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# Burden of typhoid fever in Sulaimania, Iraqi Kurdistan

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SUMMARY

*Background:* Typhoid fever imposes a high disease burden worldwide, but resource limitations mean that the burden of typhoid fever in many countries is poorly understood.
*Methods:* The authors conducted a prospective surveillance study at the adult and pediatric teaching hospitals in Sulaimania, Iraqi Kurdistan. All patients presenting with an undifferentiated febrile illness consistent with typhoid were eligible for enrollment. Enrolled patients had blood cultures and Brucella serologies performed. Incidence was calculated with reference to census data.
*Results:* Both typhoid fever and brucellosis were common, and the incidence of typhoid fever was 21 cases/100 000 patient-years. Classic disease symptoms were uncommonly observed.
*Discussion:* Cost-effective surveillance projects to calculate disease burden of typhoid fever are practical and replicable. Typhoid has successfully adapted to the healthcare environment in Sulaimania. Additional work in the region should focus on antibiotic resistance and other enteric pathogens such as *Brucella spp*.
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## 1. Introduction

*Salmonella* Typhi and *Salmonella* Paratyphi are human-adapted pathogens that cause enteric fever.[1] The disease burden worldwide is estimated at over 20 million cases per year, with more than 200 000 deaths.[2–4] A significant proportion of this burden is carried by children and young adults who are non-immune.[5] Complicating clinical management is the increase in recent years of antibiotic resistance among strains of *Salmonella* Typhi, a development that threatens to overwhelm the diagnostic and surveillance capabilities of many health systems in developing countries.[6,7]

Incidence rates are an important part of the basis for strategic decisions on expenditures of scarce funds for infectious disease control and prevention. Prospective surveillance for patients presenting with an undifferentiated febrile syndrome, using blood culture, can provide a realistic estimate of the disease burden of typhoid.[8] Surveillance efforts of this kind concentrated at sites used by the population under study have recently been piloted as a suitable and low cost approach.[9] This has also been used to compare the burden of vaccine-preventable diseases such as *Salmonella* Typhi, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b.[10] The data from such studies can be used to inform health policy decisions on vaccination programs, particularly those for children.

Sulaimania is the provincial capital of the Sulaimania Governorate, one of three provinces forming the Kurdish Autonomous Region in northern Iraq. The region is culturally and linguistically distinct from the rest of Iraq, and suffered from ethnic cleansing including the use of chemical weapons prior to the overthrow of the Ba'ath regime in 2003.[11,12] The consequences of war, chemical weapons use, and repression still impact the health of the population today.[13]

The central district of Sulaimania, demarcated by a peripheral ring road, has a health system that includes university teaching hospitals for adults and for children, as well as public and private

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clinics. A well-resourced microbiology laboratory is located inside the central district near the main teaching hospitals. The central district had a population census determined by the Kurdish government in December 2009, thereby facilitating population-based surveillance.

This paper presents the results of a prospective, population-based study to measure the burden of disease of typhoid fever in Sulaimania, Iraqi Kurdistan. To our knowledge it is the first collaborative effort of its kind between American and Kurdish physicians, and the first effort to calculate the burden of typhoid and enteric fever in Iraqi Kurdistan.

## 2. Methods

A prospective study was conducted during May–September 2011 of patients suspected to have typhoid fever, who presented for evaluation to the emergency department or inpatient floors of the adult and pediatric teaching hospitals of the Sulaimania College of Medicine. Eligible patients were those with an illness of more than 2 days duration that included fever >38 °C, who were clinically suspected by the examining physician to have typhoid fever. Exclusion criteria were illness with localizing signs or symptoms suggesting an alternative diagnosis and residency in areas outside the central district of Sulaimania. Enrollment was conducted by medical residents who were part of the project staff, and enrollment occurred 24 h daily, 7 days per week, during the study.

Patients eligible for enrollment were invited to participate. The clinician completed a form recording key demographic and clinical information, and documented the patient's verbal consent. A single blood sample was obtained and sent to the participating private microbiology laboratory, using a courier service when necessary to prevent delays in culture processing. Results from the microbiology laboratory were recorded on the enrollment form, which had no patient identifiers. The enrolling physicians maintained a key that allowed relevant results (e.g., positive blood cultures) to be linked back to the individual patients for use in their care. The key was destroyed after the study was completed to protect patient anonymity.

Brain heart infusion (BHI) broth was used for blood cultures. Positive blood cultures were subjected to organism identification using API strips (bioMérieux, 20E). All enrolled patients were also screened for *Brucella spp* with the Rose-Bengal slide agglutination test using *Brucella abortus* antigen (LINEAR Chemicals, Spain). Serial dilution was used to detect the prozone effect. Patients with positive test results had additional confirmatory testing with a 2-mercaptoethanol (2ME) test (Bio Basic, Canada).

