
REVIEW ARTICLE

Part I. Analysis of data gaps pertaining to *Salmonella enterica* serotype Typhi infections in low and medium human development index countries, 1984–2005

J. A. CRUMP^{1*}, P. K. RAM¹, S. K. GUPTA¹, M. A. MILLER² AND E. D. MINTZ¹

¹ Enteric Diseases Epidemiology Branch, National Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

² Fogarty International Center, National Institutes of Health, Bethesda, MD, USA

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SUMMARY

There are only 10 contemporary, population-based studies of typhoid fever that evaluate disease incidence using blood culture for confirmation of cases. Reported incidence ranged from 13 to 976/100 000 persons per year. These studies are likely to have been done preferentially in high- incidence sites which makes generalization of data difficult. Only five of these studies reported mortality. Of these the median (range) mortality was 0% (0–1·8%). Since study conditions usually involved enhanced clinical management of patients and the studies were not designed to evaluate mortality as an outcome, their usefulness for generalizing case-fatality rates is uncertain. No contemporary population-based studies reported rates of complications. Hospital-based typhoid fever studies reported median (range) complication rates of 2·8% (0·6–4·9%) for intestinal perforation and case-fatality rates of 2·0% (0–14·8%). Rates of complications other than intestinal perforation were not reported in contemporary hospital-based studies. Hospital-based studies capture information on the most severe illnesses among persons who have access to health-care services limiting their generalizability. Only two studies have informed the current understanding of typhoid fever age distribution curves. Extrapolation from population-based studies suggests that most typhoid fever occurs among young children in Asia. To reduce gaps in the current understanding of typhoid fever incidence, complications, and case-fatality rate, large population-based studies using blood culture confirmation of cases are needed in representative sites, especially in low and medium human development index countries outside Asia.

INTRODUCTION

The global incidence of typhoid fever was estimated to be about 21 650 000 illnesses in 2000 and varies greatly between regions. Typhoid fever incidence is

* Author for correspondence: J. A. Crump, MB, ChB, DTM&H, Medical Epidemiologist, Enteric Diseases Epidemiology Branch, National Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.
(Email: jcrump@cdc.gov)

This is the first of three papers, appearing in successive issues of the Journal, reviewing the analysis of data gaps pertaining to infections in low and medium human development index (HDI) countries.

highest among infants and children living in South Central and South East Asia [1]. Typhoid fever is a severe systemic illness that is characterized by sustained fever, systemic toxicity and abdominal pain [2]. *S. Typhi* colonizes only humans. The disease is acquired by consuming water or food contaminated by the faeces of a person who has typhoid fever or who is a carrier [3]. While transmission via sexual relations between men has also been reported [4], true person-to-person transmission is rare. The ID₅₀ of *S. Typhi* is about 10⁶ organisms by ingestion, but varies considerably with gastric acidity. The risk of

Table 1. *Terms used in literature search to identify gaps in data on enteric disease burden*

Burden of disease
Epidemiology
Morbidity
Mortality
Disease outbreaks
Incidence
Prevalence
Seasons
Population surveillance
Age distribution
Longitudinal survey
Pathogen-specific terms for typhoid fever
Typhoid
Typhoid fever
Enteric fever
<i>Salmonella Typhi</i>

infection increases as the size of the inocula increases [5].

Salmonella enterica subspecies *enterica* serotype Typhi (*Salmonella Typhi*) belong to the family of Enterobacteriaceae and are Gram-negative, motile, non-lactose-fermenting bacilli. Although most *S. enterica* serotypes cannot be distinguished by biochemical reactions, *S. Typhi* can be provisionally identified by its production of only trace amounts of hydrogen sulphide and being less active biochemically than other serotypes within the subspecies. Confirmation depends on the detection of surface antigens using specific antisera. *S. Typhi* belongs to *Salmonella* serogroup D and possesses somatic antigen O9, a single flagellar antigen Hd, and the polysaccharide virulence antigen Vi. Resistance to traditional first-line antimicrobial agents, such as ampicillin, chloramphenicol, and trimethoprim-sulfonamide combinations has emerged worldwide. More recently isolates with reduced susceptibility to fluoroquinolones and third-generation cephalosporins (i.e. ceftriaxone) have been increasingly recovered [6].

