

POPULATION-BASED SURVEILLANCE OF TYPHOID FEVER IN EGYPT

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Abstract. Credible measures of disease incidence are necessary to guide typhoid fever control efforts. In Egypt, incidence estimates have been derived from hospital-based syndromic surveillance, which may not represent the population with typhoid fever. To determine the population-based incidence of typhoid fever in Fayoum Governorate (pop. 2,240,000), we established laboratory-based surveillance at five tiers of health care. Incidence estimates were adjusted for sampling and test sensitivity. Of 1,815 patients evaluated, cultures yielded 90 (5%) *Salmonella* Typhi isolates. The estimated incidence of typhoid fever was 59/100,000 persons/year. We estimate 71% of typhoid fever patients are managed by primary care providers. Multidrug-resistant (MDR) *Salmonella* Typhi (resistant to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole) was isolated from 26 (29%) patients. Population-based surveillance indicates moderate typhoid fever incidence in Fayoum, and a concerning prevalence of MDR typhoid. The majority of patients are evaluated at the primary care level and would not have been detected by hospital-based surveillance.

INTRODUCTION

Typhoid fever is estimated to cause 21 million illnesses and 200,000 deaths annually worldwide.¹ Ingestion of contaminated drinking water and food is the most common route of disease transmission.^{2–4} Although typhoid fever is common in many regions of the world, the actual burden of disease is poorly defined in most endemic countries. The widespread prevalence of multidrug-resistant typhoid fever⁵ also influences the true impact of disease in these regions. With the advent of new vaccines for typhoid fever,⁶ there is a need for timely and accurate assessment of disease burden in typhoid-endemic countries to guide decisions about the allocation of scarce resources for disease control and prevention programs.

To better define the burden of typhoid fever, we first need credible measures of disease incidence. Because the diagnosis of typhoid is based on blood or bone marrow culture, determining the incidence of disease is inherently challenging in many endemic countries, where laboratory capacity is frequently limited.⁷ In Egypt, current estimates of typhoid fever incidence are derived from case reports received from passive hospital-based surveillance, without laboratory confirmation of disease. In the year 2000, the estimated incidence of typhoid fever in Egypt was 15 cases per 100,000 persons per year (Egyptian national syndrome-based surveillance, unpublished data). However, this estimate may not reflect the true incidence of disease, as less than 1% of these cases were culture-confirmed. Furthermore, as many patients may never be hospitalized, hospital-based surveillance may not accurately represent the population with typhoid fever.

In 2001, the Egyptian Ministry of Health and Population (MOHP), the U.S. Naval Medical Research Unit-3 (NAMRU-3), and the Centers for Disease Control and Prevention (CDC) piloted a rapid, community-based surveillance method to measure the incidence of typhoid fever and other causes of acute febrile illnesses in Bilbeis district (population 664,000) in Lower Egypt. Surveillance was conducted at multiple levels of service providers to more accurately measure

disease incidence and characterize the population with disease. The estimated incidence of typhoid fever was calculated to be 13 cases per 100,000 persons per year, much lower than initially anticipated.⁸ To develop a better understanding of the burden of typhoid fever in Egypt, we refined this surveillance method to characterize disease incidence in a larger governorate in Upper Egypt and ascertain the prevalence of multidrug-resistant disease among patients with typhoid fever in this region.

MATERIALS AND METHODS

Study site. The study site, Fayoum Governorate (Fayoum), is located 150 km southwest of Cairo and had an estimated population of 2,240,000 in 2002 (Fayoum Governorate Census, 2002). The governorate spans 1,827 km² and is composed of five rural districts and Fayoum City. Each district is composed of several villages that rely primarily on an agrarian economy. Fayoum City, the urban center of the governorate, consists primarily of single- and multi-story dwellings and commercial establishments. Fayoum is a man-made oasis region that is surrounded by desert, separating it from surrounding districts and limiting residents from traveling outside the governorate for medical care. Fayoum is one of the poorer governorates of Egypt; the GDP per capita in 2001 was US\$785 and the adult literacy rate was 48%.⁹ Of 27 governorates in Egypt, Fayoum is ranked 22nd by the central government on a human development index scale.⁹

