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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.

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 influenza* 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

that policymakers are seeking to change. Indeed, optimally accurate community-based surveillance identifies people who are ill early in the course of their illness and then provides appropriate algorithmic-based treatment, but these steps alter the course of illness and so underestimate severe disease.

4. Combining facility-based surveillance with health utilization surveys

Combining facility-based surveillance with health utilization surveys generates population level estimates of severe disease at costs that are substantially less than prospective cohort studies. To conduct this type of hybrid surveillance, the surveillance team first characterizes the catchment population, that is they identify the geographic area where most of the patients with enteric fever who use the facility live. Some patients will be from very far away, but a more accurate estimate of incidence will be generated if it is focused on those communities where the bulk of patients live. This catchment area may be somewhat different for inpatients and outpatients, and is typically substantially larger for the former. If outpatients will be included in the surveillance, the outpatient catchment population should be separately assessed. Reviewing the addresses of between 75 and 200 blood culture confirmed cases and placing these on a spot map can provide a visual picture of the referral area that people who are familiar with the surrounding communities in hospital can use to help identify meaningful borders. At times, we have found it easier to send a field worker home with discharged patients to take a GPS measurement, rather than attempting to reconstruct addresses using medical records [43]. Using well known political borders or geographic divisions to delimit catchment areas makes it easier to identify whether subsequent patients live within or outside the catchment area.

Once the catchment area is defined, the number of people who live within this catchment area is estimated. If official statistics are recent and accurate, they can be used. Alternatively, fieldworkers can select a geographically based random sample and estimate the population density within that area. The surveillance team then extrapolates that population density to the total population within the catchment area. One straightforward approach to capture a representative sample using a cluster sampling approach is to review a satellite photograph of the catchment area. A virtual grid can be projected over the catchment area, the rectangles within the grid enumerated and a random subset of them selected [43]. Fieldworkers can review the satellite photographs and include each household whose front door is within the selected rectangle for surveying.

The next step is to assess the health seeking behavior of people who have symptoms consistent with enteric fever within the catchment area of the facility. In crowded urban areas where official statistics are often outdated and a total census would be prohibitively expensive, obtaining a geographically based random sample using satellite photography as described above is one low-cost method. Fieldworkers then visit each selected household within the sample and ask about the health seeking behavior of all members of the household for symptoms that are consistent with, though not specific for, enteric fever. Questions that we have used in prior studies include “Within the last 2 months did this person have any illness with fever that prompted you to bring him/her to someone to treat?” or “within the last 12 months did this person have any illness with fever that resulted in him/her being hospitalized?” If the answer to either question is yes, then follow-up questions assess where the person sought care. Importantly, these questions asked where people actually received care, rather than where they think they might go if they became ill. Sample size is relatively large, because hospitalization for a specific syndrome is uncommon. The surveillance team should reevaluate the size of the population catchment and health care utilization every few years to capture changes.

Within the surveillance facility, clinicians are encouraged to draw blood cultures for all patients who meet a clinical case definition of suspected enteric fever before initiating therapy. This approach can be restricted to hospitalized patients or extended to include the outpatient clinic. The consistency of the application of the case definition and ordering of blood cultures can be checked by reviewing the medical records. The laboratory uses a standardized approach to blood culture. It is important to distinguish between *Salmonella* Typhi and Paratyphi for vaccine planning purposes; the Vi polysaccharide vaccine only targets Typhi, while the Ty21a live oral vaccine may have efficacy against at least Paratyphi B [44]. Antimicrobial susceptibility testing is an important component of enteric fever surveillance, which may inform empiric antibiotic use among suspected cases. Among all patients who are blood culture positive and in a subset of patients who meet the clinical case definition, surveillance officers can assess whether or not the patients live within the catchment area and abstract clinical information from the chart. If patients have already been discharged and the address information is indefinite, surveillance officers may need to call patients to clarify whether or not they fit within the surveillance area. Because patients reports of antimicrobial use is characteristically unreliable [45], in a systematic subset of the population, the microbiology laboratory assesses what proportion of patients with a diagnosis of suspected enteric fever have evidence of receiving antimicrobials prior to the blood culture being collected, by assessing whether or not patient urine inhibits the growth of sensitive bacteria [46].

