Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Evaluating and introducing pneumococcal conjugate vaccines (PCV) into the UK infant immunisation programme

1. Summary of the impact

A programme of work undertaken jointly between the UCL Institute of Child Health (ICH) Vaccine Evaluation Laboratory headed by Professor David Goldblatt and the Health Protection Agency (now Public Health England [PHE]) led by Professor Liz Miller, has led directly to the introduction of pneumococcal conjugate vaccines (PCV) into the UK infant immunisation schedule. These vaccines have reduced the burden of invasive disease in the UK saving many lives and reducing morbidity from these devastating infections. This work has also provided the evidence for other countries to introduce PCV with fewer than the originally recommended doses, thus improving cost effectiveness and hastening the implementation of these vaccines worldwide. Goldblatt has also contributed to a WHO programme to roll out PCV in developing countries; by July 2013 this programme had vaccinated around 10 million children.

2. Underpinning research

Since 1993, the Goldblatt laboratory has had a leading role in global efforts aimed at establishing and standardising pneumococcal assays for the purpose of assessing and licensing pneumococcal vaccines **[1]**.

In 2002 the laboratory was designated one of only two World Health Organisation (WHO) Reference Laboratories for Pneumococcal Serology in recognition of its role in standardising pneumococcal assays and establishing correlates of protection to license second generation pneumococcal conjugate vaccines **[2]**. The WHO funded the laboratory to develop assays, teach and train staff from organisations around the world in the conduct of such assays and to transfer materials and technology to other laboratories to facilitate global efforts to rapidly introduce pneumococcal vaccines in areas of the world most in need. The laboratory has just finished leading an international effort to develop a new Pneumococcal Standard Reference serum to replace the dwindling stocks of an existing standard. The new Standard will enable assays to be quality-controlled for the next 50 years **[3]**.

The first PCV, a seven-valent formulation, was licensed in 2000 but initially only used in the USA where it was administered, according to a four-dose schedule. In collaboration with PHE, we were the first in the world to formally assess the utility of a three-dose, rather than the licensed four-dose schedule and to predict the efficacy of the reduced schedule based on the data generated in this study **[4]**. A three-dose schedule was desirable in the UK to facilitate introduction into an already crowded immunisation programme and to address the issue of cost-effectiveness. The results of this study led directly to the decision in the UK to introduce PCV into the infant immunisation schedule with only three doses (September 2006).

ICH and PHE subsequently proceeded to establish the immunological basis for the effectiveness of the response to a three-dose schedule and to refine the understanding of pneumococcal correlates of protection **[5]**.

Underpinning research at ICH continues to inform the evolving use of PCV. The Goldblatt laboratory has led a study of PCV administration with the first dose at birth, to assess safety and likely efficacy of early vaccination in developing countries where up to a quarter of pneumococcal deaths under the age of 2 years occur before infants are eligible for their first vaccine **[6]**.

3. References to the research

[1] Plikaytis BD, **Goldblatt D**, Frasch CE, Blondeau C, Bybel MJ, Giebink GS, Jonsdottir I, Kayhty H, Konradsen HB, Madore DV, Nahm MH, Schulman CA, Holder PF, Lezhava T, Elie CM, Carlone GM. An analytical model applied to a multicenter pneumococcal enzyme-linked immunosorbent assay study. J Clin Microbiol. 2000 Jun;38(6):2043-50. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC86724/

[2] Jodar L, Butler J, Carlone G, Dagan R, **Goldblatt D**, Kayhty H, Klugman K, Plikaytis B, Siber G, Kohberger R, Chang I, Cherian T. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. Vaccine. 2003 Jul 4;21(23):3265-72. http://dx.doi.org/10.1016/S0264-410X(03)00230-5

[3] **Goldblatt D**, Plikaytis BD, Akkoyunlu M, Antonello J, Ashton L, Blake M, Burton R, Care R, Durant N, Feavers I, Fernsten P, Fievet F, Giardina P, Jansen K, Katz L, Kierstead L, Lee L, Lin J, Maisonneuve J, Nahm MH, Raab J, Romero-Steiner S, Rose C, Schmidt D, Stapleton J, Carlone GM. Establishment of a new human pneumococcal standard reference serum, 007sp. Clin Vaccine Immunol. 2011 Oct;18(10):1728-36. http://dx.doi.org/10.1128/CVI.05252-11

[4] **Goldblatt D**, Southern J, Ashton L, Richmond P, Burbidge P, Tasevska J, Crowley-Luke A, Andrews N, Morris R, Borrow R, Cartwright K, Miller E. Immunogenicity and boosting after a reduced number of doses of a pneumococcal conjugate vaccine in infants and toddlers. Pediatr Infect Dis J. 2006 Apr;25(4):312-9 http://dx.doi.org/10.1097/01.inf.0000207483.60267.e7

