Institution: University of Liverpool

Unit of Assessment: UoA1

Title of case study: Reducing infant deaths from rotavirus diarrhoea in sub-Saharan Africa

Period when the underpinning research was undertaken: 2005-2020

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

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Nigel Cunliffe	Professor of Medical Microbiology	1996 - present
Neil French	Professor of Infectious Diseases	2011 - present
Miren Iturriza-Gomara	Professor of Virology	2012 - 2020
Naor Bar-Zeev	Reader in Paediatric Infectious Diseases	2011 - 2017
Dan Hungerford	Tenure Track Fellow	2015 - present
Khuzwayo Jere	Tenure Track Fellow	2013 - present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Rotavirus is the leading cause of severe gastroenteritis, responsible for 250,000 annual childhood deaths in Africa prior to introduction of rotavirus vaccine. A UoL-led clinical trial of rotavirus vaccine in Malawi informed a WHO recommendation in 2009 that children in low income, high mortality countries should receive rotavirus vaccine. Subsequent introduction of a childhood vaccination program in Malawi was used as an exemplar to demonstrate impact, safety and cost-effective health protection. By reducing hospital diarrhoea admissions and diarrhoea deaths by a third, it is estimated that the vaccine program in Malawi has averted 1,505 deaths since 2013. Our demonstration of programmatic impact has informed international policy with rotavirus vaccination programs now introduced in 38 African countries, preventing an estimated 169,400 deaths over the same period.

2. Underpinning research

Background

The University of Liverpool (UoL) has led studies of rotavirus diarrhoea in Malawi since 1997, designed to facilitate and accelerate the introduction of rotavirus vaccines into childhood Expanded Programme on Immunisation (EPI) programmes in Malawi and other low-income African countries. Rotavirus vaccines developed by GSK (RV1) and Merck (RV5) were known to work well in high income countries, but their ability to protect children in the world's poorest countries was unknown. Live, orally administered vaccines against other enteric diseases (e.g. cholera, typhoid) performed less well in the poorest settings, for reasons that are unclear.

After describing a high burden of rotavirus disease among children under two years of age in Malawi, Professor Cunliffe subsequently led a pivotal, Phase III clinical trial of the RV1 rotavirus vaccine in Malawi. This first trial of a modern rotavirus vaccine in Africa showed that severe rotavirus diarrhoea episodes were reduced by half[3.5] leading to a WHO recommendation in 2009 that all the world's children should receive rotavirus vaccine, with a particularly strong recommendation for those countries with a high burden of diarrhoea deaths.

Demonstration of vaccine impact, effectiveness and safety

The RV1 vaccine was added into Malawi's infant immunisation schedule in October 2012. This enabled UoL (in partnership with the Malawi Ministry of Health) to undertake detailed,

prospectively conducted studies to demonstrate the impact, safety and cost-effectiveness of rotavirus vaccination across the country.

Case control studies in 2012 - 2014 demonstrated that national vaccination was more than 60% effective in preventing severe rotavirus diarrhoea episodes among infants in urban Malawi, with population incidence of rotavirus hospitalisations reduced by over 40%[3.4]. A large, prospectively conducted cohort study of 48,672 live births, then demonstrated that rotavirus vaccination reduced infant diarrhoea deaths by a third in rural Malawi, the first evidence from a low-income country that rotavirus vaccination saves lives[3.1]. The UoL also demonstrated that rotavirus vaccination provides cost-effective health protection in Malawi[3.3].

Through its work in Malawi, UoL contributed to a multi-country African study led by the Centers for Disease Control and Prevention, USA which demonstrated that rotavirus vaccination did not result in the development of intussusception (blockage of the small bowel) in African infants; this is an important finding given the association of this rare side effect with rotavirus vaccination in more developed settings, and is perhaps related to earlier age of vaccination and reduced vaccine "take" in this setting [3.2].

