Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care

Title of case study: Influencing the widespread adoption of pneumococcal conjugate vaccines in low- and middle-income countries

1. Summary of the impact

A trial of a pneumococcal conjugate vaccine (PCV) coordinated by Greenwood (LSHTM) and conducted in Gambian infants, showed a significant reduction in invasive pneumococcal disease, severe pneumonia, hospital admissions and deaths in vaccinated children. These results played an important role in encouraging WHO to recommend the introduction of a PCV into the routine immunisation programme of all countries with a high child mortality. Fifty-one GAVI eligible countries have now introduced, or made a commitment to introduce, a PCV into their routine infant immunisation programme with the consequent saving of many young lives.

2. Underpinning research

Pneumonia causes over 1m deaths each year in children, with nearly all occurring in the developing world. *Streptococcus pneumoniae* (the pneumococcus) is the most important cause of severe pneumonia in children. Developing a vaccine that could prevent pneumococcal infections in young children is, therefore, a high public health priority. Initial vaccines based on the capsular polysaccharide of the pneumococcus were not effective as they induced only a poor immune response in young children. Coupling of capsular polysaccharides to a protein to produce a PCV overcame this problem. Initial trials of a 7-valent PCV (Prevenar®) in the USA showed that this vaccine was highly effective in protecting vaccinated infants and unvaccinated members of their family by preventing nasopharyngeal carriage and thus interrupting transmission. Whether a PCV would be equally effective in developing countries was unknown. To investigate this, a trial of a 9-valent PCV was undertaken in The Gambia, West Africa,[3.1] the first large-scale trial of a PCV to be undertaken in a low-income country (a parallel study was undertaken in Soweto, South Africa).

The Gambian phase 3 trial built on many years of background work, including a series of phase 2 trials of prototype PCVs conducted during the period 1994–1999. These trials, funded largely by NIH, were coordinated by Brian Greenwood who was director of the MRC Unit, The Gambia until 1996 when he took up a chair at LSHTM. These pilot trials demonstrated the safety and immunogenicity of PCVs in African infants for the first time.[3.2,3.3,3.4] They also showed that PCVs reduced nasopharyngeal carriage of pneumococci of vaccine serotype but that these bacteria were replaced in the nasopharynx by pneumococci of serotypes not represented in the vaccine,[3.3] the first description of a phenomenon known as 'serotype replacement' which has subsequently posed a major challenge to the effectiveness of PCVs in many countries, including the UK.

The Gambian phase 3 PCV trial undertaken in Upper River Region during 2000–2004 was a partnership between the MRC Laboratories, The Gambia and LSHTM. It was designed and planned by Greenwood. The study was led by Felicity Cutts (honorary LSHTM staff). Professor Shabbar Jaffar (joined LSHTM 1996, then Lecturer) provided statistical support on study design and undertook the trial analysis. During the trial, 17,437 infants were given either three doses of a 9-valent PCV or placebo at the ages of approximately 6, 10 and 14 weeks.[3.1] The vaccine was safe and immunogenic.[3.5] During 30 months of follow-up, the vaccine reduced invasive pneumococcal disease of vaccine serotype by 77%, severe pneumonia by 37%, hospital admissions by 15% and mortality by 16%. The vaccine reduced nasopharyngeal carriage of pneumococci of vaccine serotype with an increase in carriage of pneumococci of non-vaccine serotype.[3.6] The trial provided data that allowed the cost effectiveness of introducing PCVs to be evaluated.

3. References to the research

3.1 Cutts, FT, Zaman, SMA, Enwere, G, Jaffar, S, Levine, OS, Okoko, JB, Oluwalana, C, Vaughan, A, Obaro, SK, Leach, A, McAdam, KP, Biney, E, Saaka, M, Onwuchekwa, U, Yallop, F, Pierce, NF, Greenwood, BM & Adegbola, RA 2005, 'Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind,

placebo-controlled trial', *Lancet*; vol. 365, no. 9465, pp.1139-1146, doi:10.1016/S0140-6736(05)71876-6. Citation count:432

3.2 Leach, A, Ceesay, SJ, Banya WAS and Greenwood, BM (1996) Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants, *Pediatric Infectious Disease Journal*, 15(4): 333–339, doi:10.1097/00006454-199604000-00010. Citation count: 71

3.3 Obaro, SK, Adegbola, RA, Banya, WAS and Greenwood, BM (1996) Carriage of pneumococci after pneumococcal vaccination, *Lancet*, 348(9022): 271–272, doi:10.1016/S0140-6736(05)65585-7. Citation count: 218

3.4 Obaro, SK, Adegbola, RA, Chang, I, Banya, WAS, Jaffar S, McAdam KWJP and Greenwood, BM (2000) Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM197 administered simultaneously but in a separate syringe with diphtheria, tetanus and pertussis vaccines in Gambian infants, *Pediatric Infectious Disease Journal*, 19(5): 463–469, http://journals.lww.com/pidj/pages/articleviewer.aspx?year=2000&issue=05000&article=00014&type=abstract (accessed 23 September 2013). Citation count: 55

3.5 Saaka, M, Okoko, BJ, Kohberger, RC, Jaffar, S, Enwere, G, Biney, EE, Oluwalana, C, Vaughan, A, Zaman, SMA, Asthon, L, Goldblatt, D, Greenwood, BM, Cutts, FT and Adegbola RA (2008) Immunogenicity and serotype-specific efficacy of a 9-valent pneumococcal conjugate vaccine (PCV-9) determined during an efficacy trial in The Gambia, *Vaccine*, 26(29–30): 3719–3726, doi:10.1016/j.vaccine.2008.04.066. Citation count: 24

