Journal of Infection (2014) 68, S38—S50

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

The challenge of enteric fever

Claire S. Waddington, Thomas C. Darton, Andrew J. Pollard*

Department of Paediatrics, University of Oxford, Children's Hospital, Oxford OX3 9DU, United Kingdom

Accepted 20 September 2013
Available online 8 October 2013

KEYWORDS
Enteric fever;
Typhoid;
Paratyphoid;
S. Typhi;
S. Paratyphi;
Controlled human infection;
Challenge studies;
Disease control;
Vaccine

Summary Enteric fever, a non-specific, systemic infection caused by *S.* Typhi or Paratyphi A, B or C, is common in resource-limited regions of the world, where poor sanitation infrastructure facilitates faeco-oral transmission. Prompt treatment with appropriate antibiotics minimises illness severity, but presentation to health care facilities is often delayed because of the non-specific nature of the symptoms and the lack of reliable diagnostic tests. Disease prevention requires significant investment in provision of clean water and sanitation in the long term; vaccination offers a more realistic strategy for medium term control. However, implementation of existing vaccines and development of more efficacious vaccines has been hindered by the lack of an established correlate of protection and under appreciation of the true disease burden. Human microbial infection studies could provide a vehicle for the rapid evaluation of novel vaccines and investigation of the immunobiology of enteric infection.

Introduction

Enteric fever is a systemic infection caused by *Salmonella enterica* subspecies *enterica* serovars Typhi (*S.* Typhi, causing typhoid fever) or Paratyphi A, B or C (*S.* Paratyphi A, B or C, causing paratyphoid fever). Enteric fever is common in resource-poor regions of the world, where poor sanitation and inadequate clean water provision facilitate the spread of infection via faeco-oral transmission.

Enteric fever produces a wide range of non-specific symptoms and is clinically indistinguishable from many other diseases, both infectious and non-infectious. Prompt treatment minimises illness severity, but late presentation to health care facilities often delays initiation of appropriate antibiotic therapy. Treatment delay is compounded by a lack of reliable diagnostic tests.

Although typhoid could be controlled by improvements in public infrastructure (for example, clean water and separate sewage systems), the significant funding investments required in many regions are unlikely to be forthcoming in the near future. Fortunately, disease control in the interim may be possible through effective vaccination. Indeed, prevention of typhoid fever has been attempted through vaccination for over 100 years.[1] Three licensed

* Corresponding author. University of Oxford, Room 02-46-07, Level 2, Children's Hospital, Oxford OX3 9DU, United Kingdom. Tel.: +44 (0) 1865 231693.
E-mail addresses: claire.waddington@paediatrics.ox.ac.uk (C.S. Waddington), thomas.darton@paediatrics.ox.ac.uk (T.C. Darton), andrew.pollard@paediatrics.ox.ac.uk (A.J. Pollard).

0163-4453/$36
http://dx.doi.org/10.1016/j.jinf.2013.09.013

vaccines for typhoid fever exist, but are only moderately efficacious and unsuitable for infant immunisation. There are currently no licensed vaccines to prevent paratyphoid infection. The implementation of existing vaccines and development of new efficacious vaccines has been hindered by a lack of understanding of typhoid immunobiology. *S.* Typhi and Paratyphi are human restricted pathogens and require a relatively high dose to cause infection. Consequently the development of a suitable vaccine could lead to the eradication of enteric fever. To reach this goal, an improved understanding of the immunobiology of typhoid fever is needed.

Epidemiology

Typhoid fever is estimated to affect at least 26.9 million people per year, of whom 1% will die.[2] Paratyphoid fever has been estimated to affect 5.4 million people per year,[3] and appears to be increasingly prevalent, with recent reports attributing up to half of all enteric fever cases to paratyphoid infection in some Asian countries.[4,5] The incidence of paratyphoid fever in returning travellers is also increasing.[6,7] The majority of the global disease burden is borne by children and adolescents in resource-poor settings, particularly in Asia.[8] The distribution of disease is changing however, with increasing recognition of a significant disease burden in Africa.[2,9]

