Am. J. Trop. Med. Hyg., 73(2), 2005, pp. 392–399

HOSPITAL-BASED SURVEILLANCE FOR ACUTE FEBRILE ILLNESS IN EGYPT: A FOCUS ON COMMUNITY-ACQUIRED BLOODSTREAM INFECTIONS

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Abstract. Acute febrile illness (AFI) is a common syndrome in Egypt. However its etiologies are not well characterized. To determine the relative frequency of pathogen etiologies and possibly improve diagnostic, clinical management and public health measures, we implemented laboratory-based surveillance in a network of infectious disease hospitals throughout Egypt. Admitted patients with AFI provided background details and a blood sample for bacterial culture and serologic analysis. Case definitions were based on laboratory results. Of 10,130 patients evaluated between 1999 and 2003, 5% were culture positive for *Salmonella enterica* serogroup Typhi, 3% for *Brucella*, and 2% for other pathogens. An additional 18% of patients had positive serologic results for typhoid and 11% for brucellosis. Risk factor analysis identified availability of municipal water to be significantly ($P < 0.05$) associated with protection against typhoid. Animal contact and consumption of raw dairy products were significantly associated with brucellosis. The surveillance network identified typhoid fever and brucellosis as the most common bacterial causes of AFI in Egypt, allowed better description of their epidemiology, and may lead to the development of targeted prevention strategies.

INTRODUCTION

Acute undifferentiated febrile illness is a common clinical syndrome among patients seeking hospital care in Egypt. The main causes and patterns of acute febrile illness (AFI) are not well characterized and many patients with AFI are empirically diagnosed as having typhoid fever, one of the most frequently reported communicable diseases in Egypt. Although not routinely diagnosed, brucellosis is reported in all domestic animals in the Near East region, including Egypt. The highest incidence of human brucellosis is reported in Saudi Arabia, Iran, the Palestinian Authority, Syria, Jordan, and Oman.[1] The most common *Brucella* species reported in Egypt is *B. melitensis*.[1] Confirmation of the diagnosis of typhoid fever and brucellosis requires the recovery of pathogens from a suitable clinical specimen. Blood cultures detect pathogens in approximately 70% of patients with suspected typhoid fever (three 5-mL cultures/patient). *Salmonella enterica* serogroup Typhi (ST) organisms can also be recovered from bone marrow (85–95%), bile, and stool cultures (45–65%), although the practicality and sensitivity of sources other than blood prevents them from being used as a first-line diagnostic method.[2]

Serodiagnosis of typhoid fever has routinely used methods that were first described more than 100 years ago by Widal and Secard.[3] Many studies indicate that a single Widal test has a relatively high sensitivity among patients with acute typhoid fever. However, this test has a variable range of sensitivity and specificity in different populations, factors that preclude its acceptance as the definitive diagnostic assay.[3–5] Attempts have been made to develop better serologic assays. However, most techniques have been disappointing and the attempt to replace bacterial culture remains a laudable but elusive goal. Taking into consideration constraints with current serologic assays, coupled with interest in ensuring completeness of reporting, the Egyptian Ministry of Health and Population (MOHP) uses a case definition of probable typhoid fever for patients with a positive Widal agglutination test result.

Brucellosis is an important health problem in Egypt and an important cause of AFI. In a series of 270 fever patients admitted to two large urban hospitals in Cairo over a two-year period, 5% had *Brucella* infections.[6] National data in the Egyptian MOHP communicable disease program shows there has been an increase in the number of patients with brucellosis over the past five years (although this increase may be an artifact related to more frequent testing being done.). Veterinary studies of sheep and goats showed that 2–5% have antibody when tested by serum agglutination, complement fixation, and Abortus Bang Ring tests.[7] Laboratory isolation and identification provides confirmation of the diagnosis of brucellosis. Blood cultures are conducted in standard media with blind subcultures in five days. However, it may take up to 2–6 weeks to isolate the organism. Prior use of antibiotics may interfere with growth of *Brucella* spp. and bone marrow culture may give higher yields.[8]

Several serologic assays have been developed to diagnose brucellosis. However, there are limitations to their use and interpretation of the results. Brucellosis can be effectively excluded from diseases having similar clinical features by highly sensitive and specific agglutination tests.[9,10] In this assay, antibody titers ≥ 1:160 are associated with infection. Assays to detect IgM antibody to *Brucella* species have been developed; however, they are not widely used in the clinical setting.

