Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Rotavirus Vaccine Evaluation and Introduction in Africa

1. Summary of the impact

Rotavirus is the leading cause of acute gastroenteritis in infants and young children worldwide, causing 500,000 deaths annually. Prof Cunliffe at the University of Liverpool (UoL) has conducted rotavirus studies in Malawi since 1997, including descriptive epidemiology and the first clinical trial of a human rotavirus vaccine in Africa. Based upon the results of this clinical trial in Malawi, where vaccination was shown to reduce severe rotavirus disease caused by diverse strains by 50%, a global recommendation for rotavirus vaccine use was issued by WHO in 2009. African countries are now introducing rotavirus vaccines into their childhood immunization schedules with introduction in Malawi in 2012.

2. Underpinning research

The UoL research was designed to facilitate and accelerate the introduction of rotavirus vaccines into childhood immunisation programmes in Africa. Rotavirus is responsible for approximately half a million childhood deaths from acute gastroenteritis each year, with the majority of deaths occurring in infants in Africa and Asia. Prior to the completion of this research, the ability of current rotavirus vaccines to protect children in the world's poorest countries was unknown and therefore WHO did not recommend their use in such populations.

1. Through a competitive Wellcome Trust Research Training Fellowship (1996-2001), to NA Cunliffe [UoL, supervisor CA Hart - now deceased]), the first detailed investigation of rotavirus infections in HIV-infected children was undertaken. The findings were published in several leading journals including the *Lancet* [1] and *AIDS*. The seminal observation of natural rotavirus infections being of similar severity in HIV-infected and HIV-uninfected children encouraged the subsequent evaluation of live, oral rotavirus vaccines in HIV-exposed and HIV- infected infants.

2. In ongoing studies since 1997 to the present, funded by the Wellcome Trust, WHO and GSK Biologicals, NA Cunliffe and CA Hart (UoL) have described the disease burden and epidemiological features of rotavirus infections in Malawian children, published in *Journal of Infectious Diseases* [2], *Journal of Clinical Microbiology* [3], *Virology*, *Emerging Infectious Diseases* and *Journal of General Virology*. These studies have highlighted the high burden of rotavirus disease amongst impoverished populations and have described particular epidemiological features relevant to rotavirus vaccine programmes. For example, the rotavirus disease burden in early infancy is very high – so effective vaccines need to provide early protection in this and similar settings. The description of a wide diversity of rotavirus strains, including novel serotype G8 strains, has highlighted the requirement for effective rotavirus vaccines to provide cross-serotype protection in African countries.

3. Consequent to the above studies, and in partnership with the Program in Appropriate Technology for Health (PATH), USA and GlaxoSmithKline Biologicals (GSK), Belgium, NA Cunliffe (UoL) and SA Madhi (University of Witwatersrand, South Africa) led as Chief Principal Investigators a Phase III, placebo-controlled clinical trial of a human rotavirus vaccine in Malawian and South African children (2006-2009). This first clinical trial of a human rotavirus vaccine in Africa, including infants exposed to HIV infection, reduced severe rotavirus disease in Malawian children by 50% [4, 5]. Vaccine efficacy was lower than documented in industrialised countries; however given the substantially higher burden of disease, public health impact of rotavirus vaccination would be greater. Protection against a wide range of rotavirus strains was observed, including the prevalent G8 serotype [6].

3. References to the research

Peer-reviewed publications

1. **Cunliffe NA**, Gondwe JS, Kirkwood CD, Graham SM, Nhlane N, Thindwa BDM, Dove W, Broadhead RL, Molyneux ME, Hart CA. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. Lancet 2001;358:550-555. Citations: 52 Impact Factor: 39.060

2. **Cunliffe NA**, Ngwira BM, Dove W, Thindwa BDM, Turner AM, Broadhead RL, Molyneux ME, Hart CA. Epidemiology of rotavirus infections in children in Blantyre, Malawi, 1997-2007. Journal of Infectious Diseases 2010;202:S168-174. Citations: 16 Impact Factor: 5.848

3. **Cunliffe NA**, Gondwe JS, Graham SM, Thindwa BDM, Dove W, Broadhead RL, Molyneux ME, Hart CA. Rotavirus strain diversity in Blantyre, Malawi, from 1997 to 1999. Journal of Clinical Microbiology 2001;39:836-843. Citations: 111 Impact Factor: 4.068

4. Madhi SA*, **Cunliffe NA***, Steele AD, Witte D, Kirsten M, Louw C, Ngwira B, Victor JC, Gillard PH, Cheuvart BB, Han HH, Neuzil KM. Effect of human rotavirus vaccine on severe gastroenteritis in African infants. New England Journal of Medicine 2010;362:289-98. *Co-primary authors. Citations: 211 Impact Factor: 51.658

5. **Cunliffe NA**, Witte D, Ngwira BM, Todd S, Bostock NJ, Turner AM, Chimpeni P, Victor JC, Steele AD, Bouckenooghe A, Neuzil KM. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life. Vaccine 2012; 30:A36-43. Citations: 8 Impact Factor: 3.492

6. Nakagomi T, Nakagomi O, Dove W, Doan YH, Witte D, Ngwira B, Todd S, Steele AD, Neuzil KM, **Cunliffe NA**. Molecular characterization of rotavirus strains detected during a clinical trial of a human rotavirus vaccine in Blantyre, Malawi. Vaccine 2012; 30: A140-151. Citations: 1 Impact Factor: 3.492

Research Grants

2010-2015. **Wellcome Trust**. New childhood vaccines for Malawi: Impact of a national pneumococcal and rotavirus vaccine roll-out on child mortality and disease burden, in a region of sub-optimal strain coverage, £2.3m Programme Grant PI **NA Cunliffe** with **Neil French** and Robert Heyderman

2006-2011. **Programme in Appropriate Technology in Health (PATH) to University of Liverpool.** A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine Expanded Program of Immunisation (EPI) vaccinations in healthy Malawian infants, £2m

1996-2001. **Wellcome Trust**. Clinical features and molecular epidemiology of rotavirus diarrhoea in Malawian children with and without HIV infection. Wellcome Research Training Fellowship for **NA Cunliffe**, £330k

4. Details of the impact

All impacts generated from the UoL research have occurred since 2008.

