

Chapter 8

Diagnosis and Treatment of the Febrile Child

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INTRODUCTION

Fever is one of the most common presenting symptoms of pediatric illnesses. Fever in children under age five years signifies systemic inflammation, typically in response to a viral, bacterial, parasitic, or less commonly, a noninfectious etiology. Patients’ ages and geographic settings can help direct the appropriate diagnostic approach and treatment, if local epidemiology is well understood.

The combined proportion of deaths due to AIDS, diarrheal diseases, pertussis, tetanus, measles, meningitis/encephalitis, malaria, pneumonia and sepsis was 58.5 percent for children ages 1–59 months in 2015; it was 23.4 percent for neonates (Liu and others 2016, chapter 4 of this volume). Evidence regarding fever incidence is variable, with country-specific reports from cross-sectional surveys or weekly active case detection ranging from two to nine febrile episodes per child under age five years per year, a mean of 5.88 fever episodes per child under age five years per year (Gething and others 2010). National survey data from 42 Sub-Saharan African countries (excluding Botswana, Cabo Verde, Eritrea, and South Africa) were collected and analyzed for an estimated 655.6 million under-five fever episodes in 2007; 32 percent of these episodes occurred in 11 outpatient units in the Democratic Republic of Congo, Ethiopia, and Nigeria (Gething and others 2010). At the health facility and community levels, fever is by far the most common pediatric presenting symptom.

Multiple studies summarized in table 8.1 highlight the most common presenting symptoms at the facility and community levels.

Before the availability of affordable and accurate malaria rapid diagnostic tests (RDTs), most health care providers in malaria-endemic countries presumed that malaria was the cause of fever; the proportion of fevers due to malaria was very high in the early 1990s, and the priority was to reduce malaria mortality by any means.

The 1997 World Health Organization’s (WHO’s) initial Integrated Management of Childhood Illness (IMCI) guidelines recommended the use of injectable antimalarials and antibiotics in children in malaria-endemic areas who were suspected of having severe disease with the presence of danger signs (Gove 1997; Communicable Disease Surveillance and Response Vaccines and Biologicals 1997). Until 2010, the first edition of the WHO guidelines for the treatment of malaria recommended empiric, oral, antimalarial therapy for fever without other source in children under age five years living in malaria-endemic areas (WHO 2006). The decline of malaria incidence; rise of antimicrobial resistance; and availability of accurate, low-cost, point-of-care diagnostics have challenged the effectiveness of the presumptive treatment of febrile illnesses and reopened the discussion of the most accurate and cost-effective approaches for fever diagnosis and treatment. There are settings with very high malaria transmission and limited availability of diagnostic test where presumptive treatment would

Table 8.1 Clinical Findings and Final Classification in Studies on Integrated Management of Fevers

	Level of health care									
	Health facilities (outpatients)					Community health workers (children < 5 years)				
Reference	Gouws and others 2004	Gouws and others 2004	Gouws and others 2004	D'Acremont and others 2011	D'Acremont and others 2011	D'Acremont and others 2014	Shao and others 2011	Rowe and others 2001	Mukanga, Tiono, and Anyorigiya 2012	Mukanga, Tiono, and Anyorigiya 2012
Year(s) of study	2000	2000	2002	2007-08	2007-08	2008	2011	1997-2002	2009	2009
Country	Tanzania	Uganda	Brazil	Tanzania	Tanzania	Tanzania	Tanzania	Kenya	Uganda	Burkina Faso
Algorithm used	Original IMCI	Original IMCI	Original IMCI	Usual care	Usual care	Modified IMCI	Modified IMCI	Original IMCI	iCCM	iCCM
Age group (years)	< 5	< 5	< 5	< 5	> 5	< 10	< 5	< 5	< 5	< 5
Total number of patients	419	516	653	1,270	1,254	1,005	842	7,151	182	525
% with one or more danger signs	—	—	—	—	—	5	—	10	—	—
% who required referral	—	—	—	—	—	8	—	17	—	—
% with fever	76	81	29	84	74	100	73	88	—	—
% positive RDT results among febrile patients	—	—	—	—	—	10	3	—	78	74
% with cough	35	33	52	46	24	46	53	44	—	48
% with difficult breathing	—	—	—	2	1	2	—	—	—	—

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Table 8.1 Clinical Findings and Final Classification in Studies on Integrated Management of Fevers (continued)

Reference	Level of health care											
	Health facilities (outpatients)						Community health workers (children < 5 years)					
	Gouws and others 2004	Gouws and others 2004	Gouws and others 2004	D'Acromont and others 2011	D'Acromont and others 2011	D'Acromont and others 2014	Shao and others 2011	Rowe and others 2001	Mukanga, Tiono, and Anyorigiya 2012	Mukanga, Tiono, and Anyorigiya 2012	Mukanga, Tiono, and Anyorigiya 2012	2009
Year(s) of study	2000	2000	2002	2007–08	2007–08	2008	2011	1997–2002	2009	2009	2009	2009
% with fast breathing among those with cough	—	—	—	—	—	40	22	—	—	44	—	24
% with chest indrawing among those with cough	—	—	—	—	—	2	—	—	—	—	—	—
% with pneumonia	28	31	3	—	—	18	12	—	35	—	—	—
% with diarrhea	24	34	17	17	6	10	18	22	—	26	—	36
% with blood in stools among those with diarrhea	—	—	—	—	—	5	1	—	—	—	—	—
% with ear pain	—	—	—	2	1	1	1	—	—	—	—	—
% with measles	—	—	—	—	0.1	0	0.8	—	—	—	—	—
% with skin problems	—	—	—	7	3	8	10	—	—	—	—	—
% with more than one diagnostic classification	—	—	—	—	—	—	—	36	29	33	—	22

Source: WHO 2013a. Reproduced with permission.

Note: — = not available; iCCM = Integrated Community Case Management; IMCI = Integrated Management of Childhood Illness; RDT = rapid diagnostic test.

be most practical and cost-effective (*D'ACP3* volume 6, Babigumira, forthcoming). In 2009, experts debated whether sufficient information was available to abandon presumptive treatment guidelines and move to an emphasis on diagnosis before treatment (D'Acromont, Lengeler, and Genton 2007; D'Acromont and others 2009; English and others 2009).

Mounting evidence demonstrated the decline of *Plasmodium falciparum* infections in response to intense national and multinational initiatives to control malaria. In 2012 more than US\$2.5 billion was invested from global partners, including the Global Fund to Fight AIDS, Tuberculosis and Malaria; the World Bank Malaria Booster Program; the U.S. President's Malaria Initiative; the Bill & Melinda Gates Foundation's Malaria Control and Evaluation Partnership in Africa; and the Roll Back Malaria Partnership (D'Acromont, Lengeler, and Genton 2010; Feachem and others 2010; Leslie and others 2012; WHO 2013a). Countries with previously defined high-transmission regions are reporting decreasing malaria incidence, making the management of nonmalarial fevers critically important (Feachem and others 2010; WHO 2013a; Hertz and others 2013; Ishengoma and others 2011).

In 2010, the WHO revised its fever treatment guidelines to recommend antimalarial treatment only for those with a positive malaria test result, either point-of-care or microscopy (WHO 2010a). This new strategy is being implemented in the public sector in most Sub-Saharan African countries (Bastiaens and others 2011). However, many patients first present for care in the informal private sector, and more research is needed to better understand treatment decision making in this context and how to reduce overuse of antimicrobials and ensure appropriate care. The epidemiology of pediatric febrile illness is undoubtedly shifting; understanding the etiology of nonmalarial fevers in each context is the logical next step to improve pediatric clinical outcomes of other treatable serious febrile illnesses, such as pneumonia, sepsis, bacterial meningitis, enteric fever, rickettsioses, and influenza. Given rampant and expanding antimicrobial drug resistance globally, care must be taken to use antibiotics only when indicated and to develop careful guidelines when resources are limited. Present guidelines are based on clinical features that are unfortunately poorly predictive of the diseases causing fever. Low-cost, accurate, point-of-care diagnostics are needed to determine which children can benefit from antibacterial therapies to guide the most effective use of antibiotics.

This chapter discusses the evidence that informs current etiologies of fever, stratified by regional geography. It presents the clinical presentation, diagnosis, and treatment of the most common diseases, with special considerations for certain age groups, the burden of disease for different

conditions, classification and treatment strategies, and a review of available diagnostic tests. In addition, different health systems approaches to diagnosis and treatment of the febrile child at the community and health-facility levels are discussed, as is the evidence base for WHO-sponsored approaches such as IMCI and Integrated Community Case Management (iCCM). Fever in adults and RDT use for malaria are discussed further in volume 6 (Holmes, Bertozzi, Bloom, Jha, and Nugent, forthcoming).