Together, these findings supported the argument for widespread adoption of rotavirus vaccination in other low-income, high-burden settings which has been promoted via annual workshops with the Malawi Ministry of Health and WHO EPI representatives, as well as via the RotaCouncil and through media coverage. Professor Cunliffe led several Cochrane reviews demonstrating the safety and efficacy of rotavirus vaccines, in order to inform their continued use and inform WHO policy[3.6].

3. References to the research

3.1. **Bar-Zeev N,** King C, Phiri T, Beard J, Mvula H, Crampin AC, Heinsbroek E, Lewycka S, Tate JE, Parashar UD, Costello A, Mwansambo C, Heyderman RS, **French N**, **Cunliffe NA**; VacSurv Consortium. Impact of monovalent rotavirus vaccine on diarrhoea-associated post-neonatal infant mortality in rural communities in Malawi: a population-based birth cohort study. The Lancet Global Health. 2018 Sept;6(9):e1036-e1044. DOI: 10.1016/S2214-109X(18)30314-0 Citations: 9 Altmetric Score: 196

3.2. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, Mujuru H, Mpabalwani E, Ngwira B, Cortese MM, Mihigo R, Glover-Addy H, Mbaga M, Osawa F, Tadesse A, Mbuwayesango B, Simwaka J, **Cunliffe NA**, Lopman BA, Weldegebriel G, Ansong D, Msuya D, Ogwel B, Karengera T, Manangazira P, Bvulani B, Yen C, Zawaira FR, Narh CT, Mboma L, Saula P, Teshager F, Getachew H, Moeti RM, Eweronu-Laryea C, Parashar UD; African Intussusception Surveillance Network. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. The New England Journal of Medicine. 2018; 378:1521-28. DOI: 10.1056/NEJMoa1713909 Citations: 10 Altmetric Score: 178

3.3. **Bar-Zeev N**, Tate JE, Pecenka C, Chikafa J, Mvula H, Wachepa R, Mwansambo C, Mhango T, Chirwa G, Crampin AC, Parashar UD, Costello A, Heyderman RS, **French N**, Atherly D, **Cunliffe NA**. Cost-effectiveness of monovalent rotavirus vaccination of infants in Malawi: A post-introduction analysis using individual patient-level costing data. Clinical Infectious Diseases.2016; 62:S220-8. DOI: 10.1093/cid/civ1025 Citations: 22 Altmetric Score: 3

3.4. **Bar-Zeev N**, Kapanda L, Tate JE, **Jere KC**, **Iturriza-Gomara M**, Nakagomi O, Mwansambo C, Costello A, Parashar UD, Heyderman RS, **French N**, **Cunliffe NA**. Impact and effectiveness of monovalent rotavirus vaccine following programmatic roll-out among infants in Malawi. The Lancet Infectious Diseases. 2015; 15:422-8. DOI: 10.1016/S1473-3099(14)71060-6 Citations: 99 Altmetric Score: 28

3.5. 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. The New England Journal of Medicine. 2010; 362:289-98. * co-primary authors. DOI: 10.1056/NEJMoa0904797 Citations: 601 Altmetric Score: 23

3.6. Soares-Weiser K, Bergman H, Henschke N, Pitan F, **Cunliffe NA**. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2019 Mar 25;3:CD008521. doi: 10.1002/14651858.CD008521.pub4. Citations: 5 Altmetric Score: 25

4. Details of the impact

Part I: Context and impact of rotavirus vaccination in Malawi

Rotavirus is the leading cause of severe paediatric gastroenteritis with the largest number of rotavirus deaths occurring in sub-Saharan Africa, estimated at 121,000 deaths in 2013[5.1]. A WHO recommendation informed by UoL research led to support from Gavi, The Vaccine Alliance, for countries in Africa to introduce rotavirus vaccine into their immunisation programmes.