The long-term detailed descriptions of rotavirus gastroenteritis in Malawian children helped to progress the assessment and introduction of rotavirus vaccines in Africa by (i) demonstrating the need for rotavirus vaccines to be effective against a wide range of rotavirus strain types; (ii)

demonstrating the need for rotavirus vaccines to protect very young infants, since a high burden of rotavirus disease occurred in the first year of life; and (iii) providing an ideal trial site with a wealth of underpinning data where the pivotal rotavirus vaccine trial could be undertaken. These data were generated in collaboration with the College of Medicine, University of Malawi (Dr Bagrey Ngwira). The data were disseminated through publication in peer-reviewed journals [1-3].

Based in large part upon the results of the clinical trial in Malawi, where vaccination was shown to reduce severe rotavirus disease by 50%, a global recommendation for rotavirus vaccine use was issued in 2009 by the World Health Organisation. In countries where diarrhoeal deaths account for ≥10% of mortality among children aged <5 years, the introduction of the vaccine was strongly recommended. Effectively, this recommendation amounted to an extension of an existing recommendation from continents where vaccine efficacy had been demonstrated (Europe and the Americas) to also include developing countries in Africa and Asia (where the greatest disease burden lies but where vaccine efficacy was unknown). The clinical trial was undertaken in partnership with the Program In Appropriate Technology for Health, GlaxoSmithKline Biologicals, The University of Malawi College of Medicine, and the University of Witwatersrand. The data were presented to a WHO Strategic Advisory Group of Experts vaccine meeting and disseminated through publication in peer-reviewed journals. The results were made available to the Malawi Ministry of Health [15].

Following this global recommendation, African countries are introducing rotavirus vaccines into their childhood immunisation schedules with Malawi having introduced in November 2012. This followed the introduction of rotavirus vaccines in Botswana, Ghana, Morocco, Rwanda, South Africa, Sudan and Zambia. Early data are emerging from South Africa (where vaccine was introduced in 2009) of an effect on child health in respect of reduced hospitalisations due to rotavirus infection. For example, a recent assessment of the impact in South Africa states that "we estimate that at least 13,000 to 20,000 hospitalizations in children <2 years were prevented in the two years following rotavirus vaccine introduction" [14]. Rotavirus diarrhoea accounts for 6.5% of global deaths of children under five. Complete implementation in all GAVI eligible countries will prevent 180,000 deaths per year and avert 6 million clinic and hospital visits each year, thereby saving US $68 million annually in treatment costs [9].

In order to assess vaccine effectiveness and impact on rotavirus disease burden in Malawi (including deaths due to diarrhoea), the UoL (PI, Cunliffe) has been awarded a 5-year Programme Grant by the Wellcome Trust (2010-2015, listed in section 3 above).

A Cochrane review has highlighted the benefits of rotavirus vaccinations in all populations [13] and the UK introduced rotavirus vaccine into its childhood immunization programme in July 2013.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

7. Weekly Epidemiological Record 2009; 84: 213-236. The global vaccine recommendation and direct link to the clinical trial of rotavirus vaccine in Malawi and South Africa

8. Rotavirus vaccines. WHO Position paper - January 2013. Wkly Epidemiol Rec 2013;88: 49-64. Current WHO position paper with review of rotavirus vaccine introduction and impact

9. http://www.path.org/news/press-room/159/ Rollout of rotavirus vaccine in Malawi (PATH)

10. http://www.gavialliance.org/library/news/press-releases/2012/malawi-protect-thousands-childrens-lives-rotavirus-vaccines/ Rollout of rotavirus vaccine in Malawi (GAVI)

11. http://www.afro.who.int/en/malawi/press-materials/item/5152-malawi-introduces-the-

rotavirus-vaccine-to-reduce-diarrhea-illnesses-and-deaths-among-children.html Rollout of rotavirus vaccine in Malawi (WHO)

12. Msimang VM, Page N, Groome MJ, Moyes J, Cortese M, Seheri M, Kahn K, Chagan M, Madhi SA, Cohen C. Impact of Rotavirus Vaccine on Childhood Diarrheal Hospitalization Following Introduction into the South African Public Immunization Program. Pediatr Infect Dis J 2013. http://www.ncbi.nlm.nih.gov/pubmed/23934208

13. Soares-Weiser K, MacLehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N "Vaccines for preventing rotavirus diarrhoea: Vaccines in use. Cochrane Review. 2012. http://summaries.cochrane.org/CD008521/vaccines-for-preventing-rotavirus-diarrhoea-vaccines-in-use#sthash.toQh67x0.dpuf

14. Contact: Program in Appropriate Technology for Health, Seattle, USA

15. Contact: Department of Health, Malawi