Building on our previously published work on typhoid fever epidemiology [1], we conducted a review of the recent scientific literature to identify contemporary gaps in the understanding of the global epidemiology of typhoid fever. An improved understanding of typhoid fever epidemiology would allow policy-makers to decide how to allocate resources to typhoid fever vs. other health priorities and would allow health officials to select and monitor the

effectiveness of public health interventions. We summarize below recent available data on the morbidity and mortality burden, the age, and the geographic and temporal distribution of typhoid fever. To provide context to the global epidemiology of typhoid fever, we also describe typhoid diagnostics and pathogen-specific preventive measures. Finally, data gaps and existing research needs are discussed.

METHODS

We systematically searched the English-language scientific literature published between 1984 and 2005 using the Medline database, restricting the search to low and medium human development countries according to the United Nations Development Programme's Human Development Index (HDI) (<http://hdr.undp.org/2004>; accessed 21 March 2005). A set of articles including the relevant epidemiological terms were cross-linked with a set of articles including the relevant pathogen-specific terms (Table 1). The resulting cross-linked set was reviewed for publications addressing typhoid fever morbidity, mortality, age distribution, geographic distribution, temporal distribution, pathogen-specific preventive measures, and diagnostics. Particularly for morbidity and mortality burden, population-based studies with culture confirmation of cases were considered primary data sources. When these were limited, hospital- and clinic-based studies were included. Publications were then evaluated for their contribution to an understanding of the global epidemiology of typhoid fever, and gaps in the data were identified.

Crude incidence figures are given, without correction for sensitivity of blood culture, or for the proportion of febrile episodes for which blood-culture specimens were not collected. Publications were sought with information on the incidence of the infection by region according to the 21 regions of the United Nations Department of Social and Economic Affairs, Population Division (<http://esa.un.org/unpp/index.asp?panel=5>; 2004 revision, accessed 4 October 2005). We examined the correlation between the incidence of typhoid fever and the national *per capita* gross domestic product (GDP), adjusted for purchasing power parity (PPP) in year 2000 dollars, at the time that the studies were conducted (http://unstats.un.org/unsd/cdb/cdb_series_xrxx.asp?series_code=29922; accessed 28 July 2006). We searched for publications with information on the age-specific incidence, morbidity, and mortality.



Fig. 1. Geographic distribution of population-based studies of typhoid fever incidence. (Adapted from Crump *et al.* [1].) ■, High incidence (>100 episodes/100 000 per year); ▒, Medium incidence (10–100 episodes/100 000 per year); □, Low incidence (<10 episodes/100 000 per year); □, region with human development index (HDI) countries; ○, site of contributing disease incidence study.

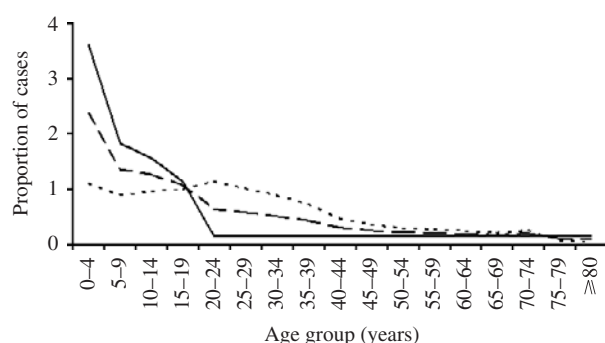


Fig. 2. Age-specific incidence of typhoid fever (from Crump *et al.* [1]). —, High (>100/100 000 per year); ---, medium (10–100/100 000 per year); ····, Low (<10/100 000 per year).

RESULTS

Morbidity

Incidence

The most recent published estimate of the global burden of typhoid fever determined that 21 650 000 illnesses occurred worldwide in 2000 [1] and that the incidence was highest in South and South East Asia and among infants and young children (Figs 1 and 2).

A computer search of the English scientific literature published between 1984 and 2005 from low- and medium-HDI countries for population-based typhoid fever incidence studies using blood culture confirmation of cases yielded 10 publications (Table 2);

three studies from Africa (South Africa and Egypt) and seven from Asia (Bangladesh, China, India, Indonesia, Nepal, and Vietnam). Five (50%) of these publications were reports of vaccine studies and all 10 were from medium-HDI countries. Crude typhoid fever incidence in these studies ranged from 13 to 976 illnesses/100 000 persons per year. Five studies included subjects of all ages; the remainder were restricted to persons within specific age ranges. Because of limitations of blood culture sensitivity for typhoid fever (Table 3) and variation of typhoid fever incidence with age (Fig. 2), it would be appropriate to adjust crude incidence for these factors when attempting to extrapolate typhoid fever incidence to the global population [1].