[5] **Goldblatt D**, Southern J, Ashton L, Andrews N, Woodgate S, Burbidge P, Waight P, Miller E. Immunogenicity of a reduced schedule of pneumococcal conjugate vaccine in healthy infants and correlates of protection for serotype 6B in the United Kingdom. Pediatr Infect Dis J. 2010 May;29(5):401-5. http://dx.doi.org/10.1097/INF.0b013e3181c67f04

[6] Scott JA, Ojal J, Ashton L, Muhoro A, Burbidge P, **Goldblatt D**. Pneumococcal conjugate vaccine given shortly after birth stimulates effective antibody concentrations and primes immunological memory for sustained infant protection. Clin Infect Dis. 2011 Oct;53(7):663-70. http://dx.doi.org/10.1093/cid/cir444

4. Details of the impact

Streptococcus Pneumoniae is an important cause of infection at the extremes of life. In the United Kingdom the incidence of invasive pneumococcal disease (IPD) is 37–48 per 100,000 for children under 1 year and 21–36 per 100,000 for adults >65 years. In the period July 1996 to June 2006 (prior to vaccine introduction) there were 52,579 cases of IPD identified through the UK laboratory-based surveillance system. This does not take into account the majority of pneumonia and otitis media cases **[a]**.

The first pneumococcal conjugate vaccine containing seven of the most prevalent serotypes (PCV7) was licensed in 2000 as a four-dose schedule. Adding a new vaccine to the relatively crowded UK infant immunisation schedule in the early 2000s presented significant difficulties, as infants were already receiving two injections at each immunisation visit (at 2, 3 and 4 months of age). Our demonstration that three doses were immunologically broadly equivalent to four gave the Department of Health the evidence base to introduce PCV into the routine infant immunisation programme vaccine with doses at 2, 4 and 12 months ("2+1" schedule). An initial catch-up campaign was conducted in 2006/7 with routine immunisation beginning in 2008 **[b]**.

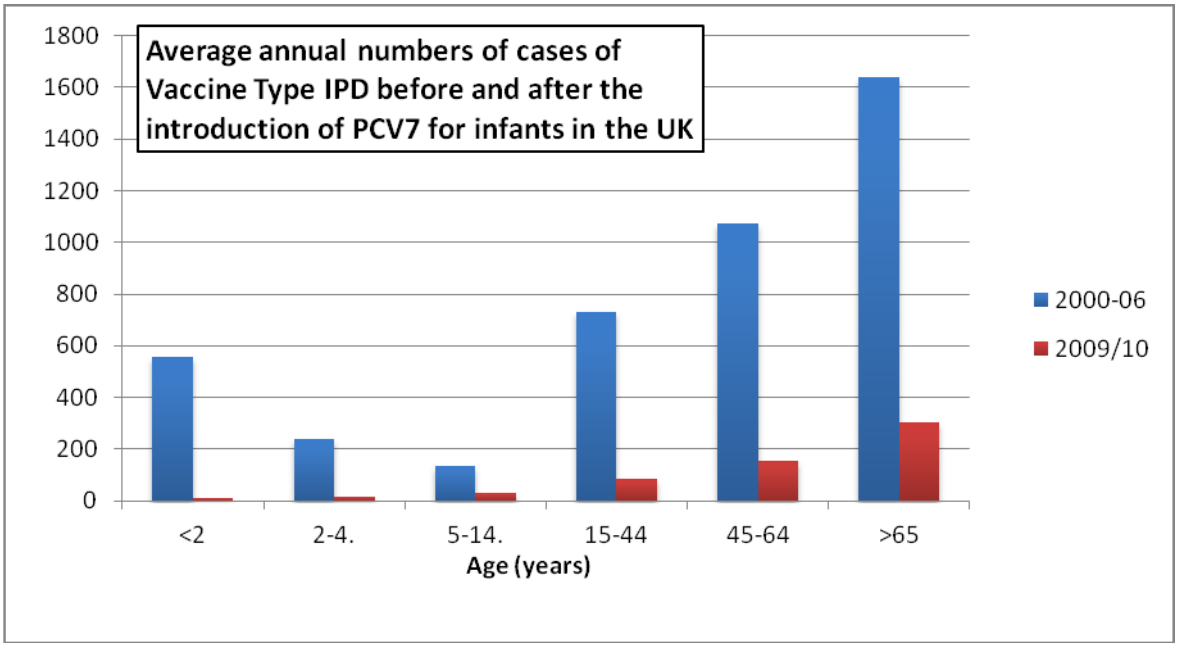
The introduction of PCV in the UK has had a clear impact on pneumococcal disease. Prior to its introduction, deaths from IPD in children under five had peaked at 797 cases/year. In 2011/12 (the last year for which there are complete data) this had reduced by 50% to 340 deaths. Notably, cases of IPD due to the seven serotypes included in the vaccine have fallen dramatically, as the following table shows:

