Typhoid in Tajikistan

A Classroom Case Study

STUDENT'S VERSION

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Note: *This case study is based on a real-life outbreak investigation undertaken in Tajikistan in 1997.[1,2] Certain aspects of the original outbreak and investigation have been altered, however, to assist in meeting the desired teaching objectives and to allow completion of the case study within the allotted time.*

Students should be aware that this case study describes and promotes one particular approach to outbreak investigation; however, procedures and policies in outbreak investigations vary by country, state, and outbreak.

The developers of this case study anticipate that the majority of outbreak investigations will be undertaken within the framework of an investigation team that includes persons with epidemiology, microbiology, and environmental health expertise. Through the collaborative efforts of this team, with each member playing a critical role, outbreak investigations are successfully completed.

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November 2010

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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STUDENT'S VERSION
Typhoid Fever in Tajikistan

Learning Objectives:

After completing this case study, the student should be able to

1. list health problems common in countries with economic hardships, deteriorating infrastructure, and displaced populations;
2. discuss the steps typically used to develop hypotheses on the source of an infectious disease outbreak;
3. interpret the results of a matched case-control study;
4. list activities that should be included in the evaluation of a public water system associated with an outbreak;
5. define surface water and groundwater;
6. list the steps in collecting water samples from a point-of-use water tap;
7. describe point-of-use water disinfection and give examples of proven approaches; and
8. describe the clinical features, epidemiology, and control of typhoid fever.

PART I. OUTBREAK DETECTION

Tajikistan is one of five Central Asian countries that were formerly part of the Soviet Union (Figure 1). Tajikistan is one of the poorest of these countries, with less than 7% of its land available for cultivation.

Figure 1. Location of Tajikistan including the country's capital and largest city, Dushanbe.

Tajikistan became an independent nation in 1991 as the result of the dissolution of the former Soviet Union. The shift in its status from being a member of a totalitarian republic to an independent nation brought with it certain challenges. Basic public services (e.g., health care, water supply, and sewer systems), previously guaranteed for even the poorest nations in the Soviet Union, were no longer supported through the Soviet cost-sharing system. Financial hardships and inadequate tariffs in Tajikistan severely limited provision of services and maintenance of equipment. Faulty design and installation of equipment while Tajikistan was still part of the Soviet Union added to these problems.

To make matters worse, shortly after becoming an independent nation, Tajikistan experienced a civil war that continued until a cease-fire occurred in 1996. During the civil war, an estimated 50,000 lives were lost and 1.2 million persons were internally displaced.[3] In addition, a substantial number of trained technical and professional workers left the country.

By 1997, the country's economy and much of its infrastructure had collapsed. Consequently, the health of the people of Tajikistan suffered. Diseases rarely seen before the dissolution of the Soviet Union reappeared in increasing numbers.

Question 1: What health problems are common in countries with displaced populations, economic hardships, and deteriorating infrastructure?

Residents of Tajikistan received primary health care at designated polyclinics on the basis of their place of residence. The polyclinics provided ambulatory care and certain acute care services but lacked surgical and post-operative care facilities. Limited hospital beds at nationally run hospitals were available for patients needing in-patient services. Cases of notifiable disease were reported each week from the polyclinics and hospitals to the Sanitary Epidemiologic Service (SES), the public health unit that monitored infectious diseases.

In February 1997, an increase in typhoid fever cases was reported in Dushanbe, the capital of Tajikistan (population approximately 600,000). Although typhoid fever was endemic in this area, more than 2,000 cases had been reported during January 29−February 11 (i.e., a 2-week period), compared with approximately 75 cases each week during the previous month. During the same 2-week period in 1996, only 23 cases had been reported.

All typhoid fever patients were hospitalized at one of six full-service hospitals in the city, as required by a central government edict. SES staff studied the situation to determine the likelihood of an outbreak.

Question 2: Besides an outbreak, what are other possible explanations for the increase in cases of typhoid fever reported to the SES? How would you go about ruling out these other explanations?

As a first step in exploring the increase in typhoid fever cases in Tajikistan, SES investigators confirmed the diagnosis of typhoid fever in a sample of patients admitted to one of the Dushanbe hospitals. They also examined laboratory testing procedures and reagents at all six hospitals. No evidence of laboratory error or contamination of cultures was identified.

SES investigators were unable to identify recent events that might have led to an increase in the completeness of case reporting. Notifiable disease reporting procedures had not changed since the early 1980s.

SES investigators noted that the civil war had resulted in the displacement of substantial numbers of Tajikistan citizens and an increase in the Dushanbe population. However, movement of the displaced persons was spread over a lengthy period and seemed an unlikely explanation for the sudden increase in typhoid fever cases during January−February of 1997.