ETIOLOGY OF FEVER IN CHILDREN UNDER AGE FIVE YEARS

Infectious etiologies of fever differ according to age and geographic region. Recent evidence from multiple health care and low- and middle-income country (LMIC) settings confirms that viral infections are predominantly responsible for fever within all age groups (Animut and others 2009; Crump and others 2013; D'Acromont and others 2014; Kasper and others 2012; Mayxay and others 2013). The studies described in table 8.2 used different study designs with significant variation in study population, case definitions, and available diagnostics. Although these studies are informative, they need to be interpreted in the context of the individual study design and context. Following are common themes across the available research:

- Predominance of acute respiratory infections (ARIs) in outpatient visits for fever
- Identification of multiple pathogens after molecular laboratory investigations, making it difficult to declare a specific diagnosis
- High proportion of fever etiologies due to viral pathogens when appropriate viral diagnostic tests are available; studies without viral diagnostics reveal a high proportion of undiagnosed febrile illnesses
- Clinically overestimated malaria, compared with RDT or microscopy-confirmed diagnosis.

Although the available evidence suggests that most viral and some specific bacterial diseases, such as rickettsiosis and leptospirosis, are likely to be underdiagnosed, data are either not available or are limited from several countries where the fever burden is highest, such as the Democratic Republic of Congo, India, and Nigeria. Ongoing surveillance of fever etiology in multiple representative geographies to establish trends in predominant pathogens and to identify emerging infections early would be ideal. Additionally, little research is available on fever etiology of young infants (age 0–2 months); a concerted research effort is underway to better understand the distribution

Table 8.2 Summary of Evidence for Etiology of Fever Studies

		World Bank region								
		Sub-Saharan Africa		South Asia						
Study		D'Acremont and others (2014)	Crump and others (2013)	Animut and others (2009)	WHO 2013a	Nijama-Meya and others (2007)	Mayxay and others (2013)	WHO 2013a	WHO 2013a	Kasper and others (2012)
Study setting		Tanzania: One urban and one rural outpatient clinic	Tanzania, hospitalized patients	Four outpatient clinics in Gojjam zone in northwest Ethiopia	Zanzibar, Tanzania	Uganda, study clinic within a referral third-level hospital	Lao PDR, two province-level hospitals	Pakistan, small peripheral clinic	Cambodia, setting unknown	Cambodia, nine outpatient clinics in south central region
Study design		N = 1,005 (younger than age 10 years with fever)	N = 467 (ages 2 months to 13 years)	N = 653 (ages 3–17 years)	N = 677 cases, 200 controls (ages 2–59 months)	N = 1,602 (less than age 10 years with fever in last 24 hours)	N = 1,938 (ages 5 months to 49 years) with fever	N = 1,248 febrile episodes, all ages	N = 1,193 febrile patients, all ages, 282 controls	N = 9,997 patients with fever, all ages, median 13 years
		Computer-generated diagnosis using history, physical, and wide array of lab investigations	Diagnoses by case definitions and convalescent serum at four to six weeks post discharge	Diagnoses by IMCI classifications plus laboratory investigations	Diagnoses by laboratory investigations	Clinical diagnoses for RDT or microscopy negative for malaria per local clinical guidelines	Case definition plus laboratory investigations	Case definition plus laboratory investigations	Tested for malaria, leptospirosis, rickettsial diseases, scrub typhus, dengue, influenza, and bacteremia	Lab investigations of respiratory secretions, blood, serum
Most common diagnoses		62 percent ARI (5 percent chest X-ray-confirmed pneumonia)	1.3 percent malaria 3.4 percent bacteremia 0.9 percent fungemia	62 percent malaria 7 percent clinical pneumonia	26 percent watery diarrhea 2 percent bloody diarrhea	10 percent diarrhea	8 percent dengue 7 percent scrub typhus	47 percent ARI 23 percent diarrhea or dysentery	32 percent RDT-confirmed malaria 68 percent RDT-negative	19.9 percent PCR-confirmed influenza 7.2 percent microscopy-confirmed malaria 6.3 percent bacteremia
		11.9 percent nasopharyngeal viral infection	Zoonotic: 2 percent brucellosis 7.7 percent leptospirosis 2.6 percent Q fever	Serologically diagnosed: 5.8 percent typhoid 5.1 percent typhus 2.6 percent brucellosis	5 percent skin infections 0.2 percent malaria 65 percent ARI's: 57 percent pneumonia 9 percent tonsillitis	47 percent URI 29 percent common cold 12 percent pharyngitis 4 percent pneumonia 1 percent otitis media	6 percent Japanese encephalitis virus 6 percent leptospirosis 2 percent bacteremia less than 3 percent malaria confirmed by microscopy or RDT	17 percent enteric fever 0.5 percent UTI 0.4 percent malaria	76 percent URI 0.6 percent LRI 17 percent enteric fever	microscopy-confirmed malaria 6.3 percent bacteremia

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Table 8.2 Summary of Evidence for Etiology of Fever Studies (continued)

		World Bank region			
		Sub-Saharan Africa		South Asia	
3.7 percent typhoid fever	7.4 percent spotted fever rickettsial disease	4 percent otitis	2 percent UTIs	Six-month testing for influenza:	
1.5 percent skin/mucosal infections	10 percent chikungunya virus	31 percent other ARI (54 percent viral, 12 percent bacterial, 18 percent unknown)	8 percent skin infections	32 percent influenza-positive	
0.2 percent meningitis					
Undiagnosed (percent)	3.2	64	15	59	62
Multiple diagnoses (percent)	22.6	Unknown	Unknown	Unknown	Unknown
Notes	Availability of extensive viral diagnostics correlated with clinical diagnoses	Limited viral testing. High prevalence of zoonoses; consider different empiric antibiotic regimens	Limited testing for bacterial illnesses such as typhoid	Role of influenza during outbreak	Clinical presentation and lab diagnoses did not always correlate; many pathogens found in similar rates in controls
		Of the viral ARIs most common PCR results: 16 percent RSV 9 percent influenza (A/B) 9 percent rhinovirus	High proportion of enteric disease	3.5 more than one pathogen identified	

Note: ARI = acute respiratory infection; IMC = Integrated Management of Childhood Illness; LRI = lower respiratory tract infection; PCR = polymerase chain reaction; RDT = rapid diagnostic test; RSV = respiratory syncytial virus; URI = upper respiratory tract infection; UTI = urinary tract infection.

of infections in young infants via the Aetiology of Neonatal Infection in South Asia research group, which is building on results from the WHO Young Infants Study Group and the WHO Young Infants Clinical Signs Study Group (YICSSG) (WHO Young Infants Study Group 1999; YICSSG 2008). Infection-related neonatal deaths contributed at least 10 percent to overall mortality in children under age five years in 2013 (Liu and others 2015).

DIAGNOSIS AND TREATMENT OF COMMON CHILDHOOD FEBRILE ILLNESSES

Febrile Illnesses in Young Infants

Infection-related mortality and morbidity for young infants from birth to age 59 days is one of the most challenging health issues to address; signs and symptoms are often nonspecific, and illnesses can rapidly progress to severe disease. Care seeking for young infant illness often occurs too late or not at all, making community-based efforts critical to increasing access to early treatment and addressing this disproportionate morbidity and mortality. Using the CHERG estimates, sepsis (15 percent) and pneumonia (6 percent) are the highest infection-related contributors to neonatal death, with tetanus and diarrheal disease both contributing approximately 1 percent (chapter 4 in this volume, Liu and others 2016). None of the etiology studies discussed in table 8.2 captures the causes of fever in the young infant age group.

Sepsis

Sepsis in young infants presents in two varieties: early onset (fewer than seven days after birth) and late onset (seven days or more). Early-onset neonatal sepsis is thought to be the result of exposure to pathogens in the maternal birth canal; late-onset sepsis is thought to be secondary to environmental exposures. Symptoms of bacteremia and related sepsis in young infants are often vague and may include fever, hypothermia, poor tone, jaundice, or inability to suck. A decrease in urine production, poor perfusion, bulging fontanelle, excessive sleepiness, or alternatively, excessive irritability are signs of more serious disease. Without antibiotic treatment, many young infants will rapidly progress to severe bacterial sepsis, which may prove fatal.

A review by Ganatra and Zaidi (2010) of five neonatal sepsis studies reports incidences of blood culture-confirmed early-onset sepsis ranging from 2.2 to 9.8 per 1,000 live births, and clinical sepsis incidence ranging from 20.7 to 50 per 1,000 live births. Two of these

studies report case fatality rates (CFRs) of 18 percent and 19 percent (Ganatra and Zaidi 2010). A systematic review that included 27 hospital-based studies of the etiology of neonatal sepsis reports CFRs in children younger than 60 days as low as 3 percent in Europe and as high as 70 percent in South-East Asia (Waters and others 2011).

Although a positive blood culture is the gold standard for diagnosing bacteremia, cultures are known to lack sensitivity, especially in children, and may take several hours to days before results are available; cultures require significant laboratory infrastructure, which is a challenge in low-resource settings. Total leukocyte count, leukocyte differential, levels of acute phase reactants (for example, C-reactive protein), and screening panels using a variety of cytokine markers may provide supportive evidence of infection when abnormal, but these measures have been shown to have limited value in diagnosing bacteremia (Remington and others 2006).

