



Review

Towards sustainable public health surveillance for enteric fever

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ABSTRACT

Enteric fever that results from infection by the typhoidal *Salmonellas* (*Salmonella* Typhi and *Salmonella* Paratyphi A, B and C) is a life-threatening preventable illness. Surveillance of enteric fever is important to understand current burden of disease, to track changes in human health burden from increasing antimicrobial resistance and to assess the impact of efforts to reduce disease burden. Since enteric fever occurs predominantly in low income communities, expensive surveillance is not sustainable. Traditional hospital-based surveillance does not estimate population burden and intensive community-based cohort studies do not capture the severe disease that is crucial to policy decisions. While cohort studies have been considered the gold standard for incidence estimates, the resources required to conduct them are great; as a consequence, estimates of enteric fever burden have been highly geographically and temporally restricted. A hybrid approach combining laboratory diagnosis that is already being conducted in healthcare centers with community-based surveillance of health care facility use offers a low-cost, sustainable approach to generate policy relevant data.

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1. Importance of enteric fever surveillance

Enteric fever is a life threatening illness. Before antibiotics were available, in one hospital in Indonesia 26% of patients hospitalized with blood culture confirmed *Salmonella* Typhi died [1]. Although most patients infected with strains of *Salmonella* Typhi and *Salmonella* Paratyphi A, B and C respond well to currently available antibiotics, the emergence of widespread antimicrobial resistance has undermined the effectiveness of commonly used antimicrobials [2–4]. There is little short term prospect for development of new effective low-cost drugs [5,6]. Thus, we face a risk of emergence and widespread dissemination of strains of typhoidal *Salmonella* that lead to a much higher case fatality rate than we have experienced for the last several decades. Sound surveillance can monitor these trends and so guide an appropriate response.

Enteric fever is preventable, both through interventions to reduce fecal contamination of drinking water and improvements in sanitation [7–9] as well as with increasingly effective vaccines [10]. However, unlike rotavirus, *Haemophilus influenzae* type B or measles, enteric fever does not affect all populations globally. Rather, it is a serious problem in select places where drinking water and food is

regularly contaminated with human feces. This concentrated risk reduces the global market for a profitable vaccine, but can help target interventions. Control efforts could focus on densely populated urban communities where fecal bacteria efficiently access the drinking water supply because the water runs only intermittently [11] and enteric fever is common [12,13]. Fewer resources could be directed towards rural areas of lower population density where enteric fever is less common [14,15] and where the cost per household served is higher [16–18].

Credible estimates of disease burden permits sound assessments of the cost-effectiveness of interventions that can help government officials appropriately prioritize interventions to prevent enteric fever. Since population density and the condition of water and sanitary infrastructure are primary determinants of the efficiency of transmission of the typhoidal *Salmonellas*, estimating current burden of enteric fever, based on observations from 2 or 3 decades previously [19–21], invites substantial inaccuracies.

Between 1982 and 2010 various research groups have measured typhoid incidence in 24 small geographical areas for 1–5 years [20]. Although these cohort studies have been repeatedly used to estimate the global burden of typhoid, they do not constitute public health surveillance. The CDC defines public health surveillance as “the ongoing systematic collection, analysis, interpretation and dissemination of data...for use in public health action” [22]. The research studies that measured typhoid incidence have not been sustained efforts that have provided ongoing guidance on public health action.

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Effective enteric fever surveillance collects isolates of the bacteria responsible for the disease and characterizes its antimicrobial susceptibility. These results inform optimal choice of antimicrobial therapy. Surveillance which tracks the incidence of severe outcomes of enteric fever, can provide a dynamic assessment of the burden of disease, a burden which is at risk of increasing markedly because of the emergence and widespread transmission of strains with high-level resistance to antimicrobials.

The objective of this paper is to critically review approaches to enteric fever surveillance and suggest strategies to improve cost-effective surveillance for the future

2. Facility-based surveillance

Historically, the most common approach to understanding enteric fever burden has been review of hospital case series [23–27]. These case series published in the international scientific literature can also be used by local government officials to assess burden in the community. The World Health Organization advocates for facility-based surveillance for a number of vaccine-preventable diseases; notably enteric fever is not included in the guidance [28].