SES staff concluded that the increase in typhoid fever cases was real and likely represented an outbreak. Because previous typhoid fever outbreaks had been associated with foods and beverages sold by street vendors, the city government prohibited such sales. However, considerable debate remained about the source of the outbreak and appropriate control measures.

Question 3: How might you approach the development of hypotheses on the source of the typhoid fever outbreak?

PART II. HYPOTHESIS GENERATION

SES investigators pursued different lines of investigation to gain clues about the typhoid fever outbreak in Dushanbe. The first step was to review known information about the disease and risk factors on the basis of its epidemiology and previous outbreaks.

Question 4: How is typhoid fever transmitted? What is the incubation period? (For additional information, see Appendix A.)

SES staff then reviewed the typhoid fever cases reported through the notifiable disease surveillance system and characterized the cases by person, place, and time (i.e., performed the descriptive epidemiology).

Question 5: For this analysis, what case definition would you use for typhoid fever? Would you use a sensitive case definition or a specific case definition?

To characterize the typhoid fever cases associated with the Dushanbe outbreak, SES investigators defined a case of typhoid fever as a physician diagnosis of typhoid fever or isolation of *Salmonella* Typhi from the stool, blood, or urine of a Dushanbe resident (i.e., a relatively sensitive case definition). Investigators analyzed typhoid fever cases reported to SES with onset of illness since January 1.

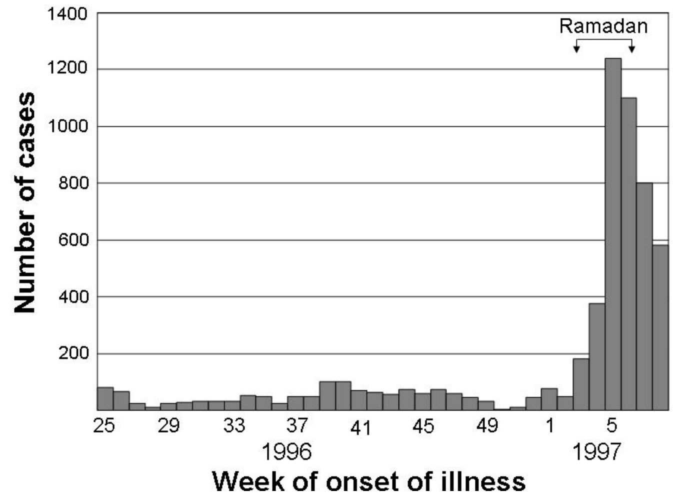
A total of 3,822 patients meeting the typhoid fever case definition had onset of illness since January 1. Of these cases, 127 had onset of illness from January 1−14 (median of 64 cases each week) and 3,695 had onset of illness from January 15 to February 18 (median of 724 cases each week) (Figure 2).

Among the cases reported during January 15−February 18, the following signs and symptoms were reported: sustained fever (91% of cases), headache (81%), weakness (76%), chills (73%), loss of appetite (67%), abdominal pain (51%), vomiting (39%), diarrhea (30%), and rose-colored spots (6%). Blood, stool, or urine cultures confirmed 1,145 (31%) of the cases.

The median age of patients was 16 years (range: <1−80 years); 51% were male. Cases were spread across the city with varying rates of infection by polyclinic catchment area (Figure 3).

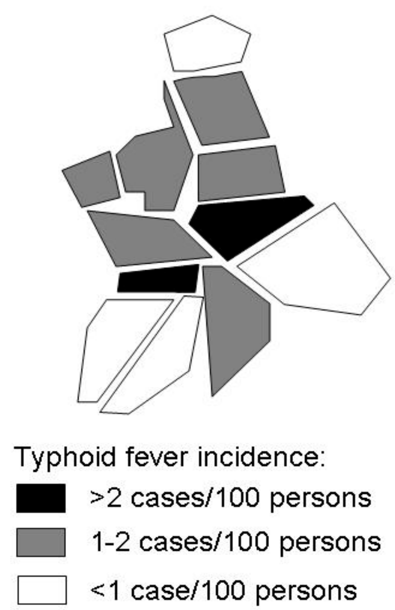
Forty-eight (1.3%) of the 3,695 patients had died. Mortality rates were lowest among patients aged <10 years (0.3%) and highest among those aged >39 years (1.4%).

Figure 2. Cases of typhoid fever by week of onset of illness, Dushanbe, Tajikistan, June 1996−February.



Source: Dushanbe SES Notifiable Disease Surveillance System.

Figure 3. Incidence rate of typhoid fever by registered polyclinic, Dushanbe, Tajikistan, January 15–February 18, 1997.



Source: Dushanbe SES Notifiable Disease Surveillance System.

