Institution: University of Nottingham		
Unit of Assessment: UoA1		
Title of case study: Transforming vaccine policy for pneumococcal disease leading to significant cost savings in the National Health Service		
Period when the underpinning research was undertaken: 2012 – present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor Wei Shen Lim	**Role(s) (e.g. job title):** Consultant Respiratory Physician (NHS) and Honorary Professor of Medicine (University of Nottingham)	**Period(s) employed by submitting HEI:** Nottingham University Hospital/University of Nottingham 2003– present
Period when the claimed impact occurred: 2015 - 2019		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Research at the University of Nottingham provided the evidence base to inform the decision by the United Kingdom (UK) Joint Committee on Vaccination and Immunisation (JCVI) to **not** offer the pneumococcal conjugate vaccination to adult populations. The change in adult vaccination policy saved 4,100,000 vaccine doses and a total projected cost of around GBP233,000,000 to the National Health Service (NHS). The data generated by the University of Nottingham was used again in 2018 to support a further decision by the JCVI to change the childhood vaccination schedule, saving the NHS an estimated GBP34,000,000 per year from 2020.

2. Underpinning research

The problem

Up until the early 2000s there was a significant burden of pneumococcal disease in the United Kingdom (UK), especially affecting very young children, the elderly and those in clinical risk groups (such as individuals suffering with chronic liver disease or heart disease). As such, in 1992 it was recommended that all those with medical conditions for whom pneumococcal infection was likely to be more serious should receive pneumococcal polysaccharide immunisation (PPV), and, in 2003, the recommendation was extended to include all those aged 65 years and over. In 2002, a pneumococcal conjugate vaccine (PCV) became available and was recommended to at-risk children under two years of age. In 2006, the PCV was added to the routine childhood vaccination programme in the UK. The PCV vaccine reduces pneumococcal carriage in children and, through herd protection, consequently reduces adult pneumococcal disease.

Prior to 2008, data on pneumococcal pneumonia was based on blood samples taken from patients admitted to hospital with pneumonia. Unfortunately, this blood test can only detect bacteraemic pneumonia, and bacteraemia is uncommon in pneumococcal pneumonia, meaning only 10% of patients admitted with pneumococcal pneumonia will have a positive blood culture result. Therefore, data being collected was skewed towards this 10%, with no data on the other 90% of patients with pneumonia. As a result, it was difficult to measure the effectiveness of the PPV and PCV vaccines which led to uncertainty on which serotypes (the different strains of disease) were causing bacteraemic and non-bacteraemic pneumococcal pneumonia, and to what extent. However, in 2008 Dr Robert George at Colindale laboratory, Public Health England (PHE), developed a urine assay which had the potential to capture data from 100% of patients.

The project

In order to monitor and collect data on the efficacy of the PVC immunisation programme, Professor Wei Shen Lim and Dr George co-founded a UK surveillance programme assessing how the prevalence of different pneumococcal strains were changed by the introduction of the childhood vaccination. The surveillance programme has been running from 2008 - present and is the only longitudinal study on pneumococcal infections in the UK and, as far as is known, the world. The programme relies on the expertise of both Professor Lim and Dr George and is a collaborative project wherein Professor Lim applies an assay – originally developed

by Dr George in 2008 (publication in 2010) and then further advanced with Professor Lim in 2014-2017 (publication in 2017) **[1]** – to a well-characterised population-based patient group of adults admitted to Nottingham hospital with community-acquired pneumonia (CAP). The UK surveillance study co-founded by Professor Lim and Dr George therefore provides invaluable information on the different serotypes of pneumococcal pneumonia, as well as revealing the similarities and differences in how the PPV and PCV vaccinations have affected bacteraemic and non-bacteraemic pneumococcal pneumonia.

The research

In **2012**, Professor Lim and Dr George led an analysis of the data (working with other staff from the Nottingham University Hospitals NHS Trust and University of Bristol), and established that the most prevalent pneumococcal serotypes are 14, 1, 8, 3 and 19A, and while serotype-specific attack rates increase with increasing age and co-morbidity group, this is more pronounced for the less invasive serotypes **[2].** It was the **first study** to describe the serotype distribution in all pneumococcal pneumonia, rather than simply invasive disease, and shows that certain serotypes preferentially cause disease in older, frailer adults.

