Review Article

The Burden of Enteric Fever

Atul Kothari, Amit Pruthi, Tulsi D. Chugh

Dr. B. L. Kapur Memorial Hospital, New Delhi, India

Abstract

Enteric fever is a disease of developing countries associated with poor public health and low socio-economic indices. Cases of enteric fever occurring in travelers returning to the United States and the UK suggest that it is present across the developing world but that the Indian subcontinent represents a hotspot of disease activity. The best figures available for the global burden of enteric fever support this and suggest that Africa (50/ 100,000) has a far lower burden of disease than Asia (274/100,000). However these figures are based mainly on data for typhoid fever in Asia and the data for returning travelers is biased by preferred travel destinations. Given that most socio-economic indices, including known risk factors for enteric fever, such as provision of safe drinking water and sanitation, are much lower in most parts of Africa than in South-East and South-Central Asia it seems remarkable that Africa has such a low burden of disease. In such a scenario, rather than comparing whole continents, it may be more relevant to estimate region-specific burden of disease. It is clear is that there is an urgent need for more population-based studies of typhoid fever incidence in different parts of Africa to clarify the typhoid fever situation for the continent and so guide public health intervention.

Key Words: *Salmonella*, typhoid fever, enteric fever, incidence, burden.

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Introduction

Typhoid fever was a major cause of morbidity and mortality in the United States and Europe in the 19th century [1]. However, with the provision of clean water and good sewage systems, there has been a dramatic decrease in the incidence of typhoid in these regions. The disease remains a serious public health problem in developing countries [2]. The disease is endemic in India and carries a significant morbidity and mortality in both paediatric and adult populations. Reliable data from which to estimate the burden of disease in these areas is difficult to obtain. Many hospitals lack facilities for blood culture and up to 90% of patients with fever are treated as outpatients. In Asia, disease burden estimates have normally relied on clinically diagnosed cases of typhoid fever compiled by governments and hospitals, usually with uncertain denominators [3]. Population-based estimates of blood culture confirmed typhoid cases are sparse. Although effective treatment with chloramphenicol was introduced in 1948 [4], the emergence of resistance to chloramphenicol, ampicillin and cotrimoxazole has been of concern [5]. Currently, fluoroquinolones and third generation cephalosporins are drugs of choice for treatment of typhoid fever. However, recent reports of decreased susceptibility to these agents have led to the prospect of re-emergence of untreatable typhoid fever and an increasing global burden.

Transmission and Risk Factors

Humans are the natural host and reservoir for *Salmonella enterica* serovar Typhi. *Salmonella* bacteria can survive for days in groundwater or seawater and for months in contaminated eggs and frozen oysters [6-9]. The infectious dose varies between 10^3-10^6 organisms given orally [10]. Transmission of infection occurs by ingestion of food or water contaminated with faeces. Other established risk factors include recent contact with a typhoid patient or carrier, eating ice cream, flavoured iced drinks or food from street vendors, and raw fruit and vegetables grown in fields fertilised with sewage [11].

A recent study from slums in Bangladesh implicated eating raw papaya as being associated

with the disease [12]. Papaya has a neutral pH and its cut surface can support the growth of various microorganisms. Hosoglu *et al*. concluded that eating lettuce salad and *cig kofte* (a traditional raw food) was significantly associated with the development of typhoid fever in Turkey [13].

While living in a crowded household was independently associated with typhoid fever [13], routinely washing vegetables [14] and using a latrine for defecation [12] has been found to be protective. Overcrowding probably represents a greater opportunity for person-to-person transmission within households. In a case-control study in Indonesia, paratyphoid fever was found to be associated with flooding and with consumption of food from street vendors [15].

Interestingly, while prior antimicrobial use has been shown in multiple epidemiological studies to increase the risk of infection with both antibiotic-resistant and drug-sensitive serotypes of *S*. Typhi [14,16,17], two recent case-control studies in Turkey and Bangladesh failed to show such a link [12,13]. It is postulated that, in addition to providing a selective advantage to resistant *S.* Typhi strains, antimicrobial exposure can lead to prolonged alterations in gastro-intestinal flora and a decreased barrier to bacterial colonisation, lowering the dose of *Salmonella* necessary to cause infection [18,19].

Bhan *et al*. have found a significant association between the presence of serum anti-*Helicobacter pylori* IgG antibodies and typhoid fever [20]. This provided empiric evidence that *H. pylori*, causing reduced gastric acidity, is associated with an increased risk of typhoid fever.

Involvement of host genetic factors is implicated in susceptibility or resistance to infection with typhoid. In Vietnam, nucleotide polymorphisms in specific HLA alleles and the TNF-alpha promoter were associated with lower risk [21]. HLA-DRB1*12 was associated with protection against complicated typhoid fever [22]. These genetic factors may be partly responsible for the wide variation in the incidence of typhoid fever among the developing countries with similar standards of public health and hygiene.