Prior to 1998, many Egyptian infectious disease hospitals had limited laboratory capacity to diagnose typhoid fever and brucellosis. However, in 1998, the MOHP implemented activities to improve epidemiology and laboratory capacity and thus strengthening infectious disease surveillance. This strategy included the upgrading of clinical and laboratory evaluations for patients with AFI. The objectives of this surveillance were to characterize the epidemiology of bacterial agents causing AFI with a special emphasis on community-acquired bloodstream infections (BSIs), and ultimately, to reduce the morbidity and mortality they caused. This report presents the results of laboratory-based AFI surveillance con-

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ducted by a network of 13 hospitals in diverse regions of Egypt during the first four years of implementation.

MATERIALS AND METHODS

The Ministry of Health in Egypt maintains 109 infectious disease hospitals distributed throughout the country. In Egypt, by law all patients with fever who come to any health facility should be referred and treated by the infectious disease hospitals after screening for mild infections such as upper respiratory tract infections and simple diarrhea. Most of the population uses the public health care system. Patients come either directly to the infectious disease hospital or are referred by primary health centers. We selected 13 infectious disease hospitals from four regions: Upper Egypt, the Delta region, the Coastal region, and Cairo Metropolitan.

Surveillance for AFI was implemented in 13 infectious disease hospitals throughout Egypt (Figure 1). In 12 of the 13 infectious disease hospitals participating in the surveillance activities, all patients meeting case definition were enrolled. We included 2 of 12 wards that admitted possible case-patients at Abbassia Fever Hospital, the largest infectious disease hospital in Egypt that serves the Cairo Metropolitan region. One adult female and pediatric ward and one adult male ward were selected to represent patients admitted to the hospital.

Seven hospitals participated for the entire four-year study period (1999–2003). Clinicians were trained to identify cases for possible inclusion and to complete a standardized clinical and laboratory evaluation of all patients who met the following case criteria: 1) > 4 years of age and admitted to the participating institution; 2) history of fever for at least two days; 3) temperature at admission > 38.5°C (oral or rectal); 4) no identified cause of fever (physicians were instructed to exclude other causes of fever such as diarrhea, hepatitis, cough and/or symptoms of respiratory tract infection, urinary tract infection, cellulitis, rheumatic fever, abscess, and/or any other known cause of fever); or 5) suspected typhoid fever or brucellosis, using the case definitions defined by the World Health Organization.[11,12]

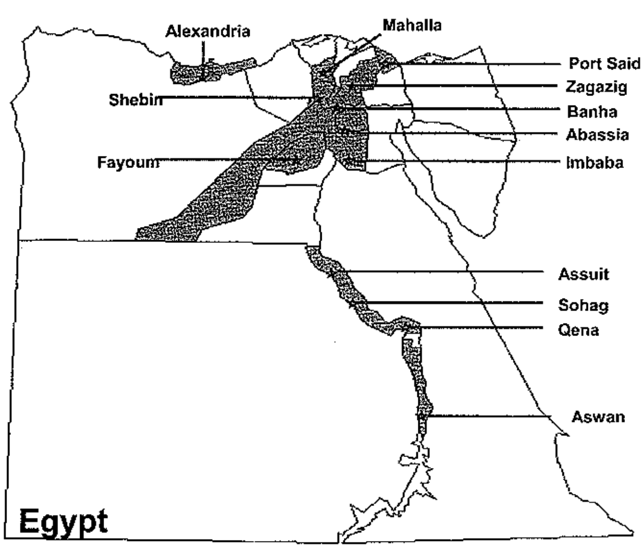

FIGURE 1. Regional hospitals participating in the sentinel surveillance network for priority diseases in Egypt, 1999–2003.

Case definitions of the World Health Organization. A suspected typhoid case was a person with two major and at least one minor of the following clinical criteria. Major criteria were 1) a sustained fever for more than two days that decreased but did not reaching baseline and 2) abdominal discomfort. Minor criteria were 1) non-productive cough and 2) relative bradycardia. A suspected brucellosis case was a person with fever for more than three days with profuse night sweating, fatigue, and malaise, plus one or more of the following: weight loss, headache, and arthralgia.

Patients meeting inclusion criteria were asked to participate. Informed, written consent was obtained from adult participants, parents, or legal guardians of minors. The U.S. Naval Medical Research Unit No. 3 Institutional Review Board reviewed and approved the study protocol (No. NAMRU3.1999.0001 [30969]) in compliance with all Federal regulations governing the protection of human subjects. All enrolled patients provided a venous blood sample for blood culture on admission; repeat cultures were obtained at the discretion of the clinician.

Epidemiologic data. For each patient, clinicians completed a surveillance questionnaire that recorded demographic, occupational, clinical, and risk factor details. Clinical information included date of onset of illness, the presence of fever or undulating fever, or other signs and symptoms. We considered a fever pattern with a long rise over a period of 7–10 days followed by a gradual fall over one week to normal temperatures as undulant fever.