A case of typhoid fever was defined as an enrolled patient with *Salmonella* Typhi bacteremia. Enteric fever was defined as an enrolled patient whose blood culture yielded *Salmonella* Typhi or *Salmonella* Paratyphi. A case of brucellosis was defined as an enrolled patient with an agglutination titer ≥1:160, as well as a positive confirmatory 2ME test.

Demographic, clinical, and microbiological data were entered into EpiInfo (Centers for Disease Control and Prevention). Univariate analysis was performed using EpiInfo; multivariate analysis was performed by logistic regression (Minitab). As described in other typhoid disease burden studies, a multiplier of two was applied to incidence calculations to adjust for blood culture sensitivity, estimated at 50%.[8,9]

The study methods and procedures were reviewed in advance and approved by the Institutional Review Board of the Memorial Hospital of Rhode Island, Lifespan Hospital network, and by the Sulaimania Directorate of Health.

## 3. Results

During the study period, 156 patients were eligible for enrollment; of these, 154 were enrolled. Patient demographic and clinical information is presented in Table 1. The median age was 20 years and 53% were male. The median duration of illness prior to presentation at the hospital was 4 days. The most common symptoms were anorexia (90%), fatigue (89%), and rigors (87%). A significant majority of patients had abdominal pain (64%) and musculoskeletal pain (72%). Diarrhea and constipation were infrequently noted. Few patients (1%) were immunosuppressed at baseline. Previous episodes of typhoid fever were reported in 29% of patients. Antibiotic use for the present illness was common, with more than half reporting that they had taken antibiotics within the preceding 48 h.

Amongst the enrolled patients, there were 27 positive blood cultures (17.5%). The distribution of pathogens in positive blood cultures was as follows: *Salmonella* Typhi ($n = 20$), *Salmonella* Paratyphi ($n = 2$), *Escherichia coli* ($n = 2$), Shigella ($n = 1$), non-typeable *Salmonella spp* ($n = 1$), and *Staphylococcus aureus* ($n = 1$). Six patients met the case definition for brucellosis and another seven patients had positive serological testing that failed to meet the definition. Cases were seen throughout the study period without apparent time clustering.

Complications among enrolled patients were rare. Only 10% of patients had hypotension requiring intravenous fluid boluses and only 2% experienced gastrointestinal bleeding. There were no intestinal perforations and no deaths during the study period. No patients were known to fail treatment. The adjusted incidence of typhoid fever in the central district of Sulaimania was 21 cases/100 000 patient-years, and for enteric fever was 24 cases/100 000 patient-years.

**Table 1**
Descriptive epidemiology of the patients enrolled

| Variable | Percentage of enrolled patients | Response (number of enrolled patients) |
|---|---|---|
| Gender, % male | 53 | 144 |
| Age, years, median (range) | 20 (0–80) | 152 |
| Current symptoms, % reporting | | |
| Duration of illness, days, median (range) | 4 (2–30) | 152 |
| Rigors | 87 | 152 |
| Diarrhea >3/day | 26 | 152 |
| Constipation | 19 | 149 |
| Anorexia | 90 | 153 |
| Abdominal pain | 64 | 147 |
| Cough | 38 | 151 |
| Fatigue | 89 | 147 |
| Confusion | 18 | 138 |
| Musculoskeletal pain | 72 | 142 |
| History and medications, % reporting | | |
| Antibiotics in last 48 h | 55 | 141 |
| Antibiotics in prior 3 months | 18 | 134 |
| History of cancer | 1 | 152 |
| On chemotherapy, steroids, or radiotherapy | 1 | 152 |
| Diarrhea in last 12 months | 18 | 145 |
| Prior typhoid fever | 29 | 144 |
| Clinical findings, % | | |
| Temperature °C, median (range) | 39 (36.7–41.2) | 142 |
| Hypotensive, requiring IV fluids | 10 | 126 |
| GI bleed | 2 | 152 |
| GI perforation | 0 | 152 |
| Palpable spleen | 15 | 138 |
| Palpable liver | 3 | 142 |
| Rash | 7 | 141 |
| Lymphadenopathy | 2 | 138 |
| Gait disturbance | 3 | 128 |

IV, intravenous; GI, gastrointestinal.

