Invasive *Salmonella* Infections and HIV in Northern Tanzania

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(See the article by Crump et al, on pages 341–348.)

Crump et al relate interesting findings on *Salmonella* Typhi bacteremic infections among adolescent and young adult patients living in an area of high human immunodeficiency virus (HIV) prevalence in northern Tanzania. Consent patients aged ≥13 years with fever admitted to either of 2 hospitals were enrolled for a comprehensive infectious disease workup that included blood cultures and HIV-status determination. Of 403 study patients, 68 yielded a clinically important organism from serovars *Salmonella* Typhimurium, *Salmonella* Enteritidis; and (3) the significantly lower incidence of isolation of *Salmonella* Typhi from HIV-infected febrile patients (1.2%) versus HIV-negative patients (9.8%).

That *Salmonella* Typhi was isolated from 9.8% of HIV-negative febrile East African patients ≥13 years of age is not surprising. Whereas the prevalence of *Salmonella* Typhi infections in adolescents and young adults is spotty in sub-Saharan Africa, there are hot spots [1]. However, because the study by Crump et al comprised only 12 months, it is also possible that the high frequency of *Salmonella* Typhi isolations was consequent to an epidemic that may have occurred during the study. Geographically dispersed typhoid outbreaks of limited duration have been described elsewhere in Africa [2, 3].

The paucity of isolation of *Salmonella* Typhimurium, *Salmonella* Enteritidis, and other NTS strains from blood cultures of febrile HIV-positive patients in this area of East Africa is notable. Strains of NTS are common causes of invasive bacterial disease among infants, toddlers, and young preschool children in East [4], West [5–7], and Southern Africa [8–10]; in low [5–7] as well as high [8–10] HIV-prevalence areas; and in both rural [5, 6] and urban [7, 10] venues. Strains of NTS also commonly cause bacteremia in HIV-positive adults [11, 12]. Because young children were not included in the Crump et al study, it is difficult to interpret the low isolation rate of NTS strains from the febrile adolescents and adults.

The most compelling observation is the selective rarity of isolation of *Salmonella* Typhi in HIV-positive patients. In the early 1990s, Gotuzzo et al reported that Peruvian patients with HIV infection were at increased risk of *Salmonella* Typhi disease [13]. However, subsequent reports addressing HIV as a risk factor for invasive *Salmonella enterica* infections in developing countries have incriminated NTS serovars rather than *Salmonella* Typhi or *Salmonella* Paratyphi. Crump et al show that in a period when *Salmonella* Typhi infections were prevalent in the community, as evidenced by the high rate of isolation from HIV-negative patients, isolations of that serovar were significantly lower among HIV-positive patients. Theoretically, a survivor treatment selection bias [14] (by which...
individuals infected with both HIV and *Salmonella* Typhi would have been less likely to seek treatment at the hospitals, due to a greater likelihood of death or disability) might have been operative in rural Tanzania; however, this seems unlikely to account for the disparity. If the rarity of typhoid fever in HIV-positive individuals, as observed by Crump et al, is corroborated, how can this be explained? Because one must assume that HIV-infected patients living in the community of study were also exposed to *Salmonella* Typhi, some characteristic of the HIV-infected host must diminish the risk of manifesting clinical typhoid fever, despite ingestion of the pathogen. One possibility is that long-term trimethoprim-sulfamethoxazole prophylaxis among the HIV-positive patients diminishes *Salmonella* Typhi (and perhaps invasive NTS) infections. Although the observed data are compatible with that explanation, Crump et al report that trimethoprim-sulfamethoxazole prophylaxis was not widely practiced by the HIV-positive patients.

Alternatively, the HIV-infected host may somehow be less prone to manifesting clinical typhoid fever, despite infection. In the pathogenesis of typhoid fever, ingested typhoid bacilli target M cells overlying gut-associated lymphoid tissue and pass to the underlying dendritic cells and macrophages. A primary bacteremia ensues and the bacilli are filtered from the blood by fixed macrophages of the reticuloendothelial system (RES), including the liver, spleen, and bone marrow, therein achieving an intracellular niche. After a long incubation (8–14 d) during which the host is unaware that *Salmonella* Typhi is residing in her/his RES, clinical symptoms appear, including fever that increases in stepwise fashion, headache, and abdominal discomfort, accompanied by a secondary bacteremia. The onset of clinical illness is also coincident with the appearance of strong cell-mediated immune (CMI) responses, including classic major histocompatibility complex (MHC) class I–restricted CD8+ cytotoxic lymphocytes that kill *Salmonella* Typhi–infected target cells [15, 16] and CD4+ T cells that elaborate helper T (T$_{H1}$) 1-type cytokines (eg, interferon-γ and tumor necrosis factor α) in response to specific antigens [16, 17]. This CMI response attacks the typhoid bacilli in their intracellular niche. Thus, the clinical symptoms of typhoid fever and its accompanying secondary bacteremia may be initiated by this potent CMI response that releases typhoid bacilli or fragments thereof from macrophages of the RES. Supporting this hypothesis, corticosteroids lessen the clinical severity of typhoid fever [18, 19], and some immunocompetent persons, following ingestion of virulent *Salmonella* Typhi, develop only silent bacteremia without clinical illness [20]. The CD4+ lymphocyte depletion and immune deficiency consequent to HIV infection could be, paradoxically, responsible for less clinical typhoid fever being observed in HIV-positive patients, because in these individuals *Salmonella* Typhi may remain quiescent in its intracellular niches without precipitating clinical illness. Because only febrile patients were enrolled into the study by Crump et al, if HIV-infected patients rarely manifest clinical typhoid fever despite exposure and infection, they would have been ineligible for enrollment.

The above hypothesis presupposes that in HIV-infected hosts, the pathogenesis of NTS (particularly *Salmonella* Typhimurium) infection, which often results in severe invasive disease, chronic infection of the RES, and clinically overt re-exacerbations [21], is distinct from the response of HIV-infected hosts to *Salmonella* Typhi. An unusual, possibly human host–restricted, multiple-locus sequence type (ST 313) of *Salmonella* Typhimurium has been described in Africa and is characterized by genomic degradation and the presence of multiple pseudogenes [22], some of which are also found in *Salmonella* Typhi and *Salmonella* Paratyphi A. Nevertheless, more classical *Salmonella* Typhimurium strains and other serovars of NTS also cause invasive disease in HIV-infected African adults and in HIV-infected persons outside Africa. Moreover, even in the United States, the case-fatality rate of invasive NTS disease varies by serovar [23]. That the pathogenesis of typhoid fever is fundamentally distinct from invasive NTS disease has long been appreciated. Some important differences in pathogenesis may occur early [24, 25], wherein *Salmonella* Typhimurium elicits a strong inflammatory response in the intestinal mucosa characterized by an influx of polymorphonuclear cells, whereas the translocation of *Salmonella* Typhi is minimally inflammatory (partly influenced by expression of Vi polysaccharide) [26, 27] and mononuclear cells are attracted [24, 25]. Crump et al may have made a hallmark observation on the interaction between 2 remarkable pathogens, HIV and *Salmonella* Typhi.

**Acknowledgments**

Potential conflicts of interest. All authors: no conflicts.

**References**