Among the 10 population-based studies, there was a non-significant relationship between typhoid fever incidence and *per capita* GDP (Fig. 3) ($R = -0.04$, $P = 0.9115$). One study that showed high typhoid incidence was done in South Africa, a country with a relatively high GDP but with considerable maldistribution of wealth. When this outlier study was excluded, a non-significant trend towards an inverse relationship between typhoid fever incidence and *per capita* GDP is seen ($R = -0.63$, $P = 0.0717$).

Complications

Intestinal perforation is an important complication of typhoid fever. Unfortunately, no population-based

Table 2. Population-based studies of typhoid fever incidence 1984–2005

Location			HDI	Year(s)	Age range (yr)	Crude incidence*	CFR (%)	Ref.
Area	Region	Country						
Africa	N Africa	Egypt	Medium	2001	All	13	n.r.	[7]
Africa	N Africa	Egypt	Medium	2002	All	59	n.r.	[45]
Africa	S Africa	South Africa	Medium	1985–88	5–15	845	n.r.	[28, 46]
Asia	E Asia	China	Medium	1995–96	3–50	21	n.r.	[37]
Asia	SC Asia	India	Medium	1995–96	All	976	0	[14]
Asia	SC Asia	Nepal	Medium	1986–87	5–44	654	1.8	[27]
Asia	SC Asia	Bangladesh	Medium	2000–01	All	390	0	[15]
Asia	SC Asia	Indonesia	Medium	1986–89	3–44	810	n.r.	[47]
Asia	SC Asia	Vietnam	Medium	1995–96	All	198	0	[24]
Asia	SC Asia	Vietnam	Medium	1998–2000	2–4	931	0	[31]

HDI, Human development index; CFR, case-fatality rate; n.r., not reported.

* Per 100 000 persons per year.

Studies excluded for high human development index country: 2 from Chile [48, 49].

Studies excluded for pre-1984: 1 from Chile [50], 2 from Egypt [51, 52]; 1 from India [53], 1 from Poland [54], 4 from the USSR [55–58], 2 from Yugoslavia [59, 60], 1 from Guyana [61], and 1 from Tonga [62].

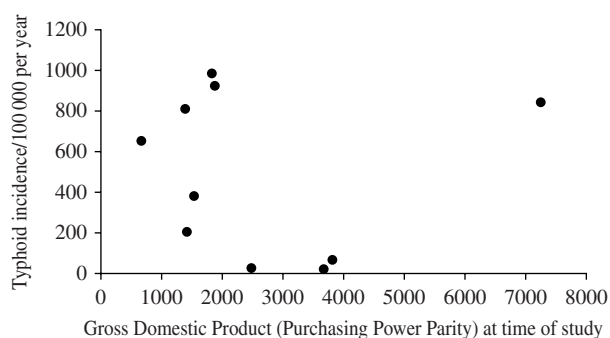


Fig. 3. Incidence of typhoid fever by *per capita* gross domestic product (adjusted for purchasing power) of low- and medium-HDI countries, 1984–2005 ($n = 10$ studies).

studies that use blood culture confirmation of *S. Typhi* infection report the rates of this or other complications. Hospital-based studies capture information on the most severe illnesses among persons who have access to health-care services and are likely to overestimate the true complication rate substantially [7]. A review of intestinal perforation rates in typhoid fever series from all countries from the pre-antibiotic era before 1950 indicate median (range) rates of 1.9% (0.8–6.3%). The same review shows a rate of intestinal perforation in developed countries of 0% (0–0%) in the post-antibiotic era after 1950 and in developing countries in the post-antibiotic era after 1950 of 3.6% (0.1–41%) [8]. Case-series published between 1984 and 2005 from low- and medium-HDI countries report median (range) intestinal

perforation rates of 2.8% (0.6–4.9%) (Table 4). Risk factors for intestinal perforation in typhoid fever include male gender, older age, inadequate antimicrobial therapy, and short duration of symptoms [8–10].

