Institution: University of Oxford		
Unit of Assessment: 1 – Clinical Medicine		
Title of case study: Typhoid vaccine introduction improves childhood health and disease control		
Period when the underpinning research was undertaken: 2011-2019		
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:**
Professor Andrew Pollard	Professor of Paediatric Infection and Immunity	2001 - Present
Professor Brian Angus	Professor in Infectious Disease	2000 - Present
Dr Merryn Voysey	Lead Statistician at the Oxford Vaccine Group	2013 - Present
Period when the claimed impact occurred: October 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Researchers at the University of Oxford developed a human typhoid challenge model, results from which accelerated the approval of the first commercially available typhoid Vi-conjugate vaccine (TCV) and led to the World Health Organisation (WHO) global recommendation on the use of this TCV for all children from 9 months to 15 years of age in areas with high typhoid transmission. This catalysed release of USD85,000,000 funding by the Global Alliance for Vaccines and Immunisation (Gavi) for low-income countries purchase and introduce the vaccine, leading to mass vaccination programmes in Pakistan (10,000,000 children) and Zimbabwe (318,000 children) in 2019. An interim analysis of an Oxford-led trial of TCV in Nepal, involving 20,000 children, has shown vaccine efficacy of 82%. Burden of disease studies lead by Oxford in Nepal supported national government policy development on typhoid control.

2. Underpinning research

In 2011, the licensed typhoid vaccines were either not immunogenic in early childhood or unsuitable for administration in children younger than 5 years. In order to accelerate typhoid vaccine introduction for children, researchers at the University of Oxford led by Professor Andrew Pollard developed a new outpatient human challenge model for typhoid infection in volunteers in Oxford [1], the first such human challenge model since 1974. Updating these studies involved changing the method of administration and combining modern molecular techniques with microbiology and immunology. The research identified that a dose of 10,000 bacteria resulted in experimental infection in two thirds of volunteers who drank a suspension of *Salmonella typhi* in a bicarbonate solution [1].

A programme of typhoid and paratyphoid challenge studies was established in 2011 and since then over 400 volunteers have been challenged in six studies in Oxford. Pollard and Angus used the model to understand the biology of typhoid infection and provide new data on diagnostics, immunity and pathogenesis in a series of papers that provide insight into the human challenge model use, including important negative data on a live attenuated oral vaccine candidate and the potential of a monoclonal antibody.

In one study, the research showed that typhoid toxin does not play a role in *S.*Typhi infection or the development of early typhoid fever symptoms [2]. The human challenge model was used to

evaluate two TCVs. To test vaccine efficacy, volunteers were vaccinated with a new vaccine or control and then deliberately infected/ "challenged" with *S.* Typhi to test vaccine efficacy one month later [3]. In a key study, published in the Lancet, a new typhoid conjugate vaccine (Typbar-TCV, developed by pharmaceutical company Bharat Biotech) was evaluated using the human challenge model and showed that the vaccine had 54% and 87% efficacy (for two definitions of typhoid fever used in field studies) [3]. The research also showed in the human challenge model that the vaccine reduced shedding of the bacteria, implying that in the field it would reduce transmission, protecting both the vaccinated and unvaccinated children in the community.

Pollard subsequently led large-scale studies of the burden of typhoid in Nepal (with Basnyat, Director of the Oxford University Clinical Research Unit (OUCRU) in Nepal, and other Oxford colleagues), Bangladesh and Malawi, involving in total 300,000 people [4]. This research provided information on the global burden of this disease, which is important for WHO and in-country decision-making on vaccine use. Pollard and other University of Oxford researchers also lead or are part of ongoing field vaccine safety and efficacy trials involving vaccination of over 80,000 children in Nepal, Bangladesh and Malawi, and interim analysis of 20,000 children in Nepal showed that the TCV provided 82% efficacy [5]. This trial is ongoing as of 2020.

Furthermore, the Pollard group have also prepared a serum standard for typhoid conjugate vaccines by vaccinating volunteers and then storing large volumes of pooled serum for freeze-drying. The pool was evaluated in collaboration with the National Institute for Biological Standards and Control (NIBSC) for potency, as described [6], and is now held at the NIBSC and is made available for vaccine development and evaluation.

