Pediatric *Salmonella typhi* infections in a Canadian pediatric hospital: An Ounce of prevention is worth a pound of cure

Jeannette L. Comeau, MD MSc[1,2],Thai Hoa Tran, MD FRCPC[1], Dorothy L. Moore, MD PhD FRCPC[1], Chi-Minh Phi, MD FRCPC[2], Caroline Quach, MD MSc FRCPC[1,3].

[1]Infectious Diseases Division, Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Québec, Canada.

[2]Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Québec, Canada.

[3]Department of Microbiology, Montreal Children's Hospital, McGill University, Montreal, Québec, Canada.

Financial Disclosure: All authors state that they have no financial relationships relevant to this article to disclose.

Short title: *S.typhi* infections in children – a 20-year review

Address correspondence to Caroline Quach MD, Infectious Diseases Division, Montreal Children's Hospital, 2300 Tupper Street, Room C-1242, Montreal, Québec, Canada, H3H 1P3. Phone: 514 412-4485. Fax: 514 412-4494. E-mail: caroline.quach@mcgill.ca

Key Words: Typhoid Fever, Travel, Immigrants, *Salmonella typhi*, Pre-travel counseling

Word count: 2,229

ABSTRACT

In developed countries, typhoid fever cases generally occur in travelers or recent immigrants from endemic areas. We aimed to describe the epidemiology of *Salmonella typhi* infections in children presenting to a pediatric teaching hospital in Montreal.

METHODS: All patients < 18 years of age presenting to the Montreal Children's Hospital between 1991 and 2011, with a laboratory-confirmed diagnosis of typhoid fever (*S.typhi* isolated from blood or stool) were included in this retrospective case series.

RESULTS: In the past 20 years, 39 cases of typhoid fever were identified (average age 7.5 years). Cases in newly arrived immigrants (4) occurred early following their arrival (median of 15.5 days). The vast majority of cases (76.9%) occurred in children who visited friends and relatives (VFRs) in their home country. None of the travelers had received typhoid fever vaccination prior to departure. All cases presented with high fever (average 40.4^0C) that lasted on average 15.8 days. Common accompanying symptoms were anorexia, abdominal pain, vomiting, and diarrhea. All *S.typhi* isolates were susceptible to third-generation cephalosporins and 7 were resistant to ciprofloxacin. Ampicillin resistance increased over time: 6 of the 10 resistant isolates occurred after 2000 (p=0.05). No death occurred.

CONCLUSION: As most cases occurred in Canadian VFR children, there is a role for increased awareness on the part of family physicians and pediatricians caring for these children to discuss travel-related infections during regular scheduled visits, as parents will not consult travel clinics or discuss their travel plans before traveling back to their home country.

Words: 248

INTRODUCTION

Typhoid fever is a systemic febrile illness caused by the bacterium *Salmonella enterica* serotype *typhi* that infects approximately 21.6 millions people annually and is responsible for more than 200,000 deaths each year worldwide (1). Overcrowded populations and poor hygienic conditions predispose developing countries to typhoid endemics with the highest incidence found in the Indian subcontinent and Southeast Asia (1). The introduction of effective antibiotic treatment radically reversed this life-threatening disease into a readily treatable condition. However, the emergence of multidrug-resistant *S. typhi* strains in recent years, the lack of rapid diagnostic tests, and the growing globalization have led to new challenges in the management of typhoid fever as a serious global public health concern.

Early studies showed that children and young adults between the age of 5 to 25 years were the most susceptible to be hospitalized for typhoid fever (2,3), and thus it was thought to be a disease affecting the school-aged and adolescent child. In 1999, however a large cohort study of more than 8,000 people in Kalkaji, Delhi, India demonstrated that 44% of culture positive cases of *S typhi* occurred in children < 5 years of age (4). More recently, an Indian study profiling hospitalized children in Chennai, South India demonstrated that almost 50% of hospitalized patients with typhoid fever were ≤ 5 years (5). In developed countries, this infection occurs generally in travelers or recent immigrants from endemic areas. Considering the population served by our hospital, the objective of this study was to describe the epidemiology of *S. typhi* infections in children presenting to the Montreal Children's Hospital (MCH) from 1991 to 2011, aiming at improving preventive strategies for this infection.