Review of hospital records has several advantages for enteric fever surveillance. In a setting where good clinical microbiology provides routine blood culture to support diagnosis, the marginal cost of systematically collecting relevant clinical information and drawing some broader conclusions is low. These low costs mean that this surveillance can be maintained over several years, even decades, without external donor support. In addition, the surveillance collects information on severe outcomes including intestinal perforation and mortality caused by enteric fever [25,29]. Although severe outcomes occur in a small minority of all cases, severe illness represents the overwhelming burden of disease. Characterizing the burden, trend, associated risk factors and patterns of antimicrobial resistance of severe illness is critical for assessing the cost-effectiveness of interventions.

Facility-based surveillance underestimates enteric fever burden for several reasons. First, a lot of sick people do not come to hospitals. Poor people are less able to afford diagnostic tests. In South Asia where enteric fever is most common [20], most healthcare costs are paid out-of-pocket [30]. This means that the most impoverished patients, presumably those at the highest risk of infection and death, are the least likely to be recognized as having enteric fever.

The second cause of underestimating enteric fever burden is that most hospital-based case series use blood culture as the basis for diagnosis. Since blood culture is insensitive [31–33], especially when patients have taken oral antibiotics before presenting to the health care facility [31], it is likely that the majority of enteric fever patients are culture negative and so are not included as part of the assessment of enteric fever. The lack of accurate, non-invasive diagnostics for enteric fever has been a long-standing barrier to accurate surveillance [34]. Unfortunately, clinical diagnosis is neither a sensitive nor specific proxy for microbiologic diagnosis of enteric fever [35].

Clinicians working in healthcare facilities use their own judgment in ordering diagnostic tests and in reaching final diagnoses. The lack of consistent case definitions and diagnostic algorithms means that for many patients who may have enteric fever, especially those with less common presentations, for example encephalitis or diarrhea, the diagnosis is not considered and so blood cultures are not collected.

Most patients with enteric fever are treated as outpatients [36,37], often in the informal sector, where untrained and unlicensed providers provide empiric antibiotics [38]. These patients

are not captured by facility-based surveillance. Moreover, the high incidence of blood culture confirmed enteric fever identified through systematic blood culture-based surveillance of patients with fever in settings where enteric fever is common [12,13,15,39] suggests that most people with enteric fever do not have a blood culture obtained for diagnosis. The burden of disease from these infections is not captured in hospital case series. Indeed, many hospitalized patients in low-income countries leave against medical advice when they are no longer able to afford the cost of hospitalization [40–42]. The subsequent outcome of these patients may be critical to the burden of disease, but are not captured in hospital records.

Nevertheless, hospital case series may also overestimate the burden of enteric fever. If enteric fever is more common in urban settings and hospitals with microbiology labs are also more common in these urban settings, then the understanding of the burden of disease may be biased. It is also possible that large public facilities which are disproportionately used by residents of communities with highly compromised water supplies may also be more likely to have operating microbiology laboratories and participate in government reporting for disease surveillance. The populations using these hospitals may represent the highest risk populations in the country, and so overestimate population disease burden.

3. Community-based active surveillance

The highest incidence of enteric fever has been identified through specific projects designed to estimate disease incidence through active case finding [12,13,15]. These cohort studies typically involve regular visits to households, usually every week, seeking anyone who has a fever and encouraging them to visit the surveillance health facility. Upon visiting the designated health center, health care workers follow a standardized case definition and collect a blood culture or other diagnostic test.

Compared with hospital case series, active community-based surveillance provides a more accurate estimate of total incidence because it captures and characterizes patients with mild disease, most of whom would not come to the attention of facilities. Identifying cases and applying diagnostic tests according to standardized procedures reduces misclassification of patients as having enteric fever or not. Active surveillance can even improve blood culture sensitivity because cases are usually enrolled prior to antibiotic treatment.

Disadvantages of active community-based surveillance include a cost that is so high that it requires external donor support to operate and maintain these research sites. Population-based surveillance requires support for surveillance infrastructure with dedicated staff, regular visits and subsidized healthcare. Its expense means that low income governments are unable to deploy this approach for sustainable surveillance and so the results are often not well connected to policymaking. The high cost also means that the assessment can only be done in a small geographic area. Because health decision makers are generally responsible for large geographical areas, the uncertain representativeness of these small surveillance sites limits their utility for decision-makers. The limited numbers of active surveillance cohort studies that have been performed for enteric fever reflect the fact that this is not a sustainable public health approach to surveillance in resource-limited settings.

Active community-based surveillance for enteric fever focuses on early detection of mild disease. The number of people who can be followed is too small to identify uncommon severe sequelae including intestinal perforation and death with precision. This is a major weakness because these severe sequelae are the primary determinant of disease burden and therefore the key outcomes

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