Global Burden of Disease

Earlier estimates of the global burden of typhoid fever indicated there are at least 16 million new cases every year with 600,000 deaths [23]. This data was first presented in 1984 and similar estimates were published around the same time [24, 25]. This data, however, excluded China and did not account for the age distribution of typhoid fever [2].

A new study in 2004 estimated that typhoid caused 21,650,974 illnesses and 216,510 deaths during the year 2000, and that paratyphoid fever caused 5,412,744 illnesses [2]. This estimate was based on blood culture positive cases in 22 population-based studies. However, this estimate was also based on data from only a few countries, with only 3 studies providing data for the entire continent of Africa. Because there is scant reliable population-based data on the incidence of paratyphoid fever, an estimate of this incidence was extrapolated from the 1997 global survey of *Salmonella* serotyping practices and results, which was conducted by World Health Organization (WHO) and the United States Centers for Disease Control and Prevention, WHO Collaborating Center for Foodborne Disease Surveillance. A conservative case-fatality rate of 1% was chosen on the basis of estimates from hospital-based typhoid fever studies, mortality data from countries with reliable national typhoid surveillance systems, and expert opinion.

Crump *et al*. [2] also relied on typhoid vaccine studies, which raise questions over data quality. To achieve favourable sample sizes, these studies are usually conducted at sites with known high incidence of typhoid fever, introducing a bias towards the final estimation of disease burden. The incidence of typhoid was high (>100 cases per 100,000 population per year) in South-Central Asia, South East Asia and Southern Africa and medium (10-100 cases per 100,000 population per year) in the rest of Asia, Africa, Latin America, Caribbean islands and Oceania [2]. The incidence of typhoid fever was estimated to be low in Europe, North America, Australia and New Zealand (<10 cases per 100,000 population per year) [2] (Table 1).

Previous typhoid fever incidence rates (IR) reported in Egypt during various vaccine trials varied from 209/100,000 in 1972-73 [26] to 48/100,000 persons [27, 28] in 1978-81. A more recent study by Crump *et al*. [29], however, reported lower IR of 13/100,000 persons.

Most cases in developed countries arise in travellers and domestically acquired disease is

infrequently reported [30, 31]. A total of 1,393 typhoid cases were reported between 1994 and 1999 in the USA, 74% of which were related to travel. The rest were acquired domestically; 7% of these cases were part of recognised outbreaks [32].

Table 1. Crude typhoid fever incidence rates by region, 2000 [2].

Area/Region	Crude Incidence*	Incidence classification
Africa		
Eastern Africa	39	Medium
Middle Africa	39	Medium
Northern Africa	33	Medium
Southern Africa	233	High
Western Africa	38	Medium
Area total	**50**	**Medium**
Asia		
Eastern Asia	12	Medium
South-central Asia	622	High
South-eastern Asia	110	High
Western Asia	33	Medium
Area total	**274**	**High**
Europe		
Eastern Europe	5	Low
Northern Europe	<1	Low
Southern Europe	2	Low
Western Europe	<1	Low
Area total	**3**	**Low**
Latin America/Caribbean	53	Medium
Caribbean	58	Medium
Central America	51	Medium
South America	**53**	**Medium**
Area total		
Northern America		
Northern America	<1	Low
Area total	**<1**	**Low**
Oceania		
Australia/New	<1	Low
Zealand	60	Medium
Melanesia	60	Medium
Micronesia	59	Medium
Polynesia	**15**	**Medium**
Area total		
Global		
Crude total	178	High
Adjusted total	355	

*Per 100,000 persons per year.

As is evident from the data, typhoid is an endemic disease in developing countries, whereas it is sporadic in more developed, industrialised nations with universal provision of safe drinking water and sanitation. In such a scenario, it may be more relevant to estimate region-specific burden of disease. In this context, it is also notable that Crump *et al*. [2] reported the crude incidence of typhoid fever cases in Africa as 50/100,000 persons and in Asia as 274/100,000 persons, which is remarkable given that most socio-economic indices, including provision of safe drinking water and sanitation, are much lower in most parts of Africa than in South-East and South-Central Asia. This anomaly may be due to the lack of available data on typhoid fever incidence for Eastern, Central and Western Africa, as regional incidences were derived from extrapolation from 3 African incidence studies [2]. It may also reflect the different environmental conditions in different parts of Asia and Africa, and the adaptability of *S*. Typhi to survive and thrive in these varying conditions. This data highlights the need for more population-based studies of typhoid fever incidence from different parts of Africa to clarify the typhoid fever situation for this continent.