In **2015** Professor Lim and those working on the surveillance programme produced original, novel data on the overall incidence of hospitalised CAP and pneumococcal CAP since the introduction of the children PCV vaccination **[3]**. The data identified that the incidence of adult pneumococcal pneumonia had declined over the last 5 years (2010-2015), with serotypes included in PCV13 declining post-PCV13 introduction, indicating early herd protection effects from PCV13 infant vaccination on adult non-bacteraemic disease. Meanwhile, between **2014** and **2017** an advanced version of the assay was developed at the Colindale lab with significant contribution (funding, clinical samples, and clinical knowledge) from Professor Lim's clinical research team in Nottingham. This development improved the assay's detection of 14 pneumococcal serotypes to 24, as well as the cell wall polysaccharide (CWP) **[1]**. The new assay replaced the previous assay that had been used in the programme from 2008-2013 for the first phase of the project, and has been in use since **2014**. The new assay was re-validated in **2019 [4].** Since then, data from the second five year phase of the project has been published in *Thorax* **[5]**.

In **2018** a team of eight Nottingham, PHE, Derby and Cambridge researchers, including the extensive efforts of Professor Lim, used the data from the surveillance programme, particularly focusing on a prospective cohort of adult patients with CAP at the two large Nottingham university hospitals Professor Lim works within, to investigate the risk of PCV-13 serotype CAP in hospitalised adults with co-morbid disease and risk factors for pneumococcal disease in the UK **[6]**. The analysis suggested that in the UK, the burden of PCV13 disease is greater in adults outside the traditional 'at-risk' groups compared to adults in 'at-risk' groups.

3. References to the research

1. Eletu SD, Sheppard CL, Thomas E, Smith K, Daniel P, Litt DJ, **Lim WS**, Fry NK. Development of an extended specificity multiplex immunoassay for detection of *Streptococcus pneumoniae* serotype-specific antigen in urine using human monoclonal antibodies. *Clin Vaccine Immunol*. **2017**. 24 (12)1-14. doi: 10.1128/CVI.00262-17
2. Bewick T, Sheppard C, Greenwood S, Slack M, Trotter C, George R, **Lim WS**. Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia. *Thorax*. **2012**; 67. 540-545. http://dx.doi.org/10.1136/thoraxjnl-2011-201092
3. Rodrigo C, Bewick T, Sheppard C, Greenwood S, **McKeever TM**, Trotter CL, Slack M, George R, **Lim WS**. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. *European Respiratory Journal*. **2015**. 45 (6) 1632-1641; DOI: 10.1183/09031936.00183614
4. Eletu S, Sheppard C, Rose S, Smith K, Andrews N, **Lim WS**, Litt DJ, Fry NK. Re-validation and update of an extended-specificity multiplex assay for detection of Streptococcus pneumoniae capsular serotype/serogroup-specific antigen and cell wall

polysaccharide in urine specimens. Access Microbiology. **2020**. 2(3). https://doi.org/10.1099/acmi.0.000094

5. Pick H, Daniel P, Rodrigo C, Bewick T, Ashton D, Lawrence H, Baskaran V, Edwards-Pritchard R, Sheppard C, Eletu S, Rose S, Litt D, Fry N, Ladhani S, Chand M, Trotter C, McKeever T, **Lim WS**. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. *Thorax*. **2020**; 75: 38-49. http://dx.doi.org/10.1136/thoraxjnl-2019-213725
6. Daniel P, Rodrigo C, Bewick T, Sheppard C, Greenwood S, **McKeever TM**, Trotter C, **Lim WS**. 13-Valent vaccine serotype pneumococcal community acquired pneumonia in adults in high clinical risk groups. *Vaccine*. **2018**. 36(12): 1614-1620. doi: 10.1016/j.vaccine.2018.02.005.