The true burden of enteric fever may be considerably higher than these estimates suggest.[2,8,10] There are significant limitations to the data used to generate morbidity and mortality estimates. Resource-poor countries frequently lack the health care and public health infrastructure to provide reliable data.[3,8,11,12] Historically, cases of clinical enteric fever have been attributed to *S.* Typhi but with the increasing burden of paratyphoid fever in many regions, this is unreliable.[13] Data from population-based blood culture studies, although specific, are few in number.[14] These studies consistently demonstrate a higher disease prevalence than that suggested by public health figures.[12] Similarly, sero-epidemiological studies based on detection of antibodies to typhoid antigens suggest higher rates of infection than studies using clinical or microbiological case detection, with up to 80% of residents in endemic regions showing evidence of past infection.[15,16] Microbiological isolation of *S.* Typhi or *S.* Paratyphi provides a definitive diagnosis, but blood culture sensitivity is limited to 50%–60% and therefore underestimates the true number of cases,[17] and bone marrow culture is rarely available.

Traditional assessments of enteric fever disease burden have focused on Asia; the incidence of disease in Africa and South America remains uncertain, although recent reports suggest it may be an increasingly recognised problem. Asian countries have previously been estimated to account for 93% of the known worldwide mortality and morbidity,[8] with current estimates of 394.2 cases per 100,000 population.[2] Correspondingly, the majority of infected travellers are returning from Asia. For example, in laboratory-based surveillance of US isolates, 65% of patients had travelled to one of four countries — India, Pakistan, Bangladesh or Haiti.[18] Encouragingly, the disease burden in some parts of Asia may be falling, particularly in areas where significant investments in infrastructure have been made. A 15 year retrospective review of blood culture results in Vietnam showed that, while *S.* Typhi had accounted for 74% of positive blood cultures in 1994, the proportion by 2008 was 6.2%.[19]

The marked decline in malaria prevalence in many regions of Africa over the last decade has promoted *S.* Typhi to one of the leading causes of severe febrile illness. A meta-analysis of community-acquired bloodstream infections across Africa estimated that *S.* Typhi accounted for 9.9% of all isolates.[9] Although this meta-analysis extrapolated limited data across a diverse continent and people, it has been supported by other data. In children under 15 years of age in Ghana, 12.4% of blood culture isolates were due to *S.* Typhi, equivalent to an incidence of approximately 190/100,000 per year.[20] Similarly, in Nigeria, *S.* Typhi accounted for 20.9% of isolates in children less than 5 years of age, despite high pre-culture antimicrobial use.[21] Disease rates in Zanzibar match those seen in many high incidence regions of Asia, with 58% of blood culture isolates identified as *S.* Typhi.[22] Although these data confirm the importance of typhoid in Africa at the clinical front-line, the false attribution of febrile illness to malaria has often hindered the recognition of enteric fever as a major cause of disease in Africa.[9,21] Comparison of blood culture isolates with clinical diagnoses in Africa showed that 55% of children with *S.* Typhi bacteraemia were diagnosed clinically with malaria,[21] supporting the idea that enteric fever is an under recognised problem in Africa and highlighting the need for better diagnostics and preventative measures in resource-poor countries.

Acute typhoid fever

Enteric fever is a highly variable, non-specific illness. Typhoid fever and paratyphoid fever cannot be distinguished on clinical grounds.[6] Fever is the most frequent and universal symptom with other frequent symptoms being malaise, chills, anorexia, diarrhoea, headache, weight loss, abdominal pain and rash.[23,24] Nausea, constipation, myalgia, arthralgia and cough are also reported.[25–27] Severity of symptoms is highly variable, with some patients able to continue normal activity and some requiring inpatient care.[27] Specific physical signs are frequently absent, but diffuse abdominal tenderness is common, and hepatosplenomegaly and/or lymphadenopathy may also be present.[12,24] Rose spots, a transient, fine, blanching maculopapular rash, usually starting on the trunk and spreading to the arms and legs, are pathognomonic for typhoid fever, but is reported with a range of frequency from as few as 3% of cases, up to 40%.[12,24] A relative bradycardia is also described.[12] *S.* Typhi and Paratyphi infection can lead to a variety of other rarer clinical entities including meningitis, septic arthritis and osteomyelitis.[28]

Chronic carriage

In 1902, Robert Koch postulated that healthy people could carry disease causing organisms and serve as reservoirs of infection.[29] Applying this idea to typhoid fever, Koch noted that humans were the only source of *S.* Typhi, and