Other complications occur, but their rates are not well quantified in either population- or hospital-based studies. A recent review of typhoid fever complications involving specific organ systems indicated that they occur with the following frequencies in hospital series: central nervous system (encephalopathy, cerebral oedema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis) 3–35%; cardiovascular system (endocarditis, myocarditis, pericarditis, arteritis, congestive cardiac failure) 1–5%; pulmonary system (pneumonia, empyema, bronchopulmonary fistula) 1–6%; bone and joint (osteomyelitis, septic arthritis) <1%; hepatobiliary system (cholecystitis, hepatic abscess, splenic abscess, peritonitis, paralytic ileus); 1–26%, and the genitourinary system (urinary tract infection, renal abscess, pelvic infection, testicular abscess, prostatitis, epididymitis) <1%. Soft tissue infections (psoas abscess, gluteal abscess, cutaneous vasculitis) and haematological complications (haemophagocytic syndrome) are rare [11].

While the geographic distribution of typhoid fever and HIV overlap, no studies have comprehensively evaluated the effect of HIV on typhoid fever incidence or complications.

Table 3. Comparison of diagnostic tests for typhoid fever

Assay name	Gold standard	Assay type	Sensitivity	Specificity	Ref.
Bone marrow culture	Bone marrow	Culture	0.90*	1.0	[40]
Blood culture	Bone marrow	Culture	0.40*	1.0	[40]
Stool culture	Bone marrow	Culture	0.37	<1.0†	[40]
Urine culture	Bone marrow	Culture	0.07	1.0	[40]
Rose spot culture	Bone marrow	Culture	0.63	1.0	[40]
Widal test	Blood culture	Antibody detection	0.64	0.76	[44]
Multi-Test Dip-S-Ticks	Blood culture	Antibody detection	0.89	0.53	[44]
TyphiDot	Blood culture	Antibody detection	0.79	0.89	[44]
TUBEX	Blood culture	Antibody detection	0.78	0.89	[44]

* Varies according to sample volume.

† Varies according to carrier prevalence in study population.

Epidemic vs. endemic disease

Large typhoid fever outbreaks make substantial contributions to the local disease burden. For example, during a large waterborne outbreak of typhoid fever in Tajikistan during 1997 more than 1200 cases of typhoid fever were detected each week during the epidemic's peak in the city of Dushanbe which had a population of about 600 000 people [12]. While large outbreaks occur, endemic typhoid fever is thought to be responsible for most typhoid fever illnesses worldwide. However, we were unable to find population-based typhoid fever surveillance studies of sufficient duration to capture incidence before, during, and after typhoid fever epidemics. Therefore, the relative contribution of epidemics to disease burden is not known.

Mortality

Five (50%) of 10 population-based studies conducted between 1984 and 2005 and representing 64 338 person-years of follow-up report mortality data. These five studies showed median (range) case-fatality rates (CFRs) of 0% (0–1.8%) (Table 2). There are several limitations to generalizing CFRs for typhoid fever from these studies. In all studies ethical requirements governing human subject research would have optimized the clinical management of patients found to have typhoid fever probably leading to lower CFRs than may be seen in the source population. Second, these studies were not designed to assess mortality as a primary outcome.

Hospital-based series provide another way to estimate typhoid fever mortality, but only capture information on the most severe illnesses among persons who have access to health-care services [7]. The

literature search identified 28 hospital-based studies reporting CFRs (Table 5): four studies from Africa, 22 from Asia, and one each from Latin America/Caribbean and Oceania. The median (range) CFR in these studies was 2.0% (0–14.8%).

A review of published typhoid fever series from the pre-antibiotic era before 1950 showed median (range) CFRs of 11% (7.5–19%). The same review shows a median (range) CFR for typhoid fever in developing countries in the post-antibiotic era after 1950 of 6.1% (0.1–41%) [8].

Appropriate antimicrobial therapy is known to reduce mortality from typhoid fever [13]. A consequence of the emergence of antimicrobial resistance in *S. Typhi* is that empiric treatment choices for typhoid fever often include antimicrobial agents to which the infecting organism is resistant. This is especially challenging in settings where laboratory capacity to isolate *S. Typhi* from blood is absent or inadequate and the prevalence of resistant *S. Typhi* at both the individual and population level is unknown.

Age distribution

Two contemporary population-based studies address the age distribution of typhoid fever and suggest that, in areas highly endemic for typhoid fever, infection is more common in infants and pre-school children than in older persons [14, 15]. The age distribution of typhoid fever has been modelled for typhoid fever at high (>100/100 000 per year), medium (10–100/100 000 per year), and low (<10/100 000 per year) incidence countries using data from studies evaluating the age distribution of the infection [14, 15] and using surveillance data [7]. The resulting age distribution curves are reproduced in Figure 2 [1].

