CHALLENGING TIMES

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While we anticipate good health for our children, living as we do in one of the wealthiest nations of the world in the 21st Century, this wasn't always the case. At the foundation of Leicester Literary and Philosophical Society in the 19th Century, there was a huge burden of infectious diseases driving high levels of child morbidity and mortality and typhoid was much feared at that time and would have been familiar to George Shaw, one of the Founders of the Society. Sadly, still today, among regions of the world with poor infrastructure, typhoid remains one of the most commonly identified bacterial infections in childhood. Developments in vaccine prevention, supported by our research efforts, are set to fight the disease and improve the quality of childhood among some of the world's most vulnerable children.

William ("Willie") Wallace Lincoln died on 20th February 1862 at the age of 11 years after he and his brother, Tad, became unwell with a fever. Thomas ("Tad") died 9 years later of heart failure at the age of 18 and another sibling, Edward, died of tuberculosis at the age of 4 in 1850. Only one of the 4 siblings, Robert, survived to adulthood. We would probably not know the story of this tragic family, even though it is by no means an unusual one for the time, if their father had not been such a prominent figure of the time who was responsible for shaping the future of the United States. Their parents were Abraham and Mary Lincoln, and it is said that they developed "melancholy" after Willie died, which we would now know as clinical depression. Three years later the pair attempted to emerge from their sadness and took a trip to Ford's Theatre to watch the farce "Our American Cousin", best known as being the play at which the President was assassinated by the confederate sympathiser, John Wilkes Booth. The White House drew its water from the Potomac River, which became contaminated with sewage from a military camp on its shores, and it is thought that this was the source of the typhoid which killed poor Willie[a].

Here in England, at almost the same time, Prince Albert is widely believed to have succumbed to typhoid in 1861 at Windsor Castle, a death which had a profound effect on his wife, Queen Victoria[(1)]. Although in neither case can we be certain that typhoid was the cause, as modern microbiological identification was not available, the symptoms are consistent, and the disease was common. The Physician in Ordinary to the Prince of Wales, Sir William Jenner, attended to Albert and his analysis of the case is as reliable as is possible in view of his expertise on the disease, exemplified by the treatise "*On the Identity or Non-Identity of Typhoid and Typhus Fever*" which he wrote and which was published in 1850[(2)].

Such stories were commonplace in the mid 19th Century because of the poor quality of drinking water and inadequate sanitation. Indeed, it is highly likely that the founder of Leicester Literary and Philosophical Society in 1835, my ancestor, George Shaw, would have been very familiar with the disease, and may even have been thinking of such cases during his presidential address in 1838 entitled "*The moral and physical condition of the working classes*".

While the disease is now largely unknown in developed countries, except among travellers, as a result of accessibility of clean water, flush toilets and well-maintained sewage systems, there is a huge burden in the developing world, with 14 million cases still thought to occur each year[(3)].

Typhoid is a disease which presents with various non-specific features including fever, malaise, abdominal pain, an enlarged liver and spleen, constipation (can be diarrhoea in children), a rash (Rose spots) and fits or coma in severe cases, with onset about

5-15 days after ingestion of contaminated food or water[4]. The bacteria, *Salmonella* typhi ("typhoid") and Paratyphi ("paratyphoid"), collectively cause the syndrome of "enteric fever". Deaths are particularly associated with severe inflammation in the gut resulting in intestinal perforation several weeks after disease onset. Before antibiotics became available up to 20% of those who were infected would die, but this is thought to be around 1% today with the use of antibiotics. However, some recent evidence from emerging economies indicates that availability of antibiotics has a profound impact on deaths from the disease, but only improvement in water and sanitation, which is harder to achieve, will result in a reduction in cases[5].

Perhaps the most famous typhoid case is Mary Fallon, an Irish cook in New York who became known as "Typhoid Mary"[1]. She developed chronic carriage of typhoid, which is thought to occur in up to 3% of individuals who have the acute infection. Such individuals continue to shed large amounts of the bacteria in their faeces after recovery from the initial infection, as a result of gall bladder carriage of the bacteria, and can infect others readily if they have poor personal hygiene. Mary infected 53 individuals, with 3 deaths, while working as a cook at the turn of the 1900s and was imprisoned for 3 years as a public health measure. Despite assuring the authorities that she would avoid food-handling, she went back to work as a cook, when she was released and further cases led to her arrest and incarceration for the next 23 years until her death. Treatment with powerful antibiotics today can prevent the onset of chronic carriage.

