CHAPTER 13
Febrile Illness in Adolescents and Adults

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Heading styles

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Abstract

(100 words)

Declines in malaria in many areas and wider use of malaria diagnostic tests demonstrate that malaria overdiagnosis is common among febrile patients. Diagnostic services for causes of non-malaria fever are complex and not widely available, and, with a few exceptions, preventive measures for specific infections are poorly developed or difficult to implement. Causes of fever have rarely been examined collectively, but emerging data suggest considerable national and subnational variation and mismatches between etiology and empiric management guidelines. Febrile illness poses substantial direct and indirect costs on patients and families. Identifying cost-effective empiric management and diagnostic strategies will be needed to improve outcomes.

Top Messages: 1. Declines in malaria in many areas and wider use of malaria diagnostic tests demonstrate that malaria overdiagnosis is common among febrile patients; 2. Diagnostic services for causes of non-malaria fever are complex and not widely available; 3. Identifying cost-effective empiric management and diagnostic strategies will be needed to improve outcomes.

Keywords: Bacteremia, fever, fungi, malaria, parasites, virus diseases, zoonoses

Introduction

Fever is one of the most common symptoms reported by patients seeking health care in low-resource areas in the tropics, where it may occur either in isolation or in association with other common symptoms, such as cough or diarrhea (Feikin and others 2011; Prasad, Sharples, and others 2015). Fever without localizing features presents a particular challenge to health care workers and health systems because it may be caused by a wide range of bacterial, fungal, parasitic, and viral infections (Crump and others 2013; Mayxay and others 2013), as well as by noninfectious conditions. Clinical assessment has limited accuracy for both identifying the likely cause and the early recognition of patients who will progress to serious or fatal disease. Compounding the limitations of clinical assessment is the dearth of available epidemiologic data on common causes of fever (Crump 2014) and a shortage of clinical laboratory services in many areas (Archibald and Reller 2001; Petti and others 2006).

Given its prevalence and severity, malaria has been the common default diagnosis for fever without localizing features in the tropics for decades (WHO 2006). However, a growing number of fever etiology studies (Reyburn and others 2004) and more widespread use of malaria diagnostic tests (WHO 2010b) have served to unmask the problem of malaria overdiagnosis among febrile patients in many areas. Documented declines in malaria since 2004 (Murray and others 2014; WHO 2013), combined with widespread use of malaria diagnostic tests (WHO 2010b), mean that health care workers face a growing proportion of patients with fever and negative malaria diagnostic tests. This is problematic because patients presenting to hospitals with a fever not due to malaria are as like to die as those who have malaria (Reyburn and others 2004).

This chapter identifies key challenges, issues for diagnosis and treatment of relevant infections, and data gaps for health care workers and policy makers regarding nonmalarial fever management and cost-effectiveness. We highlight the needs for etiologic research, for restructuring of burden-of-disease estimates to recognize nonmalarial fever, and for approaches to evaluating clinical interventions aimed at improving patient outcomes.

Burden of Disease from Nonmalarial Febrile Illness

There is no estimate of the global burden of disability and death due to febrile illnesses without localizing features. Consequently, this group of infections has lacked collective prominence. By extension, estimating the effect size of interventions for fevers is challenging. Disability-adjusted life years (DALYs) and deaths from diarrhea and pneumonia are estimated at the syndrome level before being assigned to individual causes by the World Health Organization (WHO) and the Institute for Health Metrics and Evaluation.[1] However, these sources estimate the individual disease burdens of some causes of fever such as malaria, dengue, and enteric fever but not for others, including chikungunya, leptospirosis, and Q fever.

As such, the organizational structures of global, national, and academic public health institutions rarely include cross-cutting expertise addressing fever across the range of responsible pathogens. Similarly, fever etiology research has tended to focus on one or a small number of pathogens rather than studying a broad range of causes (Prasad, Murdoch, and others 2015).

Also contributing to the difficulty in estimating the global burden of death from febrile illnesses is the inadequacy of autopsy procedures. Verbal autopsy has been criticized for overattribution of febrile deaths to malaria (Butler 2010) and is likely to perform poorly for identifying the specific cause. Complete diagnostic autopsy is not widely available in low-resource areas, but minimally invasive autopsy approaches are being studied as a means to reduce uncertainty regarding causes of death in developing countries (Bassat and others 2013).

Nonmalarial Fever in Adolescents and Adults

Since 2010, WHO guidelines recommend that malaria treatment decisions be based on the result of a malaria diagnostic test (WHO 2010b). For patients with a positive malaria diagnostic test, health care workers would prescribe antimalarial treatment and consider coinfections, as described in detail in chapter XX. However, for those patients with a negative malaria diagnostic test, health care workers often lack the epidemiologic information or laboratory services necessary to support rational diagnostic and management decisions (Crump, Gove, and Parry 2011).

Etiology of Nonmalarial Fever

Annex _A lists studies conducted from 1980 through 2013 of the etiology of severe febrile illness among, predominantly, adolescents and adults. **[[AQ: Annex number to be completed when chapter numbers are finalized.]]** Key features of studies undertaken in Africa (n=16), and South and Southeast Asia (n=11) are listed below (Prasad, Murdoch, and others 2015). These studies illustrate both many data gaps as well as sufficient geographical heterogeneity in the etiology of fevers to require subnational empiric treatment guidelines (White and others 2012).

Africa. Considerable data gaps exist in our understanding of the etiology of severe febrile illness in Africa. Few studies investigate more than one or a small group of pathogens, and many countries and some regions lack contemporary studies. Furthermore, standard laboratory-based case definitions are not widely used, and study designs rarely include control groups or other approaches to estimate attributable fractions.

Reddy, Shaw, and Crump (2012) conducted a systematic review of prospective studies of the etiology of community-acquired bloodstream infection in Africa. Their findings were as follows:

- Of 58,296 patients enrolled in 22 eligible studies conducted in 34 locations from 1984 through 2006, 2,051 (13.5 percent) of 15,166 adolescents and adults had nonmalarial bloodstream infections, yielding 2,078 bloodstream isolates.
- Of these isolates, 1,019 (49.0 percent) were Enterobacteriaceae, including 878 (42.3 percent) *Salmonella enterica*; 553 (63.0 percent) *Salmonella* serovar Typhi;

5 (less than 1.0 percent) *Salmonella* serovar Paratyphi A; and 291 (33.1 percent) nontyphoidal *Salmonella*.

- Among the Enterobacteriaceae, *Salmonella* Typhi predominated in North Africa, whereas nontyphoidal *Salmonella* predominated in East Africa, West and Central Africa, and Southern Africa.

- Among the 141 (6.8 percent) non-*Salmonella* Enterobacteriaceae, *Escherichia coli* accounted for 77 (54.6 percent), *Klebsiella* species (spp.) for 24 (17.0 percent), *Proteus mirabilis* for 17 (12.1 percent), and *Shigella* spp. for 10 (7.1 percent).

- Other Gram-negative organisms caused 341 bloodstream infections (16.4 percent), of which *Brucella* spp. accounted for 275 (80.6 percent), occurring predominantly in North Africa; *Neisseria* spp. for 22 (6.5 percent); *Acinetobacter* spp. for 16 (4.7 percent); and *Pseudomonas* spp. for 15 (4.3 percent).

- Of the 336 (16.2 percent) Gram-positive isolates, *Streptococcus pneumoniae* accounted for 198 (58.9 percent); *Staphylococcus aureus* for 111 (33.0 percent); and other streptococci for 21 (6.3 percent).

- Yeasts caused 39 bloodstream infections (1.9 percent of the total), of which *Cryptococcus* spp. accounted for 31 (79.5 percent) and *Candida* spp. for 5 (12.8 percent). *Histoplasma capsulatum* is sometimes isolated from blood culture (Archibald and others 1998), but urine antigen testing detects more cases (Lofgren and others 2012).

- Mycobacterial bloodstream infections were found in 173 of the patients tested, of which 166 (96.0 percent) were due to *Mycobacterium tuberculosis* complex, and 2 (1.2 percent) to *M. avium* complex.

The bacterial zoonoses brucellosis, leptospirosis, Q fever, and rickettsial infections are also important causes of febrile illness in Africa. Brucellosis appears to be particularly common in North Africa (Afifi and others 2005; Jennings and others 2007; Reddy, Shaw, and Crump 2010), but it also occurs in sub-Saharan Africa (Dean and others 2012). Although often not studied, leptospirosis is a common cause of febrile illness in Africa, identified as the cause of fever in up to 20 percent of inpatients in some studies (Parker and others 2007). Q fever caused 2–9 percent of febrile hospitalizations, according to a systematic review of African inpatient studies (Vanderburg and others 2014). Spotted fever group rickettsioses and, in some locations, typhus group rickettsioses are also common among febrile inpatients (Prabhu and others 2011). Viral infections including influenza (Yazdanbakhsh and Kremsner 2009) and arbovirus infections such as chikungunya, dengue, Rift Valley fever, and others also may occur.

South and Southeast Asia. Even though a relatively large number of studies have examined the epidemiology of single diseases in Asia—for example typhoid, scrub typhus, and melioidosis (discussed further below)—they cover relatively few sites concentrated in Southeast Asia (Acestor and others 2012). As for China and India, vast knowledge gaps persist. In these countries, no studies have looked at a diversity of pathogens stratified by patient age, outpatient or inpatient status, and disease severity.

Deen and others (2012) identified 17 studies of the etiology of community-acquired bloodstream infection in South and Southeast Asia. Among those, pathogenic organisms were isolated from 12 percent of adults. Of adults with bloodstream infections, *Salmonella enterica* serotype Typhi was the most common bacterial pathogen (30 percent). Other commonly isolated organisms in adults were *Staphylococcus aureus*, *Escherichia coli*, and other Gram-negative organisms. China was excluded from the review, and no reports were found from peninsular India, representing an enormous gap in our knowledge.

In the Kathmandu valley of Nepal, Blacksell, Sharma, and others (2007) and Murdoch and others (2004) identified the importance of typhoid, dengue, leptospirosis, scrub typhus, and murine typhus. In Papua, Indonesia, Punjabi and others (2012) found—among 227, predominantly adult, patients hospitalized with negative malaria diagnostic tests—that the most common etiological diagnoses were typhoid, leptospirosis, rickettsioses, and dengue.

In a large study of patients aged 7–49 years at three health centers in rural Cambodia, Mueller and others (2014) identified at least one pathogen in 73.3 percent of febrile patients. The most frequent pathogens were the malaria parasites. *Plasmodium vivax* (33.4 percent) and *P. falciparum* (26.5 percent). Others included pathogenic *Leptospira* spp. (9.4 percent), influenza viruses (8.9 percent), dengue viruses (6.3 percent), and *Orientia tsutsugamushi* (3.9 percent). However, in the control group consisting of non-febrile persons accompanying febrile patients to health centers, a potential pathogen was identified in 40.4 percent of patients, most commonly malaria parasites and *Leptospira* spp.

In a similar study, but without a control group, Mayxay and others (2013) investigated the etiology of fever in patients aged 5–49 years presenting at two provincial hospitals in rural northern and southern areas of the Lao People's Democratic Republic. They identified at least one pathogen in 41 percent of patients at diagnosis, most commonly dengue (8 percent), scrub typhus (7 percent), Japanese encephalitis virus (JEV) (6 percent), leptospirosis (6 percent), and bacteraemia (2 percent). Influenza diagnostics were available for one site, where influenza B was the most frequently detected type (87 percent). However, as described in Cambodia (Kasper and others 2010), 50 percent of cases of influenza B would not have been identified by surveillance for influenza-like illness. In rural Lao PDR, the contribution of bacteremia diagnosed by conventional blood cultures was relatively low (2 percent). The etiology in children and adults were similar, but the data were not stratified by outpatients and inpatients.

Mayxay and others (2013) estimated that azithromycin, doxycycline, ceftriaxone, and ofloxacin would have had substantial efficacy for 13 percent, 12 percent, 8 percent, and 2 percent of patients, respectively. They suggested that empiric treatment with doxycycline for patients with undifferentiated fever and negative rapid diagnostic tests for malaria and dengue could be an appropriate strategy for rural health workers in Lao PDR. Because JEV, usually without encephalitis, was an important cause of fever, JEV vaccination is likely to have a substantial effect on reducing the frequency of patients presenting with fever as well as those developing encephalitis (Mayxay and others 2013).

Despite many data gaps and uncertainties, the evidence highlights the importance of typhoid, dengue, scrub typhus, leptospirosis, and influenza viruses in South and Southeast Asia. Relative to Africa, brucellosis and Q fever appear to be less important. There is a great need for consensus on designing fever studies that emphasize, for example, the inclusion of control groups especially when sampling sites that are not normally sterile and standardized reporting. The studies' variation in inclusion criteria and age stratification make it difficult to summarize and compare data between sites. The lack of reports from China and India are especially troubling because, presumably, most persons in Asia developing fevers live in these two countries.

The lack of an evidence base for development and testing of diagnostic accuracy and cost-effectiveness of algorithms of empirical treatment creates much uncertainty for policy makers. A major impediment to better understanding the epidemiology of diverse infections across the continent has been the dearth of quality-assured diagnostic facilities in rural Asia—including the substantial expense and human and technical capacity required for these. The situation suggests that a new model is needed for infectious disease diagnostic facilities in the rural tropics—not copied from high-income countries (HICs) but designed for the local pathogens and environment.

Special Groups. Specific issues arise when considering certain subgroups of patients with fever—particularly pregnant women, individuals infected with the human immunodeficiency virus (HIV), people with diabetes, malaria patients, and people at increased risk for occupational or other types of exposure to certain nonmalarial

pathogens. Infections and considerations affecting these special groups are described in table _.1

Table _.1 Febrile Illness Considerations for Special Groups

Group	Disease	Comments	References
Pregnant women	*Plasmodium falciparum*, *Listeria monocytogenes* more common	Few data on etiology and impact of nonmalarial fevers on mother, fetus, and infant	Gravett and others 2012; Kourtis, Read, and Jamieson 2014; Say and others 2014; Machado and others 2013; McGready and others 2010; Louie and others 2010
	Hepatitis E and herpes simplex virus disease, malaria, influenza more severe	Some antimicrobials important for treatment of bacterial pathogens contraindicated in pregnancy	
	Dengue, scrub typhus, and typhoid fever may be more severe.		
	Obstetric sepsis		
HIV infection	Invasive bacterial and fungal infections, including *Cryptococcus neoformans, C. grubii*, nontyphoidal *Salmonella enterica*, and *Mycobacterium tuberculosi*s more common	Knowledge of patient's HIV infection status assists in differential diagnosis of febrile illness; provider-initiated HIV testing recommended	WHO and UNAIDS 2007; Reddy, Shaw, and Crump 2010; Huson and others 2014; Sanders and others 2014
	Acute HIV infection may be	Few data on interaction between HIV and	

	common among persons seeking care for fever in areas with concentrated or generalized epidemics.	several febrile illnesses	
Diabetes	Tuberculosis, infections with Enterobacteriaceae, lower respiratory tract infection, urinary tract infection, skin and mucous membrane infection, and meliodosis more common	Hyperglycemia impairs antibacterial function of neutrophils and T cell-mediated immune response	Kapur and Harries 2013; Knapp 2013; Suputtamongkol and others 1999; Muller and others 2005; Thomsen and others 2005; Esper, Moss, and Martin 2009; Faurholt-Jepsen and others 2013; Van den Berghe and others 2006; Park and others 2011, Figueiredo and others 2010
	Poorer outcomes with tuberculosis, infections with Enterobacteriaceae	Few data from low-resource settings	
		Few data on interaction between diabetes and several febrile illnesses such as leptospirosis and rickettsial infections	
Malaria	Nontyphoidal *S. enterica* bloodstream infection and other bacteremias more common	Positive malaria film may mean malaria is the cause of current illness, a cofactor in a concurrent infection, or an incidental finding.	Abba and others 2011; Kyabayinze and others 2008; Feasey and others 2012; Nadjm and others 2010
		P. falciparum malaria rapid diagnostic tests may remain positive for a month or more	

		after clearance of parasites.	
Occupational and other exposures	Rural residence increases risk for leptospirosis, meliodosis, scrub typhus, and spotted fever group rickettsioses.	Knowledge of patient's occupational and exposure history assists in differential diagnosis of febrile illness.	
	Pastoralist animal husbandry practices increase risk for brucellosis.		
	Q fever more common among livestock keepers, abattoir workers		
	Urban residence associated with enteric fever and murine typhus		

Sources: Shirima and others, 2007; Breiman and others, 2012; Cheng and others, 2005; Wardrop and others, 2013; Vallee and others, 2010.

Note: HIV = human immunodeficiency virus.

Diagnosis and Treatment of Specific Infections

The initial challenge for managing the febrile patient is selecting the most appropriate empiric treatment. Making an etiologic diagnosis allows rationalization and correction of initial treatment. Considerations for diagnosis and treatment of specific infections are summarized in table _.2.

Table _.2 Nonmalarial Febrile Diseases: Exposures, Diagnosis, and Treatment

Disease type	Subgroup	Exposure	Diagnosis	Treatment
Arbovirus infections	Dengue	Arthropod vectors	• Detection of antibody and NS1 antigen • Fourfold rise in antibody titer • Demonstration of virus in tissue by immunohistochemistry or nucleic acid amplification test	Supportive
	Japanese encephalitis virus	Arthropod vectors	• Culture or nucleic acid amplification test from serum, cerebrospinal fluid (CSF), or tissue • Detection of virus-specific IgM in CSF confirmed by plaque reduction assay • Demonstration of virus in tissue by immunohistochemistry or nucleic acid amplification test	Supportive
Bloodstream infection	Enteric fever	Fecally contaminated water or food	Blood culture	Fluoroquinolones, extended-spectrum cephalosporins, or

				azithromycin, according to local patterns of susceptibility
	Meliodosis	Exposure to contaminated soil and water	• Blood culture • Culture of throat swab, pus, and other bodily fluids	• Ceftazidime • Carbapenems (for example, meropenem) usually reserved for severe infections or treatment failures • Amoxicillin-clavulanic acid as second-line therapy; Trimethoprim-sulfamethoxazole alone for eradication phase
	Other	Miscellaneous	Blood culture	Antimicrobials according to local patterns of susceptibility
Brucellosis	n.a.	Exposure to infected animals and their products	• Fourfold rise in antibody titer by microagglutination test • Nucleic acid amplification test • Blood culture	Doxycycline plus gentamicin or streptomycin, or doxycycline plus rifampin, for six weeks

Leptospirosis	n.a.	Exposure to urine or environments contaminated by the urine of infected animals	• Fourfold rise in antibody titer by microagglutination test • Nucleic acid amplification test • Culture of blood or urine using special media	Doxycycline, penicillin, cephalosporins
Q fever	n.a.	Exposure to infected animals, their products, and environments	• Fourfold rise in antibody titer by immunofluorescence assay • Nucleic acid amplification test • Culture	Tetracyclines
Rickettsioses	n.a.	Arthropod vectors, vary by pathogen species	• Fourfold rise in antibody titer by immunofluorescence assay • Nucleic acid amplification test • Culture	Tetracyclines

Note: n.a. = not applicable. NS1 = nonstructural protein 1. IgM = immunoglobulin M. "Supportive" treatment refers to measures to Treatment given to prevent, control, or relieve complications

Other challenges concerning diagnosis and treatment of febrile patients involve the quality of diagnostics and medicine in general regarding many of the pathogens considered in this chapter. These issues can be divided into two groups: inadequate diagnostic capacity and poor quality diagnostics and therapeutic products.

Inadequate Diagnostic Capacity. Given the relative paucity of investment and understanding of febrile diseases, there are inadequate accurate, accessible point-of-care tests (POCTs) and insufficient evaluations of their diagnostic accuracy and cost-effectiveness. Although whole-genome sequencing of pathogens is now commonly performed, no accurate, simple, and affordable diagnostic tests are available for key infections such as typhoid, scrub typhus, and leptospirosis in peripheral health care facilities (Peacock and Newton 2008). This is in part because of intrinsic difficulties such as low bacterial blood load (Dittrich and others 2014) but also because of a lack of investment in targeted research. We will not be able to understand and provide evidence to guide health policy without a surge in investment in accurate, simple, and affordable diagnostic tests for these neglected diseases. The success of nonstructural protein 1 (NS1)-based dengue POCTs in assisting with dengue diagnosis in rural facilities suggests that this can be done.

Poor Quality of Diagnostic and Therapeutic Products. The diagnostic tests, vaccines, and medicines necessary to reduce the burden of fevers are often of poor quality, especially in countries with insufficient regulation (Caudron and others 2008; Mori, Ravinetto, and Jacobs 2011; Newton and others 2006). The evidence regarding

antimalarials suggests severe quality issues (Tabernero and others 2014), but limited data exists regarding diagnostic tests, vaccines, and other classes of medicines.

The only long-term sustainable solution is the dramatic strengthening of medicine regulatory authorities in the 30 percent or so of countries without functional capacity (Newton and others 2009). Health care providers should exercise caution in using diagnostic tests, in case the instructions either inflate the products' claims for diagnostic accuracy or are of poor quality, and be aware that poor patient outcomes may reflect poor-quality medicines rather than the disease process *per se*.

Integrated Management of Adolescent and Adult Febrile Illness

Management at First-Level Health Facilities. The WHO Integrated Management of Adolescent and Adult Illness (IMAI) guidelines for health workers at first-level facilities, specifically health centers and district outpatient clinics, provide guidance on the management of febrile patients (WHO 2009). Managementof the febrile adolescents and adults at first-level facilities is based on the current WHO guidelines for the treatment of malaria (WHO 2010b).

Management at the District Hospital. The WHO IMAI district clinician manual provides guidelines for the hospital care of adolescents and adults in low-resource areas (WHO 2011a). The manual has been subject to few evaluations to date (Rubach and others 2015). The district clinician manual assumes availability of a minimum level of human resources (medical officer, clinical officer, or senior nurse) and a limited range of essential drugs, equipment, and laboratory and other investigations at the hospital level. Emergency management includes the use of antibacterials

(ceftriaxone) and antimalarials (parenteral artesunate) if sepsis or severe malaria is suspected.

Adherence to Guidelines. Considerable evidence indicates that the WHO practice recommendations and diagnostic technologies are often not adopted and used in low-resource areas (English and others 2014). The reasons include poor dissemination, limited training and monitoring, and limitations of human and other resources.

Diagnostic Approaches

Laboratory services have been neglected components of health services in low-resource areas (Archibald and Reller 2001; Petti and others 2006), and therefore patient management has been based predominantly on syndromic approaches (WHO 2009, 2011a). Notable exceptions have been assays in support of programs for the diagnosis and management of HIV, tuberculosis, and malaria (WHO 2010a, 2010 b, 2010c). Experts have recommended clinical laboratory services that should be available at various tiers of the health service in low-resource areas (WHO 2008). However, these services remain widely unavailable.

Knowledge of the HIV serostatus of a febrile patient is useful. Many rapid HIV antibody tests have high sensitivity and specificity in established HIV infection (WHO 1997). Further risk stratification for specific HIV coinfections may be based on the results of a CD4-positive T-lymphocyte count when available.[2]

Culture of a sufficient volume of blood is useful for the diagnosis of bloodstream infections (Lee and others 2007). Once available, the results of blood culture may be

used to refine initial antimicrobial management. In addition, aggregate data provide useful information about the local prevalence of pathogens causing bloodstream infection as well as patterns of antimicrobial resistance. Continuously monitored blood culture systems may shorten the time to detection and improve sensitivity compared with manual blood culture methods, but they are much more expensive. Special blood culture bottles optimize the recovery of organisms with particular growth requirements including some yeasts, mycobacteria, anaerobes, and leptospires.

Diagnostic tests for many febrile illnesses other than malaria remain complex, expensive, and limited to a few supranational reference laboratories mostly in high-income countries. Their use has been restricted to a few centers, often in large cities, where conditions differ from those in the vast areas of *terra incognita* (Acestor and others 2012). Newer diagnostics often lack standardization of both operation and interpretation and have not been sufficiently validated in the range of settings where they will be used.

Independent evaluations of diagnostic tests are vital because key information is often missing from the details provided by the manufacturers, which may claim high sensitivity and specificity without appropriate justification (Blacksell, Bell, and others 2007). For example, high sensitivity and specificity of a dengue POCT for a sample taken seven days after fever onset has minimal clinical utility.

A consensus statement—perhaps linked to Standards for Reporting of Diagnostic Accuracy (STARD) (Bossuyt and others 2003) but dedicated to evaluation of infectious disease diagnostic tests, especially POCTs—could help improve the current

situation. Because estimates of the sensitivity and specificity of diagnostic tests based on evaluation against a known but imperfect gold standard may be imprecise, Bayesian latent class models may be helpful in improving their evaluation (Lim and others 2013). Imaginative use of filter paper as a storage matrix for both serological and molecular diagnosis may be a practical way forward in low-and-middle-income countries (LMICs) (Smit and others 2014).

Despite these limitations, we would expect that common pathogens, especially if sharing routes of transmission and risk factors, would result in a substantial incidence of mixed or concurrent infections (Phommasone and others 2013). However, the laboratory diagnosis and management of mixed infection is vexed. Reports of mixed infections often use only serological criteria. However, the problems of antibody persistence and interspecies cross-reaction raise uncertainty as to whether these results represent true mixed infections, sequential infections, or cross-reactions. Hence, reports of mixed infections should include an explicit discussion of the likely specificity and sensitivity of the diagnostic assays used and the likelihood that the observations represent true concurrent mixed infections (Phommasone and others 2013).

The incidence of mixed infections, including pathogens such as *Salmonella* Typhi and *Streptococcus pneumoniae*, will also be highly influenced by vaccination coverage. The management of mixed infections has received little attention. Concerning bacterial mixed infections, a key consideration is that although doxycycline is likely to be efficacious for pathogens such as scrub typhus and leptospirosis, it would not be for other common pathogens such as typhoid fever and melioidosis. Combination

therapy may be problematic if bacteriostatic and bacteriocidal antimicrobials are given in parallel.

Costs of Febrile Illness and Cost-Effectiveness of Diagnostics and Treatments

This section briefly reviews the evidence on the costs of febrile illness in adolescents and adults and the cost-effectiveness of interventions to improve their management. It then summarizes three new cost-effectiveness evaluations of interventions for the management of fever in hospitals, first-level health facilities, and the community. It concludes with a discussion of how future economic evaluations could improve on common limitations in the existing literature.

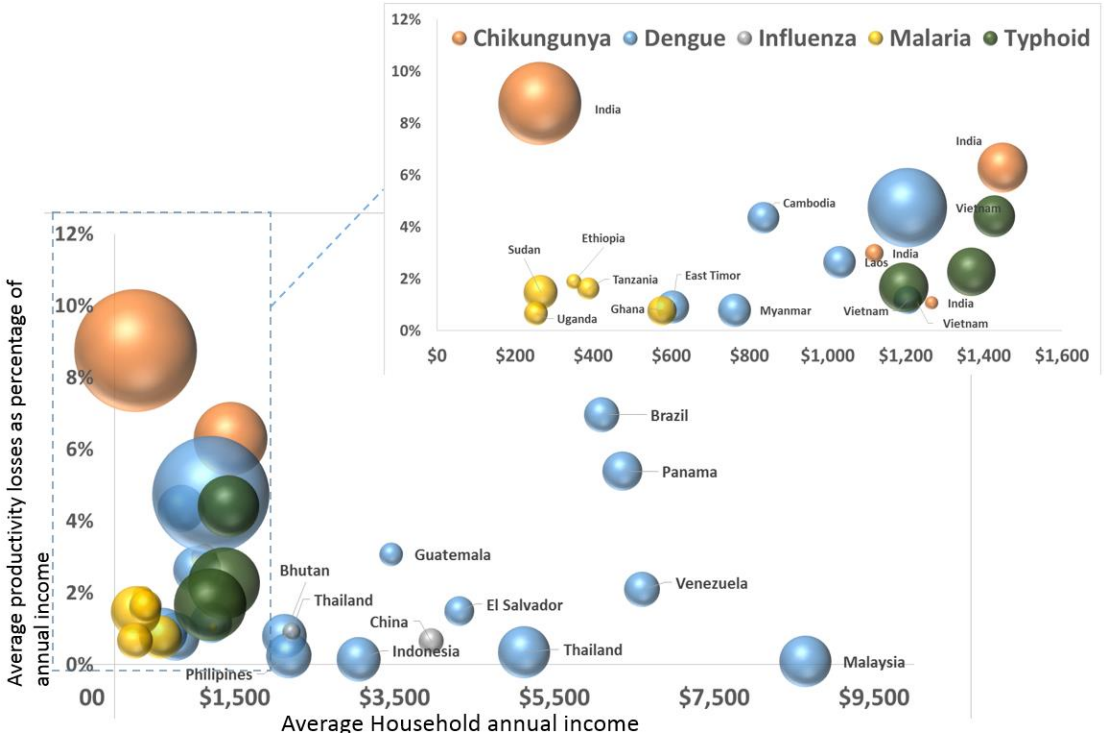
Costs to Households and Health Care Providers

As a dominant reason for seeking medical care, febrile illnesses are a key driver of health expenditures and productivity losses. However, no data are available on the economic impact of common diseases such as scrub typhus and brucellosis on either households or health care systems. For other diseases such as melioidosis, limited data are available from hospital settings (where the visible burden of confirmed cases is likely a small fraction of the full burden) because pathogens such as *Burkholderia pseudomellei* and *Orientia tsutsugamushi* are unlikely to be detected outside well-equipped hospital settings.

Although methodological differences among cost-of-illness studies impede comparison of the relative cost burden of different diseases, some general trends can be detected (figure _.1 and annex _B). The largest impact is often associated with

household productivity losses rather than direct medical costs, a particular concern of adult patients. For melioidosis, the known burden is concentrated among adult agricultural workers, therefore the economic impact on rural households can be particularly hard hitting. In hospitalized typhoid fever cases in India and Indonesia, productivity losses have been as high as 15–20 percent of annual income (Bahl and others 2004; Poulos and others 2004).

Figure _.1 Direct and Indirect Costs of Febrile Illness in Adolescents and Adults, by Illness, 2012



Source: xxxxxxxxx. **[[AQ: Add figure and/or data source(s) here.]]**

Note: Circle size indicates the direct cost of illness, which include both household and provider direct medical and non-medical costs per febrile episode, relative to household income. The largest circle on the top-left, for instance, represents the direct cost of an episode of Chikungunya, which in this rural Indian setting is equivalent to 18% of households' annual income. Most malaria episodes on the bottom-left consumed an equivalent of 1-3% of household income, as indicated by the smaller circles. These episodes also resulted in relatively fewer productivity losses, as indicated by their lower vertical positioning. As would be expected, direct costs of illness are regressive, consuming a larger proportion of household income in lower-income settings. However, as indicated by the inverse relationship between household income and productivity losses, these indirect costs also appear to be regressive, with households in lower-income settings losing higher proportions of their income per episode of febrile illness.

Tellingly, the household and provider costs are lower for malaria than for other febrile illnesses in both ambulatory and admitted patients. This finding is evident from both indirect cost-of-illness comparisons and from studies comparing the cost of malaria and nonmalarial cases in the same setting (Ansah and others 2013; Batwala and others 2011; Deressa, Hailemariam, and Ali 2007; Kyaw and others 2014; Morel and others 2008; Mustafa and Babiker 2007; Rammaert and others 2011;Yukich and others 2010). One such study compared household costs for patients diagnosed clinically as having malaria, with and without subsequent confirmation of parasitemia, finding that patients incorrectly diagnosed with malaria were more likely to remain symptomatic at three weeks' follow-up and had a higher risk of reattendance at a health facility (Hume and others 2008). Severe malaria admissions have also been found to be less costly than nonmalarial diseases with similar presentations on the same wards because of lower medication costs and shorter durations of admission (Ayieko and English 2007; Lubell and others 2010).

These differences in cost could be explained by the concentration of malaria-related studies in low-income sub-Saharan African countries. However, the differences could also indicate a genuine trend for two reasons: First, with extensive donor support, malaria diagnostics and treatments have become increasingly available across the endemic world at low cost. Second, the strengthening of distribution mechanisms in the public and private sectors has helped to ensure access to rapid diagnosis and effective treatment. Thus, patients suffering from malaria may fare better than those with fever from other causes that often go undiagnosed, or for which effective treatment is unavailable, resulting in a longer duration of illness and higher expenses for repeated seeking of medical care (Reyburn and others 2004).

The high costs of nonmalarial febrile illnesses to households and health care systems suggest considerable scope for cost-effective investment to reduce these illnesses' impact through prevention, diagnosis, and treatment. Households might also be willing to pay for such interventions should they become available, as has been found regarding a typhoid vaccine in Bangladesh and leptospirosis prevention in the Philippines (Arbiol and others 2013; Cook and others 2007). However, there is virtually no guidance as to the cost-effectiveness of diagnostics and treatments for febrile illnesses other than malaria.

Cost-Effectiveness Analyses of Diagnostics and Treatments of Undifferentiated Febrile Illness

Recent major policy changes by WHO (WHO 2010b) in the diagnosis and treatment of malaria were well supported by evidence of their cost-effectiveness. For example, the paradigm shift from empiric treatment of fever with antimalarials toward parasitological confirmation was accompanied by numerous economic evaluations (Ansah and others 2013; Batwala and others 2011; de Oliveira, Castro, and Toscano 2010; Lubell, Hopkins, and others 2008; Shillcutt and others 2008; White and others 2011; Zurovac and others 2006). Several economic evaluations have also compared treatments for uncomplicated malaria, demonstrating the superiority of artemisinin-based combination therapies (ACTs) over preexisting monotherapies (Chanda and others 2007; Wiseman and others 2006) and of artesunate overquinine for severe malaria (Lubell and others 2009, 2011). Reviews of the cost-effectiveness of preventive interventions for malaria such as insecticide-treated nets, indoor residual spraying, and intermittent preventive treatment can be found elsewhere (White and others 2011).

Only a handful of economic evaluations have been carried out on diagnoses and treatments of nonmalarial fevers in the context of LMICs (detailed in web annex _C). This scarcity stems from the dearth of relevant point-of-care (POC) diagnostics and treatments that warrant evaluation; other than recent dengue and influenza POCTs, no tests have been deemed sufficiently accurate and suitable for use in routine care. For the treatment of nonmalarial fevers, with the exception of new combination therapies for visceral leishmaniasis, there have been few advances in recent years.

The few available evaluations include cost-effectiveness analyses of the following:

- Leptospirosis tests compared with empiric treatment with doxycycline (Supputamongkol and others 2010);
- Influenza POCTs for the detection of influenza A(H1N1) in Mexico City (González-Canudas and others 2011);
- Eflornithine compared with melarsoprol for the treatment of human African trypanosomiasis (Robays and others 2008);
- Combination treatments over monotherapy for leishmaniasis (Meheus and others 2010; Olliaro and others 2009); and
- Yet-undeveloped prereferral rectal antimicrobial suppositories for severe febrile illness, both alone and in combination with an antimalarial suppository (Buchanan and others 2010).

These studies represent the scant evidence on the cost-effectiveness of diagnostics and treatments for nonmalarial causes of fever. We next extend this limited body of

evidence, summarizing three evaluations of diagnostic tools for the management of febrile episodes and sepsis in the hospital, first-level, and community settings.

Surveillance of Bloodstream Infections for Sepsis Management in Low-Resource Settings. A leading cause of mortality among febrile patients in LMICs is bacterial sepsis, but blood culture services are not widely available. Consequently, empiric antimicrobial management of suspected bloodstream infection is based on generic guidelines that are rarely informed by local data on etiology and antimicrobial resistance patterns.

To evaluate the cost-effectiveness of surveillance of bloodstream infections to inform empiric management of suspected sepsis in low-resource areas, Penno, Baird, and Crump (2015) compared costs and outcomes of generic antimicrobial management with management informed by local data on etiology and patterns of antimicrobial resistance across all of Africa. Applying a decision-tree model to a hypothetical population of febrile patients presenting at the district hospital level in Africa, the authors found that the evidence-based regimen saved an additional 534 lives per 100,000 patients with fever at an increase in cost of US$25.35 per life saved, which corresponded to an incremental cost-effectiveness ratio (ICER) of US$4,749.[3] Although this number compares favorably to standard cost-effectiveness thresholds, it should ultimately be compared with other relevant policy alternatives to confirm whether routine surveillance for bloodstream infections is a cost-effective strategy in the African context.

POCT for Sepsis among Patients with Febrile Illness in Low-Resource Settings. Similarly, distinguishing patients with sepsis from those with other illnesses remains a challenge. Currently management decisions are based on clinical assessment using algorithms such as WHO's Integrated Management of Adolescent and Adult Illness (IMAI) guidelines (WHO 2009, 2011a).

Efforts to develop and evaluate POCTs for sepsis to guide decisions on the use of antimicrobials are under way. To establish the minimum performance characteristics of such a test, Penno, Crump, and Baird (2015) varied the characteristics required for cost-effectiveness of a hypothetical POCT for sepsis and applied similar methods to the bloodstream infection surveillance analysis of Penno, Baird, and Crump (2015). The existing clinical assessment algorithms were compared with the POCT.

Based on a clinical assessment for sepsis with the established sensitivity of 83 percent and specificity of 62 percent, the authors found that a POCT for sepsis with a specificity of 94 percent and a sensitivity of 83 percent was cost-effective, resulting in parity or equivalence with clinical assessment in terms of survival but costing US$1.14 less per life saved. A POCT with sensitivity and specificity of 100 percent, equivalent to the best malaria rapid diagnostic tests, was both cheaper and more effective than clinical assessment. Overall, this work helps establish performance targets for POCTs for sepsis in low-resource areas.

Diagnosis and Treatment Strategies for the Management of Febrile Patients in the Community. This analysis considers the implications of using pathogen specific tests for dengue and scrub typhus, as compared with testing for a biomarker of host-

inflammation, C-Reactive Protein (CRP), to inform management of fever in the community. Using data on causes of fever in outpatients in rural Laos PDR (ref Mayxay and others 2013), we model the proportion of patients that would be correctly treated with an antimicrobial under each of the approaches and the cost-effectiveness of the tests.

After accounting for the accuracy of the tests, the following assumptions are made regarding how their results would be used to inform treatment practices:

- Patients with a positive dengue test result are not prescribed an antimicrobial
- Patients with a positive scrub typhus test result are prescribed an antimicrobial
- Where a pathogen specific test is negative, antimicrobials are prescribed at random at a rate of 38% resembling current practice
- Patients with CRP levels below the threshold of 20 milligrams per litre do not receive an antimicrobial, and those above the threshold do.

We first evaluate the approaches in terms of their ability to classify patients as requiring treatment, and then go on to incorporate their ability to inform as to the choice of antimicrobials, with regards to pathogen susceptibility to the different drugs. Patients with a positive scrub typhus test are therefore assumed to receive doxycycline, whereas for other treated patients the choice of antimicrobial is taken at random based on the frequency of their use in current practice.

The analysis suggests that use of either pathogen specific test offered modest improvements over current practice in terms of the ability to classify patients as requiring an antimicrobial (Figure 2). The dengue RDT implied a reduction in

antimicrobials prescribed to viral infections but a larger proportion of bacterial infections going untreated, while the inverse was true for the scrub typhus test. Use of the CRP test implied reductions in both use of antimicrobials in viral infections as well as less bacterial infections going untreated. These advantages were consistent despite variation in all model parameters, including the incidence of infections, baseline antimicrobial prescription practices, and when accounting for the uncertainty surrounding the accuracy of the tests (left hand panel of Figure 2).

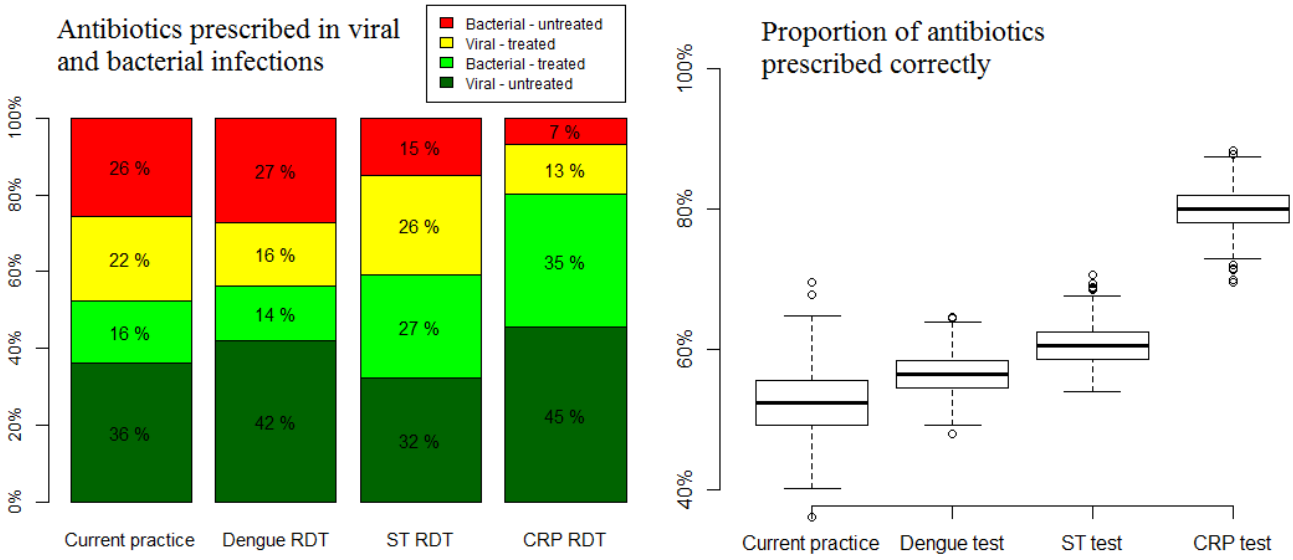


Figure 1: Antimicrobial targeting using the Laos PDR data (left) and across a range of simulated incidences and test accuracies (right)

The incremental costs and DALYs averted from 500 simulation outputs and the corresponding cost-effectiveness acceptability curves are shown in Figure 3, illustrating that either the scrub typhus or CRP tests are likely to be cost-effective, despite the considerable uncertainty surrounding many model parameters.

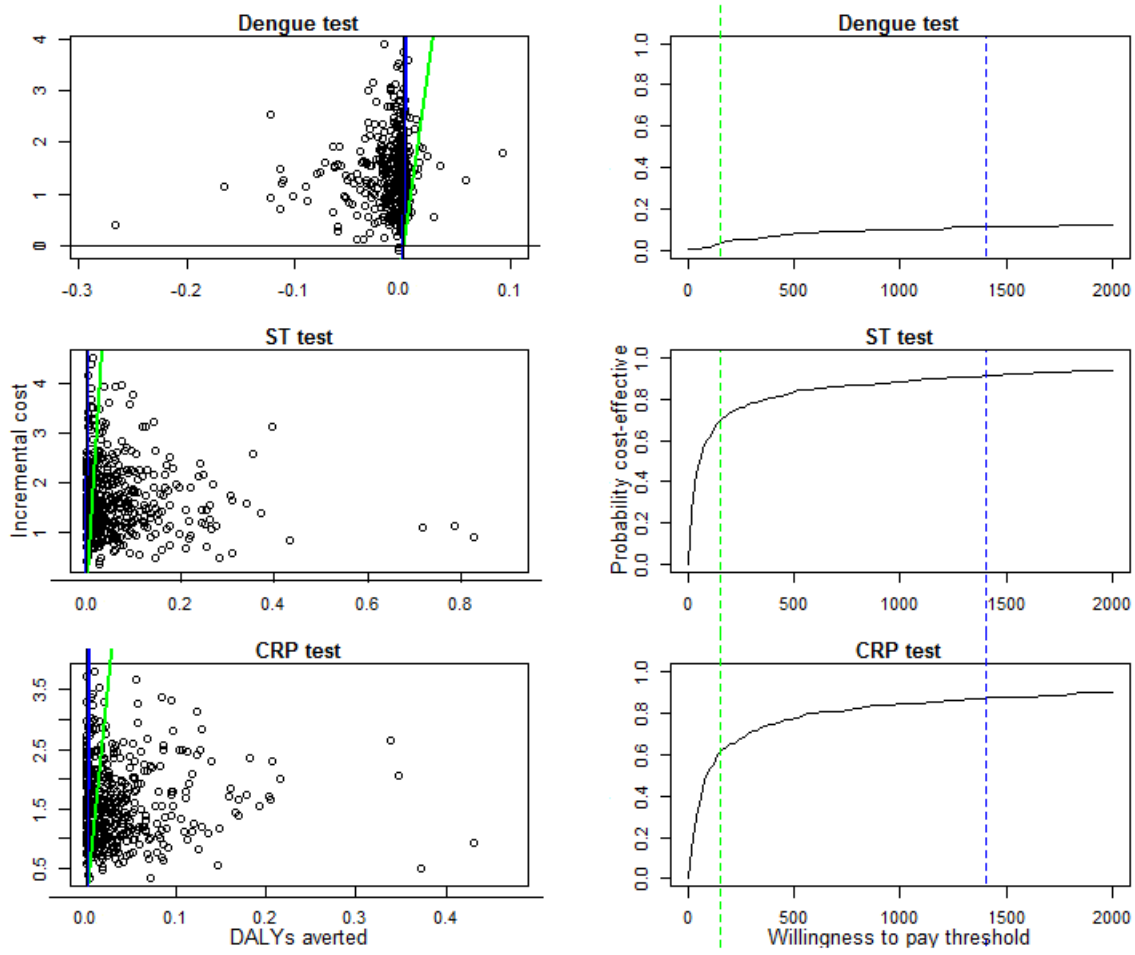


Figure 2: Cost-effectiveness plane and cost-effectiveness probability curves for the three strategies when compared with a baseline of current practice. *The blue lines indicate a wiliness to pay threshold of $1400, approximating the Laos PDR 2012 GDP/capita, while the green line is a much more conservative willingness to pay threshold of $150. The Dengue test in most instances was associated with worse health outcomes and higher costs. The scrub typhus and CRP tests averted on average 0.07 and 0.05 DALYs as compared with current practice, with a median ICER of $59 and $110, respectively.*

The analysis suggests that testing for pathogens for which there are no immediate treatment implications such as dengue might not offer a direct health benefit over current practice, although this does not account for factors such as patient reassurance

in having a confirmed diagnosis, raising awareness for possible danger signs, or initiating measures for vector control. Testing for bacterial pathogens can guide the use of an appropriate antimicrobials therefore this could be a cost-effective approach, but the cost-effectiveness varies widely depending on local etiology. Testing for biomarkers of inflammation could offer a cost-effective approach to targeting antimicrobials in rural settings that is robust to heterogeneous in causes of fever typical of the rural tropics.

Future Research Needs

Fever Etiology Research

To provide a clearer picture of the relative importance of relevant causes of nonmalarial febrile illness, fever etiology research is needed that takes into account geographic and ethnic diversity, includes a broad range of pathogens, employs standardized case definitions and diagnostic assays, and uses a control group to estimate attributable fractions. The findings of such research would better inform health care workers about the prior probability of specific infections in their area and would contribute data relevant to burden-of-disease estimation for infections that currently lack robust estimates of illness and death.

Researchers should also consider structuring the burden-of-disease estimates for febrile illness similarly to the estimates for diarrhea and pneumonia. Data from fever etiology research could be applied to the syndrome-wide envelope of disability-adjusted life years (DALYs) and deaths for febrile illness to develop pathogen-specific estimates. Such an approach would provide the basis to estimate the effects of interventions, including robust cost-effectiveness analyses.

Diagnostic and Clinical Management Studies

POCTs for febrile illnesses can be classified into pathogen-specific tests and biomarker assays that might detect states such as the systemic inflammatory response associated with sepsis. Malaria rapid diagnostic tests demonstrate that a pathogen-specific diagnostic can find an important place in management algorithms for fever in low-resource areas (WHO 2010b). However, current pathogen-specific POCTs for other causes of fever do not approach the performance of the best malaria rapid diagnostic tests (WHO 2011b). Research priorities for pathogen-specific POCTs should be based on burden-of-disease data and should focus on infections for which potentially lifesaving treatments are available. Biomarker assays that identify a group of patients with severe disease or those likely to develop severe disease could have a role in triage and in targeting of antimicrobial agents. However, such tests must be at least as sensitive as clinical evaluation to avoid excess deaths and at least as specific to avoid antimicrobial overuse and excessive costs.

In addition, clinical management studies are urgently needed to inform the best empiric treatment strategies for patients with severe nonmalarial febrile illness (Crump, Gove, and Parry 2011). Studies that inform decisions at first-level health care facilities about when to use and when to withhold antimicrobial therapy are essential to optimize patient outcomes while preserving scarce health care resources and containing antimicrobial resistance.

Necessary Elements for Cost-Effectiveness Analyses

As for the design of economic evaluations of diagnostics and treatments for febrile illnesses, five elements need to be strengthened:

1. Inclusion of the intervention's implications for all febrile patients rather than for a subset with specific pathogens of interest

2. Inclusion of factors affecting the intervention's performance in real-life settings

3. Framing of the evaluations within specified etiological contexts and exploration of the implications of heterogeneity

4. Extension of the analyses, where appropriate, to include the implications for ongoing pathogen transmission

5. Accounting for the interventions' impact on development of antimicrobial resistance

Inclusion of the Intervention's Implications for All Febrile Patients. An important limitation in many evaluations of malaria diagnostics was the use of malaria-centered outcomes such as cost per malaria case diagnosed or treated. Such outcomes failed to account for the impact on other nonmalarial diseases—often affecting the majority of patients. What is needed, therefore, is a clear indication of how the intervention affects the management of febrile patients as a whole.

One of the reasons malaria POCTs were found to be cost-effective was this methodological shift toward inclusion of their potential benefit for other causes of illness. In contrast, there was apprehension that, in high-transmission areas, malaria POCTs could be detrimental to the management of nonmalarial diseases because older children and adults could be carrying malaria parasites to which they are clinically immune while suffering from a potentially severe nonmalarial illness

(Bisoffi and others 2011). These considerations will be important in other pathogen-specific tests already on the market for diseases such as dengue and scrub typhus.

Inclusion of Factors Affecting the Intervention's Performance. The performance and impact of the tests in routine settings can be affected by intermediate factors such as interpretation of and adherence to test results, stockouts, and compromised quality due to inadequate storage and handling. For malaria POCTs, the prescribing of antimalarials to patients who had tested negative for malaria was of particular concern, raising the question of whether POCTs were in fact cost-effective in routine care as opposed to trial settings and model-based evaluations.

An economic evaluation that accounted for compromised adherence demonstrated that although the cost-effectiveness of POCTs was diminished, a substantial degree of nonadherence could be absorbed while use of the tests remained cost-effective (Lubell, Reyburn, and others 2008). Models that incorporate such factors can not only provide a more realistic assessment of the interventions' cost-effectiveness in routine care, but also assist in guiding resources for training and other supportive interventions.

Framing of Evaluations within Specific Etiological Contexts. The diagnostic value of a test is not an inherent characteristic, but one that is strongly influenced by the prior probability of the condition it is designed to detect. This implies that the suitability of many pathogen-specific tests will vary by etiological setting, both seasonally and spatially. This is a challenge to effective policy making but also an opportunity to vastly improve the efficient allocation of scarce resources.

Extension of Analyses to Implications for Pathogen Transmission. One important element of concern is the degree to which the analysis should account for the impact of interventions on disease transmission, as opposed to a limited focus on direct costs and benefits to the patient. Although the latter can avoid many of the uncertainties that often pervade transmission dynamic models, the more-conservative results of such analyses could unduly penalize an intervention that would represent an efficient use of resources when considering indirect health benefits associated with reduced transmission.

Inclusion of Interventions' Impact on Antimicrobial Resistance. Perhaps most challenging, the evaluations of diagnostics and treatments for fevers could be improved by including the societal costs and consequences associated with antimicrobial resistance (Loubiere and Moatti 2010). The methodological challenges to this approach are considerable and likely explain this glaring omission (Coast, Smith, and Millar 1996). In their absence of such measurements, presumptive treatment will almost always appear dominant as long as the purchase cost of the drugs is less than that of diagnostics to inform their use, even if this analysis fails to reflect the broader societal costs and consequences of such a strategy (Girosi and others 2006).

Few attempts have been made to define the societal cost per antimicrobial consumed. One such study, in a high-income hospital setting, estimated that each defined daily dose of antimicrobial was associated with a cost of €5–12 because of its contribution to antimicrobial resistance in that hospital (Kaier and Frank 2010). Despite the

difficulties in deriving these values, the inclusion of even highly conservative estimates for these costs in the evaluation of malaria POCTs has been shown to dramatically affect their conclusions (Lubell, Reyburn, and others 2008). If not formally incorporated in the analysis, the implications of their exclusion should at the very least be addressed.

Conclusions

Declines in malaria in many areas and growing recognition of the problem of malaria overdiagnosis have focused new attention on the problem of management of fevers in low-resource areas. Comprehensive and coordinated fever etiology research is urgently needed in low-resource areas to identify priorities for improvements in management and control of causes of fever other than malaria. In the meantime, focus on the identification and management of patients with bacterial and fungal sepsis and those with tetracycline-response infections are likely to avert substantial morbidity and mortality from fever. Burden of disease structures that capture fever without localizing features as a group would greatly assist with estimating the effect size of interventions for fevers. Cost-effectiveness analyses have underpinned important policy decisions for the management and control of malaria. Early insights from cost-effectiveness analysis suggest a place for tetracyclines in the management of febrile patients in Asia, underscore the value of surveillance for bloodstream infections in low-resource areas, and identify the minimum performance characteristics of a POCT for sepsis. Gathering more cost and outcome data and improving approaches to cost-effectiveness analysis related to fever would greatly strengthen resource-stratified approaches to adoption and integration of interventions in the emerging field of non-malaria febrile illness.

Web Annex _A Etiology of Severe Febrile Illness Studies of Adolescents and Adults, by Region, 1980–2013

First Author (Reference)	Location; study dates	Total no. of patients in study	Hospital type	Age (population type)	Diagnostic tests conducted	N (%) of diseases searched in review investigated in study	Patients (%) with confirmed infection	Patients infected with HIV (proportion of patients tested)	Most common pathogens
Eastern Africa									
Aarsland and others 2012	Ethiopia, December 2009 - January 2010	102	Urban referral hospital.	1 month – 18 years. Primarily children.	DNA extraction and NAAT from malaria blood smears for *S. pneumoniae*, *Salmonella* spp, *Rickettsia* spp, *Borrelia* spp, *Leptospira* spp. (NAAT for *Salmonella* and *S.pneumoniae* did not meet case definitions)	3 (12.0%)	12 (11.8%) with positive NAAT*	n.a.	*Plasmodium* spp, *Rickettsia* spp, *Borrelia* spp*
Archibald and others 1998	Tanzania; February 1995-April 1995	517	Urban referral hospital	>15 years.	Blood culture. Thick and thin blood smears	2 (8.0%)	145 (28.9%) positive blood culture. 49 (9.8%) malaria slide positive	282 (56.2%)	*Mycobacterium tuberculosis,* Non-typhoidal *Salmonella, S.aureus,*

Bell and others 2001	Malawi; March 1998 - May 1998	238	Urban referral hospital.	>14 years. Primarily adults	Blood culture (mycobacteria), Thick and thin blood smears	2 (8.0%)	67 (28.2%) positive blood culture. 72 (31.2%) malaria slide positive	173 (75.9%)	Non-typhoidal *Salmonella, Mycobacterium tuberculosis, Cryptococcus neoformans*
Dougle and others 1997	Kenya; July 1994 - October 1994	228	Urban referral, teaching hospital.	> 5 years. Primarily adults	Blood culture. Thick and thin blood smears	2 (8.0%)	51 (22.4%) positive blood culture. 25 (11.0%) malaria slide positive	51 (22.5%)	*S enterica* serotype Typhi, *S.pneumoniae,* Non-typhoidal *Salmonella*
Gordon and others 2001	Malawi; December 1997 - November 1998	9,298	Urban referral teaching hospital.	Unspecified. Primarily adults	Blood culture	1 (4.0%)	449 (16.1%) positive blood culture	n.a.	Non-typhoidal *Salmonella*, *S.pneumoniae, E.coli*
McDonald and others 1999	Malawi; August - September 1997	128	Urban referral hospital (Malawi)	> 18 years	Mycobacterial blood culture	1 (4.0%)	14 (10.9%) positive blood culture	101 (78.9%) in Malawi.	*Mycobacterium tuberculosis*
Meremo and others 2012	Tanzania; June 2011 - December 2011	346	Urban tertiary referral hospital.	Unspecified. Primarily adults	Blood culture	1 (4.0%)	33(9.5%) positive blood culture	156 (45.0%)	Non-typhoidal *Salmonella*, *S.pneumoniae, E.coli*
Petit and others 1995	Kenya, 1990	336	Study 1 urban and referral	> 8 years. Primarily adults	Blood culture, thick and thin blood smears	2 (8.0%)	Only study 1-104 (30.9%) positive BSI. 25 (7.4%) malaria slide positive	12 (3.6%)	*Plasmodium* spp, *Salmonella* spp, *E.coli*

Ssali and others 1998	Uganda; January 2007 - April 2007	299	Urban referral, hospital	>15 years.	Blood culture (mycobacterial)	1 (4.0%)	71 (23.7%) positive blood culture	228 (76.3%)	*Mycobacterium tuberculosis, S.pneumoniae*
Lofgren and others 2012	Tanzania; August 2007 - September 2008	628	Urban referral medical center and Regional hospital.	>13 years. Primarily adults	Histoplasma urine antigen testing	1 (4.0%)	7 (1.1%) positive for histoplasmosis	n.a.	*Histoplasma* spp
Crump and others 2013	Tanzania; September 2007 - August 2008	870	Urban referral hospital.	Children (>2 years <13 years) Adults >13 years	Blood culture, thick and thin blood smears. Cryptococcal, *S.pneumoniae, H.capsulatum* antigen testing. Leptospirosis/ Brucellosis standard microscopic reciprocal test (MAT). Acute and convalescent serological investigation for Q fever and Spotted and typhus fever group rickettsiosis. NAAT for DENG, CHIKV and flavivirus	11 (44.0%)	Q fever (n=24; 5.0%) spotted fever rickettsiosis (n=36; 8.0%) typhus group rickettsiosis (n=2; 0.4%) chikungunya (n=55; 7.9%) brucellosis (n=16; 3.5%) leptospirosis (n=40; 8.8%)	n.a.	Chikungunya virus, *Leptospira, Rickettsial* spp,

					RNA				
Crump and others 2011	Tanzania; September 2007 - August 2008	403	Urban referral hospital.	>13 years. Primarily adults	Blood culture (mycobacteria), Thick and thin blood smears	2 (8.0%)	104 (25.8%) positive blood culture. 8 (2.0%) with malaria slide positive	161(39 %)	*S enterica* serotype Typhi, *S.pneumoniae, E.coli, Mycobacterium tuberculosis*
Western Africa									
Baba and others 2013	Nigeria, July 2008- December 2008	310	Urban, referral, tertiary, teaching hospital	All age groups. Primarily adults	Thick and thin blood smears, Widal test. Plaque reduction neutralization tests for CHIK, YF, DENG, WNV (Did not meet case definitions for Widal and viral tests)	1 (4.0%)	49 (15.8%) malaria slide positive	n.a.	*Plasmodium* spp
Ki-Zerbo and others 2000	Burkina Faso; January 1995 - March 1995	183	Teaching hospital	>15 years	Acute and convalescent serological investigation for Spotted and typhus group rickettsiosis and Q fever	2 (8.0%)	17 (5.5%)	n.a.	*Rickettsial* spp (SFG) *Rickettsial* spp (TG) *Coxiella* spp

North Africa									
Afifi and others 2005	Egypt; 1999 - 2003	10,130	Public infectious disease hospital	> 4 years. Primarily adults	Blood culture	1 (4.0%)	1005 (10.2%) with positive blood culture	n.a.	*Salmonella enterica* serotype Typhi, *Brucella* spp, *S.aureus*
Hyams and others 1986	Sudan; Jan 1984 - Feb 1984	100	Urban hospital	> 12 years. Primarily adults	Blood culture, virology test-isolation and acute and convalescent serological investigation for DENV, YF, WNV, CHIK, thick and thing blood smears	5 (5.0%)	25 (25%) positive blood culture, 21(21%) virus isolation, 13 (13%) malaria slide positive	n.a.	Dengue virus, *Salmonella enterica* serotype Typhi, *Plasmodium* spp
South Central Asia									
Abbasi and others 2009	Pakistan; September 2007 - January 2008	112	Urban teaching hospital	> 13 years. Primarily adults	Thick and thin blood smears. Dengue viral specific immunoglobulin detection (Did not meet dengue case definition)	1 (4.0%)	26 (23.2%) malaria slide positive	n.a.	*Plasmodium* spp

Blacksell and others 2007	Nepal, Kathmandu; July 2002 - June 2004	103	Urban, referral, community general hospital	> 17 years	Blood culture. Serology for scrub typhus, murine typhus, leptospirosis, dengue. Included only for blood culture and paired acute and convalescent sera	3 (12.0%)	29 (28.1%) positive blood culture, 14 (13.5%) confirmed serology	n.a.	*Salmonella enterica* serotype Typhi, *Salmonella enterica* Paratyphi A, *R.typhi*
Chrispal and others 2010	South India; January 2007 - January 2008	398	Tertiary care referral hospital	>16 years	Blood culture, thick and thin blood smears, serological testing for scrub typhus, Dengue virus, *Leptospira* spp, SFG rickettsiosis (did not meet serological case definitions)	1 (4.0%)	32 (8.0%) positive blood cultures, 68 malaria slide positive	n.a.	Salmonella enterica serotype Typhi, *Salmonella enterica* Paratyphi A, *Plasmodium* spp
Faruque and others 2012	Bangladesh; December 2008 - November 2009	462	Six tertiary level, teaching, referral hospital	Unspecified. Primarily adults	Malaria rapid diagnostic test. Serological testing for dengue virus (Did not meet dengue case definition)	1 (4.0%)	3 (0.6%) positive for malaria rapid diagnostic test	n.a.	*Plasmodium* spp

Murdoch and others 2004	Nepal, Kathmandu; Jan 2001 - March 2001 and July - August 2001	876	Urban, general hospital	>14 years old.	Blood culture, Urinary antigen testing, serological testing for IgM antibodies dengue virus, *Leptospira* spp, Scrub typhus and *R.typhi* (did not meet serological case definition)	1 (4.0%)	137 (15.6%) positive blood culture	n.a.	*Salmonella enterica* serotype Typhi, *Salmonella enterica* Paratyphi A
Pattanaik and others 2012	India; 2008 - 2009	67	Teaching hospital	>15 years.	Blood culture, NAAT	1 (4.0%)	No positive results	n.a.	
Zimmerman and others 2008	Nepal, Kathmandu; Jan 2001 - March 2001 and July - August 2001	756	Urban, tertiary care hospital	>14 years old	R.typhi NAAT	1 (4.0%)	50 (6.6%) positive NAAT	n.a.	*R. typhi*
South East Asia									
Archibald and others 1999	Thailand, Bangkok; February 1997 - April 1997	246	Urban, referral, infectious disease hospital.	>15 years.	Blood culture (mycobacterial)	1 (4.0%)	119 (48.4%) positive blood culture	n.a.	*C. neoformans, Mycobacterium tuberculosis,* Non-typhoidal *Salmonella*

Blair and others 2010	Cambodia; December 2006 - December 2008	4,233	Two referral hospitals	> 2 years	Blood, throat and nasal specimen. rRT-NAAT, virus isolation, HI	1 (4.0%)	1151 (27.2%) with confirmed influenza	n.a.	
McDonald and others 1999	Thailand; February 1997 - March 1997 and August - September 1997	216	Urban, referral hospital in Thailand.	> 18 years	Mycobacterial blood culture	1 (4.0%)	20 (9.3%) positive blood culture	154 (71.3%) in Thailand	*Mycobacterium tuberculosis*
Cohen and others 2007	Thailand; February 2002 - February 2003	704	Four district rural hospitals	> 6 years. Primarily adults	Acute and convalescent serological examination for dengue virus, and *Leptospira* spp	2 (8.0%)	199 (28.3%) with confirmed serology	n.a.	Dengue virus, *Leptospira* spp

Note: n.a. = not applicable. NAAT = nucleic acid amplification test. BSI = bloodstream infection. MAT = microagglutination test. SFG = spotted fever group. TG = typhus group. IgM = immunoglobulin M. rRT = real-time reverse transcriptase. HI = hemagglutination inhibition.

a. Percentage represents the proportion of patients tested.

Web annex _B Studies of Febrile Illness Costs to Households and Health Care Providers

				Ambulatory cases (or unspecified)				Hospitalized cases			
Reference	**Country**	**Disease**	**Annual HH income (US$)[a] [[AQ: OK?]]**	**HH direct cost (US$)[b] [[AQ: OK?]]**	**Provider cost (US$) [[AQ: OK?]]**	**Aggregate direct cost (US$)[c] [[AQ: OK?]]**	**Indirect cost (% monthly HH income)[d]**	**HH direct cost (US$) [[AQ: OK?]]**	**Provider cost (US$) [[AQ: OK?]]**	**Aggregate direct cost (US$) [[AQ: OK?]]**	**Indirect cost (% monthly HH income)**
Vijayakumar 2013	India	Chikungunya	1,120	9	N.A.	9	36	N.A.	N.A.	N.A.	N.A.
Seyler 2010	India	Chikungunya	263	N.A.	N.A.	46	105	N.A.	N.A.	N.A.	N.A.
Saji 2009	India	Chikungunya	1,448	100	N.A.	100	75	N.A.	N.A.	N.A.	N.A.
Nandha	India	Chikungunya	1,266	6	N.A.	6	13	N.A.	N.A.	N.A.	N.A.
Shepard 2011	Philippines	Dengue	2,179	N.A.	N.A.	51	3	N.A.	N.A.	193	21
Suaya 2009	Venezuela	Dengue	6,598	N.A.	N.A.	95	25	N.A.	N.A.	644	39
Shepard	East Timor	Dengue	603	N.A.	N.A.	16	11	N.A.	N.A.	63	69

2011											
Suaya 2009	El Salvador	Dengue	4,314	N.A.	N.A.	43	18	N.A.	N.A.	538	18
Suaya 2009	Brazil	Dengue	6,092	N.A.	N.A.	88	84	N.A.	N.A.	573	121
Shepard 2011	Malaysia	Dengue	8,642	N.A.	N.A.	265	1	N.A.	N.A.	717	31
Suaya 2009	Panama	Dengue	6,351	N.A.	N.A.	113	65	N.A.	N.A.	1,020	83
Suaya 2009	Guatemala	Dengue	3,457	N.A.	N.A.	21	37	N.A.	N.A.	521	28
Shepard 2011	Bhutan	Dengue	2,123	N.A.	N.A.	48	9	N.A.	N.A.	187	6
Shepard 2011	Vietnam	Dengue	1,205	N.A.	N.A.	24	14	N.A.	N.A.	70	13
Shepard 2011	Indonesia	Dengue	3,052	N.A.	N.A.	69	2	N.A.	N.A.	257	3
Shepard 2011	Thailand	Dengue	5,122	N.A.	N.A.	159	4	N.A.	N.A.	635	13
Tam 2012	Vietnam	Dengue	1,205	192	N.A.	192	57	N.A.	N.A.	N.A.	N.A.
Shepard 2011	Laos	Dengue	1,031	N.A.	N.A.	27	32	N.A.	N.A.	100	66

Shepard 2011	Cambodia	Dengue	835	N.A.	N.A.	21	52	N.A.	N.A.	91	55
Shepard 2011	Myanmar	Dengue	761	N.A.	N.A.	21	9	N.A.	N.A.	77	19
Lutumba	DRC	HAT	445	10	N.A.	10	483	N.A.	N.A.	N.A.	N.A.
Guo 2011	China	Influenza	3,959	29	N.A.	29	8	N.A.	N.A.	N.A.	N.A.
Guo 2012	China	Influenza	3,959	37	N.A.	37		N.A.	N.A.	N.A.	N.A.
Clague 2006	Thailand	Influenza	2,212	8	N.A.	8	11	N.A.	N.A.	N.A.	N.A.
de Souza 2011	Brazil	Leptospirosis	2,723	N.A.	N.A.	N.A.	N.A.	N.A.	620	N.A.	36
Mustafa 2007	Sudan	Malaria	265	8	N.A.	8	18	N.A.	N.A.	N.A.	N.A.
Gatton 2004	Myanmar	Malaria	2,242	N.A.	N.A.	N.A.	11	N.A.	N.A.	N.A.	N.A.
Batwala 2011	Uganda	Malaria	253	1	3	4	8	N.A.	N.A.	N.A.	N.A.
Morel 2008	Vietnam	Malaria	1,231	1	N.A.	1	12	N.A.	N.A.	N.A.	N.A.
Deressa 2007	Ethiopia	Malaria	350	2	N.A.	2	23	N.A.	N.A.	N.A.	N.A.

Yukich 2012	Tanzania	Malaria	387	1	3	5	19	N.A.	N.A.	N.A.	N.A.
Ansah 2013	Ghana	Malaria	577	1	11	12	9	N.A.	N.A.	N.A.	N.A.
Bhengsri 2013	Thailand	Melioidosis	1,220	N.A.	N.A.	N.A.	N.A.	N.A.	879	901	39
Rammaert 2011	Cambodia	Melioidosis	676	N.A.	N.A.	N.A.	N.A.	577	N.A.	N.A.	N.A.
Poulos 2011	Indonesia	Typhoid	1,426	48	14	62	53	444	N.A.	444	287
Poulos 2011	China	Typhoid	1,195	73	N.A.	73	20	231	N.A.	N.A.	64
Bahl 2004	India	Typhoid	1,368	28	53	81	27	285	547	N.A.	277

Note: All dollar amounts are in 2012 U.S. dollars. HH = household. N.A. – data not available

a. Household annual income.

b. Household direct costs, medical and non-medical expenses.

c. Provider and household direct costs, including medical and non-medical expenses.

d. Indirect costs, comprising of productivity losses for patients and/or household carers, as a percentage of monthly household income

References

Aarsland, S. J., A. Castellanos-Gonzalez, K. P. Lockamy, R. Mulu-Droppers, M. Mulu, and others. 2012. "Treatable Bacterial Infections Are Underrecognized Causes of Fever in Ethiopian Children." *American Journal of Tropical Medicine & Hygiene* 87 (1): 128–33.

Abba, K., J. J. Deeks, P. Olliaro, C. M. Naing, S. M. Jackson, and others. 2011. "Rapid Diagnostic Tests for Diagnosing Uncomplicated *P. falciparum* Malaria in Endemic Countries." *Cochrane Database of Systematic Reviews* 7 (7): CD008122. doi: 10.1002/14651858.CD008122.pub2.

Abbasi, A., N. Butt, Q. H. Sheikh, A. R. Bhutto, S. M. Munir, and others. 2009. "Clinical Features, Diagnostic Techniques and Management of Dual Dengue and Malaria Infection." *Journal of the College of Physicians and Surgeons Pakistan* 19 (1): 25–29.

Acestor, N., R. Cooksey, P. N. Newton, D. Ménard, P. J. Guerin, and others. 2012. "Mapping the Aetiology of Non-Malarial Febrile Illness in Southeast Asia through a Systematic Review—Terra Incognita Impairing Treatment Policies." *PLoS One* 7 (9): e44269.

Afifi, S., K. Earhart, M. A. Azab, F. G. Youssef, H. El Sakka, and others. 2005. "Hospital-Based Surveillance for Acute Febrile Illness in Egypt: A Focus on Community-Acquired Bloodstream Infections." *The American Journal of Tropical Medicine and Hygiene* 73 (2): 392–99.

Ansah, E. K., M. Epokor, C. J. Whitty, S. Yeung, and K. S. Hansen. 2013. "Cost-Effectiveness Analysis of Introducing RDTs for Malaria Diagnosis as Compared to Microscopy and Presumptive Diagnosis in Central and Peripheral Public Health Facilities in Ghana." *The American Journal of Tropical Medicine and Hygiene* 89 (4): 724–36.

Arbiol, J., M. Borja, M. Yabe, H. Nomura, N. Gloriani, and others. 2013. "Valuing Human Leptospirosis Prevention Using the Opportunity Cost of Labor." *International Journal of Environmental Research and Public Health* 10 (5): 1845–60.

Archibald, L. K., M. O. den Dulk, K. J. Pallangyo, and L. B. Reller. 1998. "Fatal *Mycobacterium tuberculosis* Bloodstream Infections in Febrile Hospitalized Adults in Dar es Salaam, Tanzania." *Clinical Infectious Diseases* 26 (2): 290–96.

Archibald, L. K., L. C. McDonald, S. Rheanpumikankit, S. Tansuphaswadikul, A. Chaovanich, and others. 1999. "Fever and Human Immunodeficiency Virus Infection as Sentinels for Emerging Mycobacterial and Fungal Bloodstream Infections in Hospitalized Patients >/=15 Years Old, Bangkok." *The Journal of Infectious Diseases* 180 (1): 87–92.

Archibald, L. K., and L. B. Reller. 2001. "Clinical Microbiology in Developing Countries." *Emerging Infectious Diseases* 7 (2): 302–05.

Ayieko, P., and M. English. 2007. "Case Management of Childhood Pneumonia in Developing Countries." *The Pediatric Infectious Disease Journal* 26 (5): 432–40.

Baba, M., C. H. Logue, B. Oderinde, H. Abdulmaleek, J. Williams, and others. 2013. "Evidence of Arbovirus Co-Infection in Suspected Febrile Malaria and Typhoid Patients in Nigeria." *The Journal of Infection in Developing Countries* 7 (1): 51–59.

Bahl, R., A. Sinha, C. Poulos, D. Whittington, S. Sazawal, and others. 2004. "Costs of Illness due to Typhoid Fever in an Indian Urban Slum Community: Implications for Vaccination Policy." *Journal of Health, Population and Nutrition* 22 (3): 304–10.

Bassat, Q., J. Ordi, J. Vila, M. R. Ismail, C. Carrilho, and others. 2013. "Development of a Post-Mortem Procedure to Reduce the Uncertainty Regarding Causes of Death in Developing Countries." *The Lancet Global Health* 1 (3): e125–26.

Batwala, V., P. Magnussen, K. S. Hansen, and F. Nuwaha. 2011. "Cost-Effectiveness of Malaria Microscopy and Rapid Diagnostic Tests versus Presumptive Diagnosis: Implications for Malaria Control in Uganda." *Malaria Journal* 10 (1): 372.

Bell, M., L. K. Archibald, O. Nwanyanwu, H. Dobbie, J. Tokars, and others. 2001. "Seasonal Variation in the Etiology of Bloodstream Infections in a Febrile Inpatient Population in a Developing Country." *International Journal of Infectious Diseases* 5 (2): 63–69.

Bisoffi, Z., S. B. Sirima, F. Meheus, C. Lodesani, F. Gobbi, and others. 2011. "Strict Adherence to Malaria Rapid Test Results Might Lead to a Neglect of Other Dangerous Diseases: A Cost Benefit Analysis from Burkina Faso." *Malaria Journal* 10 (1): 226.

Blacksell, S. D., D. Bell, J. Kelley, M. P. Mammen, R. V. Gibbons, and others. 2007. "Prospective Study to Determine Accuracy of Rapid Serological Assays for Diagnosis of Acute Dengue Virus Infection in Laos." *Clinical and Vaccine Immunology* 14 (11): 1458–64.

Blacksell, S. D., N. P. Sharma, W. Phumratanaprapin, K. Jenjaroen, S. J. Peacock, and others. 2007. "Serological and Blood Culture Investigations of Nepalese Fever Patients." *Transactions of the Royal Society of Tropical Medicine & Hygiene* 101 (7): 686–90.

Blair, P. J., T. F. Wierzba, S. Touch, S. Vonthanak, X. Xu, and others. 2010. "Influenza Epidemiology and Characterization of Influenza Viruses in Patients Seeking Treatment for Acute Fever in Cambodia." *Epidemiology & Infection* 138 (2): 199–209.

Bossuyt, P. M., J. B. Reitsma, D. E. Bruns, C. A. Gatsonis, P. P. Glasziou, and others. 2003. "Towards Complete and Accurate Reporting of Studies of Diagnostic Accuracy: The STARD Initiative." *BMJ* 326 (7379): 41–44.

Breiman, R.F, L. Cosmas, H. Njuguna, A Audi, B. Olack, and others. 2012. "Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa." *PLoS One*. 7: e29119.

Buchanan, J., B. Mihaylova, A. Gray, and N. White. 2010. "Cost-Effectiveness of Pre-Referral Antimalarial, Antibacterial, and Combined Rectal Formulations for Severe Febrile Illness." *PLoS ONE* 5 (12): e14446.

Butler, D. 2010. "Verbal Autopsy Methods Questioned." *Nature* 467 (7319): 1015.

Caudron, J. M., N. Ford, M. Henkens, C. Macé, R. Kiddle-Monroe, and others. 2008. "Substandard Medicines in Resource-Poor Settings: A Problem that Can No Longer Be Ignored." *Tropical Medicine & International Health* 13 (8): 1062–72.

Chanda, P., F. Masiye, B. M. Chitah, N. Sipilanyambe, M. Hawela, and others. 2007. "A Cost-Effectiveness Analysis of Artemether Lumefantrine for Treatment of Uncomplicated Malaria in Zambia." *Malaria Journal* 6: 21.

Cheng, A.C., B.J. Currie. 2005. Melioidosis: Epidemiology, Pathophysiology, and management. *Journal of Clinical Microbiology*. 18(2): 383-416.

Chrispal, A., H. Boorugu, K. G. Gopinath, S. Chandy, J. A. Prakash, and others. 2010. "Acute Undifferentiated Febrile Illness in Adult Hospitalized Patients: The Disease Spectrum and Diagnostic Predictors: An Experience from a Tertiary Care Hospital in South India." *Tropical Doctor* 40 (4): 230–34.

Coast, J., R. D. Smith, and M. R. Millar. 1996. "Superbugs: Should Antimicrobial Resistance Be Included as a Cost in Economic Evaluation?" *Health Economics* 5 (3): 217–26.

Cohen, A.L. 2007. “Rapid Diagnostic Tests for Dengue and Leptospiroisis: Antibody Detection is Insentive at Presentaton Rapid Diagnostics Tests in the Tropics. *Tropical Medicine & International Health*. 12: 47-51.

Cook, J., D. Sur, J. Clemens, and D. Whittington. 2009. "Evaluating Investments in Typhoid Vaccines in Two Slums in Kolkata, India." *Journal of Health, Population and Nutrition* 27 (6): 711–24.

Crump, J. A. 2014. "Time for a Comprehensive Approach to the Syndrome of Fever in the Tropics." *Transactions of the Royal Society of Tropical Medicine & Hygiene* 108 (2): 61–62.

Crump, J. A., S. Gove, and C. M. Parry. 2011. "Management of Adolescents and Adults with Febrile Illness in Resource Limited Areas." *BMJ* 343: d4847.

Crump, J. A., A. B. Morrissey, W. L. Nicholson, R. F. Massung, R. A. Stoddard, and others. 2013. "Etiology of Severe Non-Malaria Febrile Illness in Northern Tanzania: A Prospective Cohort Study." *PLoS Neglected Tropical Diseases* 7 (7): e2324.

Crump, J. A., H. O. Ramadhani, A. B. Morrissey, W. Saganda, M. S. Mwako, and others. 2011. "Invasive Bacterial and Fungal Infections among Hospitalized HIV-Infected and HIV-Uninfected Adults and Adolescents in Northern Tanzania." *Clinical Infectious Diseases* 52 (3): 341–48.

Dean, A. S., L. Crump, H. Greter, E. Schelling, and J. Zinsstag. 2012. "Global Burden of Human Brucellosis: A Systematic Review of Disease Frequency." *PLoS Neglected Tropical Diseases* 6 (10): e1865.

Deen, J., L. von Seidlein, F. Andersen, N. Elle, N. J. White, and others. 2012. "Community-Acquired Bacterial Bloodstream Infections in Developing Countries in South and Southeast Asia: A Systematic Review." *The Lancet Infectious Diseases* 12 (6): 480–87.

de Oliveira, M. R., G. A. de Castro, and C. M. Toscano. 2010. "Cost Effectiveness of OptiMal® Rapid Diagnostic Test for Malaria in Remote Areas of the Amazon Region, Brazil." *Malaria Journal* 9 (1): 277.

Deressa, W., D. Hailemariam, and A. Ali. 2007. "Economic Costs of Epidemic Malaria to Households in Rural Ethiopia." *Tropical Medicine & International Health* 12 (10): 1148–56.

Dittrich, S., J. Castonguay-Vanier, C. E. Moore, N. Thongyoo, P. N. Newton, and others. 2014. "Loop-Mediated Isothermal Amplification for *Rickettsia typhi* (the Causal Agent of Murine Typhus): Problems with Diagnosis at the Limit of Detection." *Journal of Clinical Microbiology* 52 (3): 832–28.

Dougle, M. L., E. R. Hendriks, E. J. Sanders, and J. W. Dorigo-Zetsma. 1997. "Laboratory Investigations in the Diagnosis of Septicemia and Malaria." *The East African Medical Journal* 74 (6): 353–56.

English, M., D. Gathara, S. Mwinga, P. Ayieko, C. Opondo, and others. 2014. "Adoption of Recommended Practices and Basic Technologies in a Low-Income Setting." *Archives of Disease in Childhood* 99 (5): 452–56.

Esper, A. M., M. Moss, and G. S. Martin. 2009. "The Effect of Diabetes Mellitus on Organ Dysfunction with Sepsis: An Epidemiological Study." *Critical Care* 13 (1): R18.

Faruque, L. I., R. U. Zaman, A. S. Alamgir, E. S. Gurley, R. Haque, and others. 2012. "Hospital-Based Prevalence of Malaria and Dengue in Febrile Patients in Bangladesh." *The American Journal of Tropical Medicine and Hygiene* 86 (1): 58–64.

Faurholt-Jepsen, D., N. Range, G. PrayGod, K. Jeremiah, M. Faurholt-Jepsen, and others. 2013. "Diabetes Is a Strong Predictor of Mortality during Tuberculosis Treatment: A Prospective Cohort Study among Tuberculosis Patients from Mwanza, Tanzania." *Tropical Medicine & International Health* 18 (7): 822–29.

Feasey, N. A., G. Dougan, R. A. Kingsley, R. S. Heyderman, and M. A. Gordon. 2012. "Invasive Non-Typhoidal *Salmonella* Disease: An Emerging and Neglected Tropical Disease in Africa." *The Lancet* 379 (9835): 2489–99.

Feikin, D. R., B. Olack, G. M. Bigogo, A. Audi, L. Cosmas, and others. 2011. "The Burden of Common Infectious Syndromes at the Clinic and Household Level from Population-Based Surveillance in Rural and Urban Kenya." *PLoS ONE* 6 (1): e16085.

Figueiredo, M. A., L. C. Rodrigues, M. L. Barreto, J. W. Lima, M. C. Costa, and others. 2010. "Allergies and Diabetes as Risk Factors for Dengue Hemorrhagic Fever: Results of a Case Control Study." *PLoS Neglected Tropical Diseases* 4 (6): e699.

Girosi, F., S. S. Olmsted, E. Keeler, D. C. Burgess, Y. W. Lim, and others. 2006. "Developing and Interpreting Models to Improve Diagnostics in Developing Countries." *Nature* 444 (suppl 1): 3–8.

González-Canudas, J., J. M. Iglesias-Chiesa, Y. Romero-Antonio, C. Chávez-Cortes, J. G. Gay-Molina, and others. 2011. "Cost-Effectiveness in the Detection of Influenza H1N1: Clinical Data versus Rapid Tests." *Revista Panamericana de Salud Pública* 29 (1): 1–8.

Gordon, M. A., A. L. Walsh, M. Chaponda, D. Soko, M. Mbvwinji, and others. 2001. "Bacteremia and Mortality among Adult Medical Admissions in Malawi: Predominance of Non-Typhi Salmonellae and *Streptococcus pneumoniae*." *Journal of Infection* 42: 44–49.

Gravett, C. A., M. G. Gravett, E. T. Martin, J. D. Bernson, S. Khan, and others. 2012. "Serious and Life-Threatening Pregnancy-Related Infections: Opportunities to Reduce the Global Burden." *PLoS Medicine* 9 (10): e1001324.

Hume, J. C., G. Barnish, T. Mangal, L. Armázio, E. Streat, and others. 2008. "Household Cost of Malaria Overdiagnosis in Rural Mozambique." *Malaria Journal* 7: 33.

Huson, M. A., S. M. Stolp, T. van der Poll, and M. P. Grobusch. 2014. "Community-Acquired Bacterial Bloodstream Infections in HIV-Infected Patients: A Systematic Review." *Clinical Infectious Diseases* 58 (1): 79–92.

Hyams, K. C., E. C. Oldfield, R. M. Scott, A. L. Bourgeois, H. Gardiner, and others. 1986. "Evaluation of Febrile Patients in Port Sudan, Sudan: Isolation of Dengue Virus." *The American Journal of Tropical Medicine and Hygiene* 35 (4): 860–65.

Jennings, G. J., R. A. Hajjeh, F. Y. Girgis, M. A. Fadeel, M. A. Maksoud, and others. 2007. "Brucellosis as a Cause of Acute Febrile Illness in Egypt." *Transactions of the Royal Society of Tropical Medicine & Hygiene* 101 (7): 707–13.

Kaier, K., and U. Frank. 2010. "Measuring the Externality of Antibacterial Use from Promoting Antimicrobial Resistance." *Pharmacoeconomics* 28 (12): 1123–28.

Kapur, A., and A. D. Harries. 2013. "The Double Burden of Diabetes and Tuberculosis: Public Health Implications." *Diabetes Research and Clinical Practice* 101 (1): 10–19.

Kasper, M. R., T. F. Wierzba, L. Sovann, P. J. Blair, and S. D. Putnam. 2010. "Evaluation of an Influenza-Like Illness Case Definition in the Diagnosis of Influenza among Patients with Acute Febrile Illness in Cambodia." *BMC Infectious Diseases* 10 (1): 320.

Ki-Zerbo, G. A., F. Tall, K. Nagalo, E. Ledru, G. Durand, and others. 2000. "Séroprévalence des rickettsioses et de la fièvre Q chez les patients fébriles à l'hôpital de Bobo-Dioulasso (Burkina Faso)." *Médicine et Maladies Infectieuses* 30 (5): 270–74.

Knapp, S. 2013. "Diabetes and Infection: Is There a Link? A Mini-Review." *Gerontology* 59: 99–104.

Kourtis, A. P., J. S. Read, and D. J. Jamieson. 2014. "Pregnancy and Infection." *New England Journal of Medicine* 370 (23): 2211–18.

Kyabayinze, D. J., J. K. Tibenderana, G. W. Odong, J. B. Rwakimari, and H. Counihan. 2008. "Operational Accuracy and Comparative Persistent Antigenicity of HRP2 Rapid Diagnostic Tests for *Plasmodium falciparum* Malaria in a Hyperendemic Region of Uganda." *Malaria Journal* 7: 221.

Kyaw, S. S., T. Drake, R. Ruangveerayuth, W. Chierakul, N. J. White, and others. 2014. "Cost of Treating Inpatient *falciparum* Malaria on the Thai-Myanmar Border." *Malaria Journal* 13: 416.

Lancet. 2012. "New Estimates of Malaria Deaths: Concern and Opportunity." *The Lancet* 379 (9814): 385.

Lee, A., S. Mirrett, L. B. Reller, and M. C. Weinstein. 2007. "Detection of Bloodstream Infections in Adults: How Many Blood Cultures Are Needed?" *Journal of Clinical Microbiology* 45 (11): 3546–48.

Lim, C., P. Wannapinij, L. White, N. P. Day, B. S. Cooper, and others. 2013. "Using a Web-Based Application to Define the Accuracy of Diagnostic Tests when the Gold Standard Is Imperfect." *PLoS ONE* 8 (11): e79489.

Lofgren, S. M., E. J. Kirsch, V. P. Maro, A. B. Morrissey, L. J. Msuya, and others. 2012. "Histoplasmosis among Hospitalized Febrile Patients in Northern Tanzania." *Transactions of the Royal Society of Tropical Medicine & Hygiene* 106 (8): 504–07.

Loubiere, S., and J. P. Moatti. 2010. "Economic Evaluation of Point-of-Care Diagnostic Technologies for Infectious Diseases." *Clinical Microbiology and Infection* 16 (8): 1070–76.

Louie, J. K., M. Acosta, D. J. Jamieson, M. A. Honein, and California Pandemic (H1N1) Working Group. 2010. "Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California." *New England Journal of Medicine* 362 (1): 27–35.

Lubell, Y., H. Hopkins, C. J. Whitty, S. G. Staedke, and A. Mills. 2008. "An Interactive Model for the Assessment of the Economic Costs and Benefits of Different Rapid Diagnostic Tests for Malaria." *Malaria Journal* 7: 21.

Lubell, Y., A. J. Mills, C. J. Whitty, and S. G. Staedke. 2010. "An Economic Evaluation of Home Management of Malaria in Uganda: An Interactive Markov Model." *PLoS ONE* 5 (8): e12439.

Lubell, Y., H. Reyburn, H. Mbakilwa, R. Mwangi, S. Chonya, and others. 2008. "The Impact of Response to the Results of Diagnostic Tests for Malaria: Cost-Benefit Analysis." *BMJ* 336 (7637): 202–25.

Lubell, Y., A. Riewpaiboon, A. M. Dondorp, L. von Seidlein, O. A. Mokuolu, and others. 2011. "Cost-Effectiveness of Parenteral Artesunate for Treating Children with Severe Malaria in Sub-Saharan Africa." *Bulletin of the World Health Organization* 89 (7): 504–12.

Lubell, Y., S. Yeung, A. M. Dondorp, N. P. Day, F. Nosten, and others. 2009. "Cost-Effectiveness of Artesunate for the Treatment of Severe Malaria." *Tropical Medicine & International Health* 14 (3): 332–27.

Machado, C. R., E. S. Machado, R. D. Rohloff, M. Azevedo, D. P. Campos, and others. 2013. "Is Pregnancy Associated with Severe Dengue? A Review of Data from the Rio de Janeiro Surveillance Information System." *PLoS Neglected Tropical Diseases* 7 (5): e2217.

Mayxay, M., J. Castonguay-Vanier, V. Chansamouth, A. Dubot-Pérès, D. H. Paris, and others. 2013. "Causes of Non-Malarial Fever in Laos: A Prospective Study." *The Lancet Global Health* 1 (1): e46–54.

McDonald, L. C., L. K. Archibald, S. Rheanpumikankit, S. Tansuphaswadikul, B. Eampokalap, and others. 1999. "Unrecognised *Mycobacterium tuberculosis* Bacteraemia among Hospital Inpatients in Less Developed Countries." *The Lancet* 354 (9185): 1159–63.

McGready, R., E. A. Ashley, V. Wuthiekanun, S. O. Tan, M. Pimanpanarak, and others. 2010. "Arthropod Borne Disease: The Leading Cause of Fever in Pregnancy on the Thai-Burmese Border." *PLoS Neglected Tropical Diseases* 4 (11): e888.

Meheus, F., M. Balasegaram, P. Olliaro, S. Sundar, S. Rijal, and others. 2010. "Cost-Effectiveness Analysis of Combination Therapies for Visceral Leishmaniasis in the Indian Subcontinent." *PLoS Neglected Tropical Diseases* 4 (9): e818.

Meremo, A., S. E. Mshana, B. R. Kidenya, R. Kabangila, R. Peck, and others. 2012. "High Prevalence of Non-Typhoid *Salmonella* Bacteraemia among Febrile HIV Adult Patients Admitted at a Tertiary Hospital, North-Western Tanzania." *International Archives of Medicine* 5 (1): 28.

Morel, C. M., N. D. Thang, N. X. Xa, L. X. Hung, L. K. Thuan, and others. 2008. "The Economic Burden of Malaria on the Household in South-Central Vietnam." *Malaria Journal* 7: 166.

Mori, M., R. Ravinetto, and J. Jacobs. 2011. "Quality of Medical Devices and In Vitro Diagnostics in Resource-Limited Settings." *Tropical Medicine & International Health* 16 (11): 1439–49.

Mueller, T. C., S. Siv, N. Khim, S. Kim, E. Fleischmann, and others. 2014. "Acute Undifferentiated Febrile Illness in Rural Cambodia: A 3-Year Prospective Observational Study." *PLoS ONE* 9 (4): e95868.

Muller, L. M., K. J. Gorter, E. Hak, W. L. Goudzwaard, F. G. Schellevis, and others. 2005. "Increased Risk of Common Infections in Patients with Type 1 and Type 2 Diabetes Mellitus." *Clinical Infectious Diseases* 41 (3): 281–88.

Murdoch, D. R., C. W. Woods, M. D. Zimmerman, P. M. Dull, R. H. Belbase, and others. 2004. "The Etiology of Febrile Illness in Adults Presenting to Patan Hospital in Kathmandu, Nepal." *The American Journal of Tropical Medicine and Hygiene* 70 (6): 670–75.

Murray, C. J., K. F. Ortblad, C. Guinovart, S. S. Lim, T. M. Wolock, and others. 2014. "Global, Regional, and National Incidence and Mortality for HIV, Tuberculosis, and Malaria during 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013." *The Lancet* 384 (9947): 1005–70.

Mustafa, M. H., and M. A. Babiker. 2007. "Economic Cost of Malaria on Households during a Transmission Season in Khartoum State, Sudan." *Eastern Mediterranean Health Journal* 13 (6): 1298–307.

Nadjm, B., B. Amos, G. Mtove, J. Ostermann, S. Chonya, and others. 2010. "WHO Guidelines for Antimicrobial Treatment in Children Admitted to Hospital in an Area of Intense *Plasmodium falciparum* Transmission: Prospective Study." *BMJ* 340: c1350. doi: 10.1136/bmj.c1350.

Newton, P. N., F. M. Fernandez, M. D. Green, J. Primo-Carpenter, and N. J. White. 2009. "Counterfeit and Substandard Anti-Infectives in Developing Countries." In *Antimicrobial Resistance in Developing Countries*, edited by A. de J. Sosa, D. K. Byarugaba., C. F. Amábile-Cuevas, P-R. Hsueh, S. Kariuki, and I. N. Okeke, 413–46. New York: Spinger.

Newton, P. N., M. D. Green, F. M. Fernández, N. P. Day, and N. J. White. 2006. "Counterfeit Anti-Infective Drugs." *The Lancet Infectious Diseases* 6 (9): 602–13.

Olliaro, P., S. Darley, R. Laxminarayan, and S. Sundar. 2009. "Cost-Effectiveness Projections of Single and Combination Therapies for Visceral Leishmaniasis in Bihar, India." *Tropical Medicine & International Health* 14 (8): 918–25.

Park, S-W., C. S. Lee, C. K. Lee, Y. G. Kwak, C. Moon, and others. 2011. "Severity Predictors in Eschar-Positive Scrub Typhus and Role of Serum Osteopontin." *The American Journal of Tropical Medicine and Hygiene* 85 (5): 924–30.

Parker, T. M., C. K. Murray, A. L. Richards, A. Samir, T. Ismail, and others. 2007. "Concurrent Infections in Acute Febrile Illness Patients in Egypt." *The American Journal of Tropical Medicine and Hygiene* 77 (2): 390–92.

Pattanaik, S. S., R. Tripathy, A. K. Panda, A. N. Sahu, and B. K. Das. 2012. "Bacteraemia in Adult Patients Presenting with Malaria in India." *Acta Tropica* 123 (2): 136–38.

Peacock, S. J., and P. N. Newton. 2008. "Public Health Impact of Establishing the Cause of Bacterial Infections in Rural Asia." *Transactions of the Royal Society of Tropical Medicine & Hygiene* 102 (1): 5–6.

Penno, E. C., S. J. Baird, and J. A. Crump. 2015. "Cost-Effectiveness of Surveillance for Bloodstream Infections for Sepsis Management in Low-Resource Settings." *The American Journal of Tropical Medicine and Hygiene*: in press. **[[AQ: Update info when published.]]**

Penno, E. C., J. A. Crump, and S. J. Baird. 2015. "Performance Requirements to Achieve Cost-Effectiveness of Point-of-Care Tests for Sepsis among Patients with Febrile Illness in Low-Resource Settings." *The American Journal of Tropical Medicine and Hygiene*: in press. **[[AQ: Update info when published.]]**

Petit, P. L., J. V. Haarlem, M. Poelman, M. C. Haverkamp, and I. A. Wamola. 1995. "Bacteraemia in Patients Presenting with Fever." *The East African Medical Journal* 72 (2): 116–20.

Petti, C. A., C. R. Polage, T. C. Quinn, A. R. Ronald, and M. A. Sande. 2006. "Laboratory Medicine in Africa: A Barrier to Effective Health Care." *Clinical Infectious Diseases* 42 (3): 377–82.

Phommasone, K., D. H. Paris, T. Anantatat, J. Castonguay-Vanier, S. Keomany, and others. 2013. "Concurrent Infection with Murine Typhus and Scrub Typhus in Southern Laos: The Mixed and the Unmixed." *PLoS Neglected Tropical Diseases* 7 (8): e2163.

Poulos, C., R. Bahl, D. Whittington, M. K. Bhan, J. D. Clemens, and others. 2004. "A Cost-Benefit Analysis of Typhoid Fever Immunization Programmes in an Indian Urban Slum Community." *Journal of Health, Population and Nutrition* 22 (3): 311–21.

Prabhu, M., W. L. Nicholson, A. J. Roche, G. J. Kersh, K. A. Fitzpatrick, and others. 2011. "Q Fever, Spotted Fever Group, and Typhus Group Rickettsioses among Hospitalized Febrile Patients in Northern Tanzania." *Clinical Infectious Diseases* 53 (4): e8–e15.

Prasad, N., D. R. Murdoch, H. Reyburn, and J. A. Crump. 2015. "Etiology of Severe Febrile Illness in Low- and Middle-Income Countries: A Systematic Review." *PLoS ONE* 10 (6): e0127962.

Prasad, N., K. J. Sharples, D. R. Murdoch, and J. A. Crump. 2015. "Community Prevalence of Fever and Relationship with Malaria among Infants and Children in Low-Resource Areas." *The American Journal of Tropical Medicine and Hygiene* 93 (1): 178–80.

Punjabi, N. H., W. R. Taylor, G. S. Murphy, S. Purwaningsih, H. Picarima, and others. 2012. "Etiology of Acute, Non-Malaria, Febrile Illnesses in Jayapura, Northeastern Papua, Indonesia." *The American Journal of Tropical Medicine and Hygiene* 86 (1): 46–51.

Rammaert, B., J. Beauté, L. Borand, S. Hem, P. Buchy, and others. 2011. "Pulmonary Melioidosis in Cambodia: A Prospective Study." *BMC Infectious Diseases* 11: 126.

Reddy, E. A., A. V. Shaw, and J. A. Crump. 2010. "Community-Acquired Bloodstream Infections in Africa: A Systematic Review and Meta-Analysis." *The Lancet Infectious Diseases* 10 (6): 417–32.

Reyburn, H., R. Mbatia, C. Drakeley, I. Carneiro, E. Mwakasungula, and others. 2004. "Overdiagnosis of Malaria in Patients with Severe Febrile Illness in Tanzania: A Prospective Study." *BMJ* 329 (7476): 1212–15.

Riley, L. W., M. L. Cohen, J. E. Seals, M. J. Blaser, K. A. Birkness, and others. 1984. "Importance of Host Factors in Human Salmonellosis Caused by Multiresistant Strains of *Salmonella*." *The Journal of Infectious Diseases* 149 (6): 878–83.

Robays, J., M. E. Raguenaud, T. Josenando, and M. Boelaert. 2008. "Eflornithine Is a Cost-Effective Alternative to Melarsoprol for the Treatment of Second-Stage Human West African Trypanosomiasis in Caxito, Angola." *Tropical Medicine & International Health* 13 (2): 265–71.

Rubach, M. P., V. P. Maro, J. A. Bartlett, and J. A. Crump. 2015. "Etiologies of Illness among Patients Meeting Integrated Management of Adolescent and Adult Illness District Clinician Manual Criteria for Severe Infections in Northern Tanzania: Implications for Empiric Antimicrobial Therapy." *The American Journal of Tropical Medicine and Hygiene* 92 (2): 454–62.

Sanders, E. J., P. Mugo, H. A. Prins, E. Wahome, A. N. Thiong'o, and others. 2014. "Acute HIV-1 Infection Is as Common as Malaria in Young Febrile Adults Seeking Care in Coastal Kenya." *AIDS* 28 (9): 1357–63.

Say, L., D. Chou, A. Gemmill, O. Tunçalp, A. B. Moller, and others. 2014. "Global Causes of Maternal Death: A WHO Systematic Analysis." *The Lancet Global Health* 2 (6): e323–33.

Shillcutt, S., C. Morel, C. Goodman, P. Coleman, D. Bell, and others. 2008. "Cost-Effectiveness of Malaria Diagnostic Methods in Sub-Saharan Africa in an Era of Combination Therapy." *Bulletin of the World Health Organization* 86 (2): 101–10.

Shirima, G.M. S. Cleveland, R.R. Kazwala, D.M. Kambarage, N. French, and others. 2007. Seroprevalence of brucellosis in smallholder dairy, agropastoral, pastoral, beef ranch and wildlife animals in Tanzania. *Bulletin of Animal Health and Production in Africa.* 55: 13-21.

Smit, P. W., I. Elliott, R. W. Peeling, D. Mabey, and P. N. Newton. 2014. "An Overview of the Clinical Use of Filter Paper in the Diagnosis of Tropical Diseases." *The American Journal of Tropical Medicine and Hygiene* 90 (2): 195–210.

Ssali, F. N., M. R. Kamya, F. Wabwire-Mangen, S. Kasasa, M. Joloba, and others. 1998. "A Prospective Study of Community-Acquired Bloodstream Infections among Febrile Adults Admitted to Mulago Hospital in Kampala, Uganda." *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 19 (5): 484–89.

Suputtamongkol, Y., W. Chaowagul, P. Chetchotisakd, N. Lertpatanasuwun, S. Intaranongpai, and others. 1999. "Risk Factors for Melioidosis and Bacteremic Melioidosis." *Clinical Infectious Diseases* 29 (2): 408–13.

Suputtamongkol, Y., W. Pongtavornpinyo, Y. Lubell, C. Suttinont, S. Hoontrakul, and others. 2010. "Strategies for Diagnosis and Treatment of Suspected Leptospirosis: A Cost-Benefit Analysis." *PLoS Neglected Tropical Diseases* 4 (2): e610.

Tabernero, P., F. M. Fernández, M. Green, P. J. Guerin, and P. N. Newton. 2014. "Mind the Gaps: The Epidemiology of Poor-Quality Anti-Malarials in the Malarious World: Analysis of the WorldWide Antimalarial Resistance Network Database." *Malaria Journal* 13: 139.

Thomsen, R. W., H. H. Hundborg, H. H. Lervang, S. P. Johnsen, H. C. Schønheyder, and others. 2005. "Diabetes Mellitus as a Risk and Prognostic Factor for Community-Acquired Bacteremia due to Enterobacteria: A 10-Year,

Population-Based Study among Adults." *Clinical Infectious Diseases* 40 (4): 628–31.

Vallée, J. T. Thaojaikong, C.E. Moore, R. Phetsouvanh, A.L Richards, and others. 2010. "Contrasting spatial distribution and risk factors for past infection with scrub typhus and murine typhus in Vientiane City, Lao PDR." *PLoS Neglected Tropical Diseases.* Dec 7(12): e909.

Van den Berghe, G., A. Wilmer, G. Hermans, W. Meersseman, P. J. Wouters, and others. 2006. "Intensive Insulin Therapy in the Medical ICU." *New England Journal of Medicine* 354 (5): 449–61.

Vanderburg, S., M. P. Rubach, J. E. Halliday, S. Cleaveland, E. A. Reddy, and others. 2014. "Epidemiology of *Coxiella burnetii* Infection in Africa: A OneHealth Systematic Review." *PLoS Neglected Tropical Diseases* 8 (4): e2787.

Wardrop, N.A. C.C. Kuo, H.C. Wang, A.C. Clements, F.F. Lee, and others. 2013. "Bayesian Spatial Modelling and the Significance of Argricultural Land Use to Scrub Typhus Infection in Taiwan. *Geospatial Health.* Nov 8 (1): 229-239.

White, M. T., L. Conteh, R. Cibulskis, and A. C. Ghani. 2011. "Costs and Cost-Effectiveness of Malaria Control Interventions: A Systematic Review." *Malaria Journal* 10: 337.

White, L. J., P. N. Newton, R. J. Maude, W. Pan-ngum, J. R. Fried, and others. 2012. "Defining Disease Heterogeneity to Guide the Empirical Treatment of Febrile Illness in Resource Poor Settings." *PLoS One* 7 (9): e44545.

WHO (World Health Organization). 1997. "Joint United Nations Programme on HIV/AIDS (UNAIDS)–WHO Revised Recommendations for the Selection and Use of HIV Antibody Tests." *Weekly Epidemiological Record* 72 (12): 81–88.

———. 2006. *Guidelines for the Treatment of Malaria*. Geneva: WHO.

———. 2008. "Consultation on Technical and Operational Recommendations for Clinical Laboratory Testing Harmonization and Standardization." Report of consensus meeting of major stakeholders, Maputo, Mozambique, January 22–24.

———. 2009. *Integrated Management of Adolescent and Adult Illness (IMAI) Acute Care: Guidelines for First-Level Facility Health Workers at Health Centre and District Outpatient Clinic*. WHO/CDS/IMAI/2004.1, Rev. 3. Geneva: WHO. http://www.who.int/hiv/pub/imai/acute_care.pdf?ua=1.

———. 2010a. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a Public Health Approach: 2010 Revision*. Geneva: WHO.

———. 2010b. *Guidelines for the Treatment of Malaria, 2nd Edition*. Geneva: WHO.

———. 2010c. *Guidelines for the Treatment of Tuberculosis, 4th Edition*. Geneva: WHO.

——— . 2011a. *IMAI District Clinician Manual. Hospital Care for Adolescents and Adults: Guidelines for the Management of Illnesses with Limited Resources*. Geneva: WHO.

———. 2011b. *Malaria Rapid Diagnostic Test Performance. Results of WHO Product Testing of Malaria RDTs: Round 3 (2010–2011)*. Geneva: WHO.

——— . 2013. *World Malaria Report 2013*. Geneva: WHO .

WHO (World Health Organization) and UNAIDS (Joint United Nations Programme on HIV/AIDS). 2007. *Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities*. Geneva: WHO

Wiseman, V., M. Kim, T. K. Mutabingwa, and C. J. Whitty. 2006. "Cost-Effectiveness Study of Three Antimalarial Drug Combinations in Tanzania." *PLoS Medicine* 3 (10): e373.

Yazdanbakhsh, M., and P. G. Kremsner. 2009. "Influenza in Africa." *PLoS Medicine* 6 (12): e1000182.

Yukich, J., V. D'Acremont, J. Kahama, N. Swai, and C. Lengeler. 2010. "Cost Savings with Rapid Diagnostic Tests for Malaria in Low-Transmission Areas: Evidence from Dar es Salaam, Tanzania." *The American Journal of Tropical Medicine and Hygiene* 83 (1): 61–68.

Zimmerman, M. D., D. R. Murdoch, P. J. Rozmajzl, B. Basnyat, C. W. Woods, and others. 2008. "Murine Typhus and Febrile Illness, Nepal." *Emerging Infectious Diseases* 14 (10): 1656–59.

Zurovac, D., B. A. Larson, W. Akhwale, and R. W. Snow. 2006. "The Financial and Clinical Implications of Adult Malaria Diagnosis Using Microscopy in Kenya." *Tropical Medicine & International Health* 11 (8): 1185–94.

Notes

[1] WHO estimates the global burden of disease through its Global Health Estimates (GHE) database, available at http://www.who.int/healthinfo/global_burden_disease/en/. The Institute for Health Metrics and Evaluation (IHME) produces the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study. However, some of the IHME's findings have been controversial: for example, it estimated in 2012 that 1.24 million people had died from malaria worldwide in 2010, double the WHO estimate (*The Lancet* 2012).

[2] CD4 (cluster of differentiation 4) refers to a T-lymphocyte surface antigen; CD4-positive T-lymphocytes depletion in HIV infection is associated with HIV comorbidities

[3] All costs are in 2012 U.S. dollars.