Univariate predictors of culture-confirmed enteric fever are shown in Table 2. Positive predictors included male gender (odds ratio (OR) 2.90, $p = 0.03$) and temperature >40 °C on presentation (OR 3.48, $p = 0.01$). Antibiotic use within 48 h of presentation showed a trend towards predicting enteric fever (OR 3.13, $p = 0.06$). None of the symptoms ascertained in the study predicted a positive blood culture. A self-reported history of prior typhoid predicted a negative culture result (OR 0.12, $p = 0.01$). Neither the positive predictors nor the protective effect of a history of previous typhoid reached statistical significance when analyzed by logistic regression.

## 4. Discussion

Measuring the disease burden of typhoid fever is important for several reasons. First, the disease is vaccine-preventable and disproportionately affects young individuals who comprise significant proportions of both the general population and the workforce.[14] Second, disease surveillance for typhoid fever can help set up and integrate surveillance programs for other diseases. Finally, control programs for typhoid fever such as improvements in water infrastructure can impact other enteric diseases.

The calculated incidence of typhoid and enteric fever in the present study, 21 and 24 per 100 000 patient-years, respectively, is a minimum estimate of disease, reflecting only cases severe enough to present to the hospital. Even with this caveat, our calculated incidence falls within the medium incidence range for typhoid fever.[3] Our data may not be representative of the incidence of typhoid fever in other areas of Kurdistan; a higher incidence should be expected in urban areas where sanitation and water infrastructure lag behind those of the city center of Sulaimania.[19]

We did not find an association between classic symptoms of enteric fever and culture-confirmed disease. This may be because patients presented soon after developing symptoms (median 4 days) and hence the clinical picture was one of an undifferentiated febrile syndrome. This is in contrast with the older literature in the pre-antibiotic era describing an orderly progression of signs and symptoms characteristic of typhoid fever, which has been referred to as 'step-laddering'.[15,16] We did find that high fever at presentation predicted culture-confirmed enteric fever and that prior typhoid was protective, but these failed to reach significance on multivariate analysis. This is likely because of the relatively small number of confirmed cases.

We were surprised by the high number of brucellosis cases. We used serology to identify cases because the blood culture system available in Sulaimania is not sensitive for the detection of *Brucella spp*. Our definition of brucellosis is consistent with that used during a decade of surveillance in India, where confirmatory 2ME testing was a cost-effective method for differentiating between active disease and prior exposure.[17] We found brucellosis to be the single most common confounding diagnosis for typhoid fever in Sulaimania, with cases outnumbering other common enteric pathogens. This suggests that further work should be focused on determining the incidence of active infection from *Brucella spp* in Sulaimania and the surrounding region, ideally with enhanced diagnostic techniques such as culture, PCR, or ELISA testing.

**Table 2**
Univariate predictors of enteric fever

| Variable | OR | 95% CI | *p*-Value |
|---|---|---|---|
| Gender, male | 2.90 | 1.00–8.41 | 0.03 |
| Antibiotics in last 48 h | 3.13 | 0.85–11.54 | 0.06 |
| Prior typhoid fever | 0.12 | 0.02–0.94 | 0.01 |
| Temperature >40 °C | 3.48 | 1.31–9.23 | 0.01 |

OR, odds ratio; CI, confidence interval.

Our study has important limitations. Because public health research of this type is novel in Iraqi Kurdistan and resources were limited, we used a surveillance mechanism that would only measure cases ill enough to seek hospital level care. As noted above, this would underestimate disease burden. Another limitation is the availability of antibiotic sensitivity testing in Iraqi Kurdistan. Because the methods used locally are not comparable to universally accepted standards, we cannot comment on antibiotic resistance. Finally, typhoid fever in Iraqi Kurdistan is a seasonal disease, with the majority of cases occurring in the summer months. This means that incidence calculations may vary by the time period sampled.

We think that the logistical limitations were also strengths. By utilizing the local microbiology laboratory, we aimed to build technical capacity for future surveillance efforts. By relying on Kurdish house officers to help organize and direct the data collection, we integrated the effort into their resident education and gave them experience in surveillance study design and implementation. Our project is additional evidence that surveillance work can be done in challenging environments with a simple study design and on a limited budget.[9,10]

In summary we demonstrate that typhoid poses a considerable challenge to public health in Sulaimania, a growing urban center in Iraqi Kurdistan. Clinical features at the time of presentation do not adequately distinguish typhoid from other causes of undifferentiated febrile syndromes and underscore the need for inexpensive, reliable diagnostics.[18]

Cost-effective disease surveillance such as that used in the present study can be used in developing countries to measure disease burden, track the effectiveness of public health interventions, and build capacity locally for nascent public health surveillance systems.

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