Table 4. *Hospital-based studies of typhoid fever intestinal perforation, 1984–2005*

Location				Years	Age range (yr)	No. of illnesses	No. with perforation	Perforation rate	Ref.
Area	Region	Country	HDI						
Africa	S Africa	South Africa	Medium	1993–95	All	102	5	4.9	[10]
Asia	E Asia	Taiwan	Medium	1982–95	Children	71	2	2.8	[68]
Asia	S Asia	Bangladesh	Medium	1975–86	All	552	18	3.3	[20]
Asia	W Asia	Turkey	Medium	1981–90	Children	680	4	0.6	[84]
Oceania	Melanesia	Papua New Guinea	Medium	1984–90	All	516	7	1.4	[83]

HDI, Human development index.

Table 5. *Hospital-based studies of typhoid fever mortality, 1984–2005*

Location					Age range (yr)	No. of illnesses	No. of deaths	CFR	Ref.
Area	Region	Country	HDI	Year(s)					
Africa	W Africa	Gabon	Medium	1992–96	All	71	5	7.0	[63]
Africa	S Africa	South Africa	Medium	1977–83	Children	585	12	2.1	[64]
Africa	S Africa	South Africa	Medium	1993–95	All	102	1	1.0	[10]
Africa	S Africa	Zimbabwe	Low	1984	Children < 14	100	0	0	[65]
Asia	SE Asia	Thailand	Medium	1986–2000	Children	19	0	0	[66]
Asia	SE Asia	Thailand	Medium	1977–84	Children	163	0	0	[67]
Asia	E Asia	Taiwan	Medium	1982–95	Children	71	0	0	[68]
Asia	SE Asia	Indonesia	Medium	1989–90	14–60	105	5	5	[13]
Asia	SE Asia	Vietnam	Medium	1993–94	All	293	9	0.3	[69]
Asia	SE Asia	Malaysia	Medium	1981–90	0–12	46	0	0	[70]
Asia	SE Asia	Malaysia	Medium	1984–6	Children	137	2	1.5	[71]
Asia	SE Asia	Malaysia	Medium	1975–9	All	121	2	1.7	[72]
Asia	SE Asia	Pakistan	Low	1986–9	Children	355	7	2.0	[73]
Asia	S Asia	Pakistan	Low	1988–93	Children	876	18	2.1	[74]
Asia	S Asia	Pakistan	Low	1988–93	Children	1158	19	1.6	[19]
Asia	S Asia	Pakistan	Low	1994	All	62	0	0	[25]
Asia	S Asia	Bangladesh	Medium	1975–86	All	552	24	4.3	[20]
Asia	S Asia	Bangladesh	Medium	1980–81	All	88	7	8.0	[75]
Asia	S Asia	Bangladesh	Medium	1975–83	All	323	18	5.5	[8]
Asia	SE Asia	Philippines	Medium	1994	All	422	9	2.1	[76]
Asia	W Asia	Turkey	Medium	1982–92	Children	27	4	14.8	[77]
Asia	S Asia	India	Medium	1988–92	Children	394	13	3.3	[78]
Asia	S Asia	India	Medium	1990–92	Children	172	4	2.3	[79]
Asia	S Asia	India	Medium	1990–91	All	102	1	1.0	[80]
Asia	S Asia	India	Medium	1980s	Adults	125	11	8.8	[81]
Asia	S Asia	Pakistan	Low	1986–89	Children	355	16	4.5	[73]
Latin America and Caribbean	Caribbean	Haiti	Low	1989–91	≥ 14	217	20	9.2	[82]
Oceania	Melanesia	Papua New Guinea	Medium	1984–90	All	374	52	13.9	[83]

HDI, Human development index; CFR, case-fatality rate.

No population-based study has evaluated age-specific mortality for typhoid fever. Although by no means benign [15], typhoid fever is thought to be less

severe in children [16–18] than in adults. Hospital in-patient series show that infants are at greater risk of dying from typhoid fever than older children [19, 20].