Question 6: Interpret the descriptive epidemiology of the typhoid fever cases. Are signs and symptoms among patients consistent with typhoid fever? Are patients clustered by selected demographic characteristics? What is the course of the epidemic and does it appear to be over?

Detailed hypothesis-generating interviews were conducted to detect common and suspicious exposures among a sample of the typhoid fever patients. Interviews were undertaken with 10 patients who had culture-confirmed illness. These patients lived in the catchment areas of five different polyclinics and ranged in age from 5 to 69 years. Six of the patients were female. All of the patients had had onset of symptoms during the first 2 weeks of February.

Hypothesis-generating interviews revealed that all of the patients had purchased groceries from state-approved markets. However, four of the patients had also purchased food from local street vendors, with fruits and vegetables being the most commonly purchased items. No market, street vendor, restaurant, or social event was identified in common among the patients.

The households of all patients included in hypothesis-generating interviews were supplied with public water. All but one patient reported that the water was often cloudy and occasionally had a foul smell.

Only one patient had traveled outside the city during the previous 6 weeks; seven patients had had visitors who normally resided outside Dushanbe staying in their home because of Ramadan (i.e., a month-long Muslim observance involving a fast from food and water from sunrise to sunset that began on January 10). None of the patients knew each other. Two patients knew someone else who had been similarly ill.

Question 7: Using information available to you at this point, state your leading hypotheses on the mode of transmission, the source of the outbreak, and the period of interest.

SES investigators suspected the public water supply as the source of the Dushanbe typhoid fever outbreak. The widespread occurrence of cases throughout the city, affecting both sexes and all age groups, was indicative of a waterborne outbreak. Complaints during the hypothesis-generating interviews about the quality of the public water further heightened their suspicions.

Investigators initiated both epidemiologic and environmental health studies to confirm their hypothesis.

PART III. AN EPIDEMIOLOGIC STUDY TO TEST THE HYPOTHESIS

SES investigators conducted a case-control study to test the hypothesis that the public water system was the source of the typhoid fever outbreak in Dushanbe.

Beginning March 24, patients hospitalized with typhoid fever in Dushanbe were recruited to participate in the case-control study. For the study, a case was defined as an illness in a person that included the following:

Clinical criteria

- sustained fever (i.e., oral temperature ≥ 101.5° F [38.5°C] for ≥7 days), and
- one or more other signs and symptoms indicative of typhoid fever (e.g., weakness, stomach pains, headache, loss of appetite, or rose-colored rash), and
- culture of stool or blood positive for *Salmonella* Typhi.

Restrictions on time, place, and person

- onset of symptoms after February 1,
- resident of Dushanbe, and
- person with earliest onset of symptoms in household.

Question 8: Why did investigators use a different case definition for the case-control study than for performing the descriptive epidemiology? If cases were culture-confirmed, why did investigators include symptoms of infection in the case definition? Why did investigators include only the first case in a household in the study?

Case-patients were interviewed within 5 days of hospital admission by a trained SES interviewer, using a standardized questionnaire. Questions focused on exposures during the 30 days before onset of illness.

Within 5 days of interviewing each case-patient, investigators selected neighborhood control subjects from households in which no one had experienced fever for ≥3 consecutive days during the previous 90 days. Control subjects were recruited by going systematically from door-to-door, starting at the case-patient's house; control subjects were then matched with case-patients by age group. Two to three control subjects were identified for each case-patient.

Control subjects were interviewed by using the same standardized questionnaire as case-patients, except that exposure information was requested for the 30 days before the interview.

During March 24−April 7, a total of 45 case-patients and 123 healthy control subjects were enrolled in the case-control study. SES investigators tabulated the results and set a P value of 0.05 as the cut-off for statistical significance.

On the basis of these analyses, case-patients were similar to control subjects with respect to age, sex, and nationality (Table 1). Exposure to potential risk factors for infection with *S*. Typhi, however, differed between case-patients and control subjects (Table 2).

Tables 1. Characteristics of case-patients and control subjects, case-control study, Dushanbe, Tajikistan, 1997.

Characteristic	Case-patients (n=45)	Control subjects (n=123)
Median age (yrs)	13	14
Age range (yrs)	3−41	5−49
Male (%)	62	60
Nationality (%)		
Tajiks	80	83
Uzbek	15	11
Russian	1	1
Other	4	5

Table 2. Exposures to selected risk factors for infection with *Salmonella* Typhi, case-control study, Dushanbe, Tajikistan, 1997.