Rotavirus vaccination was introduced into Malawi's EPI schedule in 2012 resulting in immunization coverage of 81% among one-year-olds by 2013, increasing to 90% subsequently[5.2]. Vaccine rollout was informed by UoL's research findings and UoL representation on the Malawi National Immunization Technical Advisory Group (NITAG), which advises Malawi's Ministry of Health on all matters relating to vaccination in the country. Since August 2013, the program in Malawi (Under 5 population of 2,600,000) is estimated to have averted 359,100 cases of rotavirus gastroenteritis, 27,300 inpatient admissions, 1,505 deaths, and 47,600 disability-adjusted-life-years (DALYs) [derived pro-rata from estimates for the 20 year period following introduction[3.3]]. Over 20 years, the societal cost per DALY averted was estimated to be USD10 (05-2016), and the cost per rotavirus case averted was USD1 (05-2016)[3.3]. This economic evaluation of a typical African national immunisation program has encouraged vaccine introduction across additional African countries and helped to sustain commitments to enable continued vaccination.[5.3, 5.2, 5.4]

Part II: Impact across Africa

National rotavirus vaccination programs have been introduced in 38 of the 54 African countries,[5.5] preventing an estimated 24,200 deaths among children younger than 5 years in sub-Saharan Africa in 2016 alone[5.3]. Based on immunisation coverage between 2013 and 2020[5.2], the 2016 data allow estimation of the impact of these programs; since August 2013, 169,400 lives were saved across Africa, and approximately 40,400,000 cases of rotavirus gastroenteritis, 3,070,000 inpatient admissions and 5,360,000 DALYs were averted[5.3]. National data also report substantial reductions in hospitalisations due to diarrhoea following introduction of vaccine programs; for example, within two years of vaccine introduction, Zambia experienced 51% and 31% reductions in rotavirus hospitalizations for infants and over one-year olds, respectively[5.4]. In Botswana, there were 43% and 48% reductions in gastroenteritis-related hospitalizations and deaths in infants during the rotavirus season, respectively[5.4]. Likewise, Togo saw impressive results in the first rotavirus season post-introduction: 43% reduction in rotavirus hospitalizations for infants[5.4]. As these countries graduate from Gavi support they will need to self-finance continued vaccine use, highlighting the importance of demonstrating programmatic impact.

Part III: Informing ongoing policy and adoption of vaccination programs

The public health impact of rotavirus vaccination has been felt in Malawi and across Sub-Saharan Africa. This has been communicated by UoL through annual workshops held with the Ministry of Health in Malawi between 2010 and 2016. UoL disseminated research findings to the general public in Malawi across a wide range of media outlets including newspaper reports, national radio (Malawi Broadcasting Corporation Radio 2, Times Radio) and television (Malawi Broadcasting Corporation TV and Mibawa TV), with live phone-in

programmes to inform the public on the benefits of using rotavirus vaccines[5.7]. The success in Malawi has been highlighted by international press[5.8] including The Guardian (print readership: 867,000; circulation: 152,714) running the headline ' "Tipping point" hope as vaccine slashes infant deaths in Malawi' in response to the 2018 Lancet Global Health paper[3.1]. UoL's ground-breaking rotavirus research programme was highlighted by Universities UK[5.9].

Dissemination of findings relating to impact, safety, and cost-effectiveness of rotavirus vaccination from Malawi as a representative low-income African country has informed vaccine introduction more widely. Thus, UoL organized the 11th African Rotavirus Scientific Symposium in 2017, advocating vaccine use across the continent, which attracted over 300 delegates including Ministry of Health representatives of 40 African countries[5.5]. Three African countries that were represented at this meeting subsequently introduced rotavirus vaccine. The findings from Malawi have been promoted by the RotaCouncil, an International Rotavirus Advocacy Group of Experts of which Professor Nigel Cunliffe is a member[5.6]. Since 2015, most African countries that have introduced rotavirus vaccine have observed an increase in vaccine coverage, with average uptake increasing from 77% to 84% by 2018[5.2]. In addition, the evidence of vaccine impact from Malawi is being used in negotiations for introduction in new countries such as the Democratic Republic of Congo, which introduced rotavirus vaccine into their immunisation program in October 2019[5.6].