METHODS

Study Setting

Montreal, Québec, Canada is an economically and culturally diverse urban center. Its metropolitan area has a population of approximately 1.8 million people, an estimated 28% of whom are international immigrants (6). More than 120 ethnic communities are represented and statistics from 2006 reported that newly arrived immigrants came mainly from Asia (31.1%) and Africa (27.8%) (6). The Montreal Children's Hospital (MCH) is a pediatric tertiary care center, affiliated to the McGill University Health Center, located in downtown Montreal with, on average, 5,000 emergency department visits per month.

Study Population

Pediatric patients aged < 18 years with a laboratory-confirmed diagnosis of *S. typhi* infection at the MCH from January 1991 to December 2011 were studied. Cases with either a stool or blood culture positive for *Salmonella typhi* were identified using the MCH microbiology laboratory database.

Study Design

This study is a case series that describes children with typhoid fever identified at a pediatric tertiary care teaching hospital in Montreal. A retrospective chart review was performed for all identified patients. Standard data extraction forms were used to collect the following variables: patient demographics (date of birth, sex, postal code of residence), country of origin, travel destination, and vaccination status, including pre-travel counseling if available. Clinical presentation, course of illness, antimicrobial susceptibility profile of the isolate, treatment, and outcome were also collected.

Statistical Analysis

Descriptive statistics (mean, median and standard deviation), relative risk with 95% confidence interval (CI) and t-test were used for univariate analysis (SAS Institute, version 8.0, Cary NC).

RESULTS

In the past 20 years, we identified 39 children with typhoid fever who presented to the MCH. The patients' age ranged from 10 months to 17.7 years with a mean (± standard deviation [SD]) of 7.5 ± 4.8 years. The annual number of cases varied between 0 and 6, as illustrated in Figure 1.

Twenty-seven patients (69%) were born in Canada, while 12 (30.8%) were born abroad but lived in Canada at the time of presentation. Patients who had immigrated to Canada had arrived on average 4.5 years before their illness (median 2.8 years, SD 5.5 years; range 2 days – 13.5 years). Thirty (76.9%) patients had traveled abroad prior to their infection and 4 (10.2%) were recently landed immigrants or refugees from endemic areas. Date of arrival to Canada was missing for 2 patients who had immigrated to Canada and 3 subjects had no recorded travel outside Canada (one had lived in Ivujivik, Northern Quebec where typhoid has been documented (7)). Recently landed immigrants and refugees, arrived on average 16.25 ± 13.1 days before illness onset (median 15.5 days). The most common travel destinations were Bangladesh (33%), India (26%), Pakistan (17%), and Lebanon (7%) as illustrated in Figure 2. The median duration of these travels was 90 days (range 14-912 days). Of note, only one took malaria prophylaxis while traveling, and none had a record of having received a typhoid vaccine prior to departure.

Table 1 outlines the clinical presentation of patients seen at the MCH. All patients presented with elevated fever (average ± SD: 40.4 ± 0.6°C) that lasted on average 15.8 days.

Other common symptoms included anorexia (69.2%), abdominal pain (56.4%), vomiting (48.7%), and diarrhea (46.2%).

Table 2 describes patients' clinical course and management. Thirty-four children (87%) required admission, with an average length of stay (± SD) of 8.8 ± 3.3 days. Thirty-six patients (92%) were treated with a third-generation cephalosporin (ceftriaxone [33] and cefotaxime [3]). Ten patients completed their course of treatment with oral antibiotics as determined by antimicrobial susceptibility results. The average duration of total antibiotic course (± SD) was 11.8 ± 4.0 days.

