**Institution:** University of Oxford

**Unit of Assessment:** 1 – Clinical Medicine

**Title of case study:** Effective pneumoccocal disease vaccination schedules improve infant health

**Period when the underpinning research was undertaken:** Jan 2005 – Feb 2019

**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: |
|---|---|---|
| Matthew Snape | Consultant | 2009 – Oct 2019 (Category C, OUH NHS) |
| | Associate Professor in Paediatrics and Vaccinology | Oct 2019 – Present |
| Andrew Pollard | Professor of Paediatric Infection and Immunity, Director of Oxford Vaccine Group | Aug 2001 – present |
| Dominic Kelly | Clinical Lecturer | Oct 2002 - Nov 2009 |
| | Consultant in Paediatric Infectious Diseases | Dec 2009 - present (Category C, OUH NHS) |
| Mainga Hamaluba | Head of Clinical Trials Unit, KEMRI-Wellcome Trust Research Programme | Oct 2012 – present (Category C, KEMRI) |

**Period when the claimed impact occurred:** Aug 2013 – Dec 2020

**Is this case study continued from a case study submitted in 2014?** N

## 1. Summary of the impact

Invasive pneumococcal diseases, including meningitis, septicaemia and pneumonia, are a major cause of death in young children in resource poor countries, and cause serious illness in developed countries. In 2015, invasive pneumococcus disease was responsible for nearly 300,000 paediatric deaths globally, but pneumococcal vaccine programmes have improved health outcomes for children worldwide. Research on pneumococcal vaccination by University of Oxford, Oxford Vaccine Group (OVG) shaped the World Health Organisation's recommendations for pneumococcal vaccination schedules for infants and was adopted by several low and middle income countries, and directly changed national immunisation policies in the UK and Nepal. The improved UK pneumococcal immunisation strategy has both reduced the number of injections given to infants and provided estimated savings to the NHS of GBP27,500,000 annually. The immunisation strategy in Nepal has led to a 34% reduction in bacterial pneumonia in infants, and averted catastrophic expenditures for thousands of the poorest families.

## 2. Underpinning research

Pneumococcal infections, caused by *Streptococcus pneumoniae* bacteria, can cause serious invasive diseases including meningitis, septicaemia and pneumonia. Pneumococcal conjugate vaccines (PCVs) reduce pneumococcal disease burden by direct protection and by reducing nasopharyngeal carriage, thereby preventing transmission and inducing herd protection. There are many pneumococcal serotypes and vaccines have been developed against the serotypes most likely to cause serious disease. In 2010, the original pneumococcal glycoconjugate vaccine, PCV7 (7-valent, Pfizer), was replaced by PCV13 (13-valent, Pfizer) and PCV10 (10-valent, GSK) to provide protection against additional pneumococcal serotypes not covered by PCV7.

The greatest proportion of pneumococcal disease occurs in late infancy and in toddlers. Therefore, an ideal vaccine programme would protect children from disease throughout early childhood. Over the last two decades, the Oxford Vaccine Group (OVG) at the University of Oxford has led over

20 clinical research studies addressing the prevention of pneumococcal disease through vaccination.

**Disease surveillance and clinical trials in low and middle income countries**

Since 2005, the OVG has led a pneumococcal disease surveillance project at Patan Hospital, Nepal. In 2010, the team demonstrated that pneumococcus was the most common cause of meningitis, pneumonia and infant septicaemia at this hospital [1], suggesting that vaccination against pneumococcus could significantly improve the health of children in Nepal. The OVG designed and implemented a phase 4 clinical trial of the PCV10 vaccine in infants in Nepal, starting in 2010 [2]. They compared two immunisation schedules: 2 priming doses (at 6 weeks and 14 weeks old) plus 1 booster dose (at 9 months old), known as a 2+1 schedule; and a 3+0 schedule, comprising three priming doses at 6, 10 and 14 weeks old. At that time, the 3+0 schedule was included in the WHO Expanded Programme of Immunisation schedule and used in most low and middle income countries (LMICs). OVG found that the 2+1 schedule resulted in improved antibody persistence through early childhood compared with the 3+0 schedule [2], providing protection to children throughout the peak risk period of disease transmission. Administering a booster dose at 9 months also provides the opportunity for this to be given the same time as measles immunisation, which may provide logistical and economic advantages in certain settings.