Sadly, individuals living in many regions of the world, particularly in low income countries, have access only to poor quality water and inadequate or absent formal sanitation. Most of the global typhoid burden is in South Asia and sub-Saharan Africa[3], and children are especially vulnerable to the disease. To make matters worse, many of the strains of the typhoid bacteria are resistant to antibiotics, and these resistant strains have spread around the world, threatening new populations[6]. A recent outbreak in Pakistan is nearly untreatable[7]. In such a setting, vaccination has the potential to prevent infection in the first place, thereby improving the health of the population and reducing the spread of antibiotic-resistant bacteria.

Until recently there were only 2 licensed typhoid vaccines but neither was suitable for the youngest children in these populations and this hampered policy changes aimed at controlling the disease[4]. The live oral vaccine, Ty21a is given, mainly to travellers, as 3 capsules by mouth provides moderate protection, but the large capsules are not appropriate for most children[8]. An injectable vaccine, made from the polysaccharide capsule (sugar coating) of the bacteria, has been available for decades and has been the most widely used vaccine for travellers, providing protection for several years after vaccination. However, the immature immune system of children under 2 years of age, cannot respond to this vaccine and so it has not been adopted by policymakers for widespread use. Fortunately, a new generation of vaccines, the protein-polysaccharide conjugate vaccines, in which the polysaccharide from the bacterial capsule is chemically conjugated to a protein carrier, have been developed, and can induce immune responses from early infancy. These vaccines have the additional advantage that they induce memory in the immune system, resulting in booster responses, even many years later. One of these vaccines was developed in India[9], and there was good evidence that it induced strong immune responses, but there were no studies which showed that it actually prevented the disease.

To accelerate vaccine development, carefully controlled human challenge models are being used for many different diseases. In these models, volunteers are deliberately infected with bacteria or viruses (or even worms), with the aim of using infection studies in humans to assess rapidly new vaccines and antibiotics. In 2011 we obtained funding from the Wellcome Trust to develop such a model in Oxford for *Salmonella* typhi with the aim of accelerating typhoid vaccine development. In our studies to develop the model, volunteers aged 18- 60, drink 10,000 typhoid bacteria in a bicarbonate solution after fully informed consent, and about 65% will go on to develop the typical disease[10]. After setting up the model we were able to gain very detailed insight into the biology of the disease in such a controlled environment and made new observations about the early development of the disease, novel diagnostics and the consequences of infection[11-13]. All of our volunteers are treated with antibiotics within 12 hours of onset of enteric fever symptoms.

To test the new conjugate vaccine from India, funded by the Bill & Melinda Gates Foundation, we vaccinated 112 volunteers in Oxford either with a typhoid vaccine or a control vaccine (which provides no protection against typhoid) and then asked them to drink the typhoid bacteria one month later. We then monitored them closely over the next 2 weeks to see if there was any protection. We were able to show a vaccine efficacy (protection) of 54% (95% confidence intervals 27-72) using the model and were confident that this would translate to higher levels of protection in the field, since the human challenge model is a very stringent test of vaccine efficacy (gastric acid neutralized, high dose of bacteria, daily testing of the blood for infection)[14]. We also showed a very strong immune response with the new vaccine and have started to identify new potential correlates of protection which can be used in future studies to predict how well the vaccine might work in different populations. Importantly, vaccination reduced shedding of the bacteria during the infection, which means that the number of cases would likely reduce considerably in a vaccinated population as spread to unvaccinated individuals would also likely decrease[15]. The data from this study in 2017, were used to drive some critical steps in the process for the vaccine to become available for those in greatest need. The vaccine was WHO prequalified (a stamp of approval on the product) and recommended for use in high burden countries for all children from 9 months to 15 years of age by the WHO vaccine policy committee, SAGE[16]. Finally, the Global Alliance for Vaccines and Immunisation released $85 million of funding to support country introductions of the vaccine[17].

To try and provide new evidence to support country introduction, my team in Oxford has now been awarded $36 million dollars in funding from the Bill & Melinda Gates Foundation, in collaboration with the University of Maryland, to test the vaccine in children in Africa and Asia. Thus far we have vaccinated 100,000 children and early results indicate that the vaccine has led to a very substantial reduction in typhoid disease amongst our vaccinees [18].

Despite the high burden of typhoid and the worrying increase in antibiotic resistance that is emerging in these bacteria, we can be confident today, as a result of these pioneering studies, that we have the knowledge and tools to control the disease. In the next few decades, municipal engineering works that provide clean water and remove sewage effectively will control this disease, just as happened over the past century in England, if we can find the finance and political will for this important development. Until then, we have new vaccines that will ensure that families do not need to suffer the misery which was exemplified by the pain of loss experienced by the Lincolns and our own Queen Victoria.

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