Surveillance. Previous health care-seeking behavior surveys performed in Egypt have indicated that the majority of persons who develop prolonged fever seek medical care from formal sectors of health care.¹⁰ Discussions with governorate health officials and clinicians revealed that there are five formal tiers of health care in Fayoum where persons with prolonged fever generally seek medical attention: the governorate infectious disease hospital, district hospitals, infectious disease specialists, rural health units, and primary care physicians. We obtained a contemporary census of these health providers and hospitals from the Fayoum Governorate Health Directorate. The governorate infectious disease hospital, located in Fayoum City, serves as the tertiary care referral center for treatment of patients with febrile illness. The

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six district hospitals in Fayoum serve as general hospitals at the district level. The 18 infectious disease specialists in Fayoum are government and private doctors who function as infectious disease consultants. Primary health care is provided by physicians in 138 rural health units and by 186 private primary care physicians (internal medicine physicians, pediatricians, and general practitioners). We conducted surveillance for typhoid fever at the governorate fever hospital, the six district hospitals, among 16 (89%) of the infectious disease specialists, and among a random selection of 13 (9.4%) representative rural health units physicians and 18 (9.7%) primary care providers. The 18 primary care providers included 3 internists, 8 general practitioners, and 7 pediatricians.

During our study period of June 9 to October 31, 2002, all patients ≥ 1 year of age who presented to surveillance health care providers with a temperature greater than 38°C and either 1) a history of fever of more than 2 days without an identifiable cause or 2) a clinical diagnosis of suspected typhoid fever were invited to participate. After obtaining informed consent from patients, providers completed a brief case investigation form with basic demographic and clinical information and collected between 3 and 7 mL of blood for a single bacterial culture. Health care providers were trained on indications for study enrollment, sterile venipuncture technique, and needle safety. Couriers visited each provider daily to provide test results and to collect and transport laboratory specimens and case investigation forms. Approval was obtained from the institutional review boards of NAMRU-3 and the Centers for Disease Control and Prevention.

Laboratory methods. Laboratory specimens were processed at the Fayoum Infectious Disease Hospital and the Fayoum Governorate Common Laboratory. Microbiologists at both laboratories were trained in blood culture technology and retrained in basic bacteriology. The NAMRU-3 bacteriology laboratory in Cairo provided quality control on all samples and bacterial isolates and acted as a reference laboratory.

Blood cultures were done with a biphasic blood culture system (Bio-Merieux, Marcy l'Etoile, France); bottles were incubated for 21 days at 37°C and observed daily for signs of microbial growth. Growth in broth or on agar slants was examined by Gram stain and subcultured to solid media for identification. Microbiologists at NAMRU-3 laboratory performed antimicrobial susceptibility testing on all confirmed *Salmonella* Typhi isolates by disk diffusion according to the 2001 methods of the National Committee of Clinical Laboratory Standards to the following antimicrobial agents: trimethoprim-sulfamethoxazole, ampicillin, chloramphenicol, ceftriaxone, and ciprofloxacin.¹¹ A person was diagnosed with typhoid fever if *Salmonella* Typhi was isolated from blood. An *Salmonella* Typhi isolate was classified as multidrug resistant if it was resistant to all three first-line antibiotics used to treat typhoid fever: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMZ).

Incidence calculations. The annual incidence of typhoid fever was calculated after accounting for provider sampling, test sensitivity and specificity, and study period. We derived simple arithmetic multipliers to account for provider sampling by using the number of participating providers at a given health care level as the numerator and the total number of providers in Fayoum Governorate at that health care level as the denominator. Because the only fever hospital and all six

district hospitals in Fayoum were included in surveillance, no multiplier was needed for cases detected at these providers. We applied a multiplier of 1.1 to cases detected at the infectious disease specialist level, as 89% of specialist providers participated in surveillance. To account for sampling 9.4% of rural health units and 9.7% of primary care providers in Fayoum, we applied respective multipliers of 10.6 and 10.3 to cases detected at these health care levels.