Exposure*	Case-patients exposed/total cases† (%)	Control subjects exposed/total controls† (%)	Matched odds ratio	95% confidence interval	P value
Drinking water that had not been boiled	19/39 (49)	12/117 (10)	6.5	3−24	<0.001
Using water obtained from an outside tap	10/42 (24)	10/116 (9)	9.1	1.6−82	0.006
Eating food obtained from a street vendor	23/42 (55)	35/117 (30)	2.9	1.4−7.2	0.004
Boiling water in the home	30/42 (71)	108/113 (96)	0.2	0.05−0.5	<0.001
Eating apples	34/43 (79)	109/117 (93)	0.3	0.08−0.9	0.03
Eating butter	8/43 (19)	60/116 (52)	0.2	0.06−0.5	<0.001
Eating onions	21/43 (49)	81/117 (69)	0.5	0.2−1.0	0.04

*Exposure during the 30 days before becoming ill (case-patients) and during the 30 days before the interview (control subjects)
†Denominator does not always total to 45 (case-patients) or 123 (control subjects) because certain subjects could not remember if they had had the exposure.

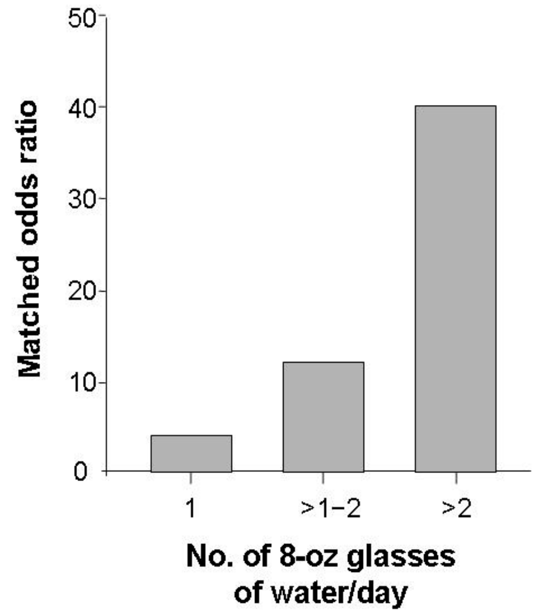
Question 9: Interpret the matched odds ratios for exposures in the case-control study.

On the basis of the matched case-control study, infection with *S*. Typhi in Dushanbe was associated with drinking water that had not been boiled during the 30 days before onset of symptoms. The odds ratio increased with the amount of water consumed each day (Figure 4). Drinking at least 1 glass of water that had not been boiled had a matched odds ratio of 3; drinking 2 glasses had a matched odds ratio of 12; and drinking > 2 glasses had a matched odds ratio of 40.

Obtaining water from a tap outside the home and eating food obtained from street vendors were also associated with illness. Using boiled water in the home and eating butter, apples, or onions were determined to be protective factors.

Factors not associated with illness (data not shown) included type of toilet facilities; drinking beverages with ice; eating or drinking at restaurants or a friend's or relative's home; traveling outside Dushanbe or receiving visitors who usually reside outside Dushanbe; and consuming raw fruits and vegetables (other than apples and onions), dairy products (other than butter), and medicines.

Figure 4. Odds ratios by amount of water consumed per day that had not been boiled, case-control study, Dushanbe,Tajikistan, 1997.



Investigators undertook a multivariate logistic regression analysis that included all exposures identified as significantly associated with infection in the univariate analysis (Table 3).

Table 3. Multivariate analysis of reported exposures to risk factors for infection with *Salmonella* Typhi, case-control study, Dushanbe, Tajikistan, 1997.

Exposure*	Matched odds ratio	95% confidence interval	P value
Using water obtained from an outside tap	16.7	2.0−138	0.009
Drinking water that had not been boiled	9.6	2.7−34	0.0005
Eating food obtained from a street vendor	1.5	0.9−5.6	0.3
Eating onions	0.6	0.5−2.1	0.2
Eating apples	0.2	0.04−0.9	0.03
Eating butter	0.1	0.04−0.4	0.001
Boiling water in home	†	†	†

*Exposure during the 30 days before becoming ill (case-patients) and during the 30 days before the interview (control subjects)

†Although significantly associated with typhoid fever in the univariate analysis, this variable was not included in multivariate logistic regression analyses because of its inverse correlation with drinking water that had not been boiled.

Question 10: Can you postulate why eating apples and butter were protective against typhoid fever? (Does an apple a day really keep the doctor [typhoid fever] away?)

PART IV. ENVIRONMENTAL STUDIES AND WATER SUPPLY INVESTIGATION

Concurrent with the case-control study, SES investigators evaluated the Dushanbe public water supply to identify factors that might have allowed introduction of pathogenic organisms into the drinking water or the survival of such organisms.

Question 11: What activities would you include in the evaluation of the public water supply? With whom would you talk? What records or data sources would you review?

