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

Unit of Assessment: 1

Title of case study: Vaccination to reduce the global burden of invasive pneumococcal disease (IPD) and pneumonia in communities

Period when the underpinning research was undertaken: 2000-2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed:
Anthony Scott	Professor	01/01/13-current
Grant Mackenzie	Associate Professor	01/10/15-current
Anna Roca	MRC Deputy Theme Leader	01/11/11-01/02/18 (MRCG), 01/02/18-current (LSHTM)
Stefan Flasche	Associate Professor	19/4/12-current
Brian Greenwood	Professor	1/1/96-current
& 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)

Clinical trials and modelling studies led by investigators at LSHTM, especially in Africa, established the safety and effectiveness of pneumococcal conjugate vaccine in preventing invasive pneumococcal disease and pneumonia, one of the leading causes of death in children under 5 years of age. This led to the life-saving vaccines being licensed and introduced worldwide, with approximately 225 million children vaccinated by the end of 2019. The research also played a leading role in establishing the importance of vaccination against pneumococcus to reduce morbidity and mortality from pneumonia, and in protecting whole communities in low-income countries via herd immunity.

2. Underpinning research (indicative maximum 500 words)

Pneumonia is a major cause of morbidity and mortality worldwide, with the majority of the disease burden occurring in the developing world. In 2013, pneumonia caused an estimated 935,000 childhood deaths worldwide. A common cause of severe pneumonia is *Streptococcus pneumoniae* and in 2015, the World Health Organization (WHO) estimated that 1.6 million deaths were caused by this bacterium annually, including between 0.7 and 1 million children aged under 5 years. Initial trials of a pneumococcal conjugate vaccine (PCV) in the USA found it was highly effective in protecting vaccinated infants and unvaccinated community members including the elderly, by preventing nasopharyngeal carriage and interrupting transmission. However, it was unknown whether a PCV would be as effective in low- and middle-income countries (LMICs). Effectiveness was demonstrated by researchers at LSHTM and MRC Unit The Gambia at LSHTM (MRCG) in a series of studies carried out with successive vaccines, led by Scott, Roca, Flasche, Mackenzie and Greenwood.

As part of the Gambian Pneumococcal Vaccine Trial Group, Greenwood co-led a randomised, placebo-controlled, double-blind trial of a 9-valent pneumococcal conjugate vaccine (PCV9) in The Gambia from 2000 to 2004 (3.1). The results demonstrated that this vaccine reduced invasive pneumococcal disease (IPD) by 77%, severe pneumonia by 37%, hospital admissions by 15%, and mortality by 16%. The trial showed for the first time that in a rural African setting, a PCV could substantially reduce hospital admissions and improve child survival.

A licensed PCV was subsequently introduced in The Gambia in 2009. Mackenzie led a study by LSHTM staff in The Gambia to monitor the impact of pneumococcal conjugate vaccination on IPD

and pneumonia in Gambian children, since the vaccines were introduced in the routine infant immunisation programme (3.2). This 2017 evaluation showed that introduction of PCV had reduced the incidence of IPD in children aged 2 to 59 months by around 55%, and of hospitalised pneumonia by 30%. This confirmed that the results achieved in the formal clinical trial setting were achievable in practice.

A further study led by Roca (MRCG) in The Gambia evaluated a multi-dose rather than a single-dose formulation of PCV in 500 participants (3.3). The multi-dose preparation was more cost-effective, and the study demonstrated that it was as effective and safe as the single-dose version, which could help to boost vaccination coverage in resource-limited settings.

An alternative PCV from the one used in The Gambia was introduced into the vaccination programme in Kenya in January 2011. The indirect protection of the 10-valent vaccine — PCV10 — in a developing country was not known at the time. This led Scott, of LSHTM, in collaboration with the Kenya Medical Research Unit/ Wellcome Trust Research Programme in Kenya, to estimate its effectiveness against carriage of vaccine serotypes and its effect on other bacteria. Scott set up the study before he moved to LSHTM, and he continued the research after joining the School in 2013 (3.4). The researchers measured the effect of PCV10 on IPD and nasopharyngeal carriage and provided the first population-level evidence of the efficacy of PCV10 in a low-income country. This study demonstrated that PCV10 resulted in IPD caused by vaccine serotypes declining by over 90%, and provided community protection to between 74% and 81%, depending on age group. This research was fully published in 2019, but ongoing data were published as live surveillance for the Global Alliance for Vaccines and Immunisation (Gavi), and the Kenyan Ministry of Health throughout the study.