3. References to the research (University of Oxford authors in bold)

1. **Waddington CS**, **Darton TC**, **Jones C**, **Haworth K**, **Peters A**, **John T**, **Thompson BA**, **Kerridge SA**, Kingsley RA, **Zhou L**, Holt KE, **Yu LM**, Lockhart S, **Farrar JJ**, **Sztein MB**, Dougan G, **Angus B**, Levine MM, **Pollard AJ** (May 2014). An outpatient, ambulant-design, controlled human infection model using escalating doses of Salmonella Typhi challenge delivered in sodium bicarbonate solution. *Clin Infect Dis.* 58(9):1230-40. DOI: 10.1093/cid/ciu078
2. **Gibani MM**, **Jones E**, **Barton A**, **Jin C**, **Meek J**, **Camara S**, **Galal U**, Heinz E, Rosenberg-Hasson Y, Obermoser G, **Jones C**, **Campbell D**, **Black C**, **Thomaides-Brears H**, **Darlow C**, **Dold C**, **Silva-Reyes L**, **Blackwell L**, Lara-Tejero M, Jiao X, Stack G, **Blohmke CJ**, **Hill J**, **Angus B**, Dougan G, Galán J, **Pollard AJ** (July 2019). Investigation of the role of typhoid toxin in acute typhoid fever in a human challenge model. *Nat Med.* 25(7):1082-1088. DOI: 10.1038/s41591-019-0505-4
3. **Jin C**, **Gibani MM, Moore M**, **Juel HB, Jones E**, **Meiring J**, **Harris V**, **Gardner J**, **Nebykova A**, **Kerridge SA**, **Hill J**, **Thomaides-Brears H**, **Blohmke CJ**, **Yu LM**, **Angus B**, **Pollard AJ.** (December 2017). Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet.* 390(10111):2472-2480. DOI: 10.1016/S0140-6736(17)32149-9
4. **Darton TC**, **Meiring JE**, **Tonks S**, Khan MA, Khanam F, **Shakya M**, Thindwa D, **Baker S**, **Basnyat B**, Clemens JD, Dougan G, **Dolecek C**, Dunstan SJ, Gordon MA, Heyderman RS, Holt KE, Pitzer VE, Qadri F, Zaman K, **Pollard AJ**; STRATAA Study Consortium (2 July 2017). The STRATAA study protocol: a programme to assess the burden of enteric fever in Bangladesh, Malawi and Nepal using prospective population census, passive surveillance, serological studies and healthcare utilisation surveys. *BMJ Open.* 7(6):e016283. DOI: 10.1136/bmjopen-2017-016283
5. **Shakya M**, **Colin-Jones R**, **Theiss-Nyland K**, **Voysey M**, Pant D, **Smith N**, **Liu X**, **Tonks S**, **Mazur O**, **Farooq YG**, **Clarke J**, **Hill J**, Adhikari A, **Dongol S**, **Karkey A**, Bajracharya B, **Kelly S**, Gurung M, Baker S, Neuzil KM, Shrestha S, **Basnyat B**, **Pollard A**, Tyvac Nepal Study Team (5 December 2019). Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine in Nepal. *New England Journal of Medicine.*381(23):2209-2218. DOI: 10.1056/NEJMoa1905047

6. Rijpkema S, Hockley J, Logan A, Rigsby P, Atkinson E, **Jin C**, Goldblatt D, Liang H, Bachtiar NS, Yang JS, Goel A, Ramasamy V, Pasetti MF, **Pollard AJ**; anti-Vi IgG working group (November 2018). Establishment of the first International Standard for human anti-typhoid capsular Vi polysaccharide IgG. *Biologicals.* 56:29-38. DOI: 10.1016/j.biologicals.2018.09.001

Funding for this work has included multiple grants since 2016 from the **Bill & Melinda Gates Foundation** (OPP1145952, USD505,702, for serum standard; OPP1141321, USD4,509,305 for enteric fever; OPP1151153, GBP5,928,918 to Oxford, led by U.Maryland, for accelerating availability and access to typhoid conjugate vaccines); a Strategic Award from the **Wellcome Trust**, 'A strategic vision to drive the control of enteric fever through vaccination', 2016-2021 (106158/Z/14/Z, GBP3,642,873); and a component of the **FP7-HEALTH** collaboration 'Advanced Immunization Technologies' (ADITEC, EUR1,590,324 to Oxford).

4. Details of the impact

Typhoid fever is a systemic infection caused by *Salmonella* Typhi, usually through ingestion of contaminated food or water. Between 11,000,000 and 21,000,000 cases and 128,000 to 161,000 typhoid-related deaths occur annually worldwide. While provision of clean water and improved sanitation could control the disease, the engineering works required to do this across low- and middle-income countries cannot be achieved quickly. Vaccines therefore offer early impact on disease while definitive investment in infrastructure is awaited. However, lack of licensed vaccines suitable for administration to children younger than five years had stalled progress towards introduction and there was no investment in the expensive field trials to help build confidence by demonstrating impact. University of Oxford researchers, under the leadership of Pollard, Angus and Basnyat, undertook key research to address this challenge. They then joined a partnership between the University of Maryland School of Medicine and PATH (an international global health non-profit organisation) to aid Gavi (Global Alliance for Vaccines and Immunisation) eligible countries in accelerating introduction of typhoid vaccines for children between 6 months and 15 years old.