According to a systematic review of 27 studies performed by Waters and others (2011), the most common documented pathogens for early-onset sepsis (N = 282 isolates) include *Escherichia coli* (16.3 percent), *Staphylococcus aureus* (11.7 percent), nonpneumococcal streptococcal species (8.5 percent), *Klebsiella* species (7.8 percent), *Pseudomonas* species (7.8 percent), Group B streptococcus (GBS; 6.7 percent), *Acinetobacter* species (6.7 percent), and *Streptococcus pneumoniae* (4.6 percent). The distribution of pathogens for late-onset sepsis (N = 1,784) was similar to early onset but with notably less GBS (1.7 percent) and a higher proportion of *Serratia* species (2.2 percent), *Salmonella* species (1.5 percent), *H. influenzae* (1.7 percent), and *Neisseria meningitidis* (0.7 percent). Overall, there was a similar proportion of gram-positive isolates (34.4 percent early onset, 34.6 percent late onset) compared with gram-negative isolates (63.8 percent early onset, 60.5 percent late-onset) (Waters and others 2011). These results suggest that empiric antibiotic regimens for both early- and late-onset sepsis should be broad spectrum to treat both gram-positive and -negative infections.

Meningitis, Herpes Simplex Virus, and Urinary Tract Infections

In addition to bacteremia, a young infant presenting with a nonfocal fever should be evaluated for meningitis and urinary tract infections (UTIs). A lumbar puncture to check for pleocytosis (an elevated number of white blood cells in cerebral spinal fluid), elevated protein, or low glucose levels can indicate whether infection is present in the central nervous system.

Herpes simplex virus-2 (HSV-2) may cause encephalitis, an infection more common in the first three

weeks of life secondary to exposure via the birth canal. HSV-2 is responsible for genital herpes, the prevalence of which is rising globally; it is of particular concern in HIV-endemic countries where genital ulcers increase risk of human immunodeficiency virus (HIV) transmission. HSV-2 seroprevalence has been measured at roughly 50 percent in many LMICs (WHO, UNAIDS, and LSHTM 2001). Many newborns are exposed to HSV-2 in asymptomatic mothers, making surveillance for neonatal HSV-2 a challenge. Further research is needed to determine whether HSV-2 is a major contributor to neonatal morbidity and mortality in LMICs.

UTIs are best evaluated by urine culture; in low-resource settings, point-of-care urinalysis can provide potentially valuable information. The presence of leukocyte esterase, blood, or nitrates may suggest a bacterial urinary infection, however, only if the urine sample is not contaminated. The difficulty of obtaining a sterile sample from a young infant has made implementation of this test less feasible in the community setting. UTIs are the most common reason for nonfocal fever in young infants; urinary vesicoureteral reflux is associated with higher risk (Byington and others 2003; Greenhow and others 2014).

Group B Streptococcus Disease

GBS (*Streptococcus agalactiae*) is a bacterium that can cause bacteremia, sepsis, pneumonia, and meningitis in newborns. GBS may present as early-onset disease, which is usually due to transmission from a colonized mother immediately before or during delivery, and late-onset disease (later than seven days of age), at which time infection may be acquired from the mother or environmental sources. Overall, the CFR tends to be high (9.6 percent), with a higher case fatality in early-onset infections (Edmond and others 2012).

Although GBS is a common cause of neonatal sepsis in high-income countries (HICs), the global burden in LMICs is less established. Variable incidence levels have been reported, with Sub-Saharan Africa reporting rates almost threefold higher than North and South America. In contrast, South-East Asian studies have reported a low incidence and even no cases of GBS. This disparity may be due to differences in study design, previous antibiotic use, and the severity of illness, with young infants dying before they can be fully evaluated. In HICs, the standard of care is to conduct surveillance cultures for GBS at 36 weeks gestation. Pregnant women colonized with GBS receive intrapartum antibiotics at least four hours before delivery to reduce the incidence of GBS neonatal illness. In the meta-analysis (Edmond and others 2012), studies that report

intrapartum prophylaxis were associated with lower incidence of early-onset GBS (0.23 per 1,000 live births [95 percent confidence interval 0.13–0.59]) compared with those with no prophylaxis (0.75 per 1,000 live births [95 percent confidence interval 0.58–0.89]). Whether this practice would be beneficial in low-resource countries is difficult to determine because of insufficient data on the burden of GBS disease in these contexts.

Acute Respiratory Infections

ARIs in young infants (age 0–59 days) are particularly dangerous because immature immune systems increase vulnerability for systemic spread, and the fatigue from the increased work of breathing is a major clinical concern. Liu and others (chapter 4 in this volume, 2016) estimate that ARIs contribute 6 percent to total all-cause neonatal mortality (0–28 days), and the WHO repository suggests 4 percent of children age 0–59 days die from ARI (WHO-CHERG 2011). It is difficult to disentangle primary respiratory infections from sepsis and other pulmonary conditions related to premature lungs and congenital anomalies. Viral respiratory infections often infect the smallest of airways—bronchioles—causing inflammation, bronchospasm, and difficulty breathing.

Febrile Illnesses in Older Infants and Young Children

Acute Respiratory Infections

ARIs became the second largest killer of children under age five years. Recent WHO-CHERG data describe ARIs as responsible for approximately 15 percent of all under-five deaths and 24 percent of mortality for ages 1–59 months (chapter 4 in this volume, Liu and others 2016). Estimates vary depending on the sources and modeling approach, with ARI-related deaths among children under five years of age ranging from 890,000 (GBD 2013 Collaborators 2015) in 2013 to approximately 922,000 in 2015 (chapter 4 in this volume, Liu and others 2016). ARIs include upper respiratory tract infections, such as the common cold, otitis media, sinusitis, and pharyngitis, as well as lower respiratory tract infections (LRIs), such as laryngitis, tracheitis, bronchitis, bronchiolitis, and pneumonia. Bronchiolitis and pneumonia are the largest contributors to child ARI deaths through progressive respiratory failure or systemic infection, inflammation, or toxins spread from the lungs.

Acute lower respiratory tract infections (ALRIs) in older infants and children under age five years are the most common reason for hospitalization. An assessment of the global burden of severe pneumonia

estimated that in 2010, 11.9 million (95 percent confidence interval 10.3 million to 13.9 million) episodes of severe and 3.0 million (95 percent confidence interval 2.1 million to 4.2 million) episodes of very severe LRI resulted in hospital admissions in young children worldwide (Nair and others 2013). This analysis uses data from 37 hospital studies reporting CFRs for severe ALRI to estimate that approximately 265,000 (95 percent confidence interval 160,000–450,000) in-hospital deaths occurred in young children; 99 percent of these deaths occurred in developing countries. These data capture the inpatient CFR; however, the at-home CFR is likely higher in areas with poor access to care. Although many children with ARI are diagnosed and treated in the private sector, data on these ARI episodes and their outcome is sorely lacking; investment to better understand the role of the informal sector in disease diagnosis and treatment is paramount.

In 2009, the WHO and UNICEF released a Global Action Plan for Prevention and Control of Pneumonia (WHO and UNICEF 2009a). In 2013, this plan was updated to include diarrheal disease control and renamed the Integrated Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea (WHO and UNICEF 2013). These calls to action outlined the research and programming priorities for ARIs to include the following:

- Etiology research to better direct antimicrobial therapy
- Vaccine development
- Scale-up of community-based programming to recognize and treat cases of severe ARI before disease progression.

The Pneumonia Etiology Research for Child Health project was designed in response to the call for enhanced understanding of the etiology of pneumonia. This multicountry case-control study of hospitalized pediatric patients in Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, and Zambia will reflect the changes in severe pneumonia etiology resulting from wider vaccine availability, the HIV/AIDS epidemic and resulting opportunistic infections, and increasing antimicrobial resistance. Results are expected in 2016–17. Annex 8A provides a summary of the current understanding of pneumonia etiology.

Respiratory viruses play a major role in infants of all ages presenting with severe ALRI, clinically known as bronchiolitis. Although these viruses exist in older children with ARIs, the clinical presentation in infants is associated with higher morbidity and

mortality. Common viral etiologies of bronchiolitis include respiratory syncytial virus, influenza (types A and B), parainfluenza, human metapneumovirus, rhinovirus, adenovirus, coronaviruses, and human bocavirus (García and others 2010).

In 2012, the WHO updated the technical guidelines for treatment of pneumonia, based on available evidence from studies reviewed by an expert panel. On the basis of recent studies, the 2014 version of the IMCI guidelines (table 8.3) recommends that pneumonia with fast breathing or chest indrawing but no other danger signs be managed at the outpatient level, potentially reducing the number of children needing referral (WHO 2012b, 2014a).

Pulse oximetry, which measures a patient's oxygen saturation, can provide important triage information—peripheral oxygen saturation of less than 90 percent predicts clinical severity and need for supplemental oxygen (WHO 2013a). To reduce mortality from ARIs, clear community-based algorithms to identify and refer children with severe pneumonia are needed, and referral-level facilities need to deliver supplemental oxygen. The cost-effectiveness of an oxygen systems strategy compares favorably with other higher-profile child survival interventions, such as new vaccines (Duke and others 2008). Although most portable oxygen systems lack sufficient oxygen flow rates to provide adequate respite for increased work of breathing in infants with bronchiolitis, oxygen concentrators provide the most consistent and least expensive source of oxygen in health facilities with reliable power supplies. Future research efforts that focus on reducing the power needs of or using alternative energy sources for oxygen concentrators will facilitate their introduction to lower levels of the health care system. The capacity to perform routine maintenance and to source necessary replacement parts locally needs to be addressed if this technology is to be sustainable at the community or facility level.