A Cochrane review led by Professor Cunliffe further validated the efficacy of rotavirus vaccination with no increased adverse risk, supporting the WHO recommended vaccination schedule in Africa[3.6]. A recent unpublished update (requested by WHO) of rotavirus vaccine effectiveness and safety, and containing expert input from Professor Cunliffe and Dr Hungerford, is being used as evidence in a pending reinforced WHO rotavirus vaccine recommendation (expected in 2020 but delayed by COVID-19).

Part IV: Conclusion

A range of independent sources have validated the UoL findings, demonstrating consistently reduced hospitalisations since the introduction of rotavirus vaccination programs, resulting in a reduction of 169,400 deaths across Africa during the between 2013 and 2020[5.3]. These benefits are expected to be sustained through continued vaccine use.

5. Sources to corroborate the impact

5.1 Jacqueline E. Tate, Anthony H. Burton, Cynthia Boschi-Pinto, and Umesh D. Parashar. Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000–2013. Clinical Infectious Diseases. 2016;62(S2):pp. S96–105. (See p.97 'Results', paragraph 2, line 6 for 121,000 figure)

5.2 World Health Organization Data Repository: Rotavirus immunisation coverage estimates by country. http://apps.who.int/gho/data/view.main.ROTACv?lang=en (re. Immunisation coverage see p.2, 'Malawi' row of the table; re. vaccine introduction across additional African countries and continued vaccination sub-Saharan countries see blue and green highlighted rows)

5.3 Christopher Troeger; Ibrahim A. Khalil; Puja C. Rao; Shujin Cao; Brigette F. Blacker; Tahmeed Ahmed; George Armah; Julie E. Bines; Thomas G. Brewer; Danny V. Colombara; Gagandeep Kang; Beth D. Kirkpatrick; Carl D. Kirkwood; Jason M.Mwenda; Umesh D. Parashar; William A. Petri Jr; Mark S. Riddle; A. Duncan Steele; Robert L. Thompson; Judd L.Walson; JohnW. Sanders; Ali H. Mokdad; Christopher J. L. Murray; Simon I. Hay; Robert C. Reiner Jr. Rotavirus Vaccination and the Global Burden of Rotavirus Diarrhea Among Children Younger Than 5 Years. JAMA Pediatrics October 2018 Volume 172, Number 10 pp -965. doi:10.1001/jamapediatrics.2018.1960 (re. Part I: see for example conclusion; Part II: see p.961, last paragraph; re. Part II)

5.4 RotaCouncil – Rotavirus Vaccine Africa Factsheet 2016 http://rotacouncil.org/wp-content/uploads/2016/10/Rotavirus-Vaccine-Africa-Factsheet-Oct-2016.pdf (Bar-Zeev et al paper (3.3 above) is reference 25. It is cited in 5.3 to illustrate 'Projected health and economic impact of rotavirus vaccine implementation'; re. Zambia, Botswana and Togo figures see p.2 'Rotavirus vaccines demonstrate substantial impact in Africa')

5.5 Mwenda JM, Mandomando I, Jere KC, Cunliffe NA, Steele AD. Evidence of reduction of rotavirus diarrheal disease after rotavirus vaccine introduction in national immunization programs in the African countries: Report of the 11th African rotavirus symposium held in Lilongwe, Malawi. Vaccine. Volume 37, Issue 23, 2019, Pages 2975-2981. (See Fig 1, p2976 'Status of Rotavirus vaccine introduction in Africa')

5.6 Rotacouncil.
Global rotavirus vaccine introduction status:
http://rotacouncil.org/vaccine-introduction/global-introduction-status/

Impact of Professor Cunliffe's work in informing WHO global vaccine recommendation:
https://rotacouncil.org/about/advisors/nigel-cunliffe/

5.7 Mixed media sources. These include Lancet Global Health Publication Dissemination. Media coverage report. 27 August 2018. (Dissemination to Malawi general public see under 'Malawi' p.1)

5.8 International press examples including the Guardian 14/08/2018

5.9 Universities UK 'Made at Uni' recognition
https://madeatuni.org.uk/university-liverpool/rotavirus-vaccine
https://www.universitiesuk.ac.uk/facts-and-stats/impact-higher-education/Documents/made-at-uni-breakthroughs.pdf (p.20)