Typhoid Fever and the Challenge of Nonmalaria Febrile Illness in Sub-Saharan Africa

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In this issue of Clinical Infectious Diseases, 2 papers shed important light on the problem of typhoid fever in Sub-Saharan Africa and stimulate reflection on the challenges raised by the syndrome of fever in low-resource settings. Neil et al [1] report the investigation of an increase in intestinal perforations from rural western Uganda. By improving the clinical microbiology services available in the outbreak area and by implementing active surveillance at healthcare facilities in the district, the research team was able to confirm Salmonella enterica serovar Typhi as the etiologic agent and estimate the typhoid fever annual incidence in the study area at 8092 cases per 100,000 persons. This very high typhoid fever incidence rate was associated not only with hundreds of hospitalizations and intestinal perforations but also with 47 deaths. Lutterloh and colleagues [2] investigated an outbreak of unexplained febrile illnesses with neurologic findings along the Malawi–Mozambique border.

Again, making diagnostic services available in the rural and remote outbreak area allowed Salmonella Typhi to be established as the cause. A careful clinical and epidemiologic investigation, including enhanced surveillance of suspected, probable, and confirmed cases of typhoid fever, characterized 40 patients with debilitating focal neurologic manifestations, including upper motor neuron signs, ataxia, and Parkinsonism, and 11 deaths.

Fever is among the most common syndromes prompting persons to seek healthcare in Sub-Saharan Africa, and the numerous causes of febrile illness are often difficult to distinguish clinically. Although malaria may be ruled out by blood film examination or a malaria rapid diagnostic test, clinicians in resource-limited areas often have few diagnostic tools to determine the etiology and inform treatment decisions for those patients without malaria [3]. With encouraging gains in malaria control in some parts of Sub-Saharan Africa [4], the proportion of febrile patients without malaria grows. Invasive bacterial diseases represent a major cause of severe illness on the continent [5]. The ability to detect invasive bacterial disease by blood culture is invaluable not only to rationalize initial broad antimicrobial therapy but also to inform empiric treatment policies and to detect outbreaks when systematically collected bloodstream infection data are aggregated for a geographic area [5]. However, in resource-limited areas, the laboratory capacity to detect invasive bacterial disease is often restricted to major referral centers and research sites. Even when available, blood culture services may not be accessible to all patients with a clinical indication, and there may be concerns about the quality of the service [6]. In both of the outbreaks described here, the complications of intestinal perforation and neurologic manifestations provided the initial clue of typhoid fever as the possible cause, in turn leading to the identification of a much larger group of patients with typhoid fever presenting with undifferentiated fever.

A typhoid rapid antibody test that has poor performance characteristics when assessed for individual patient diagnosis [7, 8] was applied during the initial stages of each investigation to help to support or rule out typhoid fever as the cause while conventional bacteriology services were being established. The application of a simple, rapid antibody test with performance characteristics that would normally preclude use for routine, individual patient management to groups of patients during the initial investigation of an outbreak of uncertain etiology in a remote area is notable and warrants further study.

The epidemiology of the invasive salmonellosis, including typhoid fever, in Sub-Saharan Africa is incompletely
understood [9]. The current estimate of the global burden of typhoid fever relies on data from only 2 countries—Egypt and South Africa—to extrapolate incidence for the entire continent of Africa [10]. Based on these studies conducted in the 1970s and 1980s, Africa is classified as a medium typhoid fever incidence area with rates between 10 and 100 cases per 100,000 persons per year. The estimate is based on studies thought to reflect endemic disease and does not attempt to incorporate illness and death associated with typhoid fever outbreaks, such as those reported by Neil et al and Lutterloh et al. Furthermore, hospital sites in Sub-Saharan Africa that have systematically studied causes of community-acquired bloodstream infection consistently identify *Salmonella enterica* as a leading pathogen, often with nontyphoidal *Salmonella* (NTS) predominating and *Salmonella* Typhi relatively uncommon [5, 11]. However, as the number of such studies grows, sites in Sub-Saharan Africa where *Salmonella* Typhi predominates over NTS across multiple years of surveillance are being identified [12–14], underscoring a complex epidemiologic picture of invasive salmonellosis on the continent, with both variable levels of endemic disease as well as outbreaks. Whereas risk for invasive NTS is associated with host factors such as young age, malnutrition, current or recent malaria, and human immunodeficiency virus (HIV) infection [15], as well as organism factors [16] in the context of an incomplete understanding of environmental sources and routes of transmission in Africa, risk for typhoid fever has been closely linked to environmental conditions and poverty [17], and does not appear to be enhanced (and may even be attenuated) by HIV infection [12, 18]. Several studies have observed declines in invasive NTS in parallel with reductions in malaria parasite prevalence [19–21], and improvements in CD4+ T-lymphocyte counts associated with the use of antiretroviral therapy also appear to reduce invasive NTS risk [22]. Although changes in host factors may currently favor declines in invasive NTS in some parts of Sub-Saharan Africa [4], the environmental conditions that place populations at risk for typhoid fever, including lack of access to safe water and sanitation, urbanization, and poverty, show fewer signs of a major reversal [17]. The recently launched Typhoid Fever Surveillance in Africa Program (TSAP), coordinated by the International Vaccine Institute, is estimating typhoid fever incidence at multiple sites in Sub-Saharan Africa in order to fill a major gap in our understanding of the global epidemiology of invasive salmonellosis and to inform typhoid control efforts, including typhoid vaccine policy decisions on the continent.