Mathematical modelling of Kenyan data led by Flasche and published in 2017 found that catch-up campaigns, where individuals who did not receive a vaccination at the recommended age were vaccinated later, were a highly dose-efficient way to accelerate protection against pneumococcal disease (3.5). A similar model was applied in Vietnam, a country that had not yet introduced PCV, by modelling the impact on carriage and IPD of routine vaccination only, and of routine vaccination with catch-up campaigns (3.6).

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

3.1 Cutts FT, Zaman SM, 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**; Gambian Pneumococcal Vaccine Trial Group. 2005. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet.* 365(9465):1139-46. doi: 10.1016/S0140-6736(05)71876-6.

3.2 Mackenzie GA, Hill PC, Sahito SM, et al. 2018. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies [published correction appears in Lancet Infectious Diseases. (7):715. *Lancet Infectious Diseases*. 17(9):965-973. doi:10.1016/S1473-3099(17)30321-3

3.3 Idoko OT, Mboizi RB, Okoye M, Laudat F, **Ceesay B**, Liang JZ, Le Dren-Narayanin N, Jansen KU, Gurtman A, Center KJ, Scott DA, Kampmann B, **Roca A**. 2017. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine (PCV13) formulated with 2-phenoxyethanol in multidose vials given with routine vaccination in healthy infants: An open-label randomized controlled trial. *Vaccine.* 35(24):3256-3263. doi: 10.1016/j.vaccine.2017.04.049.

3.4 Hammitt L, Etyang A, Morpeth S, **Ojal J**, Mutuku A, Mturi N, Moisi, J, **Adetifa I,** Karani A, Akech D, **Otiende M**, Bwanaali T, Wafula J, Mataza C, Mumbo E, Tabu C, Knoll MD, Bauni E, Marsh K, Williams TN, Kamau T, Sharif SK, Levine OS, **Scott JAG**. 2019. Effect of ten-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and nasopharyngeal carriage in Kenya: a longitudinal surveillance study. *Lancet.* 393(10186):2146-2154. doi: 10.1016/s0140-6736(18)33005-8.

3.5 Flasche S, Ojal J, **Le Polain de Waroux O**, Otiende M, O'Brien KL, Kiti M, Nokes J, **Edmunds WJ, Scott JAGS.** 2017. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. *BMC Medicine*. 15(1):113. doi: 10.1186/s12916-017-0882-9.

3.6 Le Polain De Waroux O, Edmunds WJ, Takahashi K, Ariyoshi K, Mulholland EK, Goldblatt D, Choi YH, Anh DD, Yoshida LM and **Flasche S.** 2018. Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam. *Human Vaccines & Immunotherapeutics*, 14:8, 1939-1947, doi: 10.1080/21645515.2018.1467201

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 body of evidence generated by LSHTM and partners was key in the international rollout of conjugate pneumococcal vaccines to 149 WHO member countries, via WHO recommendations and adoption in the portfolio of Gavi-supported vaccines. The research significantly contributed to the estimation of the burden of morbidity and mortality from pneumococcal disease prevented by PCV, and the role of the vaccination in herd immunity. It informed next steps in decision making for governments considering introducing and continuing this life-saving vaccine programme.

Demonstrating vaccine efficacy and effectiveness

The results of the Gambian trial and a parallel study in South Africa provided crucial information to the WHO Strategic Advisory Group of Experts' (SAGE) recommendations that PCVs should be introduced into routine infant immunisation programmes of all countries with high child mortality. This was accepted by WHO in 2007 (5.1).