In addition, patients were asked about drinking water sources in their household and exposures in the two weeks prior to illness that included consumption of raw milk, soft cheese, or yogurt, contact with animals, participation in the slaughtering of animals, or exposure to animal abortus.

Laboratory evaluations. Depending on the age of the patient, clinicians collected 2–10 mL of venous blood into a sterile Vacutainer® (Becton Dickinson, Franklin Lakes, NJ) tube prior to initiating antibiotic therapy and immediately inoculating biphasic blood culture media (PML Microbiologicals, Wilsonville, OR). An additional 3–5 mL of blood was permitted to clot and serum was collected and frozen (–20°C) for later serologic assays. All cultures taken at admission to the infectious disease hospital were considered community-acquired, even if the patient was first seen at another institution.

Laboratory personnel were trained to process blood and serum samples using aseptic techniques, universal precautions, and disposable supplies. Blood cultures were incubated at 37°C for 2–3 weeks. When growth was noted, subcultures were made onto blood, MacConkey, and chocolate agar plates. All microbiologic procedures were performed in a biosafety level 2 hood.

Positive blood cultures were characterized using standard microbiologic procedures. Serogrouping of *Salmonella* was determined using reference antisera (Becton Dickinson). During monthly site visits, positive blood cultures, isolates, and frozen sera were transported to a reference laboratory for quality control assessment and further serologic testing. Widal tests were conducted using slide agglutination methods with acute febrile antigens of *Salmonella* and controls (SA Scientific, San Antonio, TX). Serologic tests for *Brucella* were conducted by slide agglutination using *B. abortus* antigens (SA Scientific). One hospital conducted tube agglutination assays on-site using the same reagents.

Antibiotic sensitivity testing was confirmed at the reference laboratory of the U.S. Naval Medical Research Unit No. 3 in Cairo using the disk diffusion method (Kirby-Bauer). The ST organisms were considered multidrug resistant when resistance to the three antibiotics most commonly used in Egypt (ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole [TMP-SMX]) was observed.

Diagnosis. Infections were classified based on clinical presentation and laboratory results as follows. 1) Suspected typhoid/brucellosis was a patient who was compatible with the case definition. 2) Probable typhoid/brucellosis was a patient with either positive slide or tube serologic results with a titer ≥ 1:160. 3) Confirmed typhoid/brucellosis was a suspected patient with a positive blood culture. (Due to higher sensitivity and specificity of the *Brucella* agglutination test compared with the typhoid test, patients with positive serologic results for both *Brucella* and typhoid were considered probable brucellosis). 4) Other BSIs were cultures positive for organisms other than ST or *Brucella* spp. 5) Unexplained AFI was a patient with negative laboratory test results for typhoid and brucellosis and other BSIs.

Data analysis. Data was entered into a computerized database using Epi-Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA). Data were compared using chi-square and *t*-tests. Statistical significance was defined as a P value < 0.05. To evaluate seasonality of disease, analyses were restricted to hospitals that participated in the surveillance activity throughout the four-year surveillance period. Nested analyses were performed to calculate age-adjusted prevalence ratio (PR) and to identify risk factors for patients with brucellosis.

RESULTS

Between March 1999 and October 2003, 10,130 patients meeting the case definition of AFI had a clinical evaluation, a case investigation form completed, and a serologic evaluation; 9,883 (98%) patients had blood cultures prepared. Overall, 1,005 (10%) patients had positive blood cultures, which included 494 (5%) with ST infection, 275 (3%) with *Brucella*, 77 (0.5%) with *Staphylococcus aureus*, and 159 (1.5%) with other bacterial pathogens. Contaminated blood culture specimens were excluded and considered negative for culture. The other organisms cultured from patients with BSIs included *Escherichia coli*, *Enterobacter cloacae*, viridans streptococci, group C and D streptococci, *Pseudomonas aeruginosa*, yeast, *Salmonella* group B, *Pseudomonas* spp., *Klebsiella pneumoniae*, *Acinetobacter*, and *Citrobacter*. The percentage of culture-positive cases for typhoid and brucellosis among laboratory-diagnosed cases differed by hospital (range = 0–50%). Serologic testing identified an additional 1,819 patients (18%) with probable typhoid fever and 1,089 (11%) with probable brucellosis. Of the probable brucellosis cases, 163 that had positive serologic results for both tests were diagnosed as having brucellosis.