Viral Exanthems

A discussion of febrile illnesses in children is incomplete without the mention of the myriad viruses that present nonfocally and ultimately declare themselves clinically with a characteristic exanthema or rash. For example, the clinical syndromes of roseola (HHV-6), varicella, measles, parvovirus B19, and coxsackievirus may initially present with fever before erupting into a rash. Of these conditions, only measles is incorporated into the IMCI algorithms, which recommend treatment with vitamin A for uncomplicated infections, or urgent referral, a first dose of an antibiotic, and vitamin A for severe complicated measles (Gove 1997). Many other classic

Table 8.3 WHO IMCI Respiratory Illness Clinical Guidelines

IMCI classification for children age 2–59 months	Treatment	Strength of recommendation
Nonsevere pneumonia (fast breathing ^a or chest indrawing without danger signs)	Without chest indrawing and HIV-negative: Amoxicillin 40 mg/kg twice daily for three days	Weak recommendation, moderate quality of evidence
	Without chest indrawing and HIV-positive: Amoxicillin 40 mg/kg twice daily for five days	
Severe pneumonia (fast breathing with danger signs, with or without chest indrawing)	With chest indrawing: Amoxicillin 40 mg/kg twice daily for five days	Strong recommendation, moderate quality of evidence
	Children age 2–59 months: Ampicillin 50 mg/kg IV every six hours for five days OR Benzyl penicillin 50,000 IU/kg every six hours for five days AND gentamicin 7.5 mg/kg IV daily for five days Third-generation cephalosporin as second-line therapy ^b	Strong recommendation, moderate quality of evidence
Wheezing	Inhaled salbutamol delivered via metered dose inhaler with spacer devices for up to three times 15–20 minutes apart, to relieve bronchoconstriction and to assess the respiratory rate again and classify accordingly Oral salbutamol should not be used for treatment of acute or persistent wheezing, except where inhaled salbutamol is not available ^b	Strong recommendation, low quality of evidence

Source: WHO IMCI Chart Booklet 2014 (http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/).

Note: IMCI = Integrated Management of Childhood Illness; IU = international unit; IV = intravenous; mg/kg = milligrams per kilogram.

a. Fast breathing is defined as respiratory rate ≥ 50 breaths per minute in infants age 2–12 months, and ≥ 40 breaths per minute in infants age 12–59 months.

b. Expert consensus.

viral exanthema are difficult to diagnose on darker skin, are typically self limited, and do not require treatment. Measles and, to a lesser extent, varicella are highly contagious viruses and have the potential for serious sequelae. Parvovirus B19 is an important condition to consider in patients with sickle-cell disease because infection can lead to aplastic anemia. An emphasis on identifying these syndromes and prophylactic vaccination for measles is warranted in refugee or displaced populations, and in HIV-endemic areas where outbreaks could spread rapidly.

Enteric Fever

Enteric fever is an all-encompassing term for the disease caused by several serovars of *Salmonella enterica* including *S. typhi* and *S. paratyphi A*. The clinical picture of typhoid is nonspecific with symptoms of severe headache, nausea, and loss of appetite associated with sustained, high fever and few other specific signs. The Institute for Health Metrics and Evaluation (IHME)

reports a mortality burden of 190,000 for enteric fever in the 2010 Global Burden of Diseases (Lozano and others 2012). In 2015, the IHME released updated mortality estimates with disaggregated cause of death; they report an estimated 54,262 paratyphoid-caused deaths and 160,645 typhoid-caused deaths worldwide annually (GBD 2013 Collaborators 2015). These data come from 73 Gavi, the Vaccine Alliance, countries within which more than 70 percent of mortality burden comes from Asia and more than 50 percent comes from South Asia (Lozano and others 2012; GBD 2013 Collaborators 2015). CFRs, ranging from 10 percent to 30 percent without antibiotic treatment, drop to less than 1 percent to 4 percent in the antibiotic-treated patient. As part of Millennium Development Goal (MDG) 7, improvements in water, sanitation, and hygiene have reduced environmental contamination exposure to typhoid. However, treatment with antibiotics and prevention through vaccination are ultimately needed to reduce typhoid mortality and morbidity (United Nations 2013).

Malaria

Despite substantial control efforts since 2000, malaria remains responsible for substantial morbidity and mortality worldwide; in 2015, there were an estimated 214 million cases and at least 438,000 deaths (WHO 2015). Four species of *Plasmodium* are responsible for most human cases (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*), although *P. knowlesi*, a cause of primate malaria, has been identified as a cause of human infections in Malaysia and other parts of South-East Asia. Clinically, malaria ranges from asymptomatic parasitemia to uncomplicated malaria to severe malaria (typically manifested as cerebral malaria, severe anemia, hypoglycemia, and potentially multisystem organ failure). Further detail on etiology and control strategies for malaria can be found in volume 6 (Holmes, Bertozzi, Bloom, Jha, and Nugent, forthcoming).

A paradigm shift has occurred in recent years, away from the presumption that all fevers in endemic areas should be treated as malaria toward the recommendation that laboratory testing should occur before treatment. Although thick and thin blood smears have been the mainstay of diagnosis, since 2005 the use of antigen-based RDTs with high sensitivity and specificity has increased. This recommendation has not been implemented in all regions given lack of resources to acquire RDTs or provider preference for relying on clinical diagnosis or blood smears, despite a convincing body of research to support RDTs as reliable and cost-effective diagnostic tools. Artemisinin-based combination therapy (ACT) is the preferred treatment modality for uncomplicated and severe disease caused by *P. falciparum*; chloroquine remains the treatment of choice for the other three species in most regions.

Dengue and Chikungunya Virus

Dengue fever, a mosquito-borne arbovirus of the genus *Flavivirus*, has become one of the most common and rapidly spreading vector-borne diseases after malaria and is a major international public health concern. Dengue is responsible for an estimated 50 million to 100 million illnesses annually, including 250,000 to 500,000 cases of dengue hemorrhagic fever—a severe manifestation of dengue—and approximately 29,000 deaths (Lozano and others 2012; CDC 2012). Approximately 95 percent of cases occur in children younger than age 15 years; infants constitute 5 percent of all cases. Dengue has mainly been documented in Asia; data from Sub-Saharan Africa are lacking, although reports from Gabon and elsewhere are creating concern that it is an emerging disease or has been previously not recognized because of a lack of diagnostic testing (Caron and others 2013).

The grading of the severity of dengue can be based on a WHO classification system, updated in 2009 (WHO and

Special Programme for Research and Training in Tropical Diseases 2009). No specific therapeutic agents exist for dengue fever apart from analgesics and medications to reduce fever. Treatment is supportive; steroids, antivirals, or carbazochrome, which decreases capillary permeability, have no proven role. Mild or classic dengue is treated with antipyretic agents such as acetaminophen, bed rest, and fluid replacement; most cases can be managed on an outpatient basis. The management of dengue hemorrhagic fever and dengue shock syndrome is purely supportive. Aspirin and other nonsteroidal anti-inflammatory drugs should be avoided, owing to the increased risk for Reye's syndrome and hemorrhage (Simmons and others 2012).

Chikungunya, an alpha virus transmitted by mosquitoes of the *Aedes* genus, is responsible for a clinical syndrome characterized by fever, rash, headache, myalgias, and arthralgias (Thiboutot and others 2010). It can affect all ages, including young children; transplacental transmission with congenital infection has been described (Gérardin and others 2008). Although past outbreaks of chikungunya have primarily occurred in Sub-Saharan Africa and regions of South Asia and East Asia and Pacific, this vector-borne viral infection has emerged in Latin America and the Caribbean, where it spread rapidly from island to island. No specific antiviral therapy is available, and treatment is largely supportive.

DIAGNOSTIC TOOLS AVAILABLE OR UNDER DEVELOPMENT

Malaria

In many endemic areas, malaria accounts for a minority of fever episodes and is clinically indistinguishable from other common illnesses, including pneumonia, meningitis, typhoid, sepsis, and viral infections such as dengue and chikungunya. The WHO recommends that malaria case management be based on parasitological diagnosis of malaria infections before treatment (WHO 2010a, 2012a); the use of antigen-detecting RDTs is supportive of this strategy, particularly in areas where good quality microscopy cannot be maintained. The number of commercially available malaria RDTs that detect one or more of the three parasite antigens—histidine rich protein-2 (HRP-2), parasite lactate dehydrogenase (pLDH), or aldolase—have increased substantially since their introduction in the late 1990s (table 8.4). RDTs can play a key role in febrile illness management, providing they are sensitive enough to detect nearly all clinically significant cases of malaria and have a high specificity to rule out nonmalarial causes of febrile illness. Multiple rounds of laboratory-based evaluations have identified those RDTs that consistently detect malaria at low parasite densities (WHO 2012c).

Table 8.4 Average Sensitivity and Specificity of Malarial Tests

Test type	Species detected	Sensitivity (95% CI)	Specificity (95% CI)
Type 1 Pf HRP-2	<i>Plasmodium falciparum</i> only	94.8% (93.1%–96.1%)	95.2% (93.2%–96.7%)
Type 2 Pf HRP-2 and pan aldolase	<i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , <i>Plasmodium malariae</i> and <i>Plasmodium ovale</i>	96.0% (94.0%–97.3%)	95.3% (87.3%–98.3%)
Type 3 Pf HRP-2 and pan pLDH	<i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , <i>Plasmodium malariae</i> and <i>Plasmodium ovale</i>	99.5% (71.0%–100%)	90.6% (80.5%–95.7%)

Sources: Baiden and others 2012; Abba and others 2011.