We reviewed published studies of the performance of a single blood culture for the microbiological diagnosis of typhoid fever to derive a multiplier for test sensitivity. Results from multiple systematic studies suggest that the sensitivity of a single blood culture for the detection of *Salmonella* Typhi is approximately 50%.¹²⁻¹⁴ Therefore, we applied a multiplier of 2.0 to account for blood culture-negative typhoid fever. For the purposes of incidence calculations, the specificity of a single blood culture for typhoid fever was assumed to be 100%.

The surveillance study period lasted for 21 weeks, between June 9 and October 31, 2002. To adjust our findings to account for a whole year, we reviewed sentinel hospital laboratory-based febrile illness surveillance system data on monthly blood culture-confirmed typhoid fever incidence from 2000 to 2002. These data suggested that no seasonal peak in typhoid fever incidence occurs. To annualize our incidence calculations, we multiplied the number of typhoid fever cases detected during our surveillance study period by 2.5. We used population age structure data from the Egyptian Ministry of Health and Population to derive age-group-specific population estimates for Fayoum Governorate; we calculated age-group-specific typhoid fever incidence using these population estimates.

Statistical methods. Data were entered and stored in an Epi-Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA) database and analyzed with SAS version 8.2 (SAS Institute, Cary, NC). Confidence limits for incidence estimates were calculated based on the assumption that *Salmonella* Typhi specimen positivity was not seasonal; thus, the 144 days under surveillance were viewed as a random sample of the 365 days in the year. Using this assumption, the data were analyzed as a stratified random sample from the different types of health care providers.

RESULTS

Surveillance. During the study period, 1,815 patients with acute febrile illness meeting the case definition were enrolled in surveillance. Study practitioners reported that no eligible patients refused to participate. Provider data was recorded for 1,804 of the 1,815 patients; 202 (11%) were enrolled at the infectious disease hospital, 300 (17%) at one of 6 district hospitals, 548 (30%) by an infectious disease specialist, 396 (22%) at one of the participating rural health units, and 358 (20%) by one of the participating primary care physicians. Age was recorded for 1,801 patients: 48 (3%) were less than 5 years old, 278 (15%) were between 5 and 9 years old, 347 (19%) were between 10 and 14 years old, and 1,128 (63%) were older than 15 years.

Typhoid fever was diagnosed by blood culture in 90 (5%) patients; 38 (43%) were female. Patients with typhoid fever were significantly younger than all other patients enrolled in surveillance (median age 11 years versus 20 years, $P < 0.001$). Patients with typhoid fever also reported longer duration of

fever before enrollment in surveillance than other patients under surveillance (7 days versus 4 days, $P < 0.001$). Among all enrolled patients, 534 (31%) reported receiving antibiotics in the month before presenting to the participating study clinician; among typhoid fever patients, 49 (54%) reported receiving antibiotic therapy during the month before evaluation by the participating study clinician ($P < 0.001$).

Other pathogens isolated by blood culture were *Salmonella* Paratyphi A (7), *Escherichia coli* (2), *Enterobacter cloacae* (1), and other nontyphoidal *Salmonella* species (1). *Brucella* species was isolated from 43 patients; of these, 27 (63%) were clinically diagnosed with and managed for typhoid fever. Bacterial contamination of blood cultures occurred frequently throughout the study period. Contaminants were isolated in 18% of all blood cultures and consisted overwhelmingly of skin flora (coagulase-negative *Staphylococcus*, diphtheroids). The proportion of bacterial contaminants varied by provider level and ranged from 5% of specimens submitted at the fever hospital to 30% of specimens submitted at rural health units. Periodic intensive retraining of participating health providers throughout the surveillance study period reduced the rate of blood culture contamination from 24% of cultures submitted in July to 13% of cultures submitted in October ($P < 0.001$).