Numerous studies have shown that the sensitivity, specificity, and predictive values of the typhoid test vary dramatically among laboratories, which make the value of the test questionable to the clinician.[13–21] This wide variation is caused by differences in patient population, antigens, and techniques. The Widal reaction is indicative of typhoid fever in only 40–60% of patients at the time of admission. In our study, 9,883 specimens were tested by both culture and serologic analysis for typhoid. Of the 494 cases that had a positive typhoid culture, 265 were also positive by serologic analysis, giving a sensitivity of 56%. Of the 9,389 cases negative by culture, 7,405 were also negative by serologic analysis, giving a specificity of 79%. With regards to brucellosis, the serum agglutination test is the traditional gold standard and has a high sensitivity (up to 87%).[22] In our study, the sensitivity and specificity were 79% (218 of 275) and 89% (8,532 of 9,608), respectively. When confirmed and probable cases of both typhoid and brucellosis were analyzed independently, no difference was observed (Table 1).

The median age of typhoid fever patients was lower than that of patients with unexplained AFI; 53% were males (P < 0.05) (Table 1). The mean ± SD duration of hospital stay was 9 ± 9 days and low (0.2%) mortality rates were observed. The distribution of typhoid fever patients varied by hospital and location, and typhoid was found to be a more common cause of AFI in Upper Egypt than at other sites (P < 0.01) (Figure 2). Among the seven hospitals that participated in the surveillance network throughout the study period, there was variable seasonal distribution of patients with typhoid fever from year to year (Figure 3).

Nearly all (98%) patients with typhoid fever had an elevated temperature on admission, with a mean ± SD duration of fever prior to admission of 9.4 ± 8 days (Table 2). Fewer patients had headaches, vomiting, myalgia, pharyngitis, and arthralgia (Table 3). Patients who did not have typhoid fever (unexplained AFI) were more likely to have municipal water available when compared with patients with typhoid fever (6,625 of 7,817 [85%] versus 1,731 of 2,313 [75%]; age adjusted PR = 0.89, 0.87–0.91).

Seven-hundred sixty seven ST specimens were available at the Naval Medical Research Unit No. 3 laboratory for antibiotic sensitivity testing; these included 494 isolates from this study and additional 273 isolates from other studies done in the same governorates at the same time and the same infectious disease hospitals for evaluating risk factors or calculating the prevalence of typhoid. We report the sensitivity results of all available samples to provide more information. Antibiotic sensitivity testing showed that 685 (92%) were sensitive to ampicillin, 703 (95%) to chloramphenicol, 693 (93%) to TMP-SMX, 743 (99%) to ceftriaxone, and 744 (99%) to ciprofloxacin. Overall, 43 (5.6%) isolates had multidrug resistance to the three empirically used antibiotics. Rates of resis-

TABLE 1

Comparison between epidemiologic characteristics of confirmed and probable cases of typhoid and brucellosis

Characteristics	Confirmed typhoid (n = 494)	Probable typhoid (n = 1,819)	Confirmed brucellosis (n = 275)	Probable brucellosis (n = 1,089)
Median age (years)	14	20	30	30
% males	56	52	72	64
% case fatality	0.2	0.2	0.0	0.1
Mean days of hospitalization	10	8	8	7
Mean duration of fever prior to admission, days	9	9	14	13
% receiving antibiotics prior to admission	47	48	40	49

TABLE 2

Epidemiologic characteristics of patients with typhoid fever, brucellosis, other bloodstream infection (BSI), or unexplained acute febrile illness (AFI)

Characteristics	Typhoid* (n = 2,313)	Brucellosis* (n = 1,364)	Other BSI (n = 236)	Unexplained AFI (n = 6,217)
Median age (years)	18	30	26	28
% males	53	66	52	60
% case fatality	0.2	0.1	0.8	0.3
Mean days of hospitalization	9	8	8	7
Mean duration of fever prior to admission	9	13	10	9
% receiving antibiotics prior to admission	48	47	56	50

* Patients with probable or confirmed disease.

tance varied by site, with a range of 63% in one hospital to 0% in 6 hospitals. Overall, five isolates had intermediate resistance to ceftriaxone and four to ciprofloxacin; no isolates showed high levels of resistance to either of these antibiotics. Among 27 *S. aureus* isolates tested, 4 (15%) showed methicillin resistance.

Patients were diagnosed with brucellosis (positive culture or serology) in all participating rural and urban hospitals. These patients had a median age of 30 years (range = 4–90) and 65% were males. The mean ± SD duration of hospital stay was 8.2 ± 5 days and the mortality rate was low (0.1%). In contrast to patients with typhoid fever, the proportion of patients diagnosed with brucellosis was greater in the Nile Delta region than in other regions (Figure 2). Patients were reported in all months of the year with a peak in the spring and early summer, which coincides with the breeding season of domestic animals (Figure 4).