The findings of the 2017 evaluation, led by Mackenzie, showed that the vaccine had reduced the incidence of IPD in children aged 2-59 months by around 55%, and of hospitalised pneumonia by 30%. This demonstrated the considerable and sustained impact of PCV on IPD and pneumonia in Gambian children since the introduction of the vaccines in the routine infant immunisation programme. SAGE reviewed this evidence in 2017, and used it to formulate their 2017 recommendations on PCV. Their recommendations endorsed the efficacy of 2 PCVs (PCV13 and PCV10), and gave further guidance for countries on dose schedule, country-level choice of vaccine depending on prevalence of pneumococcal strains, and product-switching (5.2). Scott, Flasche, Greenwood and Mackenzie contributed to the expert consultation on optimising PCV impact in 2017. The evidence and recommendations presented fed directly into the WHO SAGE working group held immediately afterwards (5.3)

The sustained impact of the original recommendation to introduce a PCV to routine infant immunisation in 2007, plus further PCV recommendations in 2017 underpinned by LSHTM and MRCG evidence, was evident. By the end of 2019, 60 Gavi-eligible countries across 3 continents had introduced a PCV into their routine immunisation programmes, with only 3 of 54 countries in sub-Saharan Africa having not yet introduced PCV. The outcomes of the original Gambian trial still underpinned the WHO position paper in 2019, demonstrating the sustained attributable impact of the research (5.4).

According to Gavi's 2019 Annual Report, 184 million children were vaccinated by the end of 2018, with this figure projected to have reached more than 225 million children by the end of 2019. The continued scale-up of PCV was expected to prevent over 700,000 future deaths among children in Gavi-supported countries by 2020 (5.5).

Both the trial and surveillance evidence in Africa focused on PCV13 in South Africa and The Gambia. But the success of PCV10 in Kenya demonstrated by Scott and colleagues contributed to several large African countries introducing a PCV vaccine, including Nigeria, Ethiopia, Madagascar, Zambia and Uganda. The preliminary results of the study on the safety of PCV10

were submitted for prequalification to WHO in 2012, and led to the approval of the formulation for use from 2013 onwards in Gavi countries (5.6).

Catch-up campaigns

Flasche's research demonstrating the effectiveness of catch-up campaigns in Kenya was used as evidence to inform the WHO position and recommendations in both 2017 and 2019: that catch-up vaccination at the time of PCV introduction should be used to accelerate its impact on disease in children aged 1-5 years.

'*Wherever possible, catch-up vaccination at the time of introduction of PCV should be used to accelerate its impact on disease in children aged 1–5 years, particularly in settings with a high disease burden and mortality. If there is limited availability of vaccine or of financial resources for catch-up vaccination, the youngest children (e.g. <2 years of age) should be prioritised to receive catch-up doses of PCV because of their higher risk for pneumococcal disease*.' (5.2, 5.4).

In 2018, the Gavi Board approved support for catch-up vaccination campaigns as part of future introductions. Timor-Leste was the first country to benefit from this change in Gavi's programmatic support, with the catch-up campaign expected to be introduced in 2021 (5.7).

Cost saving for LMICs

Roca's research evaluating the immunogenicity of the multi-dose preparation of PCV13 led the WHO SAGE working group on PCV to recommend PCV13 for WHO prequalification in 2016. This enabled the vaccine, Prevenar 13 multi-dose vial (MDV), to be used by United Nations agencies and countries worldwide (5.8). The vaccine offered significant benefits to LMICs. Pfizer stated it resulted in a 75% reduction in the cold-chain requirements for temperature-controlled supply chain, and in UN and UNICEF shipping costs and storage requirements at national, regional and community levels. The pre-qualified multi-dose vial presentation was introduced in 2017 for shipment to countries supported by Gavi, preceded by Pfizer announcing a cost reduction from USD3.30 per dose to USD3.10 per dose in its multi-vial per-dose price, to all Gavi-eligible countries using PCV13 (5.8).

The current licensed versions of the vaccine are PCV13 and PCV10. Both PCV10 and PCV13 have substantial impacts against pneumonia, providing protection against different pneumococcal strains, and nasopharyngeal carriage. One of Gavi's aims is to encourage competition on vaccine price, and it encouraged different countries to take up PCV10 (GSK) and PCV13 (Pfizer). Following LSHTM trials and surveillance evidence of cost savings in The Gambia and Kenya of both vaccines, Gavi signed further agreements in 2017 with both manufacturers under the Advanced Market Commitment to keep the dose price no more than USD3.50 and allow countries no longer eligible for Gavi support to access the same pricing until 2025. In 2018, UNICEF (as Gavi's procurement agency) entered a new supply agreement with Pfizer to supply 19 million doses annually from 2018 for a period of 10 years (5.5).

