Are we adequately prepared for the emergence of *Salmonella enterica* serovar Paratyphi A?

Typhoid fever is a life-threatening systemic disease caused by the bacterium *Salmonella enterica* serovar Typhi (*S* Typhi). Years of focused research have resulted in a detailed, but not complete, understanding of the disease caused by this organism. Diagnostics, host susceptibility, and vaccine responses need further research and investment, but recent technological advances in immunology and high-throughput genomics are providing new insights.[1,2] Indeed, the burden of typhoid fever might be falling in parts of Asia, and the potential introduction of Vi-polysaccharide-conjugate vaccines could reduce the burden even more.[3]

Other *Salmonella* serovars and pathovars also cause invasive disease in human beings, which can be difficult to distinguish clinically from typhoid. Invasive infections with *S enterica* serovars Typhimurium and Enteritidis in young children and also adults living with HIV in parts of sub-Saharan Africa have been reported.[4] However, *S enterica* serovar Paratyphi (*S* Paratyphi) A, the main alternative cause of typhoid-like infections in most of the world, has received little attention. This knowledge gap has the potential to become an Achilles' heel in the global battle against enteric (typhoid) fever.

At the turn of the millennium, *S* Paratyphi A caused about 20% of the global burden of enteric fever.[5] In many areas, this proportion has steadily increased. In Patan Hospital in Kathmandu, Nepal, standardised surveillance of blood cultures during the past 10 years has shown annual increases in the proportions of individuals with *S* Paratyphi A. More than two-thirds of the culture-confirmed cases of enteric fever are now caused by this serovar. Increases in the proportion of enteric fever cases caused by *S* Paratyphi A have also been reported in India, Pakistan, China, and Cambodia.[6] In some locations, the proportion of enteric fever caused by *S* Paratyphi A is now greater than that caused by *S* Typhi. There is a real threat that *S* Paratyphi A could replace *S* Typhi as the main global cause of enteric fever. Clinicians often believe that *S* Paratyphi A infections are less severe than are those caused by *S* Typhi. However, in the largest comparison to date,[7] no significant differences were shown between disease severity, duration, or outcomes for infection caused by these organisms.

Both pathogens are transmitted through the faecal-oral route by ingestion of contaminated food or water. Ingestion is followed by colonisation of the small intestine, invasion of the gastrointestinal mucosal surface, and dissemination throughout the body into the liver, spleen, and bone marrow. Crucially, *S* Typhi and *S* Paratyphi A infect only human beings, and no other *Salmonella* serovar entirely mimics the infection in other hosts. Much of the understanding of pathogenesis is derived from the mouse infection model of *S enterica* serovar Typhimurium, which does not adequately replicate human infection. The absence of a suitable animal model has impaired the ability of researchers to develop diagnostic tests that take into account the specific biology of host–pathogen interactions. Researchers, therefore, rely almost solely on specimens collected from patients infected with these pathogens to understand the disease and investigate immunological responses.

S Paratyphi A could have a large effect if Vi-polysaccharide-conjugate vaccines are introduced in Asia. The absence of the Vi-polysaccharide capsule in *S* Paratyphi A is the most important microbiological discrepancy between *S* Paratyphi A and *S* Typhi; vaccines based on Vi-polysaccharide do not provide any cross-serovar immunity. At present no vaccines specific to *S* Paratyphi A are available. Conjugate vaccines using the O antigen as the main immunological component are under development.[8] However, these vaccines are some way from being licensed and made available to use in endemic locations. Whether they will provide sufficient protective efficacy and herd immunity to be a cost-effective intervention for public health remains to be established.

In the absence of improvements in sanitation, clean water, and systematic vaccination, antimicrobial therapy for acute infection is the only intervention that can contribute to control of community transmission. Available data suggest that infections with *S* Typhi and *S* Paratyphi A both respond equally well to antimicrobials when the bacteria are susceptible.[9] Unfortunately, antimicrobial resistance in all invasive *Salmonella* species is a growing threat, and *S* Paratyphi A seems to have a greater propensity than does *S* Typhi to develop resistance

to antimicrobials.[10] Multidrug resistance and intermediate susceptibility to ciprofloxacin is common in *S* Paratyphi A, and full resistance to fluoroquinolones, azithromycin, and ceftriaxone is of increasing concern. The world is not prepared for the emergence of *S* Paratyphi A. Although many lessons from research into *S* Typhi are applicable to *S* Paratyphi A, this neglected but emergent pathogen is a global health issue that needs the urgent attention of the enteric-fever research community.

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