Almost all patients with brucellosis had fever on admission, with a mean ± SD duration of 13 ± 12 days prior to admission (Table 2); 89% of the patients had headache, 71% undulant fever, 72% myalgia, 70% arthralgia, 28% pharyngitis, and 6% retro-orbital pain. Clinical symptoms of brucellosis and typhoid were similar (Table 3). When compared with patients with unexplained fever, patients with brucellosis reported a greater number of animal exposures, as well as greater consumption of dairy products (Table 4).

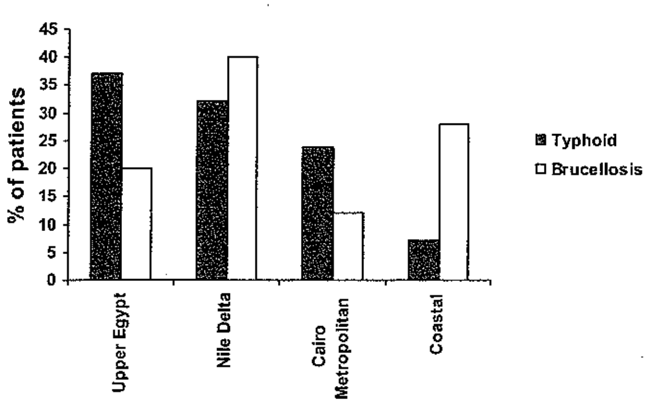

FIGURE 2. Proportion by region of Egypt of hospitalized acute febrile illness patients with laboratory-confirmed typhoid fever or brucellosis.

DISCUSSION

Identifying the etiology of AFI caused by various pathogens poses a major public health challenge in many countries because of the diversity of pathogens causing disease, limited capacity of laboratories to identify these pathogens, and fewer resources allocated to support surveillance activities. Laboratory-based surveillance requires coordination among clinicians and laboratory personnel to optimize diagnostic procedures and ensure high-quality data collection.

The development of a sentinel surveillance network in selected hospitals in Egypt is considered an efficient and low-cost option to enhance the detection and characterization of selected diseases and has led to a better understanding of the epidemiology of AFI in this country. This surveillance network has been particularly helpful in defining the epidemiology of typhoid fever and brucellosis. Community-based studies indicate that most patients with AFI in Egypt are diagnosed and managed clinically as having typhoid fever.[23] These studies, which were conducted in the Nile Delta, found that without laboratory testing, it is difficult to distinguish typhoid fever from other causes of AFI, particularly brucellosis and diseases of rickettsial origin.[23] Although patients with brucellosis were more likely to report symptoms of undulating fever, headaches, and myalgias, these symptoms also occurred in a substantial proportion of patients with typhoid fever and are not useful in making a definitive diagnosis of *Brucella* infection. In one study, approximately 87% of laboratory-confirmed cases of brucellosis were diagnosed, treated, and managed as having typhoid fever.[23] Prior to the Egyptian MOHP laboratory upgrade, AFI cases in the participating institutions were simply classified on clinical grounds as typhoid fever or fever for investigation. Laboratory-based diagnoses enable clinicians to tailor therapy to specific pathogens. Regional networking of laboratory-based detection and surveillance for AFI cases permits health professionals to track epidemiologic trends and changes in the occurrence of certain preventable diseases such as typhoid and brucellosis in the Egyptian population. Although patients with fevers in Egypt are required to be referred to infectious diseases hospitals for evaluation and treatment, many patients seek health care advice in the clinics and pharmacies. Hospital admissions, however, are limited principally to fever hospitals. By enrolling fever patients from infectious diseases hospitals from all geographic regions of Egypt, we believe the network provides data applicable to all of Egypt. In limiting surveillance to hospitals, we selected more severe fever patients who required admission. Therefore, patients who were seen outside the hospital setting and did not require referral or admission are not included. This likely results in underrepresentation of prevalence of disease in the community because milder cases were not identified.

Infection with ST causes a broad spectrum of clinical illness that include prolonged high fever, abdominal discomfort, malaise, and headache. Definitive diagnosis of typhoid is made by culture; however, many studies conducted in disease-endemic areas have shown a relatively high specificity and positive predictive value for the Widal test (slide or tube agglutination with a titer ≥ 1:160).[3,24] We used either culture or serologic results to diagnose typhoid fever, which confirmed that typhoid fever was the most common cause of AFI in Egypt. The age distribution of patients with ST infections in