Subsequently, starting in 2015, the OVG implemented a further phase 4 clinical trial of PCV10 in Nepal to compare the 2+1 schedule with immunisations at 6 weeks, 14 weeks and 9 months with an 'accelerated' 2+1 schedule with immunisations at 6 weeks, 10 weeks and 9 months [3]. The rationale for this trial was that 2 other immunisations are recommended at 14 weeks of age for infants in Nepal (pentavalent vaccine and inactivated poliomyelitis virus vaccine), and there were concerns about public acceptance of 3 immunisations being administered at 14 weeks. The trial showed comparable immune responses for both 2+1 schedules, validating use of an accelerated prime-boost schedule where logistically necessary [3].

The OVG team also initiated pharyngeal swabbing studies in Nepal. Firstly, in 2012 they enrolled 600 children to determine the local prevalence of circulating pneumococcal serotypes prior to introduction of PCV10 into the national immunisation schedule [4]. Their ongoing studies have enrolled nearly 4000 children, enabling continued surveillance of circulating pneumococcal serotypes since the introduction of PCV10.

**Pneumococcal vaccine design and UK clinical trials**

Starting in 2006, the OVG led a phase 4 randomised clinical trial in the UK of the novel PCV13 pneumococcal vaccine to assess immunogenicity and tolerability in a 2+1 schedule, given at 2, 4 and 12 months of age [5]. Their results, published in 2010, demonstrated near-universal immune response to all serotypes in PCV13, without impacting on concomitantly administered vaccines [5], providing support to the UK Department of Health and Social Care decision in 2010 to replace PCV7 with PCV13 in the national immunisation schedule.

With the introduction of meningococcal B vaccine into the UK infant immunisation schedule in 2015, there was a need to reduce the number of vaccine doses delivered without compromising disease control. In 2016, the OVG collaborated with University College London and Public Health England to lead a phase 4 randomised clinical trial to assess the effectiveness of a reduced dosing strategy for PCV13: a 1+1 schedule, with immunisations at 3 and 12 months of age [6]. Their study demonstrated an at least equivalent immune response for 9 out of 13 serotypes for this 1+1 schedule compared with the 2+1 (2, 4 and 12 month) schedule [6]. This study was the first in the world to assess a 1+1 schedule for pneumococcal vaccines.

**3. References to the research** (University of Oxford employed authors in bold)


1. **Kelly DF,** Thorson S, Maskey M, Mahat S, Shrestha U, **Hamaluba M, Williams E,** Dongol S, Werno AM, Portess H, Yadav BK, Adhikari N, Guiver M, Thomas K, Murdoch DR, **Pollard AJ.** (2011) The burden of vaccine-preventable invasive bacterial infections and pneumonia in children admitted to hospital in urban Nepal. *Int J Infect Dis.* 15(1):e17-23. DOI:10.1016/j.ijid.2010.05.021. 26 citations (WoS 03-2021)
2. **Hamaluba M, Kandasamy R,** Upreti SR, Subedi GR, Shrestha S, Bhattarai S, Gurung M, Pradhan R, **Voysey M**, Gurung S, Pradhan S, Thapa AK, Maharjan R, Kiran U, **Kerridge SA,** Hinds J, van der Klis F, **Snape MD,** Murdoch DR, **Kelly S, Kelly DF,** Adhikari N, Thorson S,

**Pollard AJ.** (2015) Comparison of two-dose priming plus 9-month booster with a standard three-dose priming schedule for a ten-valent pneumococcal conjugate vaccine in Nepalese infants: a randomised, controlled, open-label, non-inferiority trial. *Lancet Infect Dis.*15(4):405-14. DOI:10.1016/S1473-3099(15)70007-1 12 citations (WoS 03-2021)