To evaluate the Dushanbe public water supply, SES investigators first talked with the superintendent of public water and viewed maps of the watersheds for the water treatment plants. They then toured all of the water treatment plants (and associated wells) and spoke with water treatment plant operators and maintenance technicians. Investigators observed procedures used to treat the water at each plant and inspected equipment used in water treatment.

SES investigators learned that the city of Dushanbe had four water treatment plants that used surface and groundwater. The two treatment plants in the northern part of the city (i.e., the Napornaya and Samotechnaya Stations) used surface water from the Varzob River. The two treatment plants in the southern part of the city (i.e., the Kafernigan and South-West Stations) used groundwater.

Question 12: What is meant by the terms surface water and groundwater? How do the health hazards differ for the two?

The Varzob River's source is in the Hissar Mountain range, 72 km north of Dushanbe, and is fed by the Siyoma, Ojuk, Kondara, Maikhura and Tagob Rivers. Heavy rains in the winter and spring and snowmelt result in periodic flash floods along the watershed. Lack of wastewater purification facilities or storage in villages and factories along the river resulted in the discharge of communal wastes directly into the river. Within the Dushanbe city limits, water was drawn from the Varzob River through a system of canals into the surface water treatment plants (i.e., Napornaya and Samotechnaya Stations).

Typically, the water was strained and held in open sedimentation basins where particulates were allowed to settle out naturally. Chlorine was added directly to the sedimentation basins before the water was passed through sand filters to allow for adequate contact time. From the filters, water was pumped into the distribution system without further storage.

The water for the two groundwater treatment plants (i.e., Kafernigan and South-West Stations) was pumped directly from the wells into holding tanks and from the holding tanks into the public water distribution system without treatment.

Question 13A: What are the usual steps in treating a public water supply to make it safe to drink?

Question 13B: Would you make any changes to the routine water treatment processes at the surface water treatment stations in Dushanbe? At the groundwater treatment stations?

On inspection of the surface water treatment stations, investigators noted that the sedimentation basins were filled with silt and algae. Dredging machines used to remove the silt were broken. Sand filters had formed mud balls (i.e., conglomerations of filter material that form if a filter is not cleaned adequately) and displayed substantial fouling with iron-oxide that can compromise the filtration process.

Water at the surface water treatment stations had not been chlorinated regularly since December. The chlorine-producing facility in Yavan, Tajikistan, which once supplied chlorine to the entire country, had closed in 1996.

Inspections of the groundwater treatment stations were unrevealing. The wells were in good condition and wellhead seals were functioning correctly. However, approximately half of the pumps at these stations were not operational, limiting the ability to provide the city with adequate water pressure. Plant workers had scavenged spare parts to maintain the functionality of the remaining pumps.

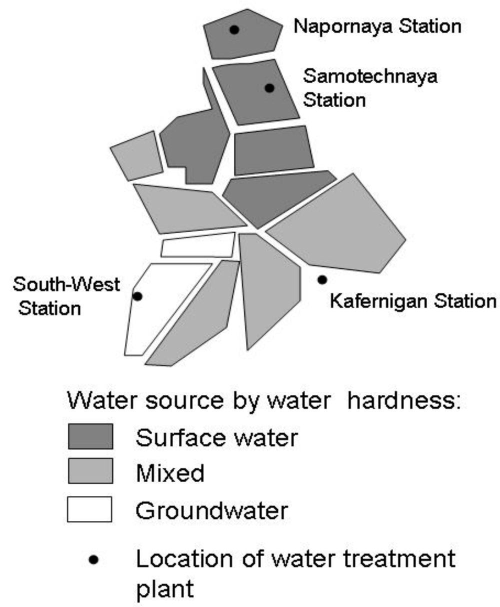
SES investigators tested treated water samples from each of the water treatment plants for turbidity and fecal coliforms.

Question 14: What is turbidity? What do fecal coliforms indicate?

The turbidity of treated water from the Napornaya Station was 150 nephelometric turbidity units (NTUs). Fecal coliforms were 132 colony forming units (CFU)/100 mL. Treated water from the Samotechnaya Station had a turbidity of 70 NTUs; fecal coliforms were 118 CFU/100 mL. Both groundwater plants pumped fecal-coliform-free water with a turbidity of 0 NTUs.

Water leaving all four water treatment plants entered an interconnected distribution system where surface and groundwater blended. To distinguish the source of water supplied to different parts of the city, SES investigators measured water hardness at the treatment plants and at a sample of consumer taps. They determined that the northern part of the city received water primarily from the surface water treatment plants. The southern part of the city received water primarily from the groundwater treatment plants. The central part of the city received water from both the surface and the ground water treatment plants (Figure 5).

Figure 5. Water source by polyclinic, Dushanbe, Tajikistan, 1997.