The outcomes of interest generally include hospitalization for enteric fever, hospitalization for drug-resistant enteric fever, intestinal perforation and death. Begin by calculating a crude incidence estimate for the outcome of interest, that is the number of cases of the outcome of interest divided by the total population within the referral area. Only count those cases in the numerator who live within primary catchment area of the hospital. Adjust this crude incidence estimate for the insensitivity of diagnostic tests (a 50% sensitivity for blood culture is a reasonable estimate [31–33]). Adjust the incidence for imperfection in application of the diagnostic algorithm. The magnitude of this correction can be determined through an audit of medical records to assess the proportion of patients who met the enteric fever clinical case definition and should have had a blood cultured collected, but were not. A third correction factor adjusts for the proportion of people with the diagnostic syndrome consistent with enteric fever who went to other facilities (Fig. 1).

One valuable enhancement to this surveillance, is a phone call to follow-up with family members 2 to 4 weeks after patients have left the facility to assess patient survival. Since patients who leave against medical advice are at increased risk of mortality, and since mortality is uncommon but extremely important for assessment of burden, attention to this measurement is crucial for generating accurate burden estimates.

A more complicated approach involves surveying more residents in the hospital’s primary catchment area about their health seeking behavior, and when patients visit the hospital, linking patient records to individuals in the community-based survey data. The proportion of hospitalized patients with enteric fever who can be linked to the community-based survey and the reported health care utilization in the community can then be used to extrapolate the size of the catchment population to estimate the incidence outcomes of interest [47]. We have found that matching names and so confirming that a hospitalized patient is the same person who the survey team identified several months earlier, is difficult, especially in countries where naming conventions and spelling varies.

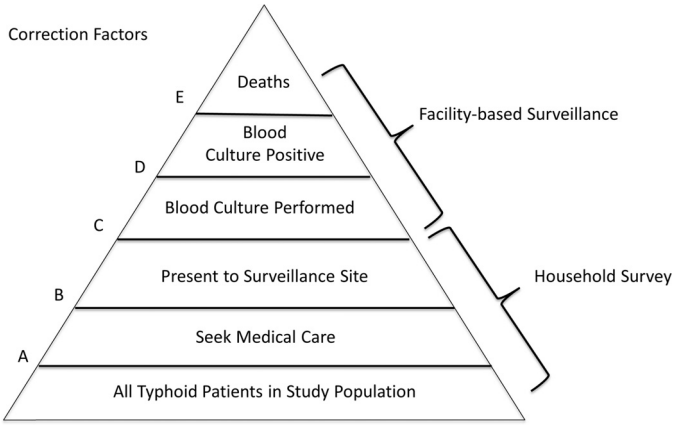

Fig. 1. Household surveys are used to estimate the (A) proportion of patients with febrile illnesses who seek medical care, and the (B) fraction of those who seek care at surveillance sites. Facility based surveillance is implemented, and review of medical records is used to estimate the (C) proportion of patients meeting enteric fever suspect definition who have blood cultures drawn. Literature based estimates are used to adjust for (D) the proportion of enteric fever cases that are culture positive. (E) Mortality is estimated by facility-based case fatality rates as well as telephone based follow up of all culture-confirmed cases.

Multiple definitions of potential matching names generate multiple different incidence estimates, and the survey becomes rapidly outdated when people move frequently. The very complexity of the linkage makes it more difficult to implement and to explain. In our experience the extra cost and effort of linking, does not provide sufficient additional information to justify this approach.

5. Strengths and weaknesses of a hybrid approach

This hybrid approach provides several advantages compared with traditional approaches to surveillance. This hybrid approach provides credible population-based estimates of severe disease attributable to enteric fever, precisely the information policy makers need to assess the priority and respond appropriately. By leveraging healthcare centers where blood culture is already being used for routine clinical diagnosis of enteric fever, this approach is much less expensive than community-based surveillance and so can be sustained with quite modest ongoing support. Indeed, such an approach can be used for multi-pathogen surveillance, that is in addition to the typhoidal *Salmonellas*, the same infrastructure can support population-based surveillance for vaccine-preventable infections, including *Haemophilus influenza* type B., pneumococcus, meningococcus and influenza. This further improves the return on investment of scarce surveillance funds and minimizes the need for specifically earmarked enteric fever surveillance funds. Because such a system can be sustained, it can provide real time information on changing circumstances, for example increased incidence of enteric fever following sudden water infrastructure failure or increased rates of mortality from spreading antimicrobial resistant strains.