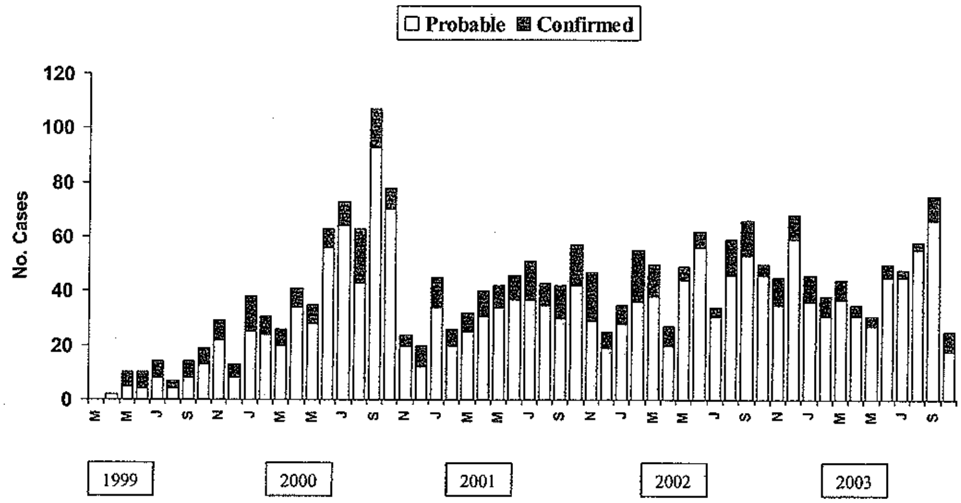

FIGURE 3. Monthly distribution of patients with probable or confirmed typhoid fever among hospitals in Egypt that conducted surveillance throughout the study period (1999–2003).

Egypt is more broadly distributed than some other regions where typhoid is highly endemic, which suggests that both endemic and epidemic transmission occur in Egypt. However, this data should be interpreted with caution since surveillance was limited to hospitalized AFI cases > 4 years of age. Data on seasonality showed peaks in case counts of ST in the summer and fall, which is consistent with transmission of other enteric diseases.

Beginning in the 1990s, strains of plasma-coded multidrug-resistant ST (MDR-ST) emerged in many developing countries, including Egypt.[25] The emergence of MDR-ST strains has been associated with more frequent severe disease and higher mortality rates, which may be a result of ineffective empirical therapy being prescribed initially.

Data from our AFI surveillance project suggests that infection with MDR-ST is not widespread but rather confined to focal geographic areas, and that antibiotic therapy for ST should be guided by an awareness of this drug resistance pattern. Thus far, our laboratory-based surveillance has shown MDR strains to occur at a low frequency and in only two of the eight networked hospitals.

Long-term ST surveillance has shown a remarkable shift back to chloramphenicol sensitivity compared with that of the early 1990s when most ST isolates were resistant.[25] In the pre-antibiotic era, case fatality among typhoid patients was ~12%. However, with the introduction of chloramphenicol, case fatality decreased to 4%. High mortality exceeding 10% continues to be reported in developing countries, despite the availability of antibiotics, whereas the case-fatality rates in developed countries are < 1%.[26] The duration of hospital stay of eight days, which is typical of typhoid response to treatment, and the lower case-fatality rates < 1% supports the finding of low-level antibiotic resistance and provides evidence of correct therapy and good case management by hospital staff. However, variation in the geographic distribution of ST infections, antibiotic use, and fluctuating ST resistance makes continued monitoring for antimicrobial resistance critical.

TABLE 3
Frequency of symptoms among patients with probable or confirmed typhoid fever and brucellosis

	Typhoid (n = 2,313)		Brucellosis (n = 1,364)	
Symptoms	No.	%	No.	%
Fever	2,273	98	1,354	99
Undulant fever	919	40	976	72
Headache	1,799	78	1,214	89
Arthralgia	812	35	953	70
Myalgia	989	43	980	72
Vomiting	1,020	44	546	40
Pharyngitis	712	31	387	28
Retro-orbital pain	202	9	82	6

The transmission of ST in disease-endemic settings occurs in association with poor sanitation and fecal contamination of water and/or food sources, and is typically observed in young school age children.[27] In Egypt, sources of drinking water and their quality and storage procedures are regionally variable. This may explain site variations in ST occurrence in AFI surveillance. In a pre-intervention survey conducted in Fayoum Governorate in the west desert 120 km from Cairo, sources of drinking water varied from a water purification plant, to compact units, to treated canal water in a few instances where pure water was unavailable. Availability of tap water ranged from being available at all times to being available for 2–3 hours/day. People store water in the home even if pure water is always available. The chlorine level in municipal water was found to be adequate even in remote areas, but there was little to no chlorine in water stored in houses, which was dependent on the length of the period of storage. Analysis of risk factors data in this study implicated a non-municipal water supply as one of the likely sources of ST infection in hospitalized AFI cases found in our surveillance network. The variable geographic distribution of typhoid fever found in this study reflects differences in access to municipal water in these diverse communities. The variability in drinking water sources, quality, and storage procedures may explain site variations in the occurrence of ST.

