901229

5.11 Joint Committee on Vaccination and Immunisation. Interim JCVI statement on adult pneumococcal vaccination in the UK. November 2015. Accessed at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/477966/JCVI_pnemococcal.pdf

- Paragraph 28, References 4, 7, 15, 25. Conclusions paragraph 35-36.

5.12 The National Institute for Health Research at Ten Years: an impact synthesis. Case Study 8.1.5 Generating the evidence to support difficult decisions around vaccination policy in a cost-constrained healthcare system (pg 173).

National Institute for Health Research Health Protection Research Unit in Immunisation. 2016. Giving 65 year olds PCV-13 pneumococcal vaccine not cost-effective. Accessed at: https://immunisation.hpru.nihr.ac.uk/news/giving-65-year-olds-pcv-13-pneumococcal-vaccine-not-cost-effective