Institution: Imperial College London

Unit of Assessment: 02 Public Health, Health Services and Primary Care

Title of case study: Evidence to Support Use of New Vaccines and Vaccination Strategies by the Global Polio Eradication Initiative

1. Summary of the impact (indicative maximum 100 words)

Research by Professor Grassly and colleagues at Imperial College on the epidemiology of poliovirus and the efficacy of new vaccines has played a critical role in the thinking and strategy of the Global Polio Eradication Initiative (GPEI). This research has supported the introduction of new vaccines, guided the timing and location of vaccination campaigns and influenced polio 'endgame' policy. This is documented in the *GPEI Strategic Plan 2010-2012*, where Imperial research informed 2 of the 4 'major lessons' concerning poliovirus epidemiology described in the executive summary that led to changes in the programme. The research has also informed our understanding of mucosal immunity induced by oral poliovirus vaccines, and led to two clinical trials of the potential role of inactivated vaccine to boost mucosal immunity. Results from one of these trials were used to support the recent World Health Organisations (WHO) recommendation for universal vaccination with inactivated vaccine following the switch to bivalent oral vaccine in routine programmes.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Nicholas Grassly, Chair in Vaccine Epidemiology (2000-present)
Professor Christophe Fraser, Chair in Theoretical Epidemiology (2000-present)
Professor Christl Donnelly, Chair in Statistical Epidemiology (2000-present)
Dr Kathleen O'Reilly, MRC Research Fellow (2009-present)
Dr Helen Jenkins, PhD student (2007-2010)

In 2004, Professors Grassly and Fraser at Imperial College London initiated a research collaboration with the Global Polio Eradication Initiative (GPEI), which is headquartered at the World Health Organisation (WHO), Geneva. The original intention of the research was to maximise the utility of routine poliovirus surveillance data by providing more sophisticated statistical and mathematical model-based analyses than were in use at the time. Over time a vaccine epidemiology research group was established at Imperial by Professor Grassly and the research effort has expanded beyond secondary analysis of data to include clinical trials of poliovirus vaccines. The group collaborates closely with field and laboratory staff in polio affected countries, and has strong international links, particularly in India. During 2004-2013 several of our research findings with a significant impact on the strategies and success of the GPEI can be highlighted:

1) In 2005 we found that the standard trivalent oral poliovirus vaccine (OPV) has extremely poor efficacy in northern India, explaining the persistence of polio at that time in the country despite frequent vaccination campaigns (1).
2) We provided the first estimate of the efficacy of serotype 1 monovalent OPV, which was licensed in 2005, showing that this vaccine was three times more efficacious per dose compared with the standard trivalent OPV in northern India (2). This finding supported the widespread use of this vaccine by the GPEI, and we have recently used similar methods to demonstrate efficacy of bivalent OPV that was licensed in 2009 (3).
3) The clinical characteristics and attack rate for a vaccine-derived poliovirus circulating in Nigeria were shown to be equivalent to that for wild-poliovirus, making it clear that vaccine-derived polioviruses can fully revert to neurovirulent and transmissible phenotypes (4).
4) Intestinal (mucosal) immunity, important for preventing infection and transmission of polioviruses, was shown for the first time to wane over time since vaccination with OPV (5).
5) Outbreaks of polio were shown to be predictable on the basis of known risk factors, allowing strategic planning of the timing and scale of pre-emptive vaccination campaigns (6).

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

(1) Grassly, N.C., Fraser, C., Wenger, J., Deshpande, J.M., Sutter, R.W., Heymann, D.L., & Aylward, R.B. (2006). New strategies for the elimination of polio from India. *Science*, 314 (5802), 1150-1153. DOI. Times cited: 90 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 31.02

(2) Grassly, N. C., Wenger, J., Durrani, S., Bahl, S., Deshpande, J.M., Sutter, R.W., Heymann, D.L., & Aylward, R.B. (2007). Protective efficacy of a monovalent oral type 1 poliovirus vaccine: a case-control study. *Lancet*, 369, 1356-1362. DOI. Times cited: 63 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(3) O'Reilly, K. M., Durry, E., Ul-Islam, O., Quddus, A., Abid, N., Mir, T.P., Tangermann, R., Aylward, R.B., & Grassly, N.C. (2012). The effect of mass immunisation campaigns and new oral poliovirus vaccines on the incidence of poliomyelitis in Pakistan and Afghanistan, 2001-2011: a retrospective analysis. *Lancet*, 380, 491-498. DOI. Times cited: 6 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 39.06