A large number of typhoid fever patients were observed with the complications of intestinal perforation and with neurologic manifestations in the Uganda and Malawi–Mozambique outbreaks, respectively. This, combined with the unusual spectrum of neurologic manifestations observed in the Malawi–Mozambique outbreak, is striking and may have a range of possible explanations. It is likely that the patients with complicated infection seeking healthcare represent a small fraction of a much larger group of patients with uncomplicated typhoid fever, an explanation supported by the very high typhoid fever incidence rate estimated during the Uganda outbreak once active surveillance was established. Furthermore, because the complicated cases prompted detection of the outbreaks, subsequent case definitions and clinic-based surveillance probably biased case detection toward identifying a larger proportion of patients with complicated disease. However, it is also possible that proportion of cases associated with complications was unusually high during this outbreak. Delays in access to appropriate antimicrobial therapy are known to be associated with increased risk for complications and death among patients with typhoid fever [23, 24]. Such delays may be particularly common in rural and remote areas [25] and where malaria is overdiagnosed and invasive bacterial disease is underappreciated as a cause of fever [26]. The possibility that host or organism factors may have contributed to the rate and character of complications is intriguing and represents a domain where research has been limited. Comparison of the sequence diversity at multiple, conserved housekeeping genes by multilocus sequence typing suggests that *Salmonella* Typhi has a relatively recent origin between 15,000 and 150,000 years ago, during the human hunter-gatherer phase [27]. Although the *Salmonella* Typhi genome shows the limited sequence diversity and considerable loss of gene function typical of a monomorphic, host-adapted pathogen [28], the possibility that some strains in the organism’s presumed homeland could be more pathogenic than others merits investigation. It is also conceivable that hitherto unknown host or environmental cofactors may contribute to the rate and phenotype of complications.

Outbreaks such as those described by Neil et al and Lutterloh et al prompt reflection on our approach to the syndrome of fever in low-resource settings. Those treating, controlling, and studying the syndromes of diarrhea and respiratory tract infection convene under syndrome-based global disease burden estimates that foster a sense of common purpose and collaboration. However, the approach to the syndrome of fever has been fragmented across a diverse group of etiologies, including invasive bacterial diseases such as the salmonellosis; malaria and other blood parasites; bacterial zoonoses such as brucellosis, leptospirosis, rickettsioses, and Q fever; and a wide range of fungal and viral infections too numerous to list. Global disease burden estimates, key data to inform disease control efforts, are available for some specific causes of fever [4, 10] but are lacking for most, and there is no estimate for the syndrome.
of fever as a whole. Clinicians, public health personnel, and researchers working on etiologic agents of febrile illness rarely have the opportunity to work together. In settings where diagnostic services are limited and epidemiologic data are sparse, uncounted numbers of persons become ill and die from non-malaria febrile illness. Beyond malaria, the invasive bacterial diseases are prominent targets for disease control efforts [29, 30]. The introduction of conjugate Haemophilus influenzae type b and pneumococcal conjugate vaccine in Sub-Saharan African countries is anticipated to provide major gains. Control of H. influenza and Streptococcus pneumoniae is likely to leave the invasive salmonelloses, NTS, and typhoid fever as the next major targets for control [5]. The reports in this issue remind us that typhoid outbreaks can be large, hidden, and associated with considerable morbidity and mortality. A coordinated approach to the syndrome of fever in low-resource settings would help to unmask the burden of a range of potential important infections and to rally control efforts for the benefits of individuals and populations.

Note

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References