Brucellosis is a zoonotic disease that occurs worldwide. It most often attributed to infection by one of three species: *B. melitensis*, *B. abortus*, and *B. suis*. Due to the concurrent high prevalence of typhoid and limited diagnostic capabilities, bru-

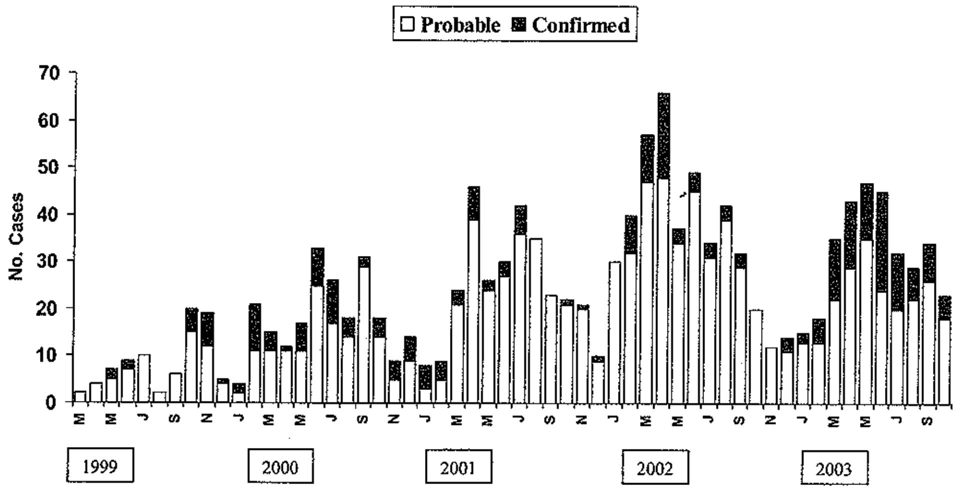

FIGURE 4. Monthly distribution of patients with brucellosis among hospitals in Egypt that participated in the surveillance project throughout the study period (1999–2003).

cellosis is a greatly underestimated cause of AFI in many countries. Annual brucellosis incidence rates in Jordan during 1986–1987 increased from 33.2/100,00 in 1986 to 46.2/100,000 in 1987.[28] The annual incidence in Kuwait during 1983–1984 was 85/100,000,[29] and in Saudi Arabia during the same period, brucellosis was the cause of 8.8% of the admissions in one Riyadh hospital.[30] The increased incidence of brucellosis may represent emerging disease, improved surveillance, or increased recognition of disease by clinicians.

Results from the Egyptian infectious disease hospital surveillance program suggest that brucellosis is a widespread and significant health problem in Egypt. The apparent high burden of disease, coupled with data implicating consumption of dairy products as a risk factor for disease, indicate a need to evaluate the effectiveness of *Brucella* control programs in Egypt. Prior to laboratory and diagnostic upgrades, brucellosis was infrequently diagnosed; with most AFI patients being classified and treated as typhoid fever, which resulted in inappropriate antimicrobial therapy. The high frequency of brucellosis as a cause of AFI, coupled with the significant overlap of symptoms among patients with brucellosis and typhoid fever, emphasize the importance of laboratory-based diagnosis of patients with AFI.

TABLE 4

Age-adjusted prevalence ratios for patients with brucellosis compared with patients with non-brucellosis

Exposure	Brucellosis (n = 1,364)		Non-brucellosis (n = 8,766)		Age-adjusted prevalence ratio (PR)	Confidence limit
	No.	%	No.	%		
Camel	45	3	34	1	3.3	2.3–4.9
Sheep	204	36	718	16	2.2	2.0–2.4
Cattle	157	28	736	17	1.8	1.6–2.0
Buffalo	168	30	694	16	1.7	1.6–1.9
Donkey	101	18	459	11	1.9	1.6–2.2
Handling animal abortus	96	17	267	6	2.9	2.4–3.4
Slaughtering animals	78	14	264	6	2.5	2.3–3.3
Handling raw meat	92	16	356	8	1.8	1.6–2.0
Drink unpasteurized milk	185	33	902	21	1.4	1.2–1.5
Eating soft cheese	427	76	2,880	66	1.2	1.1–1.2

Brucellosis is often a disease of rural communities associated with animal husbandry. The prevalence of disease in domestic animals is an important predictor of disease in humans. In this surveillance study, we found the distribution of brucellosis as a cause of AFI was similar in both rural and urban communities, with the highest frequency among patients in the Nile Delta. Animal exposure occurs in all regions of Egypt. In addition, unpasteurized dairy products are widely available throughout the country. The age group affected most included young adults with a predominance among males. Risk factor data suggest exposure to animals, animal husbandry, and consumption of raw dairy products are important risk factors for the disease in Egypt. These data are consistent with numerous studies on brucellosis in the Middle East.[28–30] The wide scale distribution of disease suggests that animal husbandry and dairy practices are promoting disease transmission throughout the country. Additional studies are needed to investigate more details on the sources of exposure to *Brucella* sp., including investigation of food sources and domestic animals.