Incidence calculations. After adjusting the number of detected typhoid fever cases for provider sampling, test sensitivity, and the 21-week study period, we estimated the annual number of typhoid fever cases in Fayoum as 1,315 and the annual incidence of typhoid fever as 59 cases per 100,000 persons per year (95% confidence interval [CI] 40–79 cases per 100,000 persons per year) (Table 1). In contrast, the calculated incidence of typhoid fever based on patients identified solely at the infectious disease hospital would be only 7 cases per 100,000 persons per year. When analyzed by source of medical provider, the majority (71%) of patients with typhoid fever in Fayoum are seen and managed at the primary level of health care (rural health units and primary care providers). The annual incidence of typhoid fever was highest among school-aged children: 5–9 (143 cases per 100,000 per year) and 10–14 years (160 cases per 100,000 per year). The annual incidence of typhoid fever among very young children (<5 years) in Fayoum was relatively low (6 cases per 100,000 per year) (Table 2).

Laboratory testing. Of the 89 *Salmonella* Typhi isolates with antimicrobial susceptibility testing, susceptibility to all three first-line antimicrobials used to treat typhoid fever (ampicillin, chloramphenicol, and TMP-SMZ) was detected

TABLE 2
Annual incidence of typhoid fever by age group: Fayoum Governorate, 2002

Age in years	Estimated annual cases typhoid*	Age-group-specific population	Annual incidence†
0–4	22	378,316	6
5–9	421	295,040	143
10–14	449	280,263	160
≥15	440	1,284,971	34

* Adjusted for health care provider sampling, 21-week study period, and blood culture sensitivity.

† Per 100,000 age-specific population.

in 58 (65%) isolates (Table 3). Twenty-six isolates (29%) were classified as MDR *Salmonella* Typhi. Among MDR *Salmonella* Typhi isolates, one isolate also demonstrated resistance to ciprofloxacin. Intermediate susceptibility to ciprofloxacin was also identified in two other isolates. Resistance to ceftriaxone was detected in one isolate, and intermediate susceptibility to this antimicrobial was detected in another isolate. Among the 26 patients with MDR typhoid, 15 (58%) were prescribed antimicrobials at the time of initial evaluation; some patients received multiple antimicrobials. Among these 15 patients, six (40%) were treated with ampicillin, 12 (80%) were treated with chloramphenicol, and eight (53%) were treated with TMP-SMZ; none were treated with a fluoroquinolone.

DISCUSSION

The results of population-based surveillance indicate the incidence of typhoid fever in Fayoum Governorate to be 59 cases per 100,000 persons per year. In contrast to the results of national, syndrome-based surveillance, these incidence calculations are based on laboratory-confirmed diagnoses and are more representative of the entire community. Our findings indicate that the majority (71%) of typhoid fever patients in Fayoum are evaluated and treated at primary levels of health care. Previous population-based surveillance efforts have also suggested that the majority of patients with typhoid fever in endemic regions are diagnosed and managed in the outpatient setting.^{15–18} During active surveillance for typhoid fever in New Delhi, less than 5% of culture-confirmed patients over 5 years of age were hospitalized for their illness.¹⁸ Our findings similarly indicate that a minority of patients with typhoid fever in Fayoum Governorate was treated at the main infectious disease hospital. If we had limited surveillance to

TABLE 1
Annual incidence typhoid fever: Fayoum Governorate, 2002

Health care provider	Crude cases typhoid	Adjusted cases typhoid*	Annualization multiplier	Test sensitivity multiplier	Annual estimated cases typhoid	Annual incidence typhoid (per 100,000)†
Fever hospital (1/1)	30	30	2.5	2	150	—
Fever specialist (16/18)	36	41	2.5	2	205	—
District hospital (6/6)	6	6	2.5	2	30	—
Rural health unit (13/135)	9	93	2.5	2	465	—
Primary care physician (18/186)	9	93	2.5	2	465	—
Fayoum Governorate total (population 2.24 million)	90	263	2.5	2	1,315	59‡

* Adjusted for health care provider sampling.