(4) Jenkins, H. E., Aylward, R.B., Gasasira, A., Donnelly, C.A., Mwanza, M., Corander, J., Garnier, S., Chauvin, C., Abanida, E.A., Pate, M.A., Adu, F., Baba, M., & Grassly, N.C. (2010). Implications of a circulating vaccine-derived poliovirus in Nigeria. *N Engl J Med*, 362, 2360-2369. DOI. Times cited: 36 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 51.65

(5) Grassly, N. C., Jafari, H., Bahl, S., Sethi, R., Deshpande, J.M., Wolff, C., Sutter, R.W., & Aylward, R.B. (2012). Waning intestinal immunity after vaccination with oral poliovirus vaccines in India. *J Infect Dis,* 205, 1554-1561. DOI. Times cited: 5 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 5.84

(6) O'Reilly, K. M., Chauvin, C., Aylward, R.B., Maher, C., Okiror, S., Wolff, C., Nshmirimana, D., Donnelly, C.A., & Grassly, N.C. (2011). A Statistical Model of the International Spread of Wild Poliovirus in Africa Used to Predict and Prevent Outbreaks. *PLoS Medicine*, 8 (10), e1001109. DOI. Times cited: 5 (as at 4th November 2013 on ISI Web of Science). Journal Impact Factor: 15.25

Key funding:

- Royal Society (2004-2012; £625,000), Principal Investigator (PI) N. Grassly, University Research Fellowship
- WHO (2008-2012; £167,000), PI N. Grassly, Mathematical models of polio immunisation.
- Medical Research Council (MRC; 2008-2013; £2.1million), PI N. Ferguson, MRC Centre for Outbreak Analysis and Modelling.
- Bill and Melinda Gates Foundation (2008-2013; £2.4million), PI N. Ferguson, Vaccine Modelling Initiative.
- WHO (2010-2013; £100,000), PI N. Grassly, Gut mucosal immunity induced by vaccine and wild-type poliovirus in India.
- Bill and Melinda Gates Foundation (2012-2014; £1.25million), PI N. Grassly, Clinical trial to treat children in India for enteric infections to improve their response to oral poliovirus vaccine.
- MRC (2012-2016; £509,000), PI K. O'Reilly, MRC Population Health Fellowship
- WHO (2013-2015; £218,000), PI N. Grassly, Statistical and mathematical analysis of polio surveillance data to support the endgame
- Bill and Melinda Gates Foundation (2013-2016; £461,000), PI N. Grassly, Mathematical modelling of poliovirus transmission to support the endgame.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare; public policy and services; international development
Main beneficiaries include: patients; WHO; GPEI

The Global Polio Eradication Initiative (GPEI) is the largest coordinated public health effort in history, with an 'endgame' budget during 2013-2018 of $5.5 billion. The four spearheading partners of the GPEI are the WHO, US Centers for Disease Control (CDC), Rotary International and

UNICEF. The vaccine epidemiology research group at Imperial College London has provided critical information that has driven strategy at the GPEI and helped to support polio eradication. In 2013 we were formally recognised as the WHO collaborating institute on polio data analysis and modelling.

Perhaps most significantly, our research has provided evidence that contributed to changing polio immunisation strategies in India, which resulted in the elimination of infection from that country in 2011. The GPEI Strategic Plan 2010-12 [1] notes that 'Compounding the problem of achieving sufficiently high population immunity to stop transmission in western Uttar Pradesh, and possibly in central Bihar, is the compromised efficacy of OPV compared with the rest of India[15]' (see page 18); citing our work demonstrating OPV failure in northern India (research reference 2). Our subsequent demonstration of the greater efficacy of monovalent and bivalent vaccines licensed in 2005 and 2009 respectively, together with the geographic and targeted approaches described in the Strategic Plan for 2010-2012, led to the eradication of polio from India, with the last case reported in January 2011 (www.polioeradication.org). Only three countries remain endemic for polio, and the group at Imperial works closely with government and WHO staff in these countries and in WHO headquarters to analyse surveillance data and optimise vaccination strategy and campaign quality. For example, Dr O'Reilly was in northern Afghanistan and Pakistan in July 2012 to monitor programme performance, drawing from her findings on vaccination coverage and efficacy.

In the GPEI Strategic Plan 2010-2012, the Executive Summary identifies at the outset four 'major lessons learned', which each led to major changes in the eradication programme. Two of these lessons drew directly from our research findings on immunity induced by newly licensed poliovirus vaccines and the epidemiology of poliovirus in endemic and re-infected countries.

