Mini-Review Article

Kathmandu, Nepal: Still an enteric fever capital of the world

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Abstract
Kathmandu, the capital city of Nepal, has been previously coined an enteric fever capital of the world. Several studies have poignantly emphasized the significant burden of enteric fever within the local population and in travellers visiting the area. The population of Kathmandu is increasing and available figures suggest that enteric fever caused by *Salmonella* serovars Typhi and Paratyphi A show no significant signs of decreasing. Furthermore, our recent research demonstrates that the ratio of disease caused by these two organisms is shifting towards *S*. Paratyphi A. Here, we outline some of the major features of enteric fever in Kathmandu, including diagnosis, seasonal variation, transmission, and some characteristics of the infecting organisms. Our findings highlight the requirement for better understanding of the disease within the city; in turn, this will aid development of a targeted control strategy.

Key Words: Kathmandu, *Salmonella* Paratyphi A, *Salmonella* Typhi, Enteric fever

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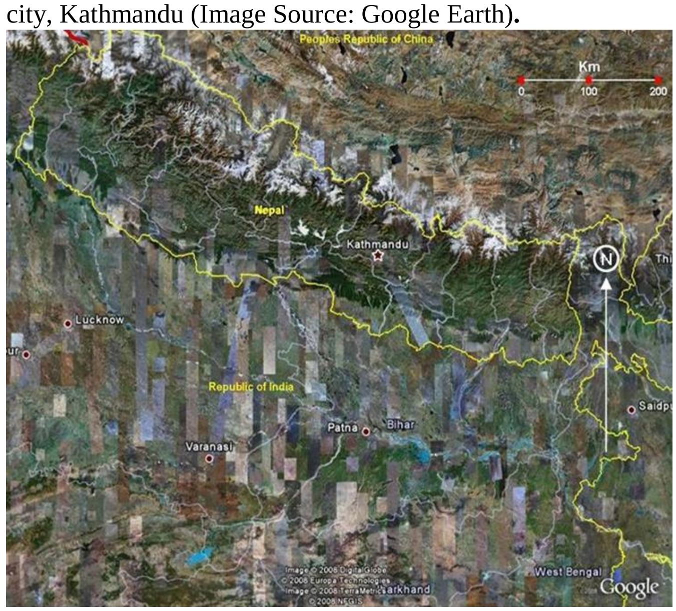
Nepal is a country of diverse geography and lies landlocked between the Republic of India to the South, East and West, and the Himalayan frontier with the Peoples Republic of China to the North (Figure 1). The climate varies dramatically from cold winter months to a hot and sticky spring, a humid monsoon season, and a temperate, dry autumn. The capital city, Kathmandu, is the largest city in Nepal and lies in the central region of the country (Figure 1). Kathmandu is nestled at an altitude of 1,300 m in the Kathmandu valley and is the most highly populated area of the country with a density of over 1,100 people per square kilometer inhabited by approximately 2,000,000 people. The population of Nepal has increased steadily over the last eight years from 24.24 million to 28.11 million (http://www.worldbank.org); this has been most prominent in Kathmandu with many people flocking to the capital in search of employment.

The World Bank calculates that Nepal has a gross per capita income of $340 (www.worldbank.org). This classifies Nepal as the 193rd poorest nation on earth and the poorest nation in Asia. The most recent assessment of poverty within the general populous calculated that 24.1% of the population survives on less than $1 a day and 68.5% survive on less that $2 a day (1990-2005 figures: http://www.undp.org). Poverty and political instability within Nepal have had obvious detrimental effects on infrastructure; while 89% of the population now has access to improved water sources, only 45% of the population has access to improved sanitary conditions (http://www.undp.org).