Laboratory-based surveillance made it possible to capture a variety of other pathogens causing BSIs in Egypt. The capacity to culture and identify these organisms is highly beneficial to clinical care and public health monitoring. Specifically a number of *S. aureus* BSIs were identified and the emergence of community-acquired methicillin-resistant *S. aureus* was documented.

Many patients had negative cultures and serologic test results for typhoid, brucellosis and other BSIs. These patients received clinical diagnoses from their physicians, which covered a broad range of symptom-based clinical syndromes. The clinical diagnosis is not always apparent during early presentation of many diseases, and clinicians often make a diagnosis based on clinical expression of the disease after hospitalization. This resulted in many patients being enrolled who subsequently received a diagnosis that should have been originally excluded, if obvious, on admission. Despite these clinical diagnoses, many patients still had unexplained AFI. The high proportion of patients with unexplained disease may be partially explained by the high frequency of pretreatment with antibiotics. Antibiotics are readily available for purchase in pharmacies, and health-seeking behavior in the community often begins at pharmacies and/or local clinics.

Studies are ongoing to evaluate other etiologies of AFI known to occur in Egypt such as rickettsioses, arboviruses, and leptospirosis. From a public health perspective, hospital-based surveillance has considerable limitations because only a fraction of patients with AFI seek hospital care. Thus, disease incidence and disease burden cannot be well characterized. Population-based surveillance in a governorate of Upper Egypt found that only 6% of typhoid fever patients were admitted to the infectious diseases hospital (Lynch M, and others, unpublished data).

From a public health perspective, hospital-based surveillance has considerable limitations because only a fraction of patients with AFI seek hospital care. Thus, disease incidence and disease burden cannot be well characterized. Despite the constraints of hospital-based surveillance, the establishment of a sentinel surveillance network has had several benefits including an increase in the reporting of patients with laboratory-confirmed disease. The overlap of symptoms between brucellosis and typhoid fever and the different treatment regimens highlight the importance of laboratory-based surveillance from a clinical perspective in making a correct diagnosis and choosing appropriate treatment regimens. The surveillance program has led to the establishment of community-based studies to better define the burden of disease. In these studies, the incidence of typhoid fever and brucellosis in a Nile Delta community was found to be 13/100,000 and 18/100,000, respectively.[9] In addition, in 2003 the incidence of typhoid fever in an Upper Egypt governorate was 81/100,000 (Lynch M and others, unpublished data) and that of brucellosis was 77/100,000 (Jennings GJ and others, unpublished data). These studies confirm the importance of risk factors identified in the hospital-based studies and serve as a platform to develop prevention strategies targeting food and water-borne diseases in Egypt.

Received September 12, 2004. Accepted for publication February 28, 2005.

Acknowledgments: We express our sincere appreciation and thanks to the many physicians, nurses, and clinical laboratory staff of the infectious disease hospitals involved in this study. We also thank Dr. Yehia Sultan, Dr. Atef Sadaka, Dr. Abdel Halim Abdel Hamid, Dr. Bothaina Bakry, Dr. Mohamed El Ragaby, Dr. Ragaa Sakr, Dr. Mohamed Abdel Hady, Dr. Mofreh Ramzy, Dr. Ahmed Ibrahim, Dr. Said Ibrahim, Dr. Mokhtar Wahba, and Dr. Abdel Fattah Ibrahim (all directors of infectious disease hospitals) for their cooperation. We also acknowledge support from the staff of the Preventive Sector and the Central Public Health Laboratory of the Ministry of Health and Population who assisted with training and monitoring the activities within the infectious disease hospitals. Appreciation is extended to the staff of the United States Agency for International Development (USAID) for their guidance, especially that of Dr. Emad Yanni and Mark White. We are especially grateful to United States Naval Medical Research Unit No. 3 staff members (Walid William, Mohamed Abdel Maksoud, Dr. Mostafa Abdel Fadeel) and to Dr. Rana Hajjeh and Dr. G. Pimentel for their critical review of the manuscript.

Financial support: The work was supported by a grant from the USAID and the Department of Defense Global Emerging Infectious Systems (DoD-GEIS) (work unit number E022).

Disclaimer: The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large, or the Egyptian Ministry of Health and Population.

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