There are important limitations to this hybrid surveillance. This approach requires a functional diagnostic laboratory. Historically, low resourced rural sites that do not conduct blood cultures have not contributed to burden estimates. With investment in capacity building, supervision and supplies some facilities can be designated centers for sentinel surveillance [48,49]. Recent advances in the development of a low cost electricity-free culture based approach [50] substantially lowers laboratory costs because it does not require a functional microbiology laboratory at each surveillance site. Costs can be further reduced by systematically testing only a portion of all patients who meet a clinical case definition, but if there is no local interest in and support for clinical diagnostics, then ongoing funding is required to sustain surveillance at such sites. Alternatively, facilities that have a high performing microbiology lab can sometimes be identified. This may be a nongovernmental charitable facility or other places where quite modest investments in equipment and training could provide sufficient improvements and laboratory diagnosis to support incidence estimates.

A second weakness to this hybrid surveillance model is that corrections to the incidence estimate are prone to error and may be controversial. For example, it is often difficult to reconstruct from a medical record whether a patient met a suspect case definition for enteric fever or not. Recent antibiotic exposure will affect the sensitivity of blood culture, will vary by site and facility type, and may require additional adjustment to that correction factor. When clearly presented, however, all stakeholders will agree that crude estimates that simply divide the blood culture confirmed cases by the population in the catchment area underestimate total incidence. Sensitivity analysis can model the effect of a range of values of these correction factors on the total incidence estimates. Those correction factors that are most controversial or have the largest impact on the incidence estimate can be further evaluated in focused studies to generate more robust empirical estimates.

Patients who come to hospitals that use blood cultures for diagnosis are different than people who do not. People who use hospitals that have the capacity for enteric fever diagnostics may be more likely or less likely to have serious enteric fever disease than the people who do not come to hospitals. Findings from the catchment population survey characterize facility users and non-users and so provide some assessment of how well facility users represent the population living in the geographic catchment. If users and non-users are similar, then the incidence estimates are more credible. If there are large differences, however, then the community assessment can assist in interpreting the data, that is understanding, for example, whether the extrapolations are likely to be an underestimate because the poorest people do not use the facility, or an overestimate because wealthy people generally seek medical care elsewhere. The differences between users and non-users could also be integrated into a more sophisticated model of incidence.

6. Looking forward

Since enteric fever occurs predominantly in low income communities, expensive surveillance via cohort studies is not sustainable. In favorable circumstances the hybrid model of enteric fever incidence provides a credible estimate of the incidence and burden of disease severe enough to require hospitalization within the catchment area. The catchment area of these facilities are not strictly representative of the broader population at risk or of the political unit that policymakers are responsible for, but they provide affordable timely data that can guide public health action.

Patients with enteric fever, medical centers with the capacity for blood cultures and government officials are all concentrated in major urban centers in low income countries. If data from these medical centers are leveraged for enteric fever surveillance then some of the most prominent politically connected physicians in the country understand enteric fever burden and can advocate for a sound prevention strategies.

Successful facility-based surveillance and reporting systems exist for a variety of infectious diseases, including measles, polio, diphtheria, tuberculosis, and leishmaniasis. The World Health Organization's antimicrobial resistance surveillance program provides additional support for characterizing drug susceptibility. To achieve population-based estimates, the apparent gaps are the proper enumeration of the facility catchment population, and the community survey of health-seeking behaviors. As is done with

surveillance for diseases such as tuberculosis and HIV, the World Health Organization and other technical support agencies could provide training to countries on data collection and analysis, and could aggregate data annually to produce regular estimates of the burden of enteric fever and enteric fever drug resistance, to inform public health planning and research agendas surrounding water, sanitation, antibiotic use, and vaccines. The overarching goal should be to move away from sporadic incidence studies and towards sustained, actionable public health surveillance.

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