Geographic distribution

The best summary of the geographic distribution of typhoid fever has been modelled from population-based incidence studies (Table 2 and earlier studies), adjusted for age-specific incidence curves (Fig. 2), and diagnostic test sensitivity (Table 3). The resulting data on geographic distribution of typhoid fever are summarized in Figure 1 [1]. The very few contemporary studies from which this figure was developed are illustrated with open symbols (○). Based on these data sources, most typhoid fever illnesses occur among infants and young children in South and South East Asia.

Temporal distribution

The incidence of typhoid fever is reputed to follow seasonal patterns [21]. In some locations a peak occurs in the hot, dry months of the year. This is often attributed to a concentration of organisms in water when supply is inadequate due to lack of rain. However, in other places, a peak is reported during the rainy season. This is often attributed to a breakdown in the systems that separate sewage from drinking water. A review of typhoid fever seasonality publications between 1984 and 2005 confirms that both seasonal patterns are reported [22–25].

Pathogen-specific preventive measures

Three licensed vaccines are available to prevent typhoid fever; parenteral inactivated whole-cell vaccines, oral attenuated *S. Typhi* Ty21a vaccine, and parenteral Vi capsular polysaccharide vaccine. These vaccines confer about 70% protection in older children and adults and do not protect young children or infants [26–30]. More recently a conjugate vaccine has been developed that binds Vi to a non-toxic recombinant protein that is antigenically identical to *Pseudomonas aeruginosa* exotoxin A (Vi-rEPA). In a clinical trial in Vietnam, the vaccine showed 90% efficacy in children aged 2–5 years [31] and this level of protection was sustained for more than 3 years after vaccination [32]. To date, routine typhoid fever vaccination has rarely been adopted in typhoid-endemic countries [33]. Reasons include cost, lack of protection for young children, difficulties integrating currently available typhoid vaccines with current expanded programme on immunization (EPI) schedules, and the need for repeated booster doses.

Non-vaccine measures for typhoid fever prevention can be divided into community measures and individual measures [3]. Community measures for typhoid fever prevention include promotion of hand washing; sanitary disposal of human faeces; provision of safe drinking water; sanitary food preparation; pasteurization or boiling of milk and dairy products; quality control procedures for the food industry; and shellfish sanitation. Individual measures for typhoid fever prevention include education of patients, convalescents, and carriers in personal hygiene; breastfeeding throughout infancy; exclusion of typhoid carriers from food handling and from patient care provision; and provision of typhoid fever vaccine to persons at high risk due to occupation or travel.

Commonly recommended measures for typhoid fever control include reporting illnesses to health authorities, use of enteric precautions for ill patients until no fewer than three stool samples have proved negative for *S. Typhi*, safe disposal of faeces, urine, and soiled articles, identification and management of the source of infection, identification and screening of exposed individuals, and specific treatment of ill persons and carriers with an effective antimicrobial agent, most often a fluoroquinolone. Identification of chronic asymptomatic carriers through serological screening of the general population in an endemic area appears not to be useful [34]. Typhoid fever epidemics are managed by epidemiological identification of the source, disinfection of drinking water, followed by control measures directed to the epidemiologically identified source, e.g. intensive search for the case or carrier, selective elimination of suspected contaminated food, pasteurization or boiling of milk [3]. In a large waterborne epidemic of typhoid fever in Dushanbe, Tajikistan, implementation of chlorination of the city water supply lead to a dramatic reduction in typhoid fever incidence [12]. The introduction of widespread sewage treatment in Santiago, Chile, in 1992 was associated with a 90% reduction of typhoid fever and hepatitis A [35, 36]. Although currently not routinely recommended, one study shows that Vi vaccine deployed in a typhoid fever epidemic provided 71% protection against infection [37].

Case-control studies indicate that the predominant route of transmission of typhoid fever varies both in time and location. For example, in Tajikistan after independence from the Soviet Union deterioration of the municipal water treatment and distribution system led to lack of chlorination, equipment failure, and back-siphonage. This was associated with

Table 6. *Data gaps and research needs for typhoid fever in low- and medium-HDI countries*