Development, regulatory approval and deployment of TCVs

The new typhoid conjugate vaccines had the potential to overcome many of the challenges that impeded uptake of earlier vaccines, including longer-lasting protection, fewer doses, and suitability for children younger than two years of age, allowing for inclusion in routine childhood immunisation programmes. However, they needed to be tested in a safe and ethical way. Conducting human challenge studies, where volunteers received an infection with a live pathogen, required the team to overcome many challenges to meet modern manufacturing, regulatory, safety and ethical standards. The development of the human challenge model of typhoid infection informed the WHO guidelines on development of new typhoid conjugate vaccines, and was prioritised by the 64th meeting of the WHO Expert Committee on Biological Standardization, 21-25 October 2013 [A]. These guidelines were made available for all manufacturers developing new vaccines for the disease.

The efficacy data on the new typhoid conjugate vaccine Typbar-TCV from the human challenge study conducted by the University of Oxford in 2016 proving a protective efficacy of 54%-87% against typhoid [3], were requested by the WHO as evidence in the prequalification of Typbar-TCV. Prequalification enabled procurement by UNICEF, Pan-American Health Organisation and Gavi. The WHO's SAGE recommendations and the prequalification of Typbar-TCV directly supported the decision by Gavi to release USD85,000,000 to support countries roll out typhoid vaccine, announced in early 2018 [B].

Learning that an approach is unlikely to be effective is important as it avoids wasted resources. Observations on the role of typhoid toxin in invasion study [2] following development of the human challenge model [1] halted further development of therapeutic monoclonal antibodies using typhoid toxin as a target and experimental vaccines based on the toxin.

Having established the human challenge model, Pollard then took the opportunity to use these volunteers' donated blood to develop a serum standard for typhoid conjugate vaccines [6], which

was approved by WHOs Expert Committee on Biological Standardisation (ECBS) for all manufacturers developing typhoid conjugate vaccines [C]. This is a biological reference material vital for international standardisation of vaccine development comparisons and immunogenicity studies. As of 14 December 2020, the NIBSC have sold 232 vials of the standard.

Health benefits through vaccination use

Field trial participants: Field trials of the Typbar-TCV were conducted in Malawi (28,000 children), Bangladesh (32,500 children) and Nepal (20,000 children). In August 2018, interim study results from the 20,000 participants aged 9 months to 15 years vaccinated in Nepal demonstrated an efficacy rate of 82% [5], and thus it can be estimated from the data that in a trial population of 80,000 vaccinated children, this should result in a reduction of 200 cases of typhoid fever per year.

Mass adoption: 2018 was the first year in which countries could apply for Gavi support for purchase and delivery of typhoid vaccines for children between 6 months and 15 years old, with the first routine immunisations taking place in 2019 [D]. Zimbabwe carried out a Gavi-funded mass Typbar-TCV vaccination campaign between February and March 2019 that targeted 318,000 children in communities affected by an ongoing typhoid outbreak in Harare [E]. A two-week vaccination campaign, targeting 10,000,000 children of 9 months to 15 years old in urban areas of the Sindh province in Pakistan with Typbar-TCV, took place in late 2019 [F], the beginning of Pakistan's introduction of the vaccine into their routine immunisation programme.

Routine immunisation: Though previously thought to be at low risk of typhoid, when it was discovered that under 3 year olds were at risk, there were concerns about how to best protect them, specifically as this age group respond less well to the previous vaccines and more to the newer conjugate vaccines. This age group is difficult to study as testing vaccines for young children requires prior testing in adults. Developing a way to test the conjugate vaccine for efficacy quickly, using the human typhoid challenge model [1, 3] was a crucial step. Following on from Pakistan's introduction of the vaccine in to their routine immunisation programme at the end of 2019, Liberia and Zimbabwe also approved the introduction of TCV into their routine childhood immunisation programmes (implementation was due to take place in 2020 but was delayed to 2021 due to COVID) [F].