Note: CI = confidence interval; Pf HRP2 = histidine rich protein-2; pLDH = parasite lactate dehydrogenase.

However, the declining malaria burden in many endemic regions and an increasing programmatic focus on malaria elimination mean that novel target antigens, use of gold nanoparticles, or other diagnostic approaches may be needed to create point-of-care tests with increased sensitivity. Several diagnostic approaches are based on selective microscopic detection of infected blood cells by methods such as third-harmonic generation imaging (Bélisle and others 2008), photoacoustic flowmetry (Samson and others 2012), and more recently, magneto-optical detection of the malaria pigment (Mens and others 2010) hemozoin using hand-held devices with polarized light and laser pulse detection of vapor nanobubbles generated by the parasite (Lukianova-Hleb and others 2014).

Respiratory and Other Bacterial Illnesses

A detailed discussion of diagnostic tools available and under development for ARI or other serious bacterial illnesses can be found in annex 8B (available online).

HEALTH SYSTEMS APPROACHES TO CHILDREN WITH FEBRILE ILLNESSES

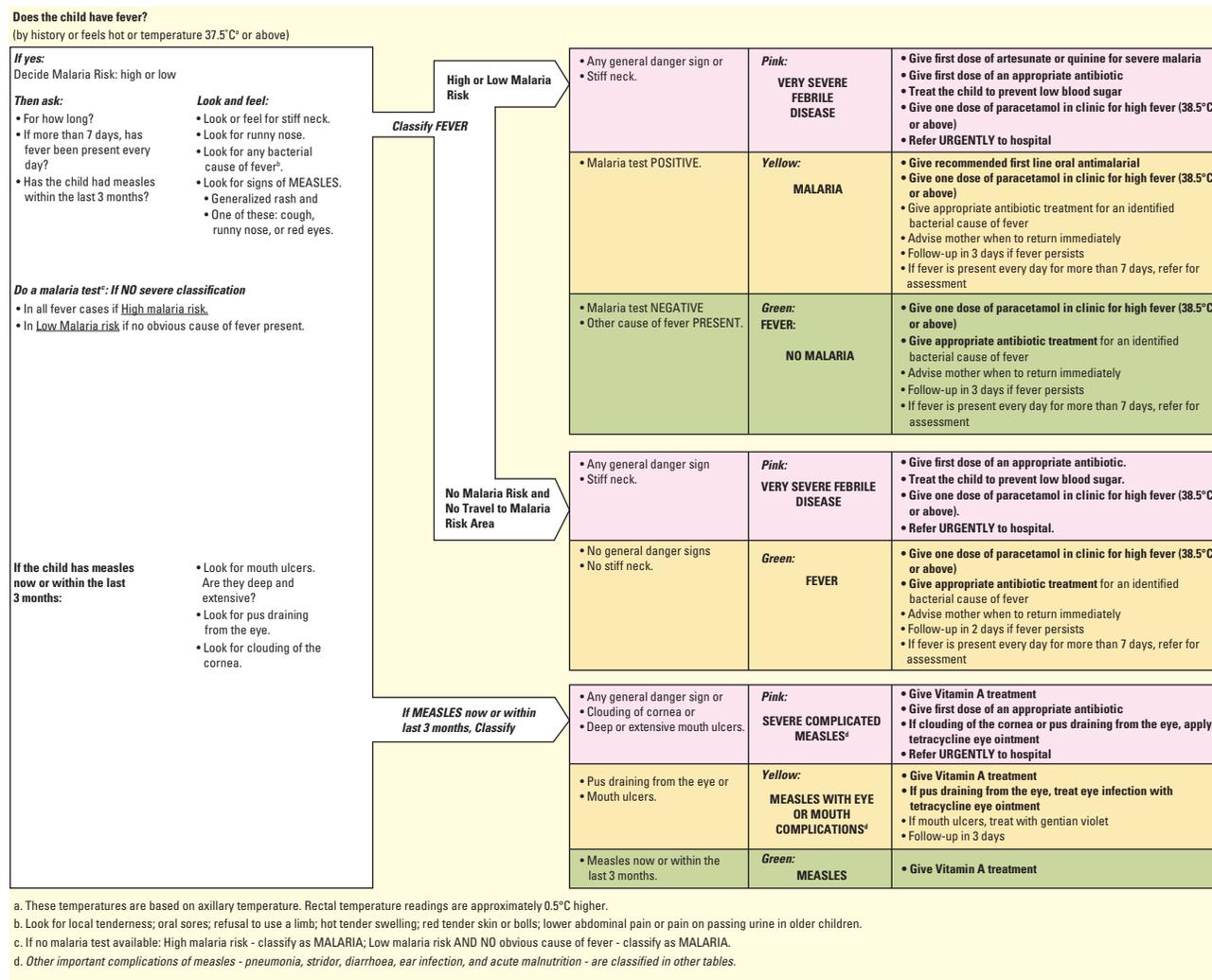
Children with fever present to all levels and sectors of the health system. Trials of algorithmic approaches have been undertaken at the community and facility levels to identify seriously ill children to indicate referral to a higher level of care. Two WHO-supported platforms to identify and treat children with fever and common pediatric illnesses are IMCI for the facility level and iCCM for the community level. Further research is needed to identify best practice models for the formal and informal private sector to create a synergistic approach to providing appropriate treatment and referral to more advanced care, when needed.

Integrated Management of Childhood Illness

The WHO developed the IMCI strategy in the 1990s to improve the quality of disease management and to reduce mortality of children under age five years (Gove 1997). Using a series of algorithms and flow charts, IMCI gives health care providers a systematic way to assess children for danger signs that trigger immediate referral or hospitalization; to classify the illness based on the level of severity for pneumonia, diarrhea, measles, fever, otitis media, and malnutrition (Tulloch 1999); and to identify those requiring antibiotic treatment. The classifications are color coded, with pink calling for hospital referral or admission, yellow for treatment at home, and green for children with mild illness who require only supportive care at home and can be counseled with return precautions (figure 8.1). IMCI has been adapted at the national level with increasing attention to HIV screening and management of illness in infants under age two months.

Several assessments of the quality of care delivered by IMCI have been performed since the early 2000s. In Bangladesh, a systematic evaluation of 669 sick children age 2–59 months, using a gold-standard physician diagnosis and treatment decision, found a sensitivity of 78 percent and specificity of 47 percent for identifying children with probable bacterial infections requiring antibiotics (Factor and others 2001). In this low malaria prevalence site, the majority of children with meningitis, pneumonia, otitis media, and UTIs fulfilled IMCI criteria for at least one classification that would have resulted in antibiotic initiation. However, many children with bacteremia, skin infections, and dysentery would not have received antibiotics. This evaluation was based on a comparison with an expert diagnosis that is subject to clinical subjectivity and the limited accuracy of available diagnostic tools. A study assessing the safety of using a slightly modified version of IMCI showed that the rate

Figure 8.1 Sample Fever Algorithm from 2014 IMCI



Source: IMCI Chart Booklet 2014 (http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/).

of clinical failure at day seven was very low (2.7 percent), and lower than in the control group (8.0 percent) in which routine care was used; only 15 percent received an antibiotic compared with 84 percent in the control group (Shao and others 2015).

A multicountry evaluation of IMCI effectiveness, cost, and impact was conducted in Bangladesh, Brazil, Peru, Tanzania, and Uganda (Bryce and others 2005). In Tanzania, the survey results demonstrate that children in IMCI districts received higher-quality care, including more thorough evaluations, a greater likelihood of being properly diagnosed and correctly treated, and better counseling and knowledge of caretakers of children in IMCI districts relative to comparison districts (Armstrong Schellenberg and others 2004). Several other

studies also show that IMCI case management training resulted in improved quality of care, especially when there were minimum standards of training quality and sufficient coverage of trained health workers (Arifeen and others 2005; Gouws and others 2004; Pariyo and others 2005; Nguyen and others 2013). The multicountry evaluation also reveals that the IMCI approach provided many benefits in addition to improved quality of care, including better record keeping and strengthened supervision. However, four of the five countries encountered challenges in expanding the IMCI strategy at the national level (Bryce and others 2005).

A multicountry study finds that the quality of child health care associated with IMCI training was similar across different cadres of health workers and that

the duration and level of preservice training did not appear to influence the quality of care (Huicho and others 2008). A cluster randomized controlled trial in Bangladesh demonstrates that IMCI implementation resulted in improved health worker skills, increased oral rehydration solution (ORS) utilization, and exclusive breastfeeding, and it reduced stunting prevalence in intervention areas relative to comparison areas (Arifeen and others 2009). IMCI implementation was also associated with a nonsignificant 13 percent reduction in mortality in children under age five years. Mortality impact is examined in two other studies. In the first, a cluster randomized controlled trial in India that used Integrated Management of Neonatal and Childhood Illness (IMNCI) and community workers to conduct postnatal home visits, the infant mortality rate was 15 percent lower (adjusted hazard ratio 0.85, 95 percent confidence interval 0.77–0.94), and the neonatal mortality rate after the first 24 hours was 14 percent lower (adjusted hazard ratio 0.86, 95 percent confidence interval 0.79–0.95) in intervention, relative to control clusters (Bhandari and others 2012). In the second, a retrospective pre/post analysis of IMCI implementation in the Arab Republic of Egypt found a nearly twofold reduction in under-five mortality (3.3 percent versus 6.3 percent) in one year (Rakha and others 2013). These three studies provide evidence to suggest that effective scale-up and implementation of IMCI can help reduce infant and under-five all-cause mortality.