Grants

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1. **2016** Pfizer unrestricted investigator initiated research grant (**£1,515,902**). Multi-centre population-based pneumonia cohort study and pneumococcal carriage study. Chief Investigator.
2. **2015** Pfizer unrestricted investigator initiated research grant (**£267,432).** Population-based pneumonia cohort study and pneumococcal carriage study. Principal Applicant.
3. **2013** Pfizer unrestricted investigator initiated research grant (**£274,348.00**). Population-based pneumonia cohort study. Principal Applicant.
4. **2011** Pfizer unrestricted investigator initiated research grant (**£397,030**). Population based adult pneumonia cohort study. Principal Applicant.
5. **2008** Unrestricted educational grant – Wyeth (**£306,240**). 2-year population-based adult pneumonia cohort study. Principal Investigator

4. Details of the impact

It was the result of Professor Lim's expertise in the field and large span of patients that he treats as a clinician at Nottingham University Hospitals, that he could co-lead and conduct the surveillance programme from two Nottingham University Hospitals. Through the novel application of the assay in the surveillance programme that has been running from 2008-present, Professor Lim and Dr George have obtained highly unique longitudinal data on adult non-invasive serotype disease, particularly community-acquired pneumonia (CAP). In **2015**, the data from the first five year phase of the programme was used to inform the Joint Committee on Vaccination and Immunisation's (JCVI) decision to not offer the PCV vaccine to adults over the age of 65 in the UK. Equally, the data has been used by the JCVI to inform decisions on childhood vaccination.

Adult vaccine: impact on UK policy

In **2015**, the CAPITA study (randomised controlled trial of Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults) raised the question of whether adults aged 65 years or older should also be offered PCV13 vaccination (Bonten, DOI: 10.1056/NEJMoa1408544). This age group was already receiving the PPV23 vaccine. In the United States, the decision was taken by the Advisory Committee on Immunization Practices (ACIP) to recommend routine use of PCV13 in series with PPV23 for all adults aged 65 or over. This decision was put to the JCVI an independent expert committee who advises UK health departments.

In order to make this decision, colleagues from PHE conducted a modelling and cost-effectiveness analyses to *'investigate the cost-effectiveness of offering PCV13 to all 65 year olds in England'*, in *'addition to the current PPV23 programme in which a dose of PPV23 is offered to any 65 year old who has not previously received a dose at any time in the past'* **[A, p.2]**. The model constructed by AJ van Hoek and Liz Miller made extensive use of the data from Professor Lim and Dr George's longitudinal study and, in particular, the data from their

2015 study **[2]**, stating that: *'To our knowledge this [meaning the Nottingham study, Rodrigo. et.al, 2015] is the largest longitudinal survey that documents the impact of PCV vaccination on vaccine-type pneumococcal pneumonia in the UK, hence we used the observations from this study in our projections'* **[A, p.3]**. The Van Hoek paper then concludes by contesting that: *'The finding of this study supported the decision of the Joint Committee for Vaccination and Immunisation (JCVI) that PCV13 will not be universally recommended for those aged 65 years and over in England'* **[A, p.12]**.

In **2015**, based on the recommendations made by Hoek and Miller's model, as well as their own reference to Professor Lim and Dr George's work (the Rodrigo paper is cited directly under point 14) **[2] [B]**, the JCVI then made the decision that PCV vaccine should **not** be offered to adults in the UK. The chair of the pneumococcal sub-committee of the JCVI confirmed that Professor Lim's research *'played a fundamental role in the decision making process of the JCVI'*, noting that the *'study is significant as the only longitudinal study on pneumococcal pneumonia in the UK'* **[C]**. The on-going data delivered by Professor Lim and his team has provided the reassuring base on which JCVI has not felt the need to make any further changes to the current policy, and it is expected that this data will be important in informing decisions made on pneumococcal vaccine policy in the future.

Adult vaccine: influencing policy in the United States

Notably, in **2019** the United States (US) Advisory Committee on Immunization Practices (ACIP) reversed their decision to recommend PCV13 to adults, with Professor Lim's research **[2]** cited by the ACIP guideline recommendations document **[D, reference 25]** as contributing towards their decision. An editorial relating to the 2020 paper published by Professor Lim and his colleagues **[5]** also commented that the *'observation that the majority of adult pneumonia secondary to serotypes effective in infant vaccines is reduced is reassuring and reinforces the need for maintaining high infant coverage. It also demonstrates that providing the same PCV as used in infants to adults is unlikely to have a big impact on CAP, an observation noted in the USA recently which led to the reversal of the former recommendation in the USA to use PCV in all adults over 65 years of age'* **[E, p.7]**.