Morbidity	<ul style="list-style-type: none"> ● Population-based surveillance for <i>Salmonella enterica</i> serotype Typhi incidence in low HDI countries ● Population-based surveillance for <i>Salmonella enterica</i> serotype Typhi incidence in sub-saharan Africa and from Central and South America
Complications	<ul style="list-style-type: none"> ● Rates of complications in population-based studies of typhoid fever ● Evaluation of the effect of HIV co-infection on typhoid fever incidence and complications
Epidemic vs. endemic disease	<ul style="list-style-type: none"> ● Assessment of contribution of outbreaks in the setting of large population-based studies of typhoid fever incidence
Mortality	<ul style="list-style-type: none"> ● Determination of case-fatality rates and mortality rates in adequately sized population-based studies ● Identification of modifiable risk factors for death through cohort studies nested in population-based disease incidence studies ● Intervention studies to ascertain the benefit of reducing mortality-associated risk factors ● Improved surveillance of antimicrobial resistance ● Treatment trials to evaluate antimicrobial agents for the treatment of drug-resistant typhoid fever
Age distribution	<ul style="list-style-type: none"> ● Surveillance among all age groups, with incidence reported for total population as well as by age group
Geographic distribution	<ul style="list-style-type: none"> ● Population-based incidence data from sub-saharan Africa and Central and South America to strengthen regional disease incidence estimates ● Population-based incidence data from most low- and medium-human development index countries to strengthen country level incidence estimates
Seasonality	<ul style="list-style-type: none"> ● Collection of data and analysis regarding temporal distribution of typhoid fever over multi-year periods, with reporting using strict case definitions that include culture confirmation and contextual environmental information such as rainfall, flooding, population density and degree of urbanization

HDI, Human development index.

widespread consumption of faecally contaminated water and a massive typhoid fever outbreak in 1997 [12]. In Pakistan, eating ice cream, eating food from a roadside cabin during the summer months, taking antimicrobials during the 2 weeks before illness onset, and drinking water at the worksite were independently associated with typhoid fever [38]. In Indonesia, recent typhoid fever in the household, not using soap for hand washing, sharing food from the same plate, and no toilet in the household were independent risk factors for typhoid fever [39]. The fraction of typhoid fever illness attributable to water, specific foods, or to typhoid fever carriers is poorly characterized both globally and at the local and regional levels. The lack of data on attribution limits the ability of policy-makers and public health officials to plan for transmission-based interventions to interrupt typhoid fever.

Diagnostics

The gold standard test for diagnosis of typhoid fever remains the culture of bone marrow. The sensitivity of this test exceeds 90 % and the specificity is 100 %, assuming that bacterial identification methods are performed correctly [40]. Because obtaining samples for culture of bone marrow is invasive and requires technical expertise and equipment, blood culture is more often used for diagnosis even though the sensitivity of a single culture is about 40 % [40–42]. Blood culture is more effected by prior antimicrobial use than bone marrow culture [42]. The sensitivity of blood culture for typhoid fever is improved by collection of larger volumes of blood [42].

The surface antigens of *S. Typhi* are shared by many other salmonellae and with other bacterial pathogens. This hampers specific serological

diagnosis. Commercially available serological assays such as Multi-Test Dip-S-Ticks (PANBIO INDX Inc., Baltimore, MD, USA), TyphiDot (Malaysian Biodiagnostic Research SDN BHD, Singapore, Malaysia), and TUBEX (IDL Biotech, Sollentuna, Sweden) all have shortcomings of both sensitivity and specificity, with the Widal test performing the worst of all (Table 3).

DISCUSSION

This review highlights the large gaps in data on the burden of typhoid fever infections for low- and medium-HDI countries (Table 6). It also identifies additional research needs with respect to the burden of disease among infants and population-based rates of typhoid fever complications and mortality. Comprehensive microbiological, clinical, and population-based epidemiological studies using blood culture confirmation of cases or using novel study designs with alternative diagnostic methods could help to address these data gaps and further inform prevention. However, the implementation of such research would lead to and would require improvements in patient management that could be expected to reduce case fatality and complication rates.

Contemporary population-based studies using blood culture confirmation of cases are lacking or are extremely limited in all socioeconomic groups and geographic regions. Data are particularly limited for populations living in low-HDI countries and those in sub-Saharan Africa and Central and South America, where laboratory diagnostic capacity for typhoid fever may not be widely available. Of the 10 contemporary, population-based studies of typhoid fever that evaluate disease incidence using blood culture for confirmation of cases the reported incidence ranges from 13 to 976/100 000 persons per year. These studies are likely to have been done preferentially in high-incidence sites that make generalization of results from a single location to a whole country or region difficult. Only two studies report typhoid fever incidence simultaneously in different age groups making the burden among infants and young children difficult to estimate [14, 15]. Preliminary evidence that the age distribution of typhoid fever varies according to disease incidence needs to be confirmed by population-based studies conducted in both low and medium typhoid fever incidence settings. A sound understanding of both incidence and mortality in different age groups is needed to make decisions

about typhoid fever vaccine policy. Although large typhoid fever epidemics are recognized to occur occasionally [12], the relative contribution of epidemic vs. endemic diseases to the overall burden of typhoid fever has not been established.