Thirty-six patients had positive blood cultures for *S. typhi* and twenty-six had positive stool cultures. The average (± SD) duration of positive blood culture was 2.3 (± 1.3) days. Among the blood isolates, twenty-six (72%) were susceptible to ampicillin and trimethoprim-sulfamethoxazole (TMS), and all were susceptible to ceftriaxone. Eight different isolates from separate cases showed antibiotic resistance to both ampicillin and TMS. Seven isolates were resistant to ciprofloxacin. The resistance patterns are shown in Figure 3. Resistance to ampicillin is seen in more recent years (4 of 18 isolates before 2000 compared to 6 of 18 afterwards; p=0.05). Ciprofloxacin resistance appears to have increased after 2000, occuring in 7 of 11 isolates tested, however ciprofloxacin susceptibility was not always reported.

Fifteen complications (38.5%) following typhoid fever were reported including hepatitis [4], coagulopathy [3], meningitis [2], cholecystitis [1], shock [1], delirium [1], and relapse requiring readmission [2]. No death was observed. One patient needed the administration of 2 doses of IVIG. Complications occurred in 33% of children under 5 years of age and in 44% of patients who had been febrile for more than 2 weeks.

DISCUSSION

Cases of typhoid fever in children presenting to the Montreal Children's Hospital were similar to the American trend with 76.9% of our typhoid cases being found in Canadians who had traveled to endemic areas, mainly to the Indian subcontinent including Bangladesh, India and Pakistan where typhoid fever incidence exceeds 600 cases per 100,000 persons per year[1].

Although proper sanitary facilities have greatly contributed to the quasi elimination of typhoid fever in the developed world, *S. typhi* infections remain a global public health concern even in developed countries. A meta-analysis of 22 population-based studies reviewed the epidemiology of typhoid fever in 2000 and found that the global burden of typhoid fever had increased in terms of annual morbidity but decreased in mortality, from 16 million cases and 600,000 deaths in 1984 to 21,650,974 cases and 216,510 deaths 16 years later (1). In North America, 453 cases of typhoid fever were recorded in 2000 (1) and occurred mainly in travelers returning from endemic countries or in new arrivals from endemic areas. It has been estimated that the incidence of typhoid fever among travelers to developing countries was 3-30 cases per 100,000 travelers (1). American data reported that 72% to 74% of persons with *S. typhi* infections had a history of recent travel prior to their illness (8,9).

Typhoid fever remains a difficult diagnosis to make clinically because of its nonspecific presentation. The most common symptoms and signs in our twenty-year retrospective study were fever (100%), anorexia (69.2%), abdominal pain (56.4%), diarrhea (46.2%), vomiting (48.7%), headache (38.5%), and hepatosplenomegaly (20.5%). Constipation (12.8%) is often present in adults; but in children, diarrhea is a more common clinical feature (10).

The definitive diagnosis of typhoid fever relies on the isolation of *S.typhi* from blood cultures that are positive in 60-85% of cases (10). Bone marrow culture has a greater sensitivity, estimated to be as high as 95%, regardless of prior antibiotic treatment or duration of illness, two factors that have been associated with reduced sensitivity of blood culture (10). Stool culture has a lower sensitivity, around 30%,(10) and becomes positive usually a week into the course of illness (11). Our study demonstrated once again the superiority of blood culture over stool culture as only 67% of typhoid fever cases had positive stool cultures.

In our study, 15 patients (38.5%) presented complications of their typhoid fever. These included hepatitis, coagulopathy, meningitis, cholecystitis, shock, delirium, relapse, and chronic *S. typhi* carrier status, requiring supportive measures and close monitoring. Compared to the literature, our rate of complications was higher but the clinical presentation was milder than what has been reported. Previous studies have reported complications in 10-15% of patients with *S. typhi* infections (10). Illness for greater than 2 weeks was highly associated with gastrointestinal bleeding (10%), intestinal perforation (1-3%), and typhoid encephalopathy (10-40%) (10). This discrepancy in complication rate may be because 60-90% of patients with *S. typhi* infections worldwide were treated as outpatients,(4,12) increasing the likelihood of losses to follow-up and non-detection of complications. None of our patients died, nor did they require surgical interventions. Recent population-based studies from South Asia suggested that children under 5 years of age had the highest incidence of complications, opposing previous reports from Latin America and Africa that had described a milder disease in infancy and childhood (5,13,14).