Question 15: Reexamine the incidence of typhoid fever by polyclinic as illustrated in Figure 3 in light of the water-quality data and water distribution maps from the four Dushanbe water treatment plants (Figure 5). Does this information provide further clues about problems within the public water supply?

The water distribution system in Dushanbe was approximately 690 km in total length and consisted mainly of steel and cast-iron pipelines. Approximately 5% of pipes were asbestos or plastic. Distribution pipes had corroded over the years, and breaks occurred intermittently throughout the city.

SES investigators undertook a community survey to assess domestic water quality and use in Dushanbe. Households were selected from each polyclinic catchment area by using a stratified random-sampling scheme. At each house or apartment, investigators recorded the number of residents, frequency of water outages and other problems, and attitudes toward water use. They also collected water from the tap for fecal coliform testing and quantified water usage.

Question 16: How would you collect a water sample from a water tap for fecal coliform testing?

SES investigators learned that low and intermittent water pressure was common across the city, resulting in water outages on a daily basis. Apartment buildings often had supplemental water pumps that were activated at times of low water pressure. Residents in households and apartment buildings without supplemental water pumps were forced to obtain water from outside taps. In addition, nonstandard connections to waterlines were commonly used to supply homes. Investigators also observed that water pipes ran inside storm drains along roadsides.

Water usage at the surveyed households was substantial. On average, 1,000 L of water were used/person/day, the majority of which was wasted. A total of 300 L/person/day were lost because of open taps within the households, and another 300 L/person/day were lost because of broken pipes or faucets within the house. An additional 400 L/person/day were wasted because of open or broken taps or pipes in public areas. (**Note:** For comparison, according to a 2006 United Nations Development Programme report,[4] water usage was approximately 575 L/person/day in the United States and 200−300 L/person/day in Europe.)

Surveyed residents considered the water supply a free commodity. Approximately 2% of domestic users paid the tariff charged by the public water utility, which by the majority of standards was quite low (i.e., US$0.004/1,000 L equivalent for domestic consumers). Residents did not consider running taps to be wasteful or as a contributing factor to the typhoid fever epidemic.

Based on the water samples collected during the survey, 97% of household and community taps throughout the city had water contaminated with fecal coliforms. The average fecal coliform concentration in water samples was 175 CFU/100 mL.

Question 17: Summarize the actions necessary to ensure safe drinking water in the city of Dushanbe. Which actions can be undertaken more quickly? Which will be longer-term efforts?

PART V. PREVENTION AND CONTROL MEASURES

Prevention and control of typhoid fever and other waterborne diseases in Dushanbe required many actions, including improved protection of the watershed of the Varzob River, repair or replacement of equipment at the water treatment plants (e.g., dredging machinery, sand filters, and pumps), thorough training of water treatment plant staff, changes to the water treatment processes, procurement of adequate amounts of chlorine and coagulant, and repair and replacement of the aging water distribution system. In addition, public education on water conservation was needed to decrease water wastage across the city.

Officials estimated that these efforts might cost at least US$150 million and require years to complete. Public health officials considered implementing point-of-use water treatment to protect the public's health while more costly improvements were being made to the water system.

Question 18: What is point-of-use water treatment? What are examples of point-of-use water treatment methods?

SES investigators worked with the Tajikistan Ministry of Health in developing a citywide public education campaign about point-of-use water treatment. A health educator from the Ministry of Health was designated to lead and coordinate campaign efforts.

Question 19: What are the likely goals of the public education campaign? What steps would you include in planning the campaign? Who might you recruit to help educate and motivate residents to use point-of-use such water treatments?

EPILOGUE

Use of multiple barriers to keep water contaminants from entering the water supply and surviving is the best approach to achieving a healthy public water supply. Development of multiple barriers to protect the water means that the system will continue to perform adequately despite the failure of part of the system.

The Dushanbe typhoid fever outbreak resulted from failures at multiple points in the water treatment and distribution process. The factors contributing to the state of water services in Dushanbe included

- chronically contaminated surface waters caused by discharge of untreated sewage into the river and heavy flooding each spring;
- inadequate treatment processes (e.g., lack of chlorination because of inadequate supplies, improperly maintained sand filters, and lack of residual chlorine levels in water leaving the water treatment stations);
- disrepair of the water treatment plants resulting from inadequate initial design, unavailable or low-quality of materials and equipment, limited financial resources, and departure of trained staff;
- frequent low and intermittent water pressure because of nonoperational water pumps at treatment facilities, breakages in the water distribution lines, and water wastage in the community; and
- inadequate monitoring of the water system to identify and correct problems.