† The annual incidence of typhoid fever was calculated for the entire Fayoum Governorate, but not by specific health care provider level because the population served by each provider level is not known.

‡ 95% confidence interval: 40–79 cases per 100,000 persons per year.

TABLE 3

Antimicrobial susceptibility patterns of *Salmonella* Typhi isolates: Fayoum Governorate, 2002 (N = 89)

Susceptibility pattern	Number N = 89	Isolates (%)
Susceptible to ampicillin, TMP-SMZ, chloramphenicol	58	(65)
Any resistance		
Chloramphenicol*	29	(33)
Ampicillin†	30	(34)
Trimethoprim-sulfamethoxazole (TMP-SMZ)	26	(29)
Ciprofloxacin*	3	(3)
Ceftriaxone‡	2	(2)
Multidrug resistance (MDR)§	26	(29)
Other resistance patterns		
Intermediate susceptibility to ampicillin and ciprofloxacin	1	(1)
Intermediate susceptibility to ampicillin, chloramphenicol, ceftriaxone, ciprofloxacin	1	(1)
Resistance to ampicillin, chloramphenicol, ceftriaxone	1	(1)
Resistance to ampicillin, chloramphenicol, TMP-SMZ, ciprofloxacin	1	(1)

* Includes two isolates with intermediate susceptibility (13–17 mm diameter for chloramphenicol; 16–20 mm for ciprofloxacin).

† Includes three isolates with intermediate susceptibility (14–16 mm).

‡ Includes one isolate with intermediate susceptibility (14–20 mm).

§ MDR classified as resistance to ampicillin (≤ 13 mm), chloramphenicol (≤ 12 mm), and TMP-SMZ (≤ 10 mm).

cases detected at the infectious disease hospital, the estimate of annual typhoid fever incidence in Fayoum would have differed by almost an order of magnitude.

The highest incidence of typhoid fever in Fayoum occurred among school-aged children, in whom rates were more than double that for the general population. Similar age distributions for typhoid fever incidence have been described in other medium-incidence endemic settings.² We did not find high rates of infection among very young children (less than 5 years old), in contrast to countries such as India or Bangladesh, where the overall incidence of typhoid fever greatly exceeds 100 cases per 100,000 persons per year.^{1,18,19} The lower rates of disease detected among young children in Fayoum may have been related to limited exposure to *Salmonella* Typhi in these age groups. However, the difficulty and reluctance of physicians to perform venipuncture on young children should also be taken into account; only 3% of all submitted specimens were collected from children younger than 5 years old. Determining the exposures associated with typhoid fever in Fayoum may help to clarify the differential rates of infection among various age groups.

Interestingly, the calculated incidence of typhoid fever in Fayoum is much higher than that determined for Bilbeis district in 2001. Although the population under surveillance in Fayoum Governorate was six times that of Bilbeis, a single district, similar surveillance methodology was used in both regions. More than 70% of the patients with typhoid fever were detected at the primary care level in Fayoum. In contrast, no cases of typhoid fever were detected at the primary care level in Bilbeis.⁸ Providers practicing at the primary level of health care enrolled 754 (42%) patients under surveillance in Fayoum. In comparison, 87 (20%) patients in Bilbeis were enrolled by primary care level providers (J. A. Crump, unpublished data). This raises the possibility that the proportion and number of patients assessed at the primary care level in Bilbeis may have been too low to accurately reflect typhoid

fever cases at this level of health care. Because incidence calculations at the primary care level are significantly affected by a multiplier to account for provider sampling, even one missed case of typhoid fever at the primary level of health care has the potential to appreciably alter the calculated disease incidence.

The differing rates of typhoid fever in Bilbeis District and Fayoum may also be due to regional socioeconomic differences. Development indices for Bilbeis suggest a higher standard of living in this district in comparison to Fayoum Governorate.⁹ Better access to safer drinking and household water in a more developed region, for example, may reduce opportunities for typhoid fever transmission and thus contribute to lower rates of disease. To develop a robust estimate of the national incidence of typhoid fever, it will be important to account for factors such as uniformity of surveillance methods and regional differences, as well as potential year-to-year variation of disease incidence.