Figure 1. Geographical positioning of Nepal and the capital city, Kathmandu (Image Source: Google Earth)**.**

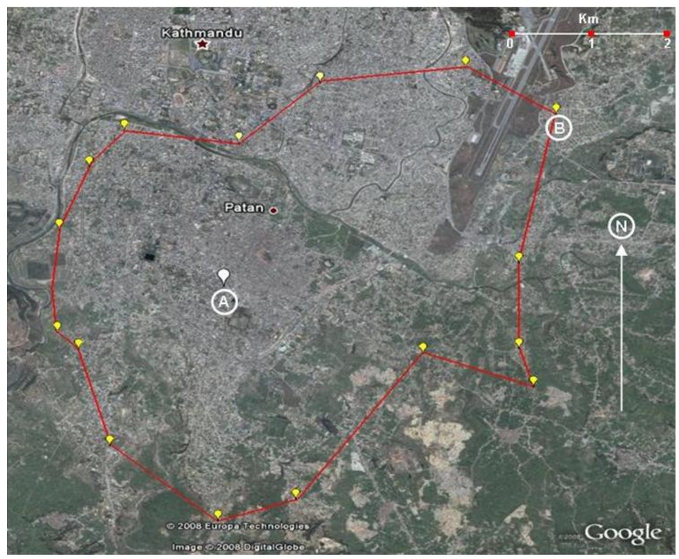


Historically, prior to the beginning of the twentieth century, typhoid (enteric) fever was a significant cause of morbidity and mortality in the overcrowded and unsanitary conditions of European and North American cities. Advances in public health, such as the provision of reliable clean water supplies and sewage systems, led to a decrease in the incidence of enteric fever in these places. Today the vast burden of disease is encountered in the developing world where poor sanitary conditions remain and facilitate transmission. While enteric fever in rural communities is not uncommon, the overwhelming focus is akin to pre-twentieth century socio-economics of the disease and affects the impoverished living in urban centres. These predisposing conditions are particularly apparent in some parts of twenty-first century Kathmandu, where living conditions appear to be optimal for constant transmission of the disease.

The majority of cases of enteric fever are attributed to the bacterium *Salmonella enterica* serovar Typhi (*S*. Typhi). However, *Salmonella enterica* serovar Paratyphi A (*S*. Paratyphi A) is now recognized as an emerging agent of enteric fever in endemic regions [1]. Accurate estimates of the burden of enteric fever (*S*. Typhi and *S*. Paratyphi A) in the context of Nepal and Kathmandu are difficult to obtain; diagnostic facilities are generally limited within the city and non-existent in many rural areas. Our experience within the Patan area of Kathmandu (Figure 2) suggests that many cases are self-treated, with patients using unprescribed drugs obtained from private pharmacies. This is also the case in many developing countries, where a wide range of medications are available prior to consultation with a physician. Those who do attend a local clinic or hospital are assessed and generally treated as out-patients. Both self-treatment and treatment as an out-patient have obvious potential detrimental consequences for the containment of the disease. There is no way of checking compliance with therapy, or, in the case of self-treatment, of knowing if the selected antimicrobial therapy is appropriate. Therefore, the opportunity of the patient to infect others in close contact is significant and the potential for relapse or re-infection of the patient is high.

The issue of infection within the community is particularly poignant with respect to enteric fever as *S*. Typhi is known to be able to survive in the gall bladder for prolonged periods and plays a pivotal role in the transmission of the pathogen [2]. The role of chronic carriage of *S* Paratyphi A, however, is less well defined and largely undescribed. We are currently assessing the role of the chronic carrier in the dissemination of organisms that cause enteric fever within Kathmandu. Persistent carriage of *S*. Typhi is a known post-treatment complication with some antimicrobial agents [3]; therefore, inadequate treatment in the community may facilitate transmission within the home.

Figure 2. The enteric fever catchment area surrounding Patan Hospital (Image Source: Google Earth).
Patan is part of the metropolitan area of greater Kathmandu and lies to the south of the city of Kathmandu, separated by the Bagmati River. This Google Earth image has been drawn to display our study catchment area surrounding Patan Hospital, labelled A. The position of residences enteric fever patients who have been enrolled in clinical studies and are farthest from the hospital in each direction have been highlighted on the map with yellow markers and joined to calculate the catchment area. B marks the location of the residence farthest from the hospital and represents a distance of 6 km; the total catchment area surrounding the hospital is approximately 28.5 km^2.



Like many other places with a high burden, enteric fever is largely diagnosed on the basis of clinical symptoms and signs in the outpatient clinics. The most common features we see at presentation are high temperature, headache, nausea, anorexia, abdominal pain and diarrhoea. Other features, such as bradycardia and splenomegaly, are uncommon. Clinical symptoms are not the most accurate diagnostic procedure, as other infections such as *Rickettsia typhi* are common in Kathmandu and offer similar clinical syndromes on presentation [4]. The culturing of bone marrow or blood are the investigations of choice, but they are not performed routinely. Blood culturing is limited as the cost is often prohibitive and many hospitals do not have adequate microbiology facilities and personnel to perform such assays. Tertiary hospitals, such as our hospital in Patan, have sufficient facilities to perform blood culturing; however, bone marrow culture is usually not performed unless it is part of a detailed investigation for a patient with fever of unknown aetiology.