The mainstay in the treatment of typhoid fever is antibiotic therapy. Historically, chloramphenicol, amoxicillin and TMS constituted the first-line therapy for uncomplicated and fully susceptible strains of *S. typhi* (15,16). However, the emergence of chloramphenicol-

resistant typhoid fever in 1972 and the subsequent resistance to all first-line agents in the late 1980s have contributed to the widespread use of fluoroquinolones (17). The efficacy of quinolones in the treatment of typhoid fever has been confirmed in multiple randomized-controlled trials in which the cure rates exceeded 96% and had been proven safe for all age groups, including children after a short-term use of fluoroquinolones (18-26). Of note, however, we do document resistance in isolates after 2007 (when our lab began routinely researching ciprofloxacin resistance) in 7 of 9 isolates. Recently, an Australian group demonstrated an increase in nalidixic acid resistance (fluouroquinolone) and suggested ceftriaxone or azithromycin as appropriate first-line agents (27).

The majority of our patients (82%) received intravenous ceftriaxone as first-line therapy. The mean fever-clearance time after inititation of antibiotics in our study population was 4.8 ± 3.6 days, comparable to the average of one week reported in randomized controlled trials using cephalosporins (21,24,25,28). Among our patients, only 2 cases relapsed (both had received ceftriaxone) requiring readmission. This relapse rate of 5% was similar to the 3-6% rate reported in the literature (21,24).

As humans are the only reservoir for *S. typhi*, control of the disease may theoretically be achieved by adequate antimicrobial treatment of both clinical cases and asymptomatic carriers. However, the role of vaccinations as a preventive measure is of greater importance in controlling the disease (29). Typhoid vaccines are available and recommended for travelers to endemic areas; yet, none of our patients had been vaccinated against typhoid prior to travel. This may be explained by the fact that the risk of infection upon traveling is considered benign, or simply not considered, by parents who lived in these endemic areas without being sick and who are returning to visit friends and relatives.

There are currently two commercially available vaccines, both offer protection ranging from 60% to 80% (29): the live, attenuated oral Ty21a vaccine and the Vi-based polysaccharide vaccine. Both are generally well tolerated. The Ty21a vaccine is a live bacterial vaccine administered orally and is contraindicated in pregnant women, in children < 5 years of age, in individuals with an acute gastrointestinal condition or inflammatory bowel disease, and in immunocompromised patients. Revaccination may be repeated after 7 years have elapsed. The Vi polysaccharide vaccine is administered as a single intramuscular dose and can be administered to travelers > 2 years of age, with a booster given if more than 2-3 years have elapsed since the previous vaccine (17,30). Routine protective measures should be practiced, such as drinking boiled or bottled water, cooking and peeling fruits and vegetables because an important phenomenon of the typhoid vaccine immunity is that it can be overcome if a large number of organisms are ingested (31).

CONCLUSION

Advances in public health strategies and sanitary resources in addition to the availability of effective pharmacologic treatment have transformed the once redoubtable, fatal typhoid fever into a readily treatable infection in the developed world. Our retrospective study on *Salmonella typhi* infections at the Montreal Children's Hospital from 1991 to 2011 has demonstrated that most cases in our centre occurred in non-immunized children returning to their native countries where typhoid fever is endemic. The diagnosis of typhoid fever remains difficult to make clinically but should be considered in a febrile traveler. The availability of two approved typhoid vaccines makes this disease potentially vaccine preventable for travelers.