The first lesson learnt was that immunity thresholds to stop polio differ, being higher in Asia than Africa, leading to a '"Geographic" strategy, with OPV campaign and monitoring strategy tailored to local circumstances. This was based on our findings that "The differential progress by country towards polio eradication globally has long suggested that the population immunity thresholds at which WPV transmission stops can differ substantially between geographic areas, with implications for programme strategy, planning, and prioritization" [1; see page 12, where research references 1 and 4 are the cited evidence]. The resulting 'process indicators' in the Strategic Plan include targets based on our estimates of vaccine-induced immunity [1; see page 15]. Our work is therefore central to this new strategy and we provide updated analysis when requested by the GPEI. As a result of these targeted approaches to polio eradication and efforts to improve vaccination campaign coverage, the global incidence of poliomyelitis is at an all time low (just 223 cases in 2012).

The second lesson drawing from our work was that 'Routes of poliovirus spread & outbreaks are now largely predictable', leading to, among others, 'Pre-planned, synchronized campaigns.' We had shown that polio outbreaks in sub-Saharan Africa could be predicted with reasonable accuracy 6 months ahead of time using a simple statistical (mathematical) model (described in research reference 6 above). The Strategic Plan notes that 'In view of the substantial resource demands of implementing this [pre-emptive vaccination campaign] strategy, a mathematical model has been developed to help prioritize countries and areas based on the risk of both an importation and a subsequent outbreak (Figure 4). Regular assessments of polio immunity among the "WPV importation belt" countries using NP AFP data, this model and other relevant information, will continue to inform this prioritization.'; Figure 4 was provided by us, based on work described in research reference 6 [1; see page 35]. We therefore continue to provide assessments and forecasts of the risk of outbreaks in sub-Saharan Africa to support immunization planning. These risk assessments allow the programme to prioritize vaccination campaigns in a time of serious resource constraints, maximising the cost-effectiveness of the programme.

The World Health Assembly (May 2012) and WHO Strategic Advisory Group of Experts (SAGE) recently recommended a switch from trivalent to bivalent OPV during routine immunisation and global cessation of vaccination with any serotype-2-containing OPV. The motivation for this switch came from the recognition of the significant burden of vaccine-associated paralytic poliomyelitis

(VAPP) and vaccine-derived poliovirus outbreaks associated with continued use of a serotype 2 OPV, when this serotype of wild-poliovirus was eradicated over 10 years previously. Our work demonstrating equivalent pathogenicity and transmissibility of serotype 2 vaccine-derived and wild-type poliovirus was an important piece of evidence underlying this decision [2].

Our work demonstrating rapid waning of intestinal mucosal immunity following vaccination with OPV and the detection of vaccine and wild-type poliovirus in stool samples collected from OPV vaccinated children provided motivation for two clinical trials on the use of inactivated poliovirus vaccine (IPV) to boost intestinal immunity (Grassly et al. J Infect Dis 2009, 2010, 2012). The first of these trials was led by WHO and enrolled 990 children in northern India [3]. Results from this trial, for which Professor Grassly is a co-investigator, were presented to WHO SAGE in November 2012 for their consideration. They provided evidence for one of the benefits of IPV that led to the WHO SAGE recommendation made in January 2013 for universal vaccination with IPV at the time of the switch from trivalent to bivalent OPV in routine programmes [4].

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

[1] Global Polio Eradication Initiative Strategic Plan 2010-2012. WHO, Rotary International, US CDC & UNICEF, 2010 (WHO/Polio/10.01). Available at: http://www.polioeradication.org/Portals/0/Document/StrategicPlan/StratPlan2010_2012_ENG.pdf Archived on 4th November 2013.

[2] 65th World Health Assembly. Resolution A65/55 Poliomyelitis: intensification of the global eradication initiative (May 2012) http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_55-en.pdf (pg 7). Archived on 4th November 2013.

[3] Mucosal immunity study - Moradabad, India. Online summary document. http://bit.ly/MAxyhk, polioeradication.org). Archived on 4th November 2013.

[4] WHO (2013). "Meeting of the Strategic Advisory Group of Experts on immunization, November 2012 – conclusions and recommendations." Wkly Epidemiol Rec 88: 1-16. http://www.who.int/wer/2013/wer8801.pdf (page 6). Archived on 4th November 2013.