Patan Hospital is one of the three general hospitals within the Kathmandu metropolitan area, and 90% of the patients attending the hospital are from the immediate Kathmandu valley and Lalitpur areas. By tracking where patients enrolled in our clinical trials reside we can identify infection “hotspots” within the vicinity (Figure 2). The focus of enteric fever diagnosed at the hospital lies within a 6-km radius, demonstrating that the local burden is concentrated in a relatively small area. Between 1993 and 2003, we isolated 9,124 *Salmonella* from 12,252 positive blood cultures [5]. Over the period of the study the overall rate of enteric fever due to *S.* Typhi and *S.* Paratyphi A more than doubled between 2001 and 2003, when compared to the three previous years. Additionally, the proportion of enteric fever cases caused by *S.* Paratyphi A increased from 17.5% in 1993 to 34% in 2003. *S.* Paratyphi A is still increasing and represents a significant proportion of all the isolates we culture from people suspected with enteric fever (our unpublished data).

There has always been an assumption that infection caused by *S.* Paratyphi A is milder than infection caused by *S.* Typhi, but in Nepal this assumption is unfounded [6]. The largest prospective study of enteric fever (609 patients), which was performed in our hospital, found that the disease syndromes caused by *S.* Paratyphi A and *S.* Typhi are clinically indistinguishable [6]. Furthermore, *S.* Paratyphi A isolates were more likely to be resistant to ofloxicin and have decreased susceptibility to ciprofloxacin. Reduced susceptibility to fluoroquinolones has become common among *S.* Typhi and *S.* Paratyphi A throughout Asia [7]. This pattern of resistance has also been demonstrated by Woods *et al.* where they isolated equivalent numbers of *S.* Typhi and *S.* Paratyphi A during an adult fever study also within Kathmandu [8]. Third-generation cephalosporins such as ceftriaxone and cefotaxime have proved to be effective alternatives for patients who respond poorly to a fluoroquinolone; however, resistance to these agents has also increased and has additionally been described in Nepal [9]. Pokharel and co-workers described the antibiotic resistance patterns of *S.* Typhi and *S.* Paratyphi isolated from blood cultures. They identified a total of 541 invasive *Salmonella* isolates, and 7% of the *S.* Paratyphi A strains were resistant to two or more antibiotics of which three strains, unusually, tested positive for ESBL production.

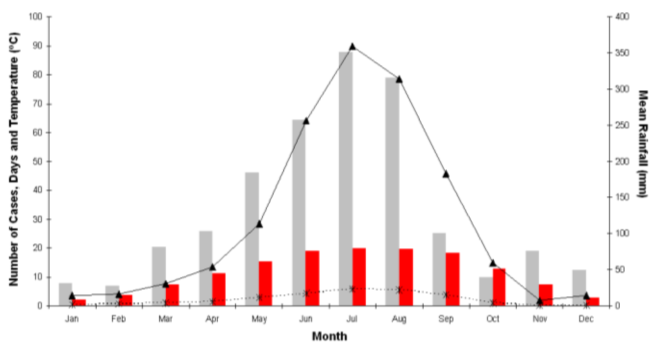
There have been several epidemiological studies identifying risk factors for contracting enteric fever [10,11]. To date there has not been such an epidemiological study undertaken in Kathmandu. This is one of the aims of our current research and our present working hypothesis is that the majority of transmission occurs through the municipal water supply. Water-borne infection seems to be the most likely transmission route as members of the genus *Salmonella* are highly adaptable and known to be capable of surviving for several days in sea and groundwater [12]. Faecal contamination of urban water supplies in Nepal has been reported; an outbreak of *S.* Typhi infecting 5,936 people in Bharatpur in 2002 was traced to the municipal water supply [13]. A study from the Terai region of southern Nepal demonstrated that coliforms were present in 61% of the provided water samples [14]. In an urban setting, Bhatta *et al*. could isolate and identify multiple drug resistant (MDR) *S.* Typhi and *S.* Paratyphi in the drinking water supply of 14% of their samples [15]. These data support our hypothesis. The majority of people living within the referral area of Patan hospital do not have access to piped water within the home and rely on taking water from the local water spouts (Figure 3). The water sources are focal points of communities within the city and are generally used for drinking, washing, cooking and recreation. The municipal water is only intermittently chlorinated and not protected from the environment; the historic nature of the waterways system suggests that the opportunity for drinking water and sewage to be mixed is high. Our preliminary data show that faecal contamination of the water sources around areas of high enteric fever burden is significant, suggesting that this is probably a major risk factor in contracting disease. Efforts to improve the water supply have been limited, due to cost, lack of infrastructure, and public opposition because of the negative effect on taste when consumed.