Family physicians and pediatricians should emphasize the risk of typhoid fever and other travel-related infections (e.g. malaria) to their patients, especially children whose parents are from endemic areas. This counseling should be part of the regular scheduled visits, as parents may not seek medical advice before traveling to their home country.

REFERENCES

1. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bulletin of the World Health Organization.* May 2004;82(5):346-353.

2. Stuart BM, Pullen RL. Typhoid; clinical analysis of 360 cases. *Arch Intern Med (Chic).* Dec 1946;78(6):629-661.

3. Huckstep RL. *Typhoid fever and other salmonella infections*. Edinburg, Scotland: E. & S. Livingstone; 1962.

4. Sinha A, Sazawal S, Kumar R, et al. Typhoid fever in children aged less than 5 years. *Lancet.* Aug 28 1999;354(9180):734-737.

5. Ganesh R, Janakiraman L, Vasanthi T, Sathiyasekeran M. Profile of typhoid fever in children from a tertiary care hospital in Chennai-South India. *Indian journal of pediatrics.* Oct 2010;77(10):1089-1092.

6. Immigration-Québec - La région de Montréal en bref. http://www.immigration-quebec.gouv.qc.ca/fr/region/montreal.html. Accessed 02-OCT-2012.

7. Martin D, Belanger D, Gosselin P, Brazeau J, Furgal C, Dery S. Drinking Water and Potential Threats to Human Health in Nunavik: Adaptation Strategies under Climate Change Conditions. *Arctic.* June 2007 2007;60(2):7.

8. Mermin JH, Townes JM, Gerber M, Dolan N, Mintz ED, Tauxe RV. Typhoid fever in the United States, 1985-1994: changing risks of international travel and increasing antimicrobial resistance. *Archives of internal medicine.* Mar 23 1998;158(6):633-638.

9. Steinberg EB, Bishop R, Haber P, et al. Typhoid fever in travelers: who should be targeted for prevention? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Jul 15 2004;39(2):186-191.

10. Wain J, Pham VB, Ha V, et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *Journal of clinical microbiology.* Apr 2001;39(4):1571-1576.

11. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. *BMJ.* Jul 8 2006;333(7558):78-82.

12. Lin FY, Vo AH, Phan VB, et al. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. *The American journal of tropical medicine and hygiene.* May 2000;62(5):644-648.

13. Brooks WA, Hossain A, Goswami D, et al. Bacteremic typhoid fever in children in an urban slum, Bangladesh. *Emerging infectious diseases.* Feb 2005;11(2):326-329.

14. Siddiqui FJ, Rabbani F, Hasan R, Nizami SQ, Bhutta ZA. Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* May 2006;10(3):215-222.

15. Woodward TE, Smadel JE, et al. Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever. *Annals of internal medicine.* Jul 1948;29(1):131-134.

16. Kadhiravan T. Typhoid fever. In: Rakel RE, Bope ET, eds. *Conn's current therapy*. Philadelphia, PA: Elsevier Saunders; 2012:179-181.

17. Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid: a global problem. *Journal of medical microbiology.* May 1996;44(5):317-319.

18. Gotuzzo E, Carrillo C. Quinolones in Typhoid-Fever. *Infect Dis Clin Prac.* Sep-Oct 1994;3(5):345-351.

19. White NJ, Parry CM. The treatment of typhoid fever. *Current opinion in infectious diseases.* 1996;9(5):298-302.

20. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Nov 1997;25(5):1196-1204.

21. Cao XT, Kneen R, Nguyen TA, Truong DL, White NJ, Parry CM. A comparative study of ofloxacin and cefixime for treatment of typhoid fever in children. The Dong Nai Pediatric Center Typhoid Study Group. *The Pediatric infectious disease journal.* Mar 1999;18(3):245-248.

22. Chinh NT, Parry CM, Ly NT, et al. A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. *Antimicrobial agents and chemotherapy.* Jul 2000;44(7):1855-1859.