3. **Kandasamy R,** Gurung M, Thorson S, **Yu LM, Galal U, Voysey M, Kelly S,** Wahl B, Berbers G, Finnegan K, Ansari I, Paudel K, Murdoch DR, O'Brien KL, **Kelly DF,** Goldblatt D, Shrestha S, **Pollard AJ.** (2019) Comparison of two schedules of two-dose priming with the ten-valent pneumococcal conjugate vaccine in Nepalese children: an open-label, randomised non-inferiority controlled trial. *Lancet Infect Dis.* 19(2):156-164. DOI:10.1016/S1473-3099(18)30568-1
4. **Kandasamy R,** Gurung M, Thapa A, **Ndimah S,** Adhikari N, Murdoch DR, **Kelly DF,** Waldron DE, Gould KA, Thorson S, Shrestha S, Hinds J, **Pollard AJ**. (2015) Multi-serotype pneumococcal nasopharyngeal carriage prevalence in vaccine naïve Nepalese children, assessed using molecular serotyping. *PLoS One.* 10(2):e0114286. DOI:10.1371/journal.pone.0114286 19 citations (WoS 03-2021)
5. **Snape MD, Klinger CL,** Daniels ED, **John TM, Layton H, Rollinson L,** Pestridge S, Dymond S, Galiza E, Tansey S, Scott DA, Baker SA, Jones TR, **Yu LM**, Gruber WC, Emini EA, Faust SN, Finn A, Heath PT, **Pollard AJ.** (2010) Immunogenicity and reactogenicity of a 13-valent-pneumococcal conjugate vaccine administered at 2, 4, and 12 months of age: a double-blind randomized active-controlled trial. *Pediatr Infect Dis* J. 29(12):e80-90. DOI:10.1097/inf.0b013e3181faa6be 74 citations (WoS 03-2021)
6. Goldblatt D, Southern J, Andrews NJ, Burbidge P, **Partington J**, Roalfe L, **Valente Pinto M,** Thalasselis V, **Plested E,** Richardson H, **Snape MD**, Miller E. (2018) Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. *Lancet Infect Dis.* 18(2), 171-179. DOI:10.1016/S1473-3099(17)30654-0 43 citations (WoS 03-2021)

## 4. Details of the impact

As the major cause of bacterial meningitis, septicaemia and pneumonia, *Streptococcus pneumoniae* is responsible for approximately 3,700,000 cases of severe disease and 500,000 deaths globally each year in young children. The schedule of immunisations is essential for effective and sustainable vaccination programmes, as the exact number and timing of doses influences efficacy, public acceptance, costs, and long-term sustainability.

**Changing global and UK healthcare policy**

***World Health Organisation, and low and middle income countries:*** In Nepal, in Nov 2013 the National Committee on Immunisation Practices (NCIP) recommended the introduction of the PCV10 pneumococcal vaccine into the national immunisation schedule for infants [A], based on the OVG's research [1, 2, 4]. Specifically, a 2+1 dosing schedule was chosen instead of 3+0, based on the OVG trial data [2]. Based on the NCIP recommendation, from 2015, PCV10 was implemented in the Nepalese infant immunisation schedule, available to more than 500,000 infants per year. Further, the OVG's research [3] validated the choice in Nepal to use an 'accelerated' 2+1 dosing schedule, which was more acceptable to the public and the research showed was as effective as the standard 2+1 schedule.

The OVG research demonstrating benefits of using a 2+1 versus a 3+0 dosing schedule in Nepal [2] was extensively referenced in a 2017 systematic review of the impact of pneumococcal conjugate vaccines, which was prepared for the WHO Special Advisory Group of Experts (SAGE) for immunisation [B]. In Feb 2019, the WHO recommended a 2+1 schedule for infant immunisation against pneumococcal disease [C], informed by this systematic review and the OVG research [2, 3] [D]. Based on these WHO recommendations, as of Nov 2020, 2+1 schedules for PCVs had been adopted for routine infant immunisations by 7 LMICs receiving support from the Global Alliance for Vaccines and Immunisations (GAVI), in addition to Nepal: India, Indonesia, Uzbekistan, Georgia, Mongolia, Kyrgyzstan and the Republic of Moldova [E]. This implementation of the 2+1 immunisation schedule applies to approximately 30,700,000 infants each year across these 8 countries. Notably, India had the world's highest number of pneumococcal deaths in 2015

and introduced routine immunisation following the 2+1 schedule in 2017 [E], prioritising states with the highest pneumonia burden.