3.6 Cheung, YB, Zaman, SMA, Nsekpong, ED, Van Beneden, CA, Adegbola, RA, Greenwood, B and Cutts, FT (2009) Nasopharyngeal carriage of *Streptococcus pneumoniae* in Gambian children who participated in a 9-valent pneumococcal conjugate vaccine trial and in their younger siblings, *Pediatric Infectious Disease Journal*, 28(11): 990–995, doi:10.1097/INF.0b013e3181a78185. Citation count: 23

Key grants

The project was funded through a consortium supported by NIAID, WHO, the Children's Vaccine Programme at PATH, USAID and the UK MRC. Vaccines were donated by Wyeth Vaccines. The grant ran from 2000–2005. The total value of the grant made to the MRC unit The Gambia was approximately US$10,000,000 with a subcontract of $557,000 to LSHTM.

4. Details of the impact

The Gambia

The Gambian phase 3 PCV trial was conducted in close collaboration with the Ministry of Health. The results of the trial were immediately available to the Ministry (2005) and it took a decision to introduce a PCV into the routine infant immunisation programme of The Gambia as soon as vaccine became available. Wyeth Lederle stopped production of the 9-valent vaccine shortly after completion of the Gambian and South African trials but made a donation of the 7-valent vaccine (Prevenar®) used in the USA to the Gambian Ministry of Health in 2009. This allowed introduction of this vaccine into the routine immunisation programme of The Gambia, only the second country in sub-Saharan Africa (after Rwanda) to take this step. In 2011, with financial support from GAVI, the seven-valent vaccine, which lacks some of the key serotypes needed for a maximally effective pneumococcal conjugate vaccine in Africa, was replaced by a 13-valent vaccine. The impact on mortality and morbidity of introducing PCVs into a national infant immunisation programme in Africa is currently being studied in detail in Upper River Region, The Gambia, with support from the Bill and Melinda Gates Foundation. It is too early to determine the extent of the impact on mortality and morbidity of this vaccine, which has now been received by nearly 100,000 Gambian infants, but it is likely that many lives have already been saved.

Internationally

The results of the Gambian phase 3 trial, together with those of the parallel study undertaken in South Africa, provided key information which led the WHO Strategic Advisory Group of Experts

(SAGE) committee to recommend to WHO that pneumococcal conjugate vaccines should be introduced into the routine infant immunisation programmes of all countries with a high child mortality. This recommendation was accepted by WHO in 2007, with the findings of the Gambian trial being influential in this decision.[5.1,5.2] The unique evidence provided from The Gambia of an effect on mortality proved especially influential. Economic data collected during the Gambian trial allowed demonstration that deployment of the vaccine in developing countries would be highly cost effective[5.3] and this information also contributed to the positive recommendation by SAGE.

Because of their complex nature, PCVs are relatively expensive and so there were concerns whether it would be possible to implement the WHO recommendation in some of the poorest countries of the world where PCVs would be most effective. However, substantial progress has been made in achieving this goal through the financial support obtained for the introduction of new vaccines in poor countries provided through GAVI and the Advanced Market Commitment[5.4] (an innovative financing method which guarantees a market if a vaccine or medicine is successfully developed). By 31 March 2013, 24 GAVI-eligible countries had introduced a PCV into their routine immunisation programme (8 of these were supported by the Advanced Market Commitment), and a further 27 countries were approved by GAVI for introduction, including nearly all countries in sub-Saharan Africa,[5.5] a dramatic uptake over a period of only three years.[5.6]

PCVs would have been introduced into most developing counties eventually, but experience with hepatitis B and *Haemophilus influenzae* type B vaccines indicates that the lag between uptake in industrialised and developing countries may be up to 15 years. PCVs are being introduced more rapidly than this as the international community has found better ways of accelerating the uptake of new vaccines. A strong case can be made that the Gambian PCV trial has played an important part in achieving this success and thus helped in saving many thousands of young lives in poor countries which would otherwise have been lost to pneumococcal infection.[5.7]

5. Sources to corroborate the impact

5.1 Coordinator, Programme and Impact Monitoring, Immunisation, Vaccines and Biologicals, WHO.

5.2 Former chair, WHO SAGE committee.

5.3 Sinha, A, Levine, O, Knoll, MD, Muhib, F and Lieu, TA (2007) Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis, *Lancet*, 369(9559): 389–396, doi:10.1016/S0140-6736(07)60195-0 (see p. 391).

5.4 Director, Vaccine Delivery, Bill & Melinda Gates Foundation.

5.5 GAVI Alliance Secretariat (2013) *Advance Market Commitment for Pneumococcal Vaccines: Annual Report 1 April 2012 –31 March 2013* (sections 2.3–2.4), http://www.gavialliance.org/funding/pneumococcal-amc/.

5.6 http://www.gavialliance.org/support/nvs/pneumococcal/ – see pneumococcal factsheet and/or http://www.gavialliance.org/results/goal-level-indicators/vaccine-goal-indicators/.

5.7 Levine, OS, Bloom, DE, Cherian, T, de Quadros, C, Sow, S, Wecker, J, Duclos, P and Greenwood, B (2011) The future of immunisation policy, implementation, and financing, *Lancet*, 378(9789): 439-448, doi:10.1016/S0140-6736(11)60406-6 (see p. 442).