23. Bethell DB, Hien TT, Phi LT, et al. Effects on growth of single short courses of fluoroquinolones. *Archives of disease in childhood.* Jan 1996;74(1):44-46.

24. Girgis NI, Butler T, Frenck RW, et al. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrobial agents and chemotherapy.* Jun 1999;43(6):1441-1444.

25. Memon IA, Billoo AG, Memon HI. Cefixime: an oral option for the treatment of multidrug-resistant enteric fever in children. *Southern medical journal.* Dec 1997;90(12):1204-1207.

26. Schaad UB, abdus Salam M, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. *The Pediatric infectious disease journal.* Jan 1995;14(1):1-9.

27. Commons RJ, McBryde E, Valcanis M, Powling J, Street A, Hogg G. Twenty-six years of enteric fever in Australia: an epidemiological analysis of antibiotic resistance. *The Medical journal of Australia.* Mar 19 2012;196(5):332-336.

28. Frenck RW, Jr., Nakhla I, Sultan Y, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* Nov 2000;31(5):1134-1138.

29. Guzman CA, Borsutzky S, Griot-Wenk M, et al. Vaccines against typhoid fever. *Vaccine.* May 1 2006;24(18):3804-3811.

30. Typhoid Vaccine - Canadian Immunization Guide - Seventh Edition - 2006 - Public Health Agency of Canada. http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-typh-eng.php#ru. Accessed 05-Oct-2012.

31. Rongkavilit C. Immunization for pediatric international travelers. *Pediatric annals.* Jul 2011;40(7):346-350.

Figure 1: Distribution of cases of typhoid fever by year

Figure 2: Number of typhoid fever cases for each [Country/region of origin] and (Travel destination)

Figure 3: Distribution of Ampicillin-sensitive and resistant strains by year (Sensitivities only available for 37 isolates)

Table 1: Clinical presentation of cases

Signs/symptoms	N	(%)
Fever:	39	(100)
• Duration (average ± SD)	15.8	± 7.9
• Maximal temperature (average ± SD)	40.4	± 0.6
Anorexia	27	(69.2)
Abdominal pain	22	(56.4)
Diarrhea	18	(46.2)
Vomiting	19	(48.7)
Headache	15	(38.5)
Constipation	5	(12.8)
Jaundice	2	(5.1)
Rash	1	(2.6)
Hepatosplenomegaly	8	(20.5)
Heart rate (average ± SD)	123.4	± 23.6
White blood cell count (average ± SD)	8.33	± 4.07

Table 2: Course of illness and management

Characteristics	N	(%)
Required admission	34	(87.2)
Length of stay (average ± SD)	8.8	± 3.3
Received antibiotics prior to admission	23	(59)
In-patient treatment		
• Ceftriaxone	33	(84.6)
• Cefotaxime	3	(7.7)
• Ampicillin	2	(5.1)
• Clindamycin	1	(2.6)
• Gentamicin	1	(2.6)
• Metronidazole	1	(2.6)
Discharged on antibiotics	21	(53.8)
• Ceftriaxone	11	(28.2)
• Amoxicillin	5	(12.8)
• TMS	3	(7.7)
• Ciprofloxacin	1	(2.6)
• Erythromycin	1	(2.6)
Complications (shock, relapse, DIC, cholecystitis, hepatitis)	15	(38.5)