***UK vaccination schedules:*** In October 2017, the UK Joint Committee for Vaccines and Immunisation (JCVI) reviewed data from the OVG-led trial comparing a 2+1 to a 1+1 schedule for PCV13 [6] and, based on this research, made a recommendation to the UK Department of Health and Social Care that the UK infant immunisation schedule should be changed from the 2+1 schedule (immunisations at 2, 4 and 12 months) to a 1+1 schedule (immunisations at 3 and 12 months) [Fi]. Public Health England announced in April 2019 that the new 1+1 schedule should be offered to all infants born on or after 1 Jan 2020 [Fii]. This was the first implementation of a 1+1 PCV13 schedule in the world. This trial and change in the UK policy is a landmark that provided credibility and reassurance to other countries that reduced dosing is safe and has cost benefits, instigating further studies in India, Vietnam, South Africa and the Gambia, funded by the Bill and Melinda Gates Foundation, to see if this reduced dose schedule is similarly immunogenic in LMICs [Gi]. Indeed, results from the study in South Africa (referencing [6]), confirmed that the 1+1 schedule was not inferior to 2+1 in a LMIC with an established PCV immunisation programme, providing the opportunity to reduce the cost of PCV procurement [Gii].

**Improving health outcomes for children**

***Decreased invasive pneumococcal disease and fewer injections for infants in the UK:*** The switch from PCV7 to PCV13 in the UK vaccination schedule in 2010, which was influenced by OVG research [5] showing that PCV13 was highly immunogenic and well tolerated in the UK schedule [H], resulting in large decreases in cases of invasive pneumococcal disease, including since August 2013. Specifically, a PHE study showed that in 2013/14 the incidence of invasive pneumococcal disease in England and Wales had decreased by 32% compared to the level before the introduction of PCV13 immunisations; this resulted in at least 1,800 fewer cases of these serious, life-threatening infections in 2013/14 [Ii]. A further PHE study showed that, in 2016/17, invasive pneumococcal disease cases resulting from PV13-type serotypes had decreased by 64% since the introduction of PCV13 [Iii]. Overall, PHE data from England and Wales, shows that pneumococcal vaccination has prevented an estimated 9,000 cases of invasive pneumococcal disease in children under 5 between 2013-2017 [Iii,iii].

Implementation of the 1+1 immunisation schedule in the UK resulted in approximately 750,000 fewer doses of pneumococcal vaccine being administered annually. Fewer injections means less distress and discomfort for infants and their parents. Mathematical modelling by PHE, based on the immunogenicity data from the trial led by the OVG [6], indicated that this reduction in discomfort through reducing the number of injections will not cause any significant loss of control of pneumococcal disease, with an estimate of only 2 additional cases of invasive pneumococcal disease in children under 2 years, over 5 a year period [J].

***Global decreases in pneumococcal deaths, severe disease and economic impacts:*** The global mortality rate for pneumococcus in 2015 was estimated to be 45 deaths (uncertainty range 29–56) per 100,000 children under the age of 5, with uncertainty in part due to the pathogen not being identified in many cases of pneumonia [K]. Overall, pneumococcal vaccine programs, including those based on OVG research, have resulted in a mean annual reduction of global paediatric deaths from invasive pneumococcal disease of 47,400 between 2010 and 2015, and an estimation that this reduction will have been at least equalled for every year since 2013 [K]. As of November 2020, 138 countries, including 58 LMICs, had introduced a pneumococcal conjugate vaccine into their national immunisation schedule [E], and a minimal estimate is that 22,800,000 children across the world have been immunised against pneumococcal infections [E]. Nepal is an illustrative example of the impact, where the vaccine programme was heavily influenced by the OVG research: in 2018 there was a 34% reduction in cases (at least 15,500 fewer cases per year) of bacterial pneumonia in children compared to the pre-vaccination period (2014-2015)[Li]; and by 2019, carriage of vaccine-serotype pneumococcus had decreased by 74% among healthy infants [Li]. Pneumococcal disease has a major economic impact on poor families, through costs of healthcare and loss of earnings; for example, in Nepal, out-of-pocket payments for pneumonia hospitalizations exceeded 40% of the monthly household spending for more than 70% of households in the three poorest quintiles [Lii]. Analysis of the impact of introduction of the PCV10

vaccination in Nepal estimated that vaccination averted 85% of catastrophic health expenditures among the poorest quintiles of the population [Liii].

