Title: The elimination of typhoid: possibility or pipe dream?

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Abstract

The elimination of typhoid would have a substantial impact on the health of millions of people living in South and Southeast Asia and sub-Saharan Africa. Like many diseases before it, there are significant challenges to elimination, including access to safe drinking water and adequate sanitation practices, the availability of a vaccine, the identification and management of chronic carriers, and the emergence of antimicrobial resistance.

While provision of clean water and adequate sanitation must remain the ultimate goal, in the short term, required to cornerstone elimination in endemic areas, is an efficacious vaccine. Recent evidence of effectiveness with a tetanus-toxoid conjugate vaccine offers an opportunity for an immunogenic and safe vaccine able to be delivered to young children. Shown to be efficacious in Nepal, where infection is endemic, it may be a viable option in public health programs moving towards elimination.

Key Points

- Public health programs aiming to eliminate typhoid will need to include an immunogenic and efficacious vaccine, in addition to addressing water and sanitation practices in endemic areas, and the role of chronic carriers
- A tetanus-toxoid conjugated Vi polysaccharide typhoid vaccine (TCV) has been shown to be efficacious, immunogenic and safe when administered to children in endemic areas

Main text (1500 words, 12 references)

Typhoid and paratyphoid fevers are illnesses caused by the pathogen *Salmonella enterica* subspecies serovars Typhi and Paratyphi A, B and C (1). These infections, often collectively referred to as enteric fever, cause a spectrum of illness, which disproportionately affects children. Non-typhoidal *Salmonella* spp usually cause a diarrhoeal illness, with bacteremia a less common feature, except in Africa. By comparison, infection caused by typhoid and paratyphoid is primarily characterised by febrile bacteremic illness, with malaise and prolonged fever characteristic, complicated by septic shock, gastrointestinal bleeding with ileus and intestinal perforation, altered conscious state, and death (1, 2).

There were 14.3 million cases of typhoid and paratyphoid fever in 2017, with an estimated global case fatality of 0.95%. Age specific incidence rates are highest in children, and disease is endemic in South and Southeast Asia, and sub-Saharan Africa (3). The illness is a significant contributor to the global burden of disease, and its elimination would improve the health of many of the world's most vulnerable populations.

Disease elimination has been the goal of many public health campaigns over the last century. The elimination of a disease as a public health threat may fall between regional control and complete elimination. Historic successes with disease elimination are paralleled by failed campaigns and disease resurgence. The ability to eliminate a disease as a public health threat is dependent on being able to address all factors including disease transmission, case identification, effective treatment, disease reservoirs and vectors. The elimination of typhoid and paratyphoid fever has long been a pipe dream, with the lack of an immunogenic and efficacious vaccine compounded by factors such as the need for clean water and adequate sanitation, complicated further by the role of chronic disease carriers and the emergence of antimicrobial resistance.

Essential to the foundation of a typhoid elimination program is a vaccine for widespread distribution in endemic areas, which can be given to young children, in whom there is a high incidence of disease. Since the development of the first vaccine against typhoid fever in 1886 by Almroth Wright, vaccination has been thought to be a key player in the quest to eliminate typhoid. At the time of the development of this first vaccine, used by the British during the Boer War in South Africa, more soldiers were dying from infectious diseases including typhoid fever than due to armed combat. A British immunologist and bacteriologist, Wright recognised the value of preventative medicine, and foresaw the challenges antimicrobial resistance would pose in the absence of disease prevention.

More than a century has passed since Wright's pioneering efforts, however significant challenges have remained in the development of appropriate vaccines for young infants and children, of whom the disease disproportionately affects. Despite the World Health Organization (WHO) recommendation for the use of vaccines against typhoid (4), vaccine-based control programs are yet to be implemented widely. The broad use of typhoid vaccines in children has been limited by poor immunogenicity of the Vi polysaccharide vaccine and impractical vaccine delivery of the oral live attenuated Ty21a vaccine, being in capsule format, which is difficult for young children to swallow. Other vaccines, such as the prototype typhoid conjugate vaccine (TCV) Vi-rEPA have a demonstrated efficacy of over 90% in children aged 2-5 years but it has not reached commercial distribution (5).