Little is known about long-term temporal trends in typhoid fever incidence in low- and medium-HDI countries and what underlies such trends. To improve understanding of long-term trends, collection of data and analysis is required over multi-year periods, with reporting using strict case definitions that include culture confirmation and contextual environmental information such as rainfall, flooding, population density and degree of urbanization.

No population-based typhoid fever study in our series reported rates of typhoid fever complications. Consequently, we calculated rates from hospital-based studies. Hospital-based typhoid fever studies showed median (range) intestinal perforation rates of 2.8% (0.6–4.9%). Rates of complications other than intestinal perforation are not consistently reported in contemporary hospital-based studies. Therefore, the total morbidity attributable to typhoid fever cannot currently be calculated. It is probable that hospital-based studies capture only the most severe illness among persons who have access to health care and therefore such studies may overestimate the rates of complications [7]. No study has systematically evaluated the effect of HIV co-infection on typhoid fever incidence and complications. Data are needed on the rates of complications from population-based studies. Such tracking might be done in areas where a discrete number of health facilities provide care for the majority of the population.

With the continued emergence of antimicrobial resistance in *S. Typhi* [43], improved surveillance for antimicrobial resistance is needed as well as continued efforts to evaluate antimicrobial agents for the treatment of drug-resistant *S. Typhi* infection.

Only five population-based studies in our series reported data that allowed calculation of the typhoid fever CFR. In these five studies, the median (range) typhoid fever CFR was 0% (0–1.8%). When using case studies to examine rates of typhoid fever complications, it is likely that the ethics of population-based typhoid fever incidence or vaccine studies will require enhanced clinical management of patients which could alter the measured CFR leading to underestimation of the CFR in such studies.

Policy-makers lack data to make decisions about pathogen-specific prevention measures for typhoid

fever. The effect of non-vaccine prevention and control measures, such as implementation of safe drinking water, has not been systematically evaluated. The fraction of typhoid fever attributable to various routes of transmission (i.e. water, food) has not been established. Furthermore, cost–benefit assessments, such as a comparison of the rapid implementation of water disinfection with the introduction of typhoid vaccines in the epidemic setting, have not been done. Finally, studies confirming the beneficial effect and feasibility of scaling up both vaccine interventions and non-vaccine measures in intervention studies would be useful to inform decisions on the distribution of resources to specific prevention programmes.

The diagnosis of typhoid fever provides an ongoing challenge both for patient care and for surveillance. The diagnosis of typhoid fever can rarely be made using clinical history and physical examination alone [7]. Bone marrow aspiration and culture is the gold-standard diagnostic test [40], but it is not practical for use in the field. Consequently, blood culture has become the practical gold standard, yet it lacks sensitivity and is also challenging to implement in the field in resource-poor settings. While a number of rapid diagnostic tests have been evaluated, none achieves the sensitivity of bone marrow culture and none has the specificity of the culture-based methods [44]. Continued efforts are needed to identify a simple, rapid diagnostic test for typhoid fever. In parallel, efforts should be made to expand access to and to improve blood culture technologies in low- and medium-HDI countries.

There are substantial gaps in the current understanding of typhoid fever epidemiology. These gaps are so large that policy-makers may have insufficient information to select the most appropriate interventions to reduce typhoid fever illnesses and death and to monitor the effects of such interventions. To address gaps in the current understanding of typhoid fever incidence, complications, and CFR, large population-based studies using blood culture confirmation of cases are needed in representative sites, especially in low-HDI countries outside Asia. Although such information is expensive to acquire, it would be invaluable for the prioritization of precious public health resources for pathogen-specific interventions, such as vaccination programmes targeting typhoid fever. Additional data regarding complications, modifiable risk factors for mortality, the burden of disease among infants, effectiveness of non-vaccine

prevention measures, and improved diagnostics would add greatly to our knowledge of typhoid fever.

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DECLARATION OF INTEREST

None.

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