**Financial benefits to the NHS**

The reduction in doses of PCV13 administered in the UK, through introduction of the 1+1 schedule from 1 Jan – 31 Dec 2020, has resulted savings to the NHS of GBP7,500,000 in vaccine administration costs alone, with additional savings through reduced vaccine purchasing costs. The 'shelf price' of this vaccine is GBP49 per dose and, although NHS purchase price is not publicly available, the total annual savings to the NHS for 2020 are estimated as at least GBP20,000,000.

**5. Sources to corroborate the impact**

A. Minutes from Meeting of National Committee on Immunization Practices, Nepal, 29 Nov 2013. Findings from OVG research discussed on page 2.

B. O'Brien, K. *et al*. Pneumococcal Conjugate Vaccine (PCV) Review of Evidence (PRIME): summary of findings from systematic review, citing [2]. Paper for WHO SAGE meeting Oct 2017, https://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pdf?ua=1

C. WHO position paper on pneumococcal vaccines in infants and children under 5 years of age, February 2019, including recommendation of 2+1 immunisation schedule.

D. Letter from former member of WHO and WHO SAGE working group on pneumococcal vaccination of infants (Dec 2020), stating that the OVG research contributed to the WHO recommendation of a 2+1 schedule.

E. Data from VIEW-hub.org, including global maps of PCV dosing schedule, number of children vaccinated and vaccine products. Accessed 25 Nov 2020.

F. Documentation of UK change to 1+1 PCV schedule: i) Minutes of the UK JCVI, October 2017. Including discussion of OVG data, and agreement to move to the 1+1 schedule in the UK; ii) PHE document: 'Changes to the infant pneumococcal conjugate vaccine schedule - Information for healthcare practitioners', (Dec 2019).

G. Evidence of international follow-up of 1+1 schedules: i) Email from Gates Foundation, Senior Program Officer Global Health, Pneumonia (Feb 2021), confirming the influence of (6) on studies in LMICs; ii) Results from clinical trial in South Africa, Madhi SA *et al*. (2020) Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. *Lancet Infectious Diseases*, DOI:10.1016/S1473-3099(20)30289-9

H. The pneumococcal chapter of the Public Health England 'Green Book' guidance for immunisation, Jan 2018. Referencing [5] with respect to introduction of PCV13.

I. PHE analyses of pneumococcal disease:
i) Waight et al. 2015, *Lancet Infectious Diseases* DOI:10.1016/S1473-3099(15)70044-7;
ii) Ladhani et al, 2018 *Lancet Infectious Diseases* DOI:10.1016/S1473-3099(18)30052-5;
iii) PHE data online at www.gov.uk, updated 8 October 2018, 'Pneumococcal disease: cases caused by strains covered by Prevenar13 vaccine', showing annual case numbers to 2018.

J. Choi YH, Andrews N, Miller E. (2019). Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1+1 in England and Wales. *PLoS Medicine,* DOI:10.1371/journal.pmed.1002845

K. Wahl et al. (2018). Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. *Lancet Global Health,* DOI:10.1016/S2214-109X(18)30247-X

L. PneumoNepal analyses of the impact in Nepal, from http://pneumonepal.org/:
i) Shrestha S et al. 'The impact of pneumococcal conjugate vaccine introduction in Nepal' (abstract); ii) PneumoNepal Assessment of Economic Impact (preliminary report); iii) Garcia C et al. 'Estimating the impact of the PCV10 program on reducing pneumococcal-associated hospitalizations and financial risk protection among Nepali children under-five' (abstract).