Figure 3. Some residents of Patan, Kathmandu, collecting water from a typical municipal drinking water spout.

Transmission through the water supply is also supported by the seasonal variation in disease incidence. The heaviest burden of enteric fever is during the monsoon months from June to August. Data taken from ~3 years of studies demonstrate an association with the average monthly rainfall and a peak in the seasonal temperatures, with an obvious increase in cases between June and August and a maximum in July (Figure 4). Seasonal variation in enteric fever has been highlighted before and tends to peak with highest temperatures in Karachi, Pakistan, and with rainfall in the Mekong Delta area of Southern Viet Nam [16,17]**.** Our theory for the incidence following seasonal change is that during the monsoon the ground water becomes saturated and the intermingling of faecal matter and the water supply becomes more frequent.

Figure 4. Seasonal variation in the number of cases of enteric fever in Kathmandu.

Data was collected from June 2005 to June 2008 and is combined from all patients enrolled in clinical studies over this period. The number of cases of clinically diagnosed and treated enteric fever is represented by the grey bar. The average minimum temperature for each month is shown by the red bar. The seasonal variation in rainfall is highlighted by the average rainfall per month (solid line with triangles) and mean number of days with rain (broken line with crosses).



Conclusion

Without doubt, the most important preventive measures required for reduction of enteric fever in Kathmandu are clean water, safe food, appropriate personal hygiene, and adequate sanitation. With the ever increasing rise of antibiotic resistance and concomitant rise of *S.* Paratyphi A infections, prevention has become imperative. While vaccination is an effective tool for prevention of typhoid fever, there is currently no vaccine for paratyphoid fever. Enteric fever caused by both *S*. Typhi and *S*. Paratyphi A is also common in travellers visiting the area [18,19]. Therefore, the lack of a vaccine for *S*. Paratyphi A combined with the rise in *S*. Paratyphi A infections poses a threat not only to the inhabitants of the endemic areas but also to travellers.

Identification of the risk factors and routes of transmission for enteric fever within Nepal will aid in the development of a rational control strategy. With accurate identification, resources should be allocated towards controlling the most important factors, namely food sold by vendors, chlorination of drinking water, construction of proper water distribution and sewage networks, identification of carriers within or outside affected households, vaccination campaigns, and hygiene education. Arguably the most dramatic reduction of enteric fever would be achieved by modernizing the water and sewage systems within the city. However, the cost of supplying all households within the city with an adequate water supply may be prohibitive and a targeted vaccination program may be a more achievable short-term goal.