Adult vaccine: NHS cost and resource savings

The JCVI's decision has saved large amounts of resources and NHS money through avoided procurement costs and immunisation delivery costs. Prospective economic analysis conducted in 2012 established that each vaccine would cost GBP56.61 (using the list price of GBP49.10 per dose and GBP7.51 administration cost) and that, based on the population figures and vaccine uptake figures, the adult vaccination policy confirmed in 2015, which Professor Lim's research helped inform, would save a total of 4,100,000 doses and around GBP233,000,000 (of which GBP202,000,000 is attributed to the vaccine and the remainder administration) **[F]**.

Supporting UK childhood vaccination policy decisions

Data from Professor Lim's surveillance study was again used to inform policy decisions made by JCVI, this time in regards to childhood vaccination. A clinical trial carried out at Oxford established that reducing the vaccine process from two primary doses and one booster (2+1) to one primary dose and one booster (1+1) would have no adverse effect on children (Goldblatt D, The Lancet, 2018). However, there were concerns that although this change in vaccination would not result in more cases of illness in children, it could decrease the protection against carriage and result in more children becoming carriers of disease and passing it to adults. Consequently, in October **2017** the JCVI made the decision to move to a 1+1 schedule in **2018**, but '*re-emphasized the need for continuing high quality surveillance to identify any change in case numbers*' **[G, p.7]**.

To model the impact on adult pneumonia, PHE used data from the Nottingham study co-led by Professor Lim (up to 2015/16), because it provided novel, applicable data **[H, p.12]**. Additionally, research data presented by Professor Lim at the ISPPD conference in Melbourne in April **2018 [I, ref.55]** was used with permission and with further communication between

Professor Lim and PHE. This *'personal communication from Dr. Wei Shen Lim, Nottingham University Hospitals NHS Trust'* further informed the modelling carried out by PHE **[H, p.12]**. The findings from this modelling suggested there would not be additional risk to adults and so the change to a 1+1 schedule in **2018** was confirmed. This decision to reduce the number of times children have to be primed with pneumococcal vaccines will open up space within the childhood vaccine schedule for other vaccines to be given and will also have a subsidiary impact on NHS costs. Health-economic analysis conducted by the UoN health economics team established that the change to the childhood pneumococcal vaccination schedule will result in NHS savings of an estimated GBP34,000,000 per year from **2020 [J]**. Although the decision to review childhood vaccines was prompted by a clinical trial at Oxford, Professor Lim's study played an important role in checking the potential secondary effects of this change in policy, confirming its influential role in informing decisions made by the JCVI.

5. Sources to corroborate the impact

[A] Van Hoek AJ, Miller E. Cost-Effectiveness of Vaccinating Immunocompetent ~65 Year Olds with the 13-Valent Pneumococcal Conjugate Vaccine in England. *PLoS ONE*. **2016**. 11(2). DOI:10.1371/journal.pone.0149540

[B] Interim JCVI statement on adult pneumococcal vaccination in the UK (November **2015**)

[C] Statement of Support from the Chair of the pneumococcal sub-committee of the JCVI (December **2019**)

[D] Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Updated Recommendations of the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Report* (*MMWR*). **2019**. 68: 1069–1075. DOI:/10.15585/mmwr.mm6846a5

[E] Goldblatt D, Miller E. Pneumococcal pneumonia. *Thorax*. **2020**. 75(1): 6–7. DOI:10.1136/thoraxjnl-2019-214135

[F] (Prospective economic analysis conducted prior to 2015): Rozenbaum MH, Van Hoek AJ, Fleming D, Trotter CL, Miller E, Edmunds WJ. **2012**. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ. **2012**. 345. DOI:10.1136/bmj.e6879

[G] JCVI minutes, October **2017** (saved in folder): https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/247634612957

[H] Choi YH, Andrews N, Miller E. Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1+1 in England and Wales: A modelling study childhood vaccine paper. **2019**. *PLoS Med*. 16(7). DOI:10.1371/journal.pmed.1002845

[I] Kwambana-Adams BA, Mulholland EK, Satzke C, and ISPPD group. State-of-the-art in the pneumococcal field: Proceedings of the 11th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-11). *Pneumonia*. **2020**. 12:2. DOI: 10.1186/s41479-019-0064-y

[J] Internal health-economic analysis Cost savings associate with moving from childhood (2+1) to a (1+1) pneumococcal vaccination schedule March 2020.