The development of a tetanus-toxoid conjugated Vi polysaccharide typhoid vaccine (TCV) offers perhaps the first vaccine option to cornerstone the development of a typhoid elimination plan. Safety and immunogenicity in young children has been shown in a phase 3 safety and immunogenicity trial (5). A stringent human challenge trial in adults in a non-endemic area showed TCV to have a protective efficacy of 54.6% (95% CI, 26.8 to 71.8) (6). Vaccine confidence was bolstered further by the results of a recent randomised control trial in Nepal with over 20,000 participants, demonstrating a vaccine efficacy of 81.6%

(95% CI, 58.8 to 91.8; P<0.001) in children aged 9 months to 16 years. Trial participants were either administered TCV (intervention arm) or a capsular group A meningococcal conjugate vaccine (MenA) (control arm), with the primary outcome being typhoid fever confirmed on blood culture. Of the 10,005 participants in the intervention arm, only 7 developed blood culture-confirmed typhoid fever (79 cases per 100,000 person years) compared with 38 of 10,014 participants who received the MenA vaccine (428 cases per 100,000 person years). The TCV vaccine was found to be immunogenic with a study subgroup examining immunogenicity demonstrating a 99% seroconversion (at least a quadrupled Vi IgG level at 28 days post vaccination) in the TVC group compared with 2% in the MenA vaccine group (7). This finding is consistent with previous immunogenicity trials in India where seroconversion rates were over 90% in children and adults at day 42 post vaccination compared with baseline titres. Additionally, the TCV group demonstrated quadrupling of the anti-Vi antibody titre 2-5 times more frequently in comparison to the Vi polysaccharide vaccine group (5). A study examining adverse events following immunisation (AEFI) after mass vaccine rollout in Hyderabad, Pakistan in children aged 6 months to 10 years reported no serious AEFI in close to 200, 000 participants (8). Inclusion of an efficacious, immunogenic and safe conjugate vaccine such as TCV that can be given to young children may play a critical role in future elimination programs.

Regardless of vaccine success, typhoid and paratyphoid elimination will not be achieved without access to safe drinking water and adequate sanitation and sewage disposal. Typhoid and paratyphoid fever is caused by faecal-oral transmission via ingestion of contaminated water or food. Historical surveillance data suggest that the disease was previously endemic in North America and Western Europe (9). Decreases in global disease burden estimates of typhoid and paratyphoid fever between 1990 and 2017 have been partially attributed to economic development enabling infrastructure improvements in water supply and sanitation (3). In developed countries, safer food practices, modern sanitation and access to treated water has largely removed typhoid as a public health problem (9).

Further complicating the development of a typhoid elimination program is the presence of chronic disease carriers. Organisms belonging to *Salmonella enterica* subspecies have no known environmental reservoir, making the chronic, asymptomatic carrier state a pillar of the continued maintenance of the bacterium in humans (10). After the resolution of clinical infection, 2-5% of patients will progress to a chronic carrier state, failing to clear the infection within 1 year (11). Localization to the biliary tract and gallbladder occurs after a breach of the intestinal epithelial barrier and evasion of early innate immune-mediated killing (12). The bacteria persist in a biofilm on gallstones and the gallbladder epithelium. These chronic carriers intermittently shed bacteria in faeces for a prolonged period of time, maintaining a reservoir of infection. The ability to identify carriers is fraught with difficulty due to their asymptomatic disease state, contributing to

their propensity to cause outbreaks, particularly when involved with food handling. A number of *S*. Typhi antigens have been found to be immunoreactive in carriers and not in controls from endemic areas (10), however implementation of this diagnostic strategy remains impractical. Furthermore, even if the chronic carriers could be identified, treatment options remain fraught with cholecystectomy an unworkable solution and antibiotic therapy with fluoroquinolones lacking complete effectiveness, especially in the context of the emergence of drug-resistant *S*. Typhi.

In areas where the disease remains endemic, managing chronic carriage has less of a critical role in public health programs. However, in low-incidence settings, the identification of carriers, particularly those involved with food production will be an important strategy in moving towards elimination.

The emergence of drug resistance poses yet another challenge to disease elimination. Antimicrobial resistance in in *S.* Typhi has been emerging since the 1970's. In 2016, an outbreak of extensively drug-resistant (XDR) *Salmonella enterica* serovar Typhi in Pakistan's Sindh province emerged, demonstrating resistance to all first-line antimicrobials including third-generation cephalosporins (3). The outbreak remains a significant public health issue in the region, resulting in a TCV rollout aiming to immunise 10 million children aged between 9 months and 15 years of age in the Sindh province in November 2019. This is followed by plans to extend to other parts of the province and neighbouring regions prior to a national rollout in 2021.

The elimination of typhoid is shifting from a pipe dream towards a possibility with the development of a tetanus-toxoid conjugated Vi polysaccharide vaccine which is efficacious and immunogenic in children in an endemic region. Elimination methodologies will need to further progress water and sanitation practices in endemic areas such as South and Southeast Asia and sub-saharan Africa; with an anticipation of an early win, while awaiting improved water quality to drive decreases in infection rates similar to those previously experienced in Western Europe and North America. Eradicating chronic carriage in an era of evolving antimicrobial resistance will be a final barrier, with methodologies to identify asymptomatic cases and subsequent treatment still requiring further development.

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