In HIV-endemic countries such as South Africa, local adaptations of the IMCI algorithm have been created to identify and manage HIV-infected children using a set of common signs and symptoms that are predictive of HIV infection, for example, recurrent or persistent diarrhea, persistent fever, or history of tuberculosis (Horwood and others 2003). The presence of three signs or a maternal report of HIV infection prompts testing for HIV in children. An evaluation of the IMCI HIV guidelines in South Africa finds that the algorithm correctly classified 71 percent of 76 HIV-infected children as suspected symptomatic HIV; approximately 20 percent were identified as HIV-exposed (Horwood and others 2009). This approach missed only 9 percent of HIV-infected children. Unfortunately, the study also finds that this approach is not being used consistently in routine clinical practice.

Although the IMCI strategy has the potential to increase the quality of care in health facilities, absolute levels of performance often are low, and adherence to the guidelines has been unsatisfactory. An assessment of health worker practices in Benin in 2000 revealed multiple problems with local adaptation of the IMCI guidelines. Problems included the failure to treat children in

accordance with the guideline (incorrect choice of drug, dosage, and duration); missed opportunities for vaccination; treatment with unnecessary and occasionally dangerous medications; prescription of a large number of drugs for some children; and failure to perform counseling tasks, including how to administer medications (Rowe and others 2001). In Uganda, even after IMCI training, only about 50 percent of the children classified as having malaria or pneumonia received complete and appropriate treatment (Pariyo and others 2005). New training strategies are necessary, especially for respiratory rate measurement and identification of danger signs.

In addition, the IMCI clinical algorithms have the advantage of being highly sensitive but the drawback of having inadequate specificity. A prospective hospital-based study in Mozambique finds substantial symptom overlap between malaria and severe pneumonia among hospitalized children (Bassat and others 2011). Some 24 percent of children were classified using IMCI as having both malaria and severe pneumonia; however, when using stricter criteria based on radiological confirmation of pneumonia and *P. falciparum* parasitemia, the authors find that fewer than 1 percent had both malaria and severe pneumonia. Similar to other studies, there was a significant association between underlying HIV infection and prevalence of severe pneumonia, duration of hospitalization, and CFRs (Lanata 2004).

For implementation of the IMCI guidelines, the WHO recommends an 11-day in-service training course for first-level (that is, primary care) health facilities, job aids, and a follow-up visit to the facility at four to six weeks to reinforce IMCI practices. As of 2009, 76 countries had scaled up IMCI beyond a few pilot districts; many countries have adapted the IMCI algorithm to their local contexts. Some countries have started to use an electronic version of IMCI called ICATT that allows easy and rapid country adaptation of the algorithm and computer-based self training (<http://www.icatt-impact.org>). Distance learning for IMCI has been developed as a strategy to increase IMCI training coverage (WHO 2014b). Other research into IMCI implementation highlights challenges related to care seeking, resources and supply chain, training, and supervision requirements to ensure implementation at large scale. Frequent staff rotation and attrition require that countries revise preservice curricula to include training on the WHO algorithms (WHO 2001, 2010b).

Management of Sick Young Infants: IMNCI and Beyond

Given the need to strengthen the capacity of health workers to identify young infants age 0–59 days with

possible serious bacterial infections, two multicountry studies were performed to provide evidence to strengthen the IMCI algorithm to include newborns and young infants. To obtain information on clinical signs of sepsis in young infants age 0–59 days, the WHO conducted a large study of the clinical features and etiologies of serious bacterial disease from 1990 to 1992 in the Philippines (Gatchalian and others 1999), The Gambia (Mulholland and others 1999), Ethiopia (Muhe and others 1999), and Papua New Guinea (Lehmann and others 1999). This information contributed to the development of the IMCI algorithms during the mid-1990s, which standardized the management of sick young infants at first-level health facilities (Gove 1997; Tulloch 1999; Weber and others 2003).

Neonates in the first week of life were still not included. Accordingly, the YICSSG designed a multicenter study to analyze recognition of young infants, including neonates younger than seven days, requiring referral to higher levels of the health system. The YICSSG found that 12 symptoms or signs showed statistical evidence of independent predictive value for severe illness requiring hospital admission in the first week of life. A decision rule requiring the presence of any of these 12 signs had high sensitivity (87 percent) and specificity (74 percent). However, a simplified algorithm that required only seven signs—history of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate ≥ 60 breaths per minute, temperature $\geq 37.5^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$, and severe chest indrawing—had a similar sensitivity (85 percent) and specificity (75 percent). This seven-sign algorithm also performed well in infants age 7–59 days (sensitivity 74 percent, specificity 79 percent) (WHO Young Infants Study Group 1999; Weber and others 2003). This clinical algorithm was validated at the community level during routine household visits in rural Bangladesh (Darmstadt and others 2011). A simplified six-sign algorithm had a sensitivity of 81 percent and specificity of 96 percent for screening neonates requiring referral, and sensitivity of 58 percent and specificity of 94 percent for identifying newborns at risk of dying.

The WHO IMCI guidelines recommend that any young infant presenting with danger signs should be referred to an appropriate level facility and treated with injectable gentamicin and ampicillin. Although data are limited, multiple reviews cite widespread resistance to ampicillin and gentamicin among sepsis-causing common pathogens *E. coli*, *S. aureus*, and *Klebsiella* species (Thaver, Ali, and Zaidi 2009; Waters and others 2011). Similarly, data from the YICSSG, which represent community-acquired bacteremia in young infants, reveals the wide distribution of multi-drug-resistant gram-negative

rods, and 11 percent of *S. aureus* isolates were methicillin resistant (Hamer and others 2015). Although broad-spectrum cephalosporins show better sensitivities to most pathogens, they are expensive and their use will increase drug pressure. Recommended antimicrobial therapies need to be regionally specific, and considerations to empirically cover for HSV-2 infections must be considered in the youngest infants. The Aetiology of Neonatal Infection in South Asia study will provide even more current data for LMICs that reflect current epidemiology and antimicrobial susceptibilities (WHO Young Infants Study Group 1999; YICSSG 2008).

A seminal study in India demonstrates a 16 percent reduction in neonatal sepsis case fatality and a 62 percent reduction in overall neonatal mortality by instituting a package of home-based newborn care services by trained community health workers (CHWs); the services included an assessment for sepsis and prereferral administration of injectable gentamicin if indicated (Bang and others 1999). A more detailed discussion of this study is provided in chapter 18 in this volume (Ashok, Nandi, and Laxminarayan 2016). In Zambia, a cluster randomized controlled trial assessed the impact of training birth attendants to perform a modified neonatal resuscitation protocol for newborns with respiratory distress and to recognize a set of cardinal symptoms and signs of possible neonatal infection. If any signs of possible serious bacterial infection were observed in the first four weeks of life, intervention-trained birth assistants were to administer a 500 milligram dose of oral amoxicillin and facilitate referral to the nearest rural health center. This combination of interventions resulted in a 45 percent reduction in neonatal mortality for all live births in intervention as compared with controls (Gill and others 2011).

Several studies from India, Nepal, and Pakistan evaluate a variety of community-based perinatal packages that deploy newborn home visitation; each trial has shown significant impact on neonatal mortality (Baqui and others 2008; Bhutta and others 2008; Kumar and others 2008). As a result of this growing body of evidence, the WHO and UNICEF released a joint statement on home visits in 2009 (WHO and UNICEF 2009b). Several countries have developed adaptations of IMNCI. The Indian IMNCI program, which integrates home visits for newborn care with improved treatment of illness, evaluated the effectiveness of this strategy in a cluster randomized controlled trial. This study demonstrated more optimal newborn care practices in intervention clusters and a significant reduction of neonatal mortality only among babies born at home receiving intervention (hazard ratio intervention/control 0.80 for home births [95 percent confidence interval 0.68–0.93]

versus 1.06 for facility births [95 percent confidence interval 0.91–1.23]) (Bhandari and others 2012).