In 2002, the World Bank began funding the Dushanbe Water Supply Project. Loans were approved to address the most critical deficiencies of the water supply, including replacement of pumps and other equipment at the treatment plants and repair of major sections of the distribution system. Despite improvements, many Dushanbe residents still had inadequate water service and outbreaks of typhoid fever reoccurred on an annual basis. In 2006, the World Bank approved additional funds to continue work on the water system. Renovations and repairs are ongoing.[5]

Although the investigation of the typhoid fever outbreak in Dushanbe presents a dramatic third world image, similar problems occur elsewhere. In 2007, the U.S. Environmental Protection Agency estimated that 240,000 water mains in the United States break each year, resulting in a loss of 1.7 trillion gallons of water.[6] These problems are attributed to factors that are reminiscent of the Dushanbe situation and include reductions in resources devoted to water treatment system maintenance, a growing backlog of needed repairs, aging treatment equipment and distribution pipes, and loss of trained personnel to maintain the systems.

In the majority of U.S. cities, water supplies have not yet been adversely affected. However, a growing number of localities have had serious problems resulting in at least a temporary loss of potable water and substantial commitment of resources to correct the problem. If steps are not taken to understand and address these growing problems, a widespread decline in drinking water quality and reliability, even in the United States, is possible.

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APPENDIX A: Typhoid and Paratyphoid Fever (by Eric Mintz)

Also available at http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/typhoid-paratyphoid-fever.aspx.

Infectious Agent

Typhoid fever is an acute, life-threatening febrile illness caused by the bacterium *Salmonella enterica* serotype Typhi. Paratyphoid fever is a similar illness caused by *S*. Paratyphi A, B, or C.

Mode of Transmission

- Humans are the only source. No animal or environmental reservoirs have been identified.

- Typhoid and paratyphoid fever are most often acquired through consumption of water or food that have been contaminated by feces of an acutely infected or convalescent individual or a chronic asymptomatic carrier.

- Transmission through sexual contact, especially among men who have sex with men, has rarely been documented.

Occurrence

- An estimated 22 million cases of typhoid fever and 200,000 related deaths occur worldwide each year; an additional 6 million cases of paratyphoid fever are estimated to occur annually.

- Approximately 400 cases of typhoid fever and 150 cases of paratyphoid fever are reported to CDC each year among persons with onset of illness in the United States, most of whom are recent travelers.

Risk for Travelers

- Risk is greatest for travelers to South Asia (6 to 30 times higher than all other destinations). Other areas of risk include East and Southeast Asia, Africa, the Caribbean, and Central and South America.

- Travelers to South Asia are at highest risk for infections that are nalidixic acid-resistant or multidrug-resistant (i.e., resistant to ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole).

- Travelers who are visiting friends or relatives are at increased risk.

- Although the risk of acquiring typhoid or paratyphoid fever increases with the duration of stay, travelers have acquired typhoid fever even during visits of less than 1 week to countries where the disease is endemic.

Clinical Presentation

- The incubation period of typhoid and paratyphoid infections is 6–30 days. The onset of illness is insidious, with gradually increasing fatigue and a fever that increases daily from low-grade to as high as 102° F–104° F (38.5° C–40° C) by the third to fourth day of illness. Headache, malaise, and anorexia are nearly universal. Hepatosplenomegaly can often be detected. A transient, macular rash of rose-colored spots can occasionally be seen on the trunk.

- Fever is commonly lowest in the morning, reaching a peak in late afternoon or evening. Untreated, the disease can last for a month. The serious complications of typhoid fever generally occur only after 2–3 weeks of illness, mainly intestinal hemorrhage or perforation, which can be life threatening.

Diagnosis

- Infection with typhoid or paratyphoid fever results in a very low-grade septicemia. Blood culture is usually positive in only half the cases. Stool culture is not usually positive during the acute phase of the disease. Bone-marrow culture increases the diagnostic yield to about 80% of cases.
- The Widal test is an old serologic assay for detecting IgM and IgG antibodies to the O and H antigens of *Salmonella*. The test is unreliable, but is widely used in developing countries because of its low cost. Newer serologic assays are somewhat more sensitive and specific than the Widal test, but are infrequently available.
- Because there is no definitive test for typhoid or paratyphoid fever, the diagnosis often has to be made clinically. The combination of a history of being at risk for infection and a gradual onset of fever that increases in severity over several days should raise suspicion of typhoid or paratyphoid fever.

Treatment

- Specific antimicrobial therapy shortens the clinical course of typhoid fever and reduces the risk for death.
- Empiric treatment of typhoid or paratyphoid fever in most parts of the world would utilize a fluoroquinolone, most often ciprofloxacin. However, resistance to fluoroquinolones is highest in the Indian subcontinent and increasing in other areas. Injectable third-generation cephalosporins are often the empiric drug of choice when the possibility of fluoroquinolone resistance is high.
- Patients treated with an appropriate antibiotic still require 3–5 days to defervesce completely, although the height of the fever decreases each day. Patients may actually feel worse during the time that the fever is starting to go away. If fever does not subside within 5 days, alternative antimicrobial agents or other foci of infection should be considered.