As of 2019, 60 countries across Africa, Asia, the Americas and the Middle East had introduced pneumococcal conjugate vaccination under the Advanced Market Commitment; 10 of these countries are using PCV10 while the remaining 50 are using PCV13. Within the REF period (2014 onwards), 22 countries introduced a PCV (16 using PCV13). In 2019, manufacturer Pfizer further reduced the price of PCV13 available to Gavi-supported countries, from USD2.95 to USD2.90 per dose. This cost reduction benefited the approximately 50 countries using PCV13 (5.5).

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

5.1 World Health Organization. Weekly Epidemiological Record. 23 March 2007. No. 12, 2007,82. Pneumococcal conjugate vaccine for childhood immunisation – WHO position paper.

- Original WHO recommendation that PCV immunisation should be included in routine infant immunisation of all countries with high child mortality, leading to mass roll out in previous and current REF period, cites Gambian trial pg 99-100

5.2 World Health Organization. Executive Summary: SAGE October 2017, Pneumococcal Conjugate Vaccine session.

- States that SAGE reviewed evidence on the impact of catch-up immunisation in Kenya and Vietnam by Flasche et al, to inform the working group of how to further optimise and update the current WHO recommendations on catch-up immunisation, pg 5 (resulting recommendations pg 17)
- Review of available evidence (including LSHTM evidence) concludes that both products (PCV13 and PCV10) have overall benefit

5.3 WHO Technical Expert Consultation Report on Optimisation of PCV Impact: Review of Evidence and Programmatic Considerations to Inform Policy. Department of Immunisations, Vaccines and Biologics. June 12-13, 2017.

- Flasche, Greenwood, Mackenzie and Scott listed as meeting participants (pg 17). The presented evidence and prioritised research recommendations were taken into consideration at the PCV SAGE working group meeting following the consultation (pg 2).

Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME): Summary of findings from systematic review, October 2017

- Evidence from Mackenzie and Roca reviewed by SAGE in 2017 in advance of their recommendations:

SAGE evidence to recommendations table: Pneumococcal Conjugate Vaccine (PCV). PICO 3: Catch-up vaccination impact, evidence citation 5, recommendations listed pg 14. October 2017.

- Evidence reviewed by WHO SAGE working group to answer question of additional value of catch-up vaccination and subsequent recommendations.

5.4 World Health Organization. Weekly Epidemiological Record. 22 February 2019. No 8, 2019,94. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper.

- Flasche research in Kenya and Vietnam referenced, pg 97 (references 40 and 41) on catch-up vaccination
- Gambia trial paper referenced, pg 87 (reference 11) for incidence of IPD and original recommendation for inclusion of PCVs in childhood immunisation programmes worldwide still stands

5.5 AMC Secretariat of Gavi, the Vaccine Alliance. Advance Market Commitment for Pneumococcal Vaccines. Annual Report. 1 January-31 December 2019.

- Lists countries that have introduced PCV up to 2019, pg 17-18, and gives details of children vaccinated and lives saved (pg 6)
- States Pfizer reduced cost of PCV13 4-dose vial to Gavi-supported countries (pg 15)

5.6 World Health Organisation. Update on two-dose presentation of preservative-free 10-valent pneumococcal conjugate vaccine from GSK (Synflorix™). 2012. Accessed at: https://www.who.int/immunization_standards/vaccine_quality/synflorix_pqnote_2dose_2012/en/

- The WHO reviewed interim data from the Kenyan surveys demonstrating benefits outweigh the potential risk, and agreed that the two-dose presentation PCV10 (Synflorix) remained prequalified

5.7 GAVI, The Vaccine Alliance. Gavi Alliance Board Meeting. 6-7 June 2018. Minutes accessed at: https://www.gavi.org/sites/default/files/board/minutes/2018/Board-2018-Mtg-01-Minutes.pdf

- Gavi Board approved a proposal to support PCV catch-up vaccination for countries that have not yet introduced the vaccine.

5.8 Pfizer press release. Pfizer receives World Health Organisation prequalification for multi-dose vial presentation of Prevenar 13. July 2016. Accessed at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_world_health_organization_prequalification_for_multi_dose_vial_presentation_of_prevenar_13