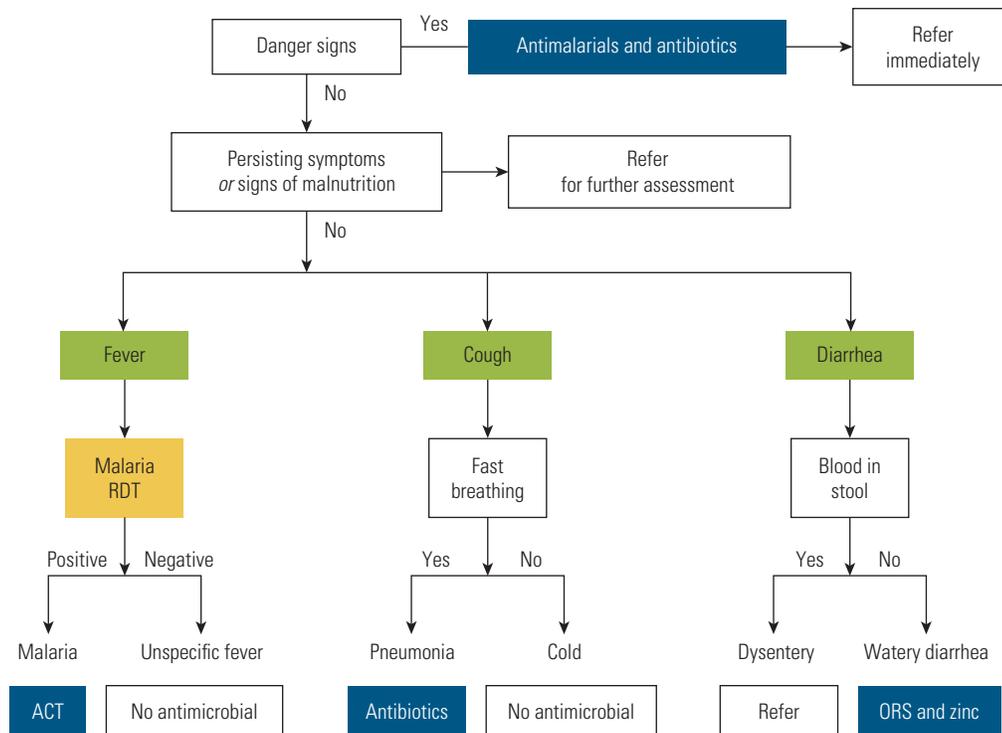
Integrated Community Case Management

In many resource-limited countries, access to health facilities for prompt, appropriate management of common childhood illnesses is limited and often complicated by shortages of essential medicines and insufficient human resources. Children in the lowest wealth quintile are less likely to receive early and appropriate treatment for malaria, pneumonia, and diarrhea (Young and Wolfheim 2012). To address this access gap and provide early access to treatment, many countries have been testing and scaling up community-based programs for the treatment of common childhood infectious diseases. iCCM provides an integrated algorithmic approach to identifying and treating ill children with limited access to health facilities. These algorithms alert CHWs to signs and symptoms of severe disease to indicate referral into the formal health system while treating minor illness in the community, serving as an extension of the formal health care system. This approach has several potential benefits, including improving the rational use of drugs

by deploying diagnostics-guided, evidence-based pediatric treatment algorithms and improving early access to effective treatment, thereby decreasing the risk that a child’s illness will progress to severe disease. The WHO and UNICEF released a joint statement justifying the need for iCCM and making recommendations on its implementation in 2012 (WHO and UNICEF 2012).

The effectiveness and feasibility of community-based management of individual disease conditions have been demonstrated for pneumonia, diarrheal disease, and malaria (Mubi and others 2011; Mukanga, Tiono, and Anyorigiya 2012; Theodoratou 2010; Yeboah-Antwi and others 2010). Home-based management of diarrhea has been practiced for decades; the WHO’s Special Programme for Research and Training in Tropical Diseases and others have extensively tested approaches to community-level management of malaria (Ajayi and others 2008; Pagnoni 2009). Studies have been conducted to assess effectiveness of the full iCCM package for management of malaria, pneumonia, and diarrhea, which is often coupled with screening for acute malnutrition. This package generally consists of training either volunteer or paid cadres of community-based health workers to follow a simple algorithm (figure 8.2) to classify and

Figure 8.2 Sample Integrated Community Case Management Algorithm



Source: WHO 2009.

Note: ACT = artemisinin-based combination therapy; ORS = oral rehydration solution; RDT = rapid diagnostic test.

treat children under age five years who present with fever, cough, difficulty breathing, or diarrhea. Necessary equipment includes a timer for counting respiratory rates and a tape for measuring mid-upper arm circumference if screening for acute malnutrition is performed; supplies include malaria RDTs, weight- and age-appropriate dose packs of an ACT, dispersible amoxicillin tablets (or cotrimoxazole because supply of amoxicillin is a frequent challenge), zinc, and low osmolarity ORS.

Quality and Safety of iCCM delivery

Several studies show that CHWs can appropriately classify and treat malaria, pneumonia, and diarrhea in children. Studies in Cambodia, Sudan, and Zambia show that with minimal training and job aids, CHWs can perform and interpret RDTs (Elmardi and others 2009; Harvey and others 2008; Mayxay and others 2004). In contrast with some studies of health workers in first-level health centers that demonstrate a tendency to ignore malaria diagnostic test results and to overprescribe ACT, several other studies clearly highlight the ability of CHWs to correctly perform RDTs and appropriately not prescribe antimalarials for RDT-negative patients (Bisoffi and others 2009; Hamer and others 2007; Harvey and others 2008; Reyburn and others 2007; Yasuoka and others 2010). Exceptions have been noted: Sudanese community volunteers have prescribed ACT in 30 percent of subjects with fever but a negative RDT result (Elmardi and others 2009), indicating that the inappropriate prescription of ACT may be an issue in some settings at the community level; lack of or inappropriate CHW training and supervision is one of several possible reasons.

A study in Zambia that evaluated two models of integrated delivery of treatment for malaria and pneumonia demonstrates that CHWs correctly classified 1,017 children who presented with fever or fast or difficult breathing as having malaria and pneumonia 94 percent to 100 percent of the time. Appropriate treatment based on disease classification was correct in 94 percent to 100 percent of episodes (Hamer and others 2012). In Uganda, a study that compared CHWs trained in integrated malaria and pneumonia management to those only trained in malaria case management demonstrated that CHWs with high illness knowledge scores used correct doses of medications for malaria and pneumonia, and correctly classified 75 percent of children with pneumonia (Kalyango, Rutebemberwa, and Alfvén 2012). However, the CHWs did not count respiratory rate accurately—only 49 percent measured respiratory rates within the bounds of the gold-standard criteria of five breaths per minute of the physician. This study

and an earlier evaluation in Kenya (Kelly and others 2001) suggest problems with pneumonia evaluation, emphasizing the need for ongoing supervision, training, and quality measurement of CHWs. This issue is further discussed in a systematic review of pneumonia community case management (CCM), which suggests that evidence on the efficacy and effectiveness of this approach in Sub-Saharan Africa is still lacking (Druetz and others 2013).

Several studies conducted in Benin, Tanzania, Uganda, and Zambia demonstrate that febrile RDT-negative children can be managed safely without antimalarial therapy (D'Acremont and others 2010; Faucher and others 2010; Msellem and others 2009; Njama-Meya and others 2007; Yeboah-Antwi and others 2010). In the Zambian study, children were evaluated five to seven days after their visit to the CHW; treatment failure at this point occurred in 9.3 percent of children (N = 1,017) in the study arm that implemented an iCCM package of malaria RDTs, ACTs, and amoxicillin. Notably, only 0.4 percent of children were hospitalized and 0.2 percent died. These findings provide additional confirmation that the WHO's guidelines for malaria treatment (WHO 2010a), which recommend treatment based on a positive diagnostic test for all patients, including children under age five years, can also be safely implemented at the community level in malaria-endemic areas of Sub-Saharan Africa.

All of the studies discussed focus on the management of children with nonsevere pneumonia at the community level. However, substantial evidence indicates that children with the former WHO-defined severe pneumonia (pneumonia with chest indrawing but no danger signs) can be managed with oral amoxicillin at the community level. In Pakistan, a five-day course of high-dose amoxicillin was shown to be equivalent to parenteral ampicillin for 48 hours, followed by a three-day course of oral amoxicillin for children with severe pneumonia (Hazir and others 2008). Subsequently, a multicountry observational study conducted in Bangladesh, Egypt, Ghana, and Vietnam demonstrated the safety and efficacy of home-based management of severe pneumonia with oral high-dose amoxicillin (Addo-Yobo and others 2011). An average of 9.2 percent of children met a rigorous definition of treatment failure at day 6 and 2.7 percent relapsed by day 14, but all children survived; only one adverse drug reaction (among 823 children) was documented. Two parallel community-based studies in rural Pakistan provide further evidence of the effectiveness and safety of the home-based management of chest indrawing pneumonia with oral amoxicillin by female health workers (Bari and others 2011; Soofi and others 2012).

Impact of iCCM

iCCM has several benefits, including early care seeking for illness; early access to appropriate treatment for children; reduced use of expensive antimalarial drugs when RDTs are used; reductions in health center attendance, which helps reduce the workload at primary health care centers; and probably decreased all-cause mortality for children under age five years.

Given the substantial workload at rural health centers, which are often understaffed, iCCM offers a potential opportunity to increase access to effective therapy at the community level (Guenther and others 2012) while decreasing the volume of health facility visits. In the Zambian study (Yeboah-Antwi and others 2010), cross-sectional household surveys on health care-seeking practices were performed before and immediately after the 12-month integrated malaria and pneumonia intervention period. A significant increase was observed in the proportion of mothers who sought care from CHWs between baseline and poststudy in both groups (empiric ACT for fever plus referral of children with pneumonia versus RDT-based ACT for malaria and amoxicillin for nonsevere pneumonia). Care seeking from CHWs increased for all types of illness, and use of health facilities and traditional healers decreased (Seidenberg and others 2012). This pattern was noted in both groups for children presenting with fever, cough, and diarrhea; however, there was a trend toward greater use of the CHWs that could provide amoxicillin for children with fast breathing or difficulty breathing relative to those CHWs who were trained to refer children with signs of pneumonia.