Asia and the Indian Subcontinent

Attempts to measure the incidence of febrile illness are hampered by problems associated with surveillance sensitivity and specificity. Although conducting surveillance at the tertiary hospital level is attractive, these approaches tend to underestimate disease incidence. While a routine door-to-door visit to identify febrile persons is a highly sensitive technique, it is limited by cost and time considerations. Similarly, syndrome based classification requires no laboratory capacity, but lacks specificity. Only a few developing countries have national typhoid fever surveillance systems, leading to an over-reliance on vaccine studies for estimates of typhoid fever incidence in these countries.

Data from Vietnam has reported an IR of typhoid fever ranging from 11.3 per 100,000 in 1991 to 12.2/100,000 in 2001 [33]. However, between 1994 and 1997, the IR shot up to 33.8, indicating the presence of both seasonal and temporal trends in typhoid fever [33]. The mean IR for typhoid in this period was 23.3/100,000 [34].

However, it is the Indian subcontinent which has the highest incidence of the disease worldwide. A previous study from Pakistan in 2006 revealed an IR of 170/100,000 (using blood culture) whereas a serology based IR was 710/100,000 (using Typhidot) [35]. Brooks *et al*. reported an overall IR of 3.9/1000 person-years in an urban slum in Bangladesh [36].

In India, there have been 6 population-based studies estimating the incidence of typhoid fever in the community [3, 37-41] (Table 2). The three studies led by Chuttani were all vaccine trials,

performed in the same urban slum between 1968 and 1974 [37-39]; Sinha *et al*. conducted their study in 1995-6 in a different urban slum in Delhi [40]. As is evident from the results, there has been little change in the IR of typhoid fever in Delhi, which is in northern India. However, Ochlai *et al*., who conducted their surveillance in an urban slum in Kolkatta in eastern India, reported a much lower incidence [3, 41].

Table 2. Incidence of typhoid fever in India: Population Studies.

Author	Year	Location	Area	Population	Age group	Incidence reported
Chuttani *et al.* [37]	1971	Delhi	Urban slum	6248	<17 years	9.6/1000 person years
Chuttani *et al.* [38]	1973	Delhi	Urban slum	6428	1-15 years	7.6/1000 person years
Chuttani *et al.* [39]	1977	Delhi	Urban slum	7292	6-17 years	7.4/1000 person years
Sinha *et al.* [40]	1999	Delhi	Urban slum	19585	0-40 Years	9.8/1000 person years
Ochiai *et al.* [41]	2005	Kolkata	-	57075	All ages	136.7 per 100000/yr
Ochiai *et al.* [3]	2008	Kolkata	Urban slum	59946	All ages	214.2 per 100000/yr

The results of these studies highlight the wide variation in incidence of disease even within the country. This could be due to various factors, including methodological differences in the studies, differences in standards of sanitation and hygiene, different geographical locations, lack of standardisation among the study populations, and impact of availability of an effective vaccine in the recent studies, to name a few. Therefore, it is important to point out that incidence in a study may not necessarily be generalized to the entire country.

In a recent multicentric study in 5 Asian countries - China, India, Indonesia, Pakistan and Vietnam - it was estimated that the incidence of typhoid ranged from 15.3 per 100,000 persons/year in China to 451.7 per 100,000/year in Pakistan [3] (Table 3). The rates were significantly higher in the south Asian sites (Pakistan and India) than in the South East & North East Asian sites (Vietnam, Indonesia, China). The previous multi-centre study by the same authors in 2005 had showed similar IRs [41] (Table 3). A vaccine trial in 2001 in southwestern China reported an IR of typhoid of 34.9/100,000 in 3-19 year old children [42]. However, several limitations existed in the study design. Recruitment strategies were different for each site, having to be adapted to local conditions. In the Indian and Pakistani sites, surveillance was supplemented by periodic home visits. In addition, the characteristics of the sites varied from rural to urban to urban slums. Finally, because the study relied on only a single blood culture for diagnosis, the observed incidence of typhoid fever is probably an underestimate.

Table 3. Incidence rate of typhoid fever in Asia: comparison of 2 multi-centre trials.

	Ochiai *et al.* [3] 2008		**Ochiai *et al.* [41] 2005**	
Country	**Incidence per 100,000 population**	**Population**	**Incidence per 100,000 population**	**Population**
Pakistan	451.7	101937	394.2	15219
India	214.2	59946	136.7	57075
Indonesia	81.7	160261	82,4	160257
China	15.3	112889	15.2	98376
Vietnam	21.3	281781	-	-

In typhoid endemic areas, hospital-based data have reported most cases in children aged 5-19 years and young adults [43-45]. However, other recent population-based studies from India, Indonesia and Vietnam suggest that in some settings, typhoid fever is also common in 1-5 year old children [40, 46-48] (Table 4). Ochiai *et al.* [3] reported in their multi-centric trial that the mean age of typhoid was significantly lower in the South Asian sites (Pakistan and India) than in the South East and North East Asian sites and suggested that there was an inverse correlation between typhoid incidence and mean age of cases.