Combating antimicrobial resistance

Vaccine rollout was given additional impetus due to the increasing problem of antimicrobial resistance, meaning in some areas typhoid had become untreatable with antibiotics. This was particularly a problem in the Sindh province of Pakistan where the Pakistan Health Authorities documented the outbreak of typhoid fever cases citing 5,274 cases of extremely drug resistant typhoid of a total of 8,188 typhoid fever cases (2016 - 2018). The vaccine efficacy data [3], amongst other University of Oxford research, is cited in the WHO position and background papers on the use of typhoid vaccines to combat resistance [Gi]. Following presentation of the interim field trial results in Nepal [5], the administration of Typbar-TCV to 10,000,000 children (detailed above) in Pakistan was approved on an emergency basis in 2019. The vaccine was specifically used here to contain the disease, due to widespread antimicrobial resistance of *S.* Typhi against ceftriaxone [H], one of the most commonly used antibiotics against typhoid fever. The impact of this effective vaccine in the control of antimicrobial resistance has been shown to be crucial, as already evidenced by the number of cases halving in areas of Pakistan following vaccination [I] (formal evidence from Pakistan delayed publishing due to COVID).

WHO recommendation for programmatic use of typhoid vaccines

Vaccine efficacy and safety data generated in the human challenge model were used to support the 2018 WHO Strategic Advisory Group of Experts on Immunisation (SAGE) global policy recommendations for TCVs [Gi]. The policy references utilising the human challenge model ([3] and two additional University of Oxford publications), in the section on Immunogenicity, efficacy and effectiveness of the TCV. This policy recommended that the vaccine is used in all high burden areas from 9 months to 15 years of age. University of Oxford research is extensively referenced in the background papers [Gii] and guidance [1, 3 and three additional University of Oxford publications] as it provided the only efficacy data available at the time the recommendations were made. Furthermore, the safety data from Oxford-led field trials in Nepal [5] were referenced in WHO Global Advisory Committee on Vaccine Safety's review of typhoid vaccines [J].

Supporting national government policy development on typhoid control

Age-stratified data on clinical and sub-clinical disease burden is important for countries to decide whether to prioritise vaccine introduction. Pollard led large-scale studies of the burden of typhoid in Bangladesh, Malawi and Nepal to inform the respective Governments on the priority of typhoid control [4]. For example, Pollard has been working in Nepal with Gavi and PATH [Ki] and has engaged with the Nepal Government to support introduction of TCV in Nepal's routine immunisation. Following discussion of the surveillance study [4] and human challenge model data [2], in 2017 the National Committee on Immunization Practices recommended "*the need for typhoid vaccine studies to be conducted in Nepal, and in the view of the huge burden of disease, Nepal should be an early adopter of typhoid conjugate vaccine once funding is available*" [Kii].

5. Sources to corroborate the impact

A: WHO guidelines on the quality, safety and efficacy of typhoid conjugate vaccines, 2013 (p34 refers to the use of the human challenge model to support vaccine development)

B: Gavi press release 3 April 2018: New typhoid vaccine to receive Gavi support. Available from https://www.gavi.org/library/news/statements/2018/new-typhoid-vaccine-to-receive-gavi-support/

C: WHO Expert Committee on Biological Standardization 2018. Lists approved serum standard with reference to the generation of the standard in Oxford volunteers (p72)

D. (i) Gavi annual progress report 2018 and (ii) Gavi annual progress report 2019, describing the role out of TVC administration in Pakistan, Zimbabwe and Liberia

E: Journal article: Olaru ID et al., Typhoid Vi-conjugate vaccine for outbreak control in Zimbabwe, *The Lancet Infectious Diseases* 2019, 19 (9): 930. DOI: 10.1016/S1473-3099(19)30425-6

F. Gavi press release 15 November 2019: Pakistan becomes first country to introduce new typhoid vaccine into routine immunisation programme. Available from https://www.gavi.org/news/media-room/pakistan-becomes-first-country-introduce-new-typhoid-vaccine-routine-immunisation

G: (i) WHO Typhoid Vaccines Position paper - March 2018 (section on TCV efficacy on page 161-2 of WHO policy recommendations);
(ii) WHO SAGE background paper on typhoid vaccine policy recommendations, September 2017 (p16 for antimicrobial resistance and p43 onwards for human challenge model)

H: Journal article: Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively Drug-Resistant Typhoid - Are Conjugate Vaccines Arriving Just in Time? The New England Journal of Medicine 2018; 379(16): 1493-5. DOI: 10.1056/NEJMp1803926

I: Corroborator 1: Associate Professor, Pediatric Infectious Disease, Aga Khan University, Karachi, Pakistan

J: WHO Global Advisory Committee on Vaccine Safety's review of typhoid vaccines (p46)

K: (i) Testimonial letter from Director of Vaccine Introduction and Impact at PATH detailing the contribution of Pollard's research, advice and other inputs to the outcome of Gavi approving support for TCV administration in Nepal, December 2020;
(ii) Minutes from March 2017 meeting of the National Committee on Immunisation Practices, Nepal, including presentation by Basnyat and Pollard on 'Studying the impact of the Vi-conjugate vaccine for typhoid fever and the road to its implementation' (p6-8).