Preventive Measures for Travelers
Vaccine

- CDC recommends typhoid vaccine for travelers to areas where there is a recognized increased risk of exposure to *S*. Typhi.
- The typhoid vaccines currently available do not offer protection against *S*. Paratyphi infection.
- Travelers should be reminded that typhoid immunization is not 100% effective, and typhoid fever could still occur.
- Two typhoid vaccines are currently available in the United States.
    - Oral live, attenuated vaccine (Vivotif vaccine, manufactured from the Ty21a strain of *S*. Typhi by Crucell/Berna)
    - Vi capsular polysaccharide vaccine (ViCPS) (Typhim Vi, manufactured by sanofi pasteur) for intramuscular use
- Both vaccines protect 50%–80% of recipients.
- Table 2-10 provides information on vaccine dosage, administration, and revaccination. The time required for primary vaccination differs for the two vaccines, as do the lower age limits.
- Primary vaccination with oral Ty21a vaccine consists of four capsules, one taken every other day. The capsules should be kept refrigerated (not frozen), and all four doses must be taken to achieve maximum efficacy. Each capsule should be taken with cool liquid no warmer than 37° C (98.6° F), approximately 1 hour before a meal. This regimen should be completed 1 week before potential exposure. The vaccine manufacturer recommends that Ty21a not be administered to infants or children<6 years of age.

- Primary vaccination with ViCPS consists of one 0.5-mL (25-µg) dose administered intramuscularly. One dose of this vaccine should be given at least 2 weeks before expected exposure. The manufacturer does not recommend the vaccine for infants and children <2 years of age.

Vaccine Safety and Adverse Reactions

Information on adverse reactions is presented in Table 2-11. Information is not available on the safety of these vaccines in pregnancy; it is prudent on theoretical grounds to avoid vaccinating pregnant women. Live, attenuated Ty21a vaccine should not be given to immunocompromised travelers, including those infected with HIV. The intramuscular vaccine presents a theoretically safer alternative for this group. The only contraindication to vaccination with ViCPS vaccine is a history of severe local or systemic reactions after a previous dose. Neither of the available vaccines should be given to persons with an acute febrile illness.

Precautions and Contraindications

Theoretical concerns have been raised about the immunogenicity of live, attenuated Ty21a vaccine in persons concurrently receiving antimicrobials (including antimalarial chemoprophylaxis), IG, or viral vaccines. The growth of the live Ty21a strain is inhibited in vitro by various antibacterial agents. Vaccination with Ty21a should be delayed for >72 hours after the administration of any antibacterial agent. Available data do not suggest that simultaneous administration of oral polio or yellow fever vaccine decreases the immunogenicity of Ty21a. If typhoid vaccination is warranted, it should not be delayed because of administration of viral vaccines. Simultaneous administration of Ty21a and IG does not appear to pose a problem.

Table(s) 2-10a. Dosage and schedule for typhoid fever vaccination
Oral, live, attenuated Ty21a vaccine (Vivotif)

Vaccination	Age (Years)	Dose/Mode of Administration	No. of Doses	Dosing Interval	Boosting Interval
Primary series	≥6	1 capsule1, oral	4	48 hrs	Not applicable
Booster	≥6	1 capsule1, oral	4	48 hrs	Every 5 years

[1]Administer with cool liquid no warmer than 98.6°F (37°C).

Table(s) 2-10b. Dosage and schedule for typhoid fever vaccination
Vi Capsular polysaccharide vaccine (Typhim Vi)

Vaccination	Age (Years)	Dose/Mode of Administration	No. of Doses	Dosing Interval	Boosting Interval
Primary series	≥2	0.50 mL,intramuscular	1	Not applicable	Not applicable
Booster	≥2	0.50 mL,intramuscular	1	Not applicable	Every 2 years

[1]Administer with cool liquid no warmer than 98.6°F (37°C).

Table 2-11. Common adverse reactions to typhoid fever vaccines

Vaccine	Fever Reactions	Headache Reactions	Local Reactions
Ty21a1	0%–5%	0%–5%	Not applicable
Vi Capsular polysaccharide	0%–1%	16%–20%	7% erythema or induration 1 cm

[1]The side effects of Ty21a are rare and mainly consist of abdominal discomfort, nausea, vomiting, and rash or urticaria.

Page last reviewed: July 27, 2009   Page last updated: July 27, 2009
Content source: Division of Global Migration and Quarantine, National Center for Preparedness, Detection, and Control of Infectious Diseases