While the 1997 Global Survey of *Salmonella* serotyping estimated an incidence of 1 case of paratyphoid fever for every 4 cases of typhoid fever, studies from India and Nepal suggest that in some settings, *S*. Paratyphi A can contribute up to

half of all cases of enteric fever [49-51]. Population surveillance had revealed an IR of *S*. Paratyphi A of 42/100,000 persons in India, 72/100,000 in Pakistan, 13.7/100,000 in Indonesia and 27/100,000 in China [41]. These figures may be due in part to the fact that current vaccines only offer protection against typhoid fever. Future vaccination strategies in these areas should include bivalent vaccines that protect against *S*. Paratyphi A as well as *S*. Typhi.

Table 4. Age-specific incidence of culture-proven typhoid fever: population-based studies.

	Age (years)	Incidence/100,000 per year
	Urban	
Indonesia [46]	3-6	1307
	7-19	1172
	20-44	182
India [40]	0-4	2730
	5-19	1170
	20-40	110
	Rural	
Vietnam [47]	2-4	358
	5-9	531
	10-14	429
	15-19	153
	20-29	149
	30-39	51
Vietnam [48]	2-4	414

Sinha *et al*. (1999) also found that the incidence of typhoid fever in India varied seasonally. The maximum incidence occurred during the monsoon (July-October) of 18.8 cases/1,000 person years while lower rates of 5.4 and 4.7 per 1,000 person years occurred during the summer and winter seasons respectively [40].

As is evident from the data presented, typhoid fever is seen predominantly in developing countries, and the Indian subcontinent is a hotspot of disease activity. Although typhoid is no longer endemic in most of the developed world, imported cases continue to occur in returning travellers, immigrants or migrant workers. Seventy-four percent of all typhoid cases occurring in the US are travel-associated, 43% of which originated in India and Pakistan. In the UK, 60% of all cases were travel related, with up to 70% of these being imported from India or Pakistan [53]. Globalisation and increasing air travel are responsible for imported cases of tropical infectious diseases occurring in industrialised nations. Vaccination should be considered for persons planning even short-term travel to high-risk areas such as the Indian subcontinent. The high prevalence of multidrug resistance among *S*. Typhi strains in South Asia further compounds the risk to travellers in this region [53].

The impact on the disease burden of multidrug resistance and emergence of recent fluoroquinolone resistance has not been estimated. However, the calculated clinical and microbiological failure rates, the median time to fever clearance, relapse rates and faecal carriage rates are higher in patients infected with drug resistant strains than for those with drug sensitive strains [54,55]. This increases the pool of patients and carriers who can potentially transmit the pathogens to household contacts and in the community, which may actually be an important factor for the persistently high prevalence of typhoid fever in regions where drug resistance is common.

Conclusions

Scarcity of diagnostic facilities in areas of high typhoid endemicity has probably led to an underestimation of the burden of typhoid fever worldwide. Population-based studies have demonstrated a wide variation in the incidence of typhoid fever both globally and within India [2,3,37-41]. Information on typhoid case fatality rate is also scant, with current estimates based on hospital data. This highlights the need for more population-based studies in different regions of the country. This would help to prioritise the use of health-care resources for disease control and target vaccination and other preventive health measures in the community.

With the widespread emergence of nalidixic acid resistant strains, fluoroquinolone resistant strains, and the sporadic occurrence of cephalosporin resistant strains of *S*. Typhi and *S*. Paratyphi A, our armamentarium of drugs active against enteric fever is rapidly shrinking. Improvements in the provision of clean water and sanitation are critical to reduce the burden of typhoid in developing countries. Use of combination chemotherapy, availability of cheap, new active drugs and wider use of effective, low-cost vaccination in endemic areas is a possible control strategy. With the new finding that a high percentage of typhoid infection occurs in children five years old and younger, the need to develop an effective conjugate Vi vaccine which can be given as part of the Expanded Program of Immunization

should be a priority. In Thailand, yearly vaccination programs for schoolchildren have reduced the incidence of typhoid fever dramatically [56]. The impact of drug resistance may improve the cost effectiveness of mass vaccination programs in typhoid endemic countries such as India.

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Corresponding Author: T. D. Chugh, Dr. B. L. Kapur Memorial Hospital, New Delhi, India, E-mail: chughtd@hotmail.com

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