Although we accounted for the sensitivity of single blood culture (~50%) in incidence calculations, it is likely that we missed microbiological confirmation of typhoid fever in some patients who presented with only a short duration (≤ 3 days) of fever. The isolation of *Salmonella* Typhi from blood culture may be higher in patients who are symptomatic for >4 days^{13,15}; in Fayoum, patients with confirmed typhoid fever presented with a significantly longer duration of fever (median 7 days). We may have also missed detecting cases of typhoid fever in bacterially contaminated cultures, as the growth of bacterial contaminants in blood cultures is likely to out-compete the growth of a pathogen such as *Salmonella* Typhi. If we considered these contaminated cultures similar to untested specimens and assumed that the rate of typhoid among persons whose cultures were bacterially contaminated would be the same as the rate of typhoid fever among persons with uncontaminated cultures, our estimated incidence of typhoid fever in Fayoum would have increased to 76 cases per 100,000 population per year (95% CI 55–97 per 100,000 per year). We were also unable to account for persons in Fayoum with febrile illness who did not seek medical care for their illness. These limitations suggest that the true incidence of typhoid fever in Fayoum is likely higher than detected through our surveillance methods.

Antimicrobial susceptibility testing revealed that close to 30% of patients diagnosed with typhoid fever in Fayoum had multidrug-resistant disease. This rate of MDR typhoid fever is much higher than that reported recently in Egypt,²⁰ and it underscores the need to promote judicious use of antimicrobials in clinical practice to prevent the further spread of resistance.²¹ Testing for nalidixic acid resistance, which may predict decreased susceptibility of an *Salmonella* Typhi isolate to fluoroquinolone therapy,²² was not performed during surveillance in Fayoum. The detection of intermediate susceptibility to ciprofloxacin in two *Salmonella* Typhi isolates in Fayoum may thus be an underestimate of the true prevalence of reduced susceptibility to fluoroquinolones in the region. Resistance to ciprofloxacin and ceftriaxone, each detected in one *Salmonella* Typhi isolate during surveillance in Fayoum, has not been previously reported in Egypt and raises concern for the development and spread of highly resistant typhoid fever that can only be managed with parenteral antimicrobial therapy.

In an area such as Fayoum, microbiological confirmation of

disease and antimicrobial susceptibility testing is not routinely available. The majority of health care providers must rely solely on clinical signs and symptoms to guide treatment decisions. If a clinical diagnosis of typhoid fever is made, use of a fluoroquinolone should be considered as an alternative to standard antimicrobial therapy (ampicillin, TMP-SMZ, or chloramphenicol) in Fayoum, given the high prevalence of MDR typhoid fever. Whatever the choice of antimicrobial therapy, close follow-up of outpatients is critical, as the failure to clinically respond should raise concern for MDR typhoid (in patients treated with first-line antimicrobial therapy) or other frequently encountered causes of febrile illness, such as brucellosis,⁸ which was misdiagnosed and managed as typhoid fever more than 50% of the time in Fayoum.

Data from multiple clinical series suggest that multidrug-resistant typhoid fever is associated with higher rates of complication and morbidity.^{23–26} The prevalence of drug-resistant disease may thus affect the burden of typhoid fever in Fayoum and other endemic settings. Accurate measurement of the mortality associated with typhoid fever is critical to understanding the true burden of disease. Published estimates of typhoid fever case-fatality rates in endemic countries vary widely and are based exclusively on hospital case series.^{27,28} To better define the health and economic consequences of typhoid fever in Fayoum and other typhoid endemic regions, it will be important to gather more representative morbidity and mortality data and examine the clinical outcomes of disease at the community level. A more accurate measurement of typhoid fever incidence in Fayoum also provides a framework to systematically investigate risk factors associated with illness. Understanding the exposures linked to typhoid fever in Fayoum will be critical to guide effective and appropriate control strategies for disease reduction.

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