Annex 8B Diagnostic Tools under Development or Commercially Available for Respiratory and Serious Bacterial Infections

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The following describes diagnostic tools under development or commercially available for respiratory and serious bacterial infections.

Respiratory Infections

The WHO IMCI algorithm recommends antibiotic treatment for all 2-59 months old children presenting with cough and or difficult breathing, who have fast breathing or chest in-drawing. However, the current UNICEF ARI timer for measurement of respiratory rate has multiple technical and implementation challenges. Multiple mHealth based tools, some of which also include oxygen saturation measurement, are also in the clinical evaluation pipeline (Pneumonia Diagnosis: Current Outlook and Perspectives 2013). Neither the IMCI algorithm nor improved ARI measurement tools can discriminate between bacterial and non-bacterial causes of pneumonia and preliminary data from several independent groups indicate that circulating host response biomarkers could potentially be translated into a bacterial versus viral pneumonia diagnostic tool, although further research is required. Biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) have been extensively evaluated in the developed world and shown to partially differentiate bacterial vs. viral infections. These biomarkers can also separate the cases of pediatric community acquired pneumonia that, regardless of etiology, do not need antibiotic treatment or, even if due to bacteria, can be treated for a shorter time than that usually recommended by the guidelines (Esposito and others 2011; Manzano and others 2010; Stocker and others 2010). However, in malaria endemic developing countries the presence of *P. falciparum* parasites increases PCT and CRP levels independently of the pneumonia-associated pathogen, questioning the diagnostic utility of these biomarkers in this population (Diez-Padrisa and others 2010).

Multiple studies have demonstrated the validity of point-of-care diagnostic tests for detecting RSV infection and influenza. In RSV, comparable specificities, but inferior sensitivity, to immunofluorescence and viral culture have been found, with quoted sensitivities generally ranging from 72 to 90 percent, while specificities are consistently greater than 90–97 percent (Khanom and others 2011; Krilov and others 1994; Mackie, Joannidis, and Beattie 2001; Slinger and others 2004). In addition, like most point-of-care tests, no formal laboratory is technically required but capabilities and familiarity with the test format may vary widely, which can have a negative impact on diagnostic accuracy. Although U.S. Food and Drug Administration (FDA) has approved 10 different rapid tests for influenza A and B, there are considerable variations in reported test performance with sensitivities ranging from 10-96 percent and specificity varying from 50 percent to 70 and 90 percent to 100 percent, respectively, compared with viral culture or RT-PCR (Rapid Diagnostic Testing for Influenza: Information for Clinical Laboratory Directors 2014). Although better test performance is observed in young children, diagnosing influenza does not exclude a bacterial disease process, potentially delaying the administration of antibiotics when they may be indicated. Until influenza RDTs can be used in combination with a biomarker

based bacterial disease diagnostic, their use in developing countries should perhaps be limited to outbreak investigations and for identifying children at risk of nosocomial infections.

Serious Bacterial infections

Serious bacterial Infections (SBIs) (e.g. sepsis due to bacteremia, urinary tract infections, meningitis, pneumonia) are a major cause of morbidity and mortality in lower to middle income countries and health outcomes can be improved through early recognition and appropriate treatment. Kain and others (2011) have identified biomarkers associated with endothelial dysfunction and inflammation (angiopoietin-2, soluble ICAM-1, soluble Flt-1, PCT, IP-10, soluble TREM-1) that, when measured at clinical presentation, have clinical utility in predicting outcome in severe sepsis (Ricciuto and others 2011) and other life-threatening infections for example, streptococcal necrotizing fasciitis and toxic shock syndrome (Page and others 2011). In one study, combinations of three or four biomarkers (for example, sEndoglin, IL18BP, PCT, ANGL3, CHI3L1, and IP10) could distinguish febrile children under-five with bacteremia or other infections requiring antibiotic therapy from children with systemic viral infections, with sensitivities of 90 percent and negative predictive values of 95 percent (Kevin Kain, personnel communication). However, further validation of these biomarkers, including evaluation of markers identified by other research groups (University of Oxford, UK & Broad Institute, MA), is required in advance of point-of-care development.

Meningitis epidemics are usually caused by *N. meningitidis* serogroup A, but meningococcal outbreaks caused by serogroups 135 and X highlight the importance of their inclusion in any diagnostic test used for bacteriological surveillance or outbreak investigation. Assessment of a recently improved point-of-care test for *N. meningitidis* serogroups A, C, W, and Y in Niger, using CSF as the clinical sample, showed comparable results to those obtained in the reference laboratory, using conventional and qPCR as the gold standards, with an overall sensitivity and specificity of 91.5 percent and 84.6 percent, respectively (Collard and others 2013).

Other notable diagnostic tests for other bacterial, protozoan, and viral infections are described in table 8.6 below.

Table 8A.1 Diagnostics for other bacterial or viral infections

Disease	Diagnostic test or mechanism	Performance	Notes	Development Status
Enteric Fever *(Salmonella enterica* - multiple serovars*)*	Tubex® Typhidot®	sensitivity 70% specificity 80% (Keddy and others 2011)	performance measurement a challenge as gold standard (blood culture) is only 50% sensitive	commercially available
Scrub typhus *(O. tsutsugamushi)*	detection of IgM or IgG response to 57KD protein (InBios, Seattle, Washington)	sensitivity 95% (Ching and others 2001; Lijuan and others 2011)		commercially available

Leptospirosis (*Leptospira* spp.)	Dual Path Platform (Chembio Diagnostic Systems, Medford, New York)	sensitivity 100% (severe disease) 73% (mild disease)		under development
Dengue (dengue virus)	Targets NS1 protein (Peeling and others 2010)	sensitivity 48.5%-58.6% specificity 92.5-99.4% (Blacksell 2012)	Avoid RDT for IgM alone as high cross-reactivity with arboviruses	commercially available
	Combined NS1 and IgM detection	sensitivity 75.5-92.9% specificity 88.8-100% (Blacksell 2012).		commercially available
Chikungunya virus	Detection of IgM via capture ELISA	sensitivity 20.5-83% specificity ~100%	ranges depend on disease stage (Arya and Agarwal 2011)	commercially available
Rotavirus (group A)	Detection of VP6 rotavirus antigens from serogroup A	sensitivity > 95% specificity > 93% (Shulman and others 2011)	results in 30 minutes,	commercially available

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