Figure 1

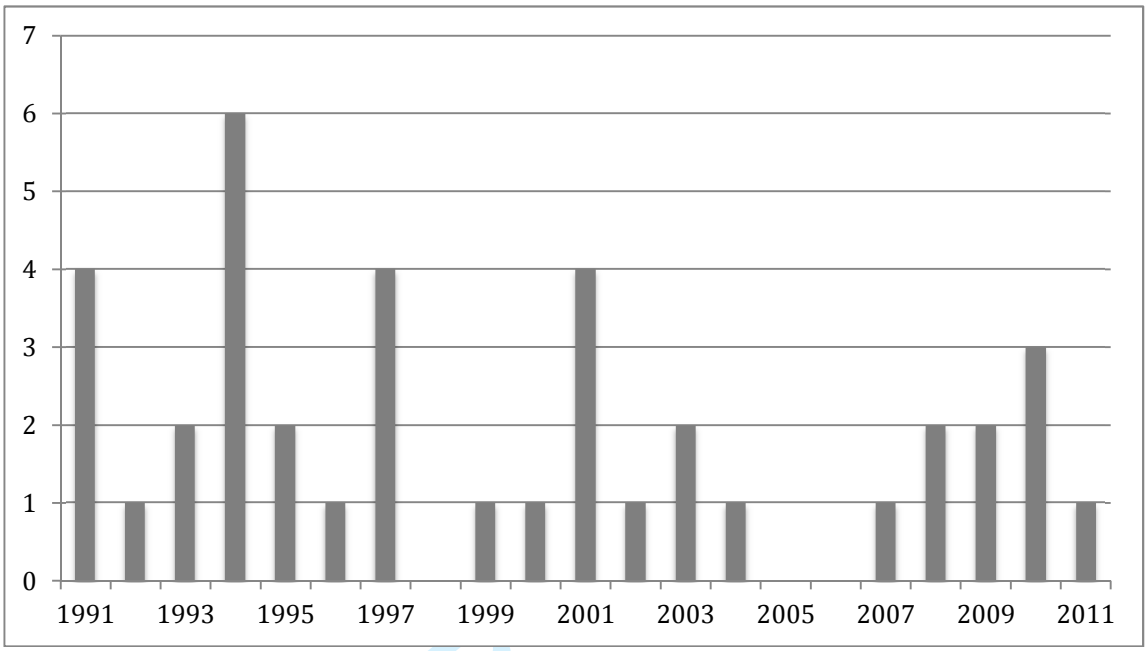

Figure 2

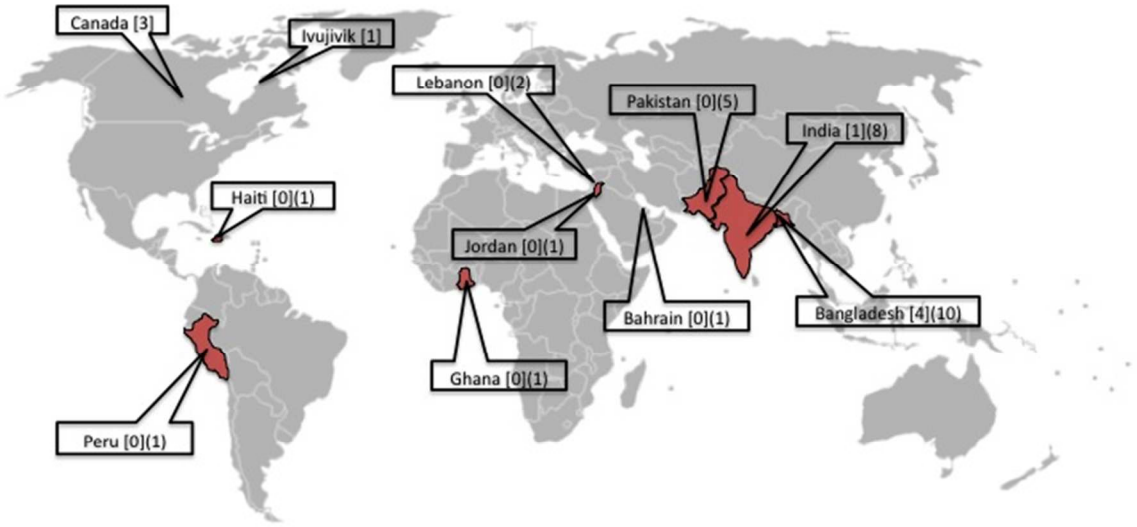

Figure 3: