Chapter **14**

Febrile Illness in Adolescents and Adults

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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 both for identifying the likely cause and for 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 absence 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). In countries historically highly endemic for malaria, fever is controlled and managed with vertical programs. However, a growing number of fever etiology studies (Prasad, Murdoch, and others 2015; 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) and expansion of nonmalarial infections such as dengue (Stanaway and others 2016), combined with widespread use of malaria diagnostic tests (WHO 2010b), mean that health care workers face a growing proportion of patients with fever and a negative malaria diagnostic test. This increase is troubling because patients presenting to hospitals with fever not due to malaria are as likely to die as those who have malaria (Reyburn and others 2004). Furthermore, vertical programs exist rarely for febrile illnesses other than malaria.

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 its cost-effectiveness. We highlight the needs for increasing etiologic research, restructuring of burden-of-disease estimates to recognize nonmalarial fever, and development of approaches to evaluating clinical interventions to improve patient outcomes.

BURDEN OF DISEASE FROM NONMALARIAL FEBRILE ILLNESS

No estimate has been made 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

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the effect size of interventions for fevers is challenging. Disability-adjusted life years (DALYs), including 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 (IHME).[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, for example, chikungunya, leptospirosis, and Q fever.

Thus, 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 on 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 limited ability to distinguish deaths caused by malaria from other conditions with fever. Verbal autopsy may classify febrile deaths as due to malaria in malaria-endemic areas. Many causes of febrile illness are not available for assignment by verbal autopsy. Even with a positive malaria diagnostic test, deaths assigned to cerebral malaria may be found to be due to other causes on autopsy (Mallewa and others 2007). 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 have recommended that malaria treatment decisions be based on the result of malaria diagnostic tests (WHO 2010b). For patients with positive malaria diagnostic tests, health care workers would prescribe antimalarial treatment and consider co-infections as described in detail in chapter 12 of this volume (Shretta and others 2017). However, for those patients with negative malaria diagnostic tests, health care workers often lack the epidemiological information or laboratory services necessary to support rational diagnostic and management decisions (Crump, Gove, and Parry 2011).

Etiology of Nonmalarial Fever

Annex 14A lists studies conducted from 1980 through 2013 of the etiology of severe febrile illness among, predominantly, adolescents and adults. Key features of studies undertaken in Africa (N = 16) and South and South-East Asia (N = 11) are described below (Prasad, Murdoch, and others 2015). These studies illustrate both many data gaps and sufficient geographic and seasonal heterogeneity in the etiology of fevers to require subnational empiric treatment guidelines (White and others 2012). The studies also confirm the need for guidelines to respond to changes over time in the etiology of febrile illness and in antimicrobial resistance of relevant pathogens.

Geography

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 estimating pathogen-specific attributable fractions.

Reddy, Shaw, and Crump (2010) conducted a systematic review of prospective studies of the etiology of community-acquired bloodstream infection in Africa. Their findings are as follows:

- Of 58,296 patients enrolled in 22 eligible studies 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*, of which 553 (63.0 percent) were *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 not often sought, 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 was responsible for 2 percent to 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 South-East Asia
Although a relatively large number of studies have examined the epidemiology of single diseases in Asia—for example, typhoid, scrub typhus, and melioidosis—they cover relatively few sites that are concentrated in South-East Asia (Acestor and others 2012). Vast knowledge gaps persist for China and India, with no studies examining the 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 South-East 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 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 ages 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 nonfebrile persons accompanying febrile patients to health centers, a potential pathogen was identified in 40.4 percent of participants, 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 ages 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 bacteremia (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 etiologies in children and adults were similar, but the data were not stratified by outpatients and inpatients.

With regard to patient management, 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 (RDTs) 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 South-East Asia. Relative to Africa, brucellosis and Q fever appear to be less important. Consensus is greatly needed 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 summarizing and comparing data between sites difficult. The lack of reports from China and India is 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 they would require. The situation suggests that a new model is needed for infectious disease diagnostic facilities in the rural tropics—not one copied from high-income countries (HICs) but a model 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 14.1.

Table 14.1 Febrile Illness Considerations for Special Groups

Group	Disease	Comments	References
Pregnant women	*Plasmodium falciparum* and *Listeria monocytogenes* are more common. Hepatitis E and herpes simplex virus disease, malaria, and influenza are more severe. Dengue, scrub typhus, and typhoid fever may be more severe. Obstetric sepsis.	Few data are available on etiology and impact of nonmalarial fevers on mother, fetus, and infant. Some antimicrobials that are important for treatment of bacterial pathogens are contraindicated in pregnancy.	Gravett and others 2012; Kourtis, Read, and Jamieson 2014; Louie and others 2010; Machado and others 2013; McGready and others 2010; Say and others 2014
HIV infection	Invasive bacterial and fungal infections, including *Cryptococcus neoformans*, *C. grubii*, nontyphoidal *Salmonella enterica*, and *Mycobacterium tuberculosis* are more common. Acute HIV infection may be common among persons seeking care for fever in areas with concentrated or generalized epidemics.	Knowledge of patient's HIV infection status assists in differential diagnosis of febrile illness; provider-initiated HIV testing is recommended. Few data are available on interaction between HIV and several febrile illnesses.	Huson and others 2014; Reddy, Shaw, and Crump 2010; Sanders and others 2014; WHO and UNAIDS 2007
Diabetes	Tuberculosis, infections with Enterobacteriaceae, lower respiratory tract infection, urinary tract infection, skin and mucous membrane infection, and melioidosis are more common. Poorer outcomes occur with tuberculosis and infections with Enterobacteriaceae.	Hyperglycemia impairs antibacterial function of neutrophils and T cell–mediated immune response. Few data are available from low-resource settings. Few data are available on interaction between diabetes and several febrile illnesses such as leptospirosis and rickettsial infections.	Esper, Moss, and Martin 2009; Faurholt-Jepsen and others 2013; Figueiredo and others 2010; Kapur and Harries 2013; Knapp 2013; Muller and others 2005; Park and others 2011; Suputtamongkol and others 1999; Thomsen and others 2005; Van den Berghe and others 2006

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Table 14.1 Febrile Illness Considerations for Special Groups (continued)

Group	Disease	Comments	References
Malaria	Nontyphoidal *S. enterica* bloodstream infection and other bacteremias are more common.	Positive malaria film may mean malaria is the cause of current illness, a cofactor in a concurrent infection, or an incidental finding. *P. falciparum* malaria rapid diagnostic tests may remain positive for a month or more after clearance of parasites.	Abba and others 2011; Feasey and others 2012; Kyabayinze and others 2008; Nadjm and others 2010
Occupational and other exposures	Rural residence increases risk for leptospirosis, melioidosis, scrub typhus, and spotted fever group rickettsioses. Pastoralist animal husbandry practices increase risk for brucellosis. Q fever is more common among livestock keepers and abattoir workers. Urban residence is associated with enteric fever and murine typhus.	Knowledge of patient's occupational and exposure history assists in differential diagnosis of febrile illness.	Breiman and others 2012; Cheng and Currie 2005; Shirima and others 2007; Vallée and others 2010; Wardrop and others 2013

Note: HIV = human immunodeficiency virus.

Diagnosis and Treatment of Specific Infections

The initial challenge for managing the febrile patient is deciding whether an antimicrobial agent is indicated and, if so, 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 14.2.

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

Inadequate Diagnostic Capacity

Because of the relative paucity of investment in and understanding of febrile illnesses, accurate, accessible point-of-care tests (POCTs) are currently inadequate, and evaluations of their diagnostic accuracy and cost-effectiveness are insufficient. Although whole-genome sequencing of pathogens is now commonly performed in research settings in both HICs and low- and middle-income countries (LMICs), 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 deficiency is in part due to intrinsic difficulties such as low bacterial blood load (Dittrich and others 2014) but also due to a lack of investment in targeted diagnostic research and development. 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 such tests can be developed.

Poor Quality of Diagnostics 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 2009). The evidence regarding antimalarials suggests severe quality issues (Tabernero and others 2014), but data regarding diagnostic tests, vaccines, and other classes of medicines are limited.

The only long-term sustainable solution to the poor quality of diagnostics and therapeutic products would be the dramatic strengthening of the authorities that regulate medicines 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. Furthermore, they should be aware that poor patient outcomes may reflect poor-quality medicines, both substandard and falsified, rather than the disease process itself.

Table 14.2 Nonmalarial Febrile Diseases: Exposure, Diagnosis, Prevention, and Treatment

Disease type	Subgroup	Exposure	Diagnosis	Prevention	Treatment
Arbovirus infections	Dengue	Arthropod vectors	• Detection of antibody and NS1 antigen • Fourfold rise in antibody titer • Demonstration of virus in blood by nucleic acid amplification test	– Mosquito avoidance – Vector control – Vaccine	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 body fluid by nucleic acid amplification test	– Mosquito avoidance – Vector control – Vaccine	Supportive
	Other (for example, chikungunya)	Arthropod vectors	• Culture or nucleic acid amplification test from serum or tissue • Fourfold rise in antibody titer • Demonstration of virus in tissue by immunohistochemistry or nucleic acid amplification test	– Mosquito avoidance – Vector control	Supportive
Bloodstream infection	Enteric fever	Fecally contaminated water or food	• Blood culture	– Improved water, sanitation, and food safety – Detection and treatment of infected persons – Vaccines	Fluoroquinolones, extended-spectrum cephalosporins, or azithromycin, according to local patterns of susceptibility
	Melioidosis	Exposure to contaminated soil and water	• Blood culture • Culture of throat swab, pus, and other bodily fluids	– Management of exposure to environmental sources – Management of predisposing conditions	• 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	– Varies by pathogen	Antimicrobials according to local patterns of susceptibility

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Table 14.2 Nonmalarial Febrile Diseases: Exposure, Diagnosis, Prevention, and Treatment (continued)

Disease type	Subgroup	Exposure	Diagnosis	Prevention	Treatment
Brucellosis	n.a.	Exposure to infected animals and their products	• Fourfold rise in antibody titer by microagglutination test • Nucleic acid amplification test • Blood culture	– Control in animal husbandry – Management of exposure among occupational groups at high risk – Food safety, including pasteurization of dairy products	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	– Control in animal husbandry and rodent control – Management of exposure among occupational groups at high risk – Management of exposure to environmental sources	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	– Control in animal husbandry – Management of exposure among occupational groups at high risk – Food safety	Tetracyclines
Rickettsioses	n.a.	Arthropod vectors, vary by pathogen species	• Fourfold rise in antibody titer by immunofluorescence assay • Nucleic acid amplification test • Culture	– Prevention of exposure to vectors – Use of prophylactic tetracyclines in very high risk groups	Tetracyclines

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

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 first-level outpatient clinics, provide guidance on the management of febrile patients (WHO 2009). Management of febrile adolescents and adults at first-level facilities is based on current WHO guidelines for the treatment of malaria (WHO 2010b) and described in detail in chapter 12 of this volume (Shretta and others 2017).

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 subjected 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 limited capacity of human and other resources.

Diagnostic Approaches

Laboratory services have been a neglected component of health services in low-resource areas (Archibald and Reller 2001; Petti and others 2006), and 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, malaria, and tuberculosis (WHO 2010a, 2010b, 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 co-infections 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 cultures 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 more expensive than manual methods. 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 and dengue remain complex, expensive, and limited to a few supranational reference laboratories mostly in HICs. In LMICs, their use has been restricted to a few studies done predominantly in large cities, where conditions differ from those in the vast rural areas (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 in which 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 has minimal clinical utility for a sample taken seven days after fever onset.

A consensus statement—perhaps linked to the Standards for Reporting of Diagnostic Accuracy (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 their evaluation (Lim and others 2013). Use of filter paper and POCTs as storage matrices for both serological and molecular diagnosis may be a practical way forward in LMICs (Fhogartaigh and others 2015; 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 common occurrence of mixed or concurrent infections (Phommasone and others 2013). However, the laboratory diagnosis and management of mixed infections is challenging. Reports of mixed infections often use only serological criteria. However, the problems of antibody persistence and interspecies cross-reaction raise uncertainty about whether these results represent true mixed infections, sequential infections, or cross-reactions. Hence, reports of mixed infections should include explicit discussions 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. With regard to 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 *Salmonella* Typhi and *Burkholderia pseudomallei.* Combination therapy may be problematic because of antagonism, such as if bacteriostatic and bactericidal antimicrobials are given in parallel, or adverse reactions.

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 its 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 key drivers of health expenditures and productivity losses. However, no data are available on the economic impact of common diseases such as brucellosis and scrub typhus 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 to be a small fraction of the full burden, because pathogens such as *B. pseudomallei* and *Orientia tsutsugamushi* are unlikely to be detected outside well-equipped hospitals.

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 14.1 and annex 14B). The largest impact is often associated with household productivity losses rather than direct medical costs, a particular concern for adult patients. For melioidosis, the known burden is concentrated among adult agricultural workers; therefore, the economic impact on rural households can be particularly hard. Among hospitalized patients with typhoid fever in India and Indonesia, productivity losses have been as high as 15 percent to 20 percent of annual income (Bahl and others 2004; Poulos and others 2004).

Tellingly, household and provider costs are lower for malaria than for other febrile illnesses among both ambulatory and admitted patients. This finding is evident from both indirect cost-of-illness comparisons and from studies comparing the costs 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 between malaria and nonmalaria illness 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 malaria-endemic world at low cost. Second, the strengthening of distribution mechanisms in the public and private sectors has helped 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 the impact of these illnesses 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 2009). However, there is virtually no guidance as to the cost-effectiveness of diagnostics and treatments for febrile illnesses other than malaria.

Figure 14.1 Direct and Indirect Costs of Febrile Illnesses in Adolescents and Adults, by Illness, 2012

Note: Average household income as reported in the original studies; where not reported, 2012 GDP per capita are used (http://data.worldbank.org/indicator/NY.GDP.PCAP.CD?). Circle size indicates the direct cost of illness, which includes both household and provider direct medical and nonmedical 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 percent of annual household income. Most malaria episodes on the bottom left consumed an equivalent of 1 percent to 3 percent 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.

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

Major policy changes by the 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 anti-malarials 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 over preexisting monotherapies (Chanda and others 2007; Wiseman and others 2006) and of

artesunate over quinine for severe malaria (Lubell and others 2009; Lubell and others 2011). Reviews of the cost-effectiveness of preventive interventions for malaria such as insecticide-treated bednets, indoor residual spraying, and intermittent preventive treatment can be found elsewhere (White and others 2011).

Only a few economic evaluations have been carried out on diagnoses and treatments of nonmalarial fevers in the context of LMICs (detailed in annex 14C). This scarcity stems from the dearth of relevant POCTs and treatments that warrant evaluation. Other than dengue and influenza POCTs, no tests have been deemed sufficiently accurate and appropriate for use in routine care. Few advances have been made in recent years for the treatment of nonmalarial fevers, with the exception of new combination therapies for visceral leishmaniasis.

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

- Leptospirosis tests compared with empiric treatment with doxycycline (Suputtamongkol 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)
- 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 non-malarial 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 first-level hospitals 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 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.

POCTs for Sepsis among Patients with Febrile Illnesses in Low-Resource Settings

Similarly, distinguishing patients with sepsis from those with other illnesses remains a challenge. Management decisions are based on clinical assessment using algorithms such as the WHO's 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 POCT-driven management.

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 equivalence with clinical assessment with regard to survival but costing US$1.14 less per life saved. A POCT with sensitivity and specificity of 100 percent, slightly superior to those of the best malaria RDTs, 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

Lubell and others (2016) considered 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 Lao PDR (Mayxay and others 2013), the proportion of patients that would be correctly treated with an antimicrobial under each of the approaches was estimated as was the cost-effectiveness of the tests.

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

- Patients with positive dengue test results are not prescribed an antimicrobial.
- Patients with positive scrub typhus test results are prescribed an effective antimicrobial, for example, tetracycline or macrolide.
- Where a pathogen-specific test is negative, antimicrobials are prescribed at random to 38 percent of patients, resembling current practice, with the choice of antibiotic resembling current practice as observed in Mayxay and others (2013).

• Patients with CRP levels below the threshold of 20 milligrams per liter do not receive an antimicrobial; those above the threshold do, with the choice of antibiotic resembling current practice.

The approaches were first evaluated for their ability to classify patients as requiring treatment. Then their ability to guide the choice of antimicrobials, with regard to pathogen susceptibility to the different drugs, was incorporated. Patients with positive scrub typhus tests are therefore assumed to receive doxycycline; for other treated patients, the choice of antimicrobial is made at random based on the frequency of their (often inappropriate) use in current practice.

The analysis suggests that use of either pathogen-specific test offered modest improvements over current practice in the ability to classify patients as requiring an antimicrobial (figure 14.2). The dengue RDT implied a reduction in antimicrobials prescribed for viral infections but a larger proportion of bacterial infections going untreated, while the reverse was true for the scrub typhus test. Use of the CRP test implied both reductions in the use of antimicrobials in viral infections and fewer bacterial infections going untreated. These advantages were consistent despite variation of all model parameters, including the incidence of infections and baseline antimicrobial prescription practices, and when accounting for the uncertainty surrounding the accuracy of the tests (figure 14.2, panel a).

The incremental costs and DALYs averted from the output of 500 simulations and the corresponding cost-effectiveness acceptability curves are shown in figure 14.3, illustrating that both the scrub typhus and the CRP tests are likely to be cost-effective, despite the considerable uncertainty surrounding many model parameters.

The analysis suggests that pathogen-specific tests can improve the management of nonmalarial fevers, but their utility and cost-effectiveness are highly sensitive to contextual factors such as heterogeneity of fever etiologies and preexisting prescription patterns. Testing for pathogens for which there are no immediate treatment implications, such as dengue, might not offer a direct health benefit over current practice. However, this approach does not account for factors such as patient reassurance in having a confirmed diagnosis, raising of awareness of possible danger signs, outbreak detection, or initiation of measures for vector control. Testing for bacterial pathogens can guide the use of appropriate antimicrobials; therefore, testing could be a cost-effective approach, but cost-effectiveness varies widely depending on local etiology. Testing for biomarkers of inflammation could offer an approach to targeting antimicrobials in rural settings that is cost-effective and robust to heterogeneity in causes of fevers

Figure 14.2 Antimicrobial Targeting Using Lao PDR Data across a Range of Simulated Incidences and Test Accuracies
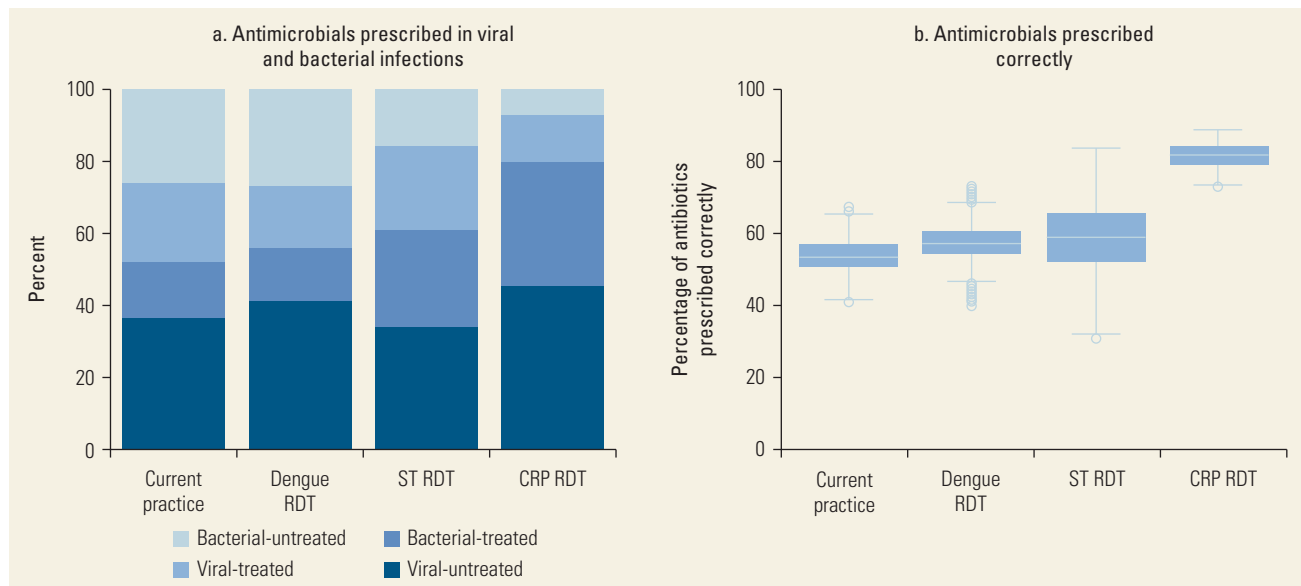
Source: Lubell and others 2016; Mayxay and others 2013.
Note: CRP = C-reactive protein; RDT = rapid diagnostic test; ST = scrub typhus. In panel b, the shaded boxes represent the interquartile ranges of simulated outputs, with the median marked by the mid-way horizontal line. The whiskers represent the simulation outputs closest to 1.5 times the interquartile range, with the remaining outliers shown as independent circles.

Figure 14.3 Cost-Effectiveness Plane and Cost-Effectiveness Probability Curves for the Three Strategies When Compared with a Baseline of Current Practice
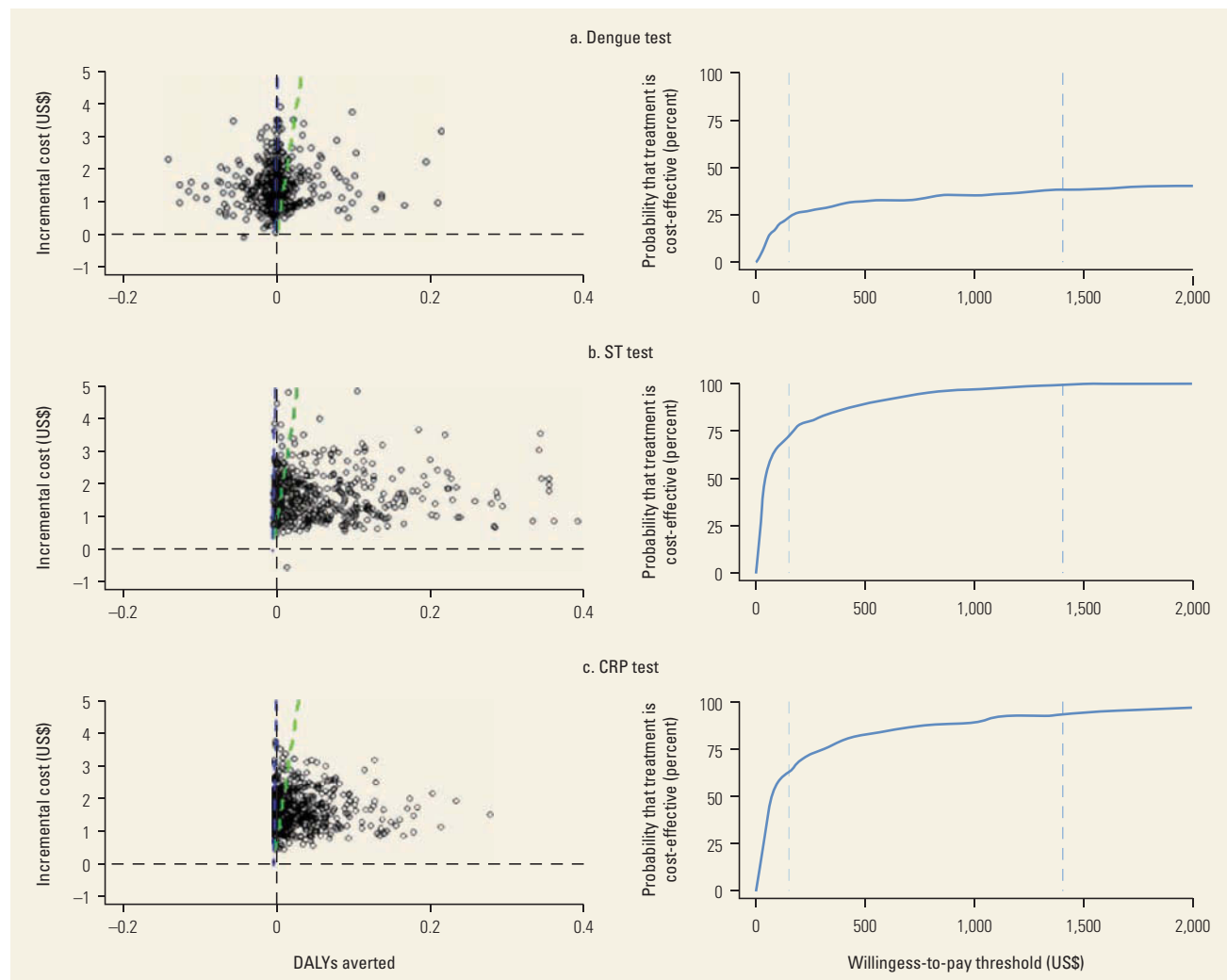
Note: CRP = C-reactive protein; DALY = disability-adjusted life year; ST = scrub typhus. The blue solid lines indicate a willingness-to-pay threshold of US$1,400, approximating Lao PDR's 2012 GDP per capita; the green dashed line is a much more conservative willingness-to-pay threshold of US$150. The dengue test in most instances was associated with worse health outcomes and higher costs. The scrub typhus test averted on average 0.07 DALYs as compared with current practice, and the CRP test averted on average 0.05 DALYs as compared with current practice, with median incremental cost-effectiveness ratios of US$59 and US$110, respectively. When accounting for parameter uncertainty, the scrub typhus and CRP tests are approximately 90 percent and 80 percent likely, respectively, to be cost-effective at a willingness-to-pay threshold of US$1,400.

and host factors typical of the rural tropics, but realizing the full potential gains of this approach requires locally appropriate empirical treatment guidelines.

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, seasonal, and ethnic diversity; includes a broad range of treatable or preventable pathogens and their antimicrobial susceptibility patterns; uses standardized case definitions and diagnostic assays; and uses a control group to estimate attributable fractions. The findings of such research would better apprise health care workers about the prior probability of specific infections in their area and would contribute data relevant to burden-of-disease assessments for infections that currently lack robust estimates of illness and death.

Researchers should also consider structuring burden-of-disease estimates for febrile illness without

localizing features similarly to estimates for diarrhea and pneumonia. Data from fever etiology research could be applied to the syndrome-wide envelope of DALYs and deaths for febrile illness to develop pathogen-specific estimates. Such an approach would provide the basis for estimating 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 RDTs 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 most other causes of fever do not approach the performance of the best malaria RDTs (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 the 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 as clinical evaluation to avoid antimicrobial overuse and excessive costs.

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

Necessary Elements for Cost-Effectiveness Analyses

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

- Inclusion of the intervention's implications for all febrile patients rather than for a subset with specific pathogens of interest
- Inclusion of factors affecting the intervention's performance in real-life settings
- Framing of the evaluations within specified etiological contexts and exploration of the implications of heterogeneity

- Extension of the analyses, where appropriate, to include the implications for ongoing pathogen transmission
- Accounting for the intervention's 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 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, such as the provision of antimicrobials to treatable bacterial infections. In contrast, there was some apprehension that the benefits of malaria POCTs were overestimated in cost-effectiveness analyses, particularly in high-transmission areas, where 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, diagnostic test 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 in 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 intervention's 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 point implies that the suitability of many pathogen-specific tests will vary by etiological setting, both seasonally and spatially. This circumstance is a challenge to effective policy making but also an opportunity to vastly improve the efficient allocation of scarce resources.

Extension of Analyses to Include Implications for Pathogen Transmission

One important 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 focus can avoid many of the uncertainties that often pervade dynamic transmission models, the more-conservative results of such analyses could unduly penalize an intervention that would be an efficient use of resources if the indirect health benefits associated with reduced transmission were to be considered.

Inclusion of Intervention's 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 the absence of such measurements, presumptive treatment will almost always dominate as long as the purchase cost of the drugs is less than that of the diagnostics employed to determine 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 US$7–17 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. We recommend the following in descending order of priority:

1. Develop accurate pathogen-specific and bacterial disease biomarker POCTs for causes of fever other than malaria.
2. Improve the identification and management of patients with bacterial and fungal sepsis and those with tetracycline-responsive infections to avert morbidity and mortality from febrile illness.
3. Undertake comprehensive, standardized, and coordinated fever etiology research in low-resource areas to identify priorities for improvements in management, such as selection of empiric antimicrobials, and for control of causes of fever other than malaria.
4. Gather more cost and outcome data and improve approaches to cost-effectiveness analyses related to fever to strengthen resource-stratified approaches to adoption and integration of interventions in the emerging field of nonmalarial febrile illness.
5. Support surveillance for bloodstream infections and antimicrobial resistance in low-resource areas.
6. Explore burden-of-disease structures that capture febrile illnesses as a group to estimate the effect size of interventions for fevers.

ANNEXES

The annexes to this chapter are as follows. They are available at http://www.dcp-3.org/infectiousdiseases.

- Annex 14A. Etiology of Severe Febrile Illness: Studies of Adolescents and Adults, by Region, 1980–2013
- Annex 14B. Studies of Febrile Illness Costs to Households and Health Care Providers
- Annex 14C. Studies Reporting the Cost-Effectiveness of Diagnostics and Treatments for Nonmalarial Fevers

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

1. The WHO estimates the global burden of disease through its Global Health Estimates 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 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-lymphocyte depletion in HIV infection is associated with HIV comorbidities.

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

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