Serotype	2003/4	2011/12
4	15	0
6B	52	1
9V	31	1
14	142	2
18C	38	4
19F	49	5
23F	25	1

Table 1: Serotype specific IPD cases for under fives in England and Wales prior to and following the introduction of PCV7 into the infant immunisation programme **[c]**

On the basis of early experience with PCV7, Goldblatt worked with international colleagues to define the first correlates of protection and then helped to draw up WHO guidelines for how PCVs should be subsequently licensed (WHO TRS 927) **[d]**. These guidelines were used to license 10- and 13-valent formulations approved in 2009/10. In 2010 the 13-valent vaccine was introduced in the UK. This vaccine addressed the burden of disease caused by the additional serotypes included in the PCV13 vaccine.

In addition to the direct impact of the vaccine on disease in the vaccinated infants, the PCV vaccine reduces the carriage of pneumococci in the nasopharynx, which thus reduces the spread of the pneumococci and impacts on invasive disease in other age groups. The figure below (adapted from HPA data **[c]**) illustrates the impact of infant vaccination on vaccine type IPD in all age groups in the UK.



The "2+1" schedule has been highly efficacious and is also more cost effective, as it uses fewer doses. For these reasons, many countries worldwide have implemented it. In 2013, WHO reports that in Europe and the Americas 23 countries are using PCV according to the schedule we developed **[e]**.

Our work has also contributed to global efforts to reduce mortality from pneumococcal disease in developing countries. Half a million children under five die each year from the condition, making it the leading vaccine-preventable cause of death among young children. In response to this issue, WHO and the GAVI alliance have initiated an innovative financing process – the Advanced Market Commitment (AMC) **[f]** – designed to make effective and affordable pneumococcal vaccines available for children in developing countries. Goldblatt chaired the committee that defined the minimum product specification (TPP) for the vaccine. This report was published in February 2008 **[g]** and in March 2010, UNICEF entered into agreements with GSK and Pfizer to supply 30 million

doses annually for 10 years **[h]**. An independent report into the AMC process reported that: *"Several interviewees praised the TPP for striking an appropriate balance between setting a high bar to ensure vaccine effectiveness and still allowing low-cost producers to compete. The TPP also proved useful in inspiring and supporting similar guidance for other prospective vaccines"* **[i]**. Since 2010, over 25 countries have begun to roll out pneumococcal vaccines under this programme; by July 2013, it was estimated that GAVI and its partners have immunised more than 10 million children **[j]**. GAVI aims to increase this to 45 countries by 2015, projecting that this will prevent more than half a million deaths in this period.

5. Sources to corroborate the impact

[a] http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1203409671876.

[b] The Green Book, chapter 25: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216088/Green-Book-Chapter-25-v4_0.pdf (References Goldblatt et al 2006; book page 311, pdf page 17)

[c] Data provided by Public Health England. Contact details provided.

[d] http://www.who.int/entity/biologicals/areas/vaccines/pneumo/Pneumo_final_23APRIL_2010.pdf . (International Reference Materials, page 6; Authors and Acknowledgements, page 34; Reference 23, page 37).

[e] WHO vaccine-preventable diseases: monitoring system. 2013 global summary http://apps.who.int/immunization_monitoring/globalsummary/schedules.

[f] GAVI alliance website detailing the pneumococcal Advance Market Commitment http://www.gavialliance.org/funding/pneumococcal-amc/about/

[g] Target Product Profile (TPP) for the Advance Market Commitment (AMC) for Pneumococcal Conjugate Vaccines: www.who.int/immunization/sage/target_product_profile.pdf. (Vaccine dosage schedule page 22, Contributors page 29, References 66 and 75).

[h] GSK press release: http://www.gsk.com/media/press-releases/2010/gsk-joins-global-vaccine-alliance-to-help-prevent-millions-of-children-from-contracting-pneumococcal-disease-in-the-worlds-poorest-countries.html

[i] The Advance Market Commitment for Pneumococcal Vaccines: Process and Design Evaluation. February 15, 2013. Dalberg Global Development Advisors. http://www.gavialliance.org/library/documents/gavi-documents/evaluations/amc-process-and-design-evaluation-full-report/. (quote page 12).

[j] http://www.gavialliance.org/support/nvs/pneumococcal/

Contact details

[c] Liz Miller, Public Health England. liz.miller@hpa.org.uk *[Provided [c] data on serotype specific IPD cases for under fives in England and Wales prior to and following the introduction of PCV7 into the infant immunisation programme]*