Limited data are available on the impact of iCCM on child mortality under age five years. Some earlier studies of the home management of malaria, based on maternal recall of a history of fever, found that home management of malaria is associated with a reduction in the development of severe malaria by more than 50 percent and all-cause mortality by 40 percent (Kidane and Morrow 2000; Sirima and others 2003). More recently, a study in Ghana that used a stepped-wedge cluster-randomized design evaluated the impact of adding amoxicillin to an antimalarial (artesunate-amodiaquine) for treating fever among children age 2–59 months on all-cause mortality. In clusters in which artesunate-amodiaquine alone was used for fever treatment, mortality decreased by 30 percent (rate ratio = 0.70, 95 percent confidence interval 0.53–0.92, $P = 0.011$) and in clusters that used both an ACT and amoxicillin, mortality was reduced by 44 percent (rate ratio = 0.56, 95 percent confidence interval 0.41–0.76, $P = 0.011$) when compared with control clusters. A 21 percent mortality reduction was observed with the addition of amoxicillin to the ACT;

however, this difference was not statistically significant (rate ratio = 0.79, 95 percent confidence interval 0.56–1.12, $P = 0.195$). This study also showed reductions in anemia, severe anemia, and severe disease among children in both study arms (Chinbuah and others 2013). Although this trial suggests a mortality benefit of both an ACT alone and the combination of an ACT with an antibiotic, its design has several limitations, including the lack of use of malaria RDTs and the empiric use of antibiotics for all children with fever, regardless of the respiratory rate in the combined arm (Chinbuah and others 2012).

A limited number of studies have evaluated the cost-effectiveness of iCCM. An economic analysis of the study in Ghana that compared an ACT to ACT plus amoxicillin (Chinbuah and others 2012) finds that the cost per DALY averted was US\$90.25 for artesunate-amodiaquine and US\$114.21 for this ACT plus amoxicillin (Nonvignon and others 2012). The authors conclude that both approaches were cost-effective. However, the diagnosis of malaria did not involve the use of RDTs; all children in the ACT plus amoxicillin arm with fever were given antibiotics, an approach that carries a high risk of antimicrobial resistance and potential adverse events among children who do not require antibiotics. A cost-effectiveness analysis of malaria case management using RDTs and artemether-lumefantrine in Zambia reveals that home-based management was more cost-effective than facility-based management (US\$4.22 per case at the home versus US\$6.12 at the facility) (Chanda and others 2011). A cost analysis from Pakistan that focuses on household costs of illness finds that home management of pneumonia by women health workers was associated with a substantially lower cost to the household than for children who were referred for treatment (Sadrudin and others 2012).

CHALLENGES AND FUTURE DIRECTIONS

The Catalytic Initiative, an evaluation in six Sub-Saharan African countries—Ethiopia, Ghana, Malawi, Mali, Mozambique, and Niger—provides a useful summary of challenges and lessons learned during the scale-up of iCCM. Some of the major challenges to delivery of iCCM include the deployment, supervision, motivation, and retention of CHWs; maintenance of reliable supply chains; demand-side barriers to utilization; inadequate monitoring and evaluation systems; and a need for supportive government policies and engagement to achieve sustainable progress (UNICEF 2012).

In 2009–10, a survey of 68 countries in the Countdown to 2015 initiative was conducted to assess CCM of childhood illnesses (de Sousa and others 2012).

Most (81 percent) of the 59 countries that responded had policies for CCM of diarrhea and malaria (75 percent); only 54 percent had CCM policies for pneumonia. Only 17 (32 percent) of the 53 malaria-endemic countries providing responses had policies for all three of these conditions. According to the survey, CHWs administered the recommended treatments for diarrhea, malaria, or pneumonia in 34 percent (17 of 50), 100 percent (41 of 41), and 100 percent (34 of 34) of the countries implementing CCM of these conditions, respectively. Many programs identified similar implementation-related concerns, including problems with drug supplies; quality of care; and CHW incentives, training, and supervision. Implementation issues around supervision, quality control, supply chain, and remuneration of CHWs are important areas of research for iCCM because best practices will inform approaches to the scale-up of iCCM.

Economic studies confirm that international guidelines for treatment of fever in children are also cost-effective. Community use of rectal artesunate for children with severe malaria during their referral to higher-level care has been shown to be cost-effective. Similarly, RDTs for malaria are cost-effective if used appropriately (where *P. falciparum* is dominant and ACTs are the appropriate therapy, and where care providers abide by test results in their prescribing behavior). Finally, IMCI was shown in one study to be cost-effective (Armstrong Schellenberg and others 2004); however, precisely because it is effective, it can increase costs to the health service as patients shift from using private clinics (needs Prinja and others 2013).

Future research needs for diagnosis and treatment approaches for the febrile child are plentiful. Box 8.1 highlights considerations for future research, policy, and programming.

Box 8.1

Future Research Needs

Epidemiology

- Ongoing surveillance of febrile illness etiology, with particular emphasis on high burden countries, such as the Democratic Republic of Congo, Ethiopia, India, and Nigeria; on regions at high risk of zoonotic illness; on regions in conflict; and on neonatal infections
- Role of HSV-2 and GBS in neonatal illness, as well as impact of HSV-2 and GBS prophylaxis on neonatal outcomes
- Patterns of antimicrobial resistance to direct empiric therapies for pediatric serious bacterial infections

Implementation

- Field evaluation of commercially available diagnostic point-of-care tools to determine feasibility, cost-effectiveness, and level of health system; various tools should be introduced
- Creation and evaluation of innovative solutions to reduce power needs or use of alternative energy sources (for example, solar power, battery

operated) for oxygen concentrators, pulse oximeters, and other tools that require power

- Operational research to determine best practices for supply chain management, training, and supervision for IMCI and iCCM when scaled up
- Qualitative and quantitative research to better understand the role of the private sector in influencing care-seeking behaviors, diagnosis, and treatment

Economics

- Cost analysis of diagnostic tools versus empiric therapy for common pediatric illnesses in newborn period, and for pneumonia, diarrheal disease, and nonfocal fevers
- Cost comparisons of investments in preventive interventions (for example, vaccines, malnutrition treatment, exclusive breastfeeding) compared with diagnosis and treatment for common pediatric illnesses

Note: GBS = Group B streptococcus; HSV-2 = herpes simplex virus-2; iCCM = integrated community case management; IMCI = Integrated Management of Childhood Illness.

CONCLUSIONS

Ample evidence suggests a shift in the etiology of pediatric febrile illnesses, especially in countries with declining rates of malaria transmission. More etiology studies are needed in LMICs with high disease burdens (for example, Democratic Republic of Congo, Ethiopia, India, Nigeria, Pakistan), particularly for young infants. Ongoing surveillance is required to track epidemiological shifts given that drug pressure and policies influence which diseases are prominent in each region. The research evidence is concentrated in a few regions of the world; thus, advocacy for research in high burden countries, regions at high risk of zoonotic illness, regions in conflict, and neonatal infections is paramount to shaping global, national, and region-specific policy. Many diagnostic tools are commercially available or are in the development pipeline, tools that could aid in narrowing differential diagnoses and that could help providers determine whether antimicrobials are indicated. However, these tools need to be evaluated in the field to assess the cost-effectiveness and utility in the clinical context.

Finally, although both WHO-sponsored IMCI and iCCM offer promising health facility and community platforms for integrated service delivery, challenges including adherence to guidelines, supply chain, supervision, and scale up while maintaining quality are barriers to successful implementation. Adaptation of these models to reflect local epidemiology and available resources is paramount. In areas without CHWs or regions with prominent informal private sectors, work needs to be done to determine how to align approaches to children with fever to ensure appropriate treatment and decrease antibiotic overuse. The role of the private informal sector has been underestimated, and careful thought is needed about how to motivate and partner with private sector drug providers.

Because febrile illnesses are still the predominant disease presentation of most pediatric illnesses, high-quality impact and process research that can inform which models work best in which contexts is needed. This research, along with expanded fever etiology surveillance and innovative technologies for low-resource diagnostics and treatment delivery, is critical for further reductions in child mortality and morbidity. A unified call for an organized agenda and framework that unites the pneumonia, malaria, measles, other febrile illnesses, and neonatal illness agendas would benefit the global child survival agenda. MDG 4 has motivated numerous national-level planning efforts and now there is substantial country-specific programming. A forum to discuss evidence for best practices would further benefit this unmet need.

ANNEXES

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

- Annex 8A. Common Etiologies of Childhood Pneumonia in Low- and Middle-Income Countries
- Annex 8B. Diagnostic Tools Available and Under Development for ARI or Other Serious Bacterial Illnesses

NOTE

For consistency and ease of comparison, *DCP3* is using the World Health Organization's Global Health Estimates (GHE) for data on diseases burden, except in cases where a relevant data point is not available from GHE. In those instances, an alternative data source is noted.

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–US\$4,125
 - b) upper-middle-income (UMICs) = US\$4,126–US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

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