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References

1. Ochiai RL, Wang X, von Seidlein L, Yang J, Bhutta ZA, Bhattacharya SK, Agtini M, Deen JL, Wain J, Kim DR, Ali M, Acosta CJ, Jodar LClemens JD (2005) *Salmonella* paratyphi A rates, Asia. Emerg Infect Dis. 11: 1764-6.
2. Levine MM, Black RE, Lanata C (1982) Precise estimation of the numbers of chronic carriers of *Salmonella* typhi in Santiago, Chile, an endemic area. J Infect Dis. 146: 724-6.
3. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ (2002) Typhoid fever. N Engl J Med. 347: 1770-82.
4. Zimmerman MD, Murdoch DR, Rozmajzl PJ, Basnyat B, Woods CW, Richards AL, Belbase RH, Hammer DA, Anderson TP, Reller LB (2008) Murine typhus and febrile illness, Nepal. Emerg Infect Dis. 14: 1656-9.
5. Maskey AP, Basnyat B, Thwaites GE, Campbell JI, Farrar JJ, Zimmerman MD (2008) Emerging trends in enteric fever in Nepal: 9124 cases confirmed by blood culture 1993-2003. Trans R Soc Trop Med Hyg. 102: 91-5.
6. Maskey AP, Day JN, Phung QT, Thwaites GE, Campbell JI, Zimmerman M, Farrar JJ, Basnyat B (2006) *Salmonella* enterica serovar Paratyphi A and *S*. enterica serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. Clin Infect Dis. 42: 1247-53.
7. Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, Van Vinh Chau N, Tuan PQ, Page AL, Ochiai RL, Schultsz C, Wain J, Bhutta ZA, Parry CM, Bhattacharya SK, Dutta S, Agtini M, Dong B, Honghui Y, Anh DD, Canh do G, Naheed A, Albert MJ, Phetsouvanh R, Newton PN, Basnyat B, Arjyal A, La TT, Rang NN, Phuong le T, Van Be Bay P, von Seidlein L, Dougan G, Clemens JD, Vinh H, Hien TT, Chinh NT, Acosta CJ, Farrar J, Dolecek C (2007) Antimicrobial drug resistance of *Salmonella* enterica serovar typhi in Asia and molecular mechanism of reduced

susceptibility to the fluoroquinolones. Antimicrob Agents Chemother. 51: 4315-23.

8. Woods CW, Murdoch DR, Zimmerman MD, Glover WA, Basnyat B, Wolf L, Belbase RH, Reller LB (2006) Emergence of *Salmonella* enterica serotype Paratyphi A as a major cause of enteric fever in Kathmandu, Nepal. Trans R Soc Trop Med Hyg. 100: 1063-7.
9. Pokharel BM, Koirala J, Dahal RK, Mishra SK, Khadga PK, Tuladhar NR (2006) Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Salmonella* enterica (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives. Int J Infect Dis. 10: 434-8.
10. Sur D, Ali M, von Seidlein L, Manna B, Deen JL, Acosta CJ, Clemens JD, Bhattacharya SK (2007) Comparisons of predictors for typhoid and paratyphoid fever in Kolkata, India. BMC Public Health. 7: 289.
11. Vollaard AM, Ali S, van Asten HA, Widjaja S, Visser LG, Surjadi Cvan Dissel JT (2004) Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. Jama. 291: 2607-15.
12. Wait DA and Sobsey MD (2001) Comparative survival of enteric viruses and bacteria in Atlantic Ocean seawater. Water Sci Technol. 43: 139-42.
13. Lewis MD, Serichantalergs O, Pitarangsi C, Chuanak N, Mason CJ, Regmi LR, Pandey P, Laskar R, Shrestha CD, Malla S (2005) Typhoid fever: a massive, single-point source, multidrug-resistant outbreak in Nepal. Clin Infect Dis. 40: 554-61.
14. Atreya K, Panthee S , Sharma P (2006) Bacterial contamination of drinking water and the economic burden of illnesses for the Nepalese households. Int J Environ Health Res. 16: 385-90.
15. Bhatta DR, Bangtrakulnonth A, Tishyadhigama P, Saroj SD, Bandekar JR, Hendriksen RS, Kapadnis BP (2007) Serotyping, PCR, phage-typing and antibiotic sensitivity testing of *Salmonella* serovars isolated from urban drinking water supply systems of Nepal. Lett Appl Microbiol. 44: 588-94.
16. Kelly-Hope LA, Alonso WJ, Thiem VD, Anh DD, Canh do G, Lee H, Smith DL, Miller MA (2007) Geographical distribution and risk factors associated with enteric diseases in Vietnam. Am J Trop Med Hyg. 76: 706-12.
17. Siddiqui FJ, Rabbani F, Hasan R, Nizami SQ, Bhutta ZA (2006) Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. Int J Infect Dis. 10: 215-22.
18. Keller A, Frey M, Schmid H, Steffen R, Walker T, Schlagenhauf P (2008) Imported typhoid fever in Switzerland, 1993 to 2004. J Travel Med. 15: 248-51.
19. Basnyat B, Maskey AP, Zimmerman MD, Murdoch DR (2005) Enteric (typhoid) fever in travelers. Clin Infect Dis. 41: 1467-72.

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