Time for a comprehensive approach to the syndrome of fever in the tropics

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Fever is a leading reason for people to seek healthcare in the tropics. Given the non-specific clinical presentation of many infections causing fever and the limited clinical microbiology services available in many low-resource areas, few patients receive an accurate and specific diagnosis and the relative importance of the various causes of fever remains unknown at the community level. Nonetheless, patients admitted to hospital with fever that is not due to malaria experience case fatality ratios at least as high as those with malaria. However, unlike diarrhea and lower respiratory infection, a syndrome-wide approach has not been taken to understanding fever. Instead, researchers studying individual pathogens or groups of pathogens causing fever have tended to work independently. Appropriately, for many decades malaria has dominated discourse on the syndrome of fever in the tropics. Apparent declines in malaria worldwide since 2004 mean that a growing proportion of patients presenting with fever do not have malaria. Furthermore, wide use of malaria diagnostic tests prior to malaria treatment unmasked a sobering level of malaria over-diagnosis in many areas.

Given the morbidity and mortality associated with infectious causes of fever, why has the global health community tended not to approach fever in a comprehensive way? The organizational structures of global, national and academic institutions of public health rarely include cross-cutting groups approaching fever across the range of responsible pathogens. Scientific meetings are often focused on individual febrile diseases as diverse as leptospirosis, invasive salmonelloses, dengue and Q fever, taking place independently or in parallel sessions at the same conference with little collaboration. Global burden of disease reports are structured to take a syndrome-based approach to diarrhea and lower respiratory infections, making syndrome-wide estimates of illness and death for each before assigning fractions to specific pathogens. However, the conditions causing fever are scattered across a range of disorders and diseases, and many remain hidden in ‘other’ disease categories. Responding to burden data, global health research funders support integrated work on diarrhoea and lower respiratory infections, but tend to take a pathogen-specific approach to the causes of fever. Consequently, studies of fever often examine just one pathogen (e.g., malaria, dengue, typhoid) or use just one diagnostic test (e.g., blood culture) resulting in lost opportunities for synergy and producing an incomplete epidemiological picture.

Tackling fever in the tropics will require a robust understanding of the etiology of febrile illness and death. Dichotomizing febrile illness into malaria and ‘non-malaria fever’ belies that non-malaria fever includes a very broad range of bacterial, parasitic, fungal and viral infections. Among the causes of fever other than malaria lies hidden the rank list diseases that need to be understood together to improve approaches to the management of the febrile patient and to inform control efforts. Integrated etiology research on diarrhoea and lower respiratory tract infection in low and middle-income countries is proving invaluable for framing a rational approach to averting childhood illness and death associated with those major syndromes. While individual fever etiology studies that take a broad look at potential pathogens are emerging from Africa and Asia, no standardized international multicenter study has been done to underpin the global fever research agenda.

What should a multicenter fever etiology study look like? A focus on severe febrile illness, such as among hospitalized patients, would most efficiently shed light on illnesses often associated with febrile deaths. It would also avoid the low diagnostic yield for some conditions and the prevalence of self-limited disease found in outpatient settings. At the same time, it is essential that research inform patient management at the community and primary healthcare level where most people with fever seek care. Close attention to conditions with high case fatality ratios (e.g., bacteremia); pathogens with distinct patient management strategies (e.g., Q fever, rickettsioses, brucellosis); and infections with vaccine and non-vaccine population control strategies (e.g., dengue, influenza) would facilitate the translation of findings into practice. Standardized case definitions and laboratory methods are necessary to ensure that results are comparable across participating study sites. The use of reference laboratory methods would allow the creation of a library of well-characterized nominal samples for evaluation of novel point of care diagnostic tests. The inclusion of a healthy community control group would allow calculation of pathogen-specific attributable fraction by accounting for the...
prevalence of background positive diagnostic test results, as may occur for malaria and some serologic assays. Healthcare utilization surveys conducted in the catchment areas of study healthcare facilities would provide a means to estimate disease incidence for responsible infections, many of which currently lack disease burden estimates. Since causes of fever are thought to vary considerably in place and time, wide geographic representation and study periods of at least 1 year are needed to understand spatial and temporal heterogeneity. Finally, consideration should be given to severe forms of some diseases such as sepsis presenting without fever; the etiologic overlap between the syndromes of diarrhea, lower respiratory infection and fever; and the possibility that some causes of fever remain to be discovered.

Research on the etiology of fever faces a number of challenges. The complexity of some conventional diagnostic methods has meant that they remain largely the province of reference laboratories. Reference diagnostic methods for several key infections require the collection of convalescent serum to demonstrate a fourfold greater rise in antibody titer. In such circumstances, a patient who dies during the acute phase of their illness cannot become a confirmed case, posing a challenge for estimating the case fatality ratio. Conversely, acute phase diagnostics for some causes of fever have shortcomings of practicality, sensitivity, specificity or combinations of these. For example, autopsy is likely to be a valuable arbiter of causes of febrile deaths, but is currently not widely used in low-resource areas for cultural, technical and human capacity reasons.

Compared with bone marrow culture, blood culture has a sensitivity of approximately 50% for the diagnosis of typhoid fever yet bone marrow culture remains too cumbersome for routine use. Similarly, nucleic acid amplification tests for leptospirosis using peripheral blood have the best sensitivity during the bacteremic phase of the illness. However, many patients with leptospirosis present during the immune phase. Other tests, such as those for malaria, do not clearly distinguish colonization, infection and disease.

Many advances are needed to avert illness and death due to fever in the tropics. However, little progress is likely without a robust and representative epidemiologic understanding of the major causes of severe febrile illness. Achieving this will require standardized, international, multicenter research. Much closer collaboration is needed across the scientific community to address tropical medicine’s most fundamental yet fragmented condition.

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References