

Innovations in the World Health Organization diagnostic and treatment guidelines for newborns and children

W. Chris Buck,¹ Nichola Connell,² Michelle Eckerle,³ Azadeh Farzin,⁴ Amy Ginsburg,⁵ Carlos Grijalva-Eternod,⁶ Matthew S. Kelly,⁷ Marko Kerac,⁸ Marie McGrath,⁹ Rashmi Patil,¹⁰ Michele Usielli,¹¹ and Eric D. McCollum,¹² for the WHO Child Health Guideline Innovation Working Group.

¹University of California Los Angeles, Department of Pediatrics, Maputo, Mozambique

²Save the Children, London, UK

³Cincinnati Children's Hospital Medical Center, Divisions of Emergency Medicine and Global Health, Cincinnati, United States

⁴Division of Neonatology, Department of Pediatrics, Johns Hopkins University School of Medicine and International Center for Maternal and Newborn Health, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States

⁵Save the Children, Seattle, United States

⁶UCL Institute for Global Health, London, UK

⁷Division of Infectious Diseases, Duke University Medical Center, Durham, United States

⁸London School of Hygiene and Tropical Medicine, Department of Population Health, London, UK

⁹ENN, London, UK

¹⁰Johns Hopkins University Bloomberg School of Public Health, Baltimore, United States

¹¹Department of Clinical Sciences and Community Health, Fondazione IRCCS

Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

¹²Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins School of Medicine and Department of International Health, Johns Hopkins Bloomberg School of Public Health, Dhaka, Bangladesh

Introduction

The Department of Maternal, Newborn, Child and Adolescent Health of the World Health Organization (WHO) is reassessing child health programming from the past two decades, with specific attention to the management of illnesses largely responsible for the morbidity and mortality of children globally. The main objective of this review is to identify evidence-based innovations in the areas of newborn health, pneumonia, diarrhea, malaria, and malnutrition that could be integrated into the current clinical guidelines, including Integrated Management of Childhood Illness (IMCI), Integrated Community Case Management (iCCM), and Pocketbook of Hospital Care for Children (Pocketbook).

Methods

We conducted a survey of 110 key informants who are content experts in neonatal and pediatric healthcare in developing countries. We also formed a WHO Child Health Guideline Innovation Working Group of 12 global health experts in the fields of newborn health and child pneumonia, diarrhea, malaria, and malnutrition. In addition to surveying the key informants, the Working Group reviewed the most recent IMCI, iCCM, and Pocketbook core guidelines, supplementary materials, and related updates. The Working Group drew upon their own expertise and the key informant survey results to identify potential innovations for integration into the current guidelines. Subsequently, the Working Group, aided by informational specialists, conducted a pragmatic non-systematic scoping review of the literature to determine whether potential guideline innovations were supported by evidence. For each innovation the Working Group subjectively assessed the literature and through a process of consensus provided an overall recommendation for whether the innovation justified incorporation into future WHO guideline revisions. The Working Group's overall recommendation was provided in one of four categories: recommended (strong), recommended (weak), not recommended (strong), or not recommended (weak). Risk-benefit tables intended to

outline the Working Group's evaluation process are referenced where applicable and provided as appendices for further detail.

A. Pneumonia Recommendations (8)

Based on survey responses and key informant interviews, eight topics were selected for comprehensive literature review. Please see Appendix 1 for the pneumonia risk-benefit summary tables and references.

1) Include pulse oximetry in the IMCI and iCCM guidelines (already included in Pocketbook)

Pulse oximeters are the standard for measuring blood oxygen levels non-invasively in children.(1, 2) A low blood oxygen level (hypoxemia) is a marker for higher pneumonia mortality risk in children.(3, 4) Oximeters lead to more appropriate use of oxygen treatment for children with hypoxemic pneumonia,(5) and hospital oxygen systems with oximetry reduce child mortality risk.(6) New evidence supporting oximetry in pneumonia care prior to hospitalization is emerging. Non-severe hypoxemia predicts treatment failure in Malawian children with pneumonia cared for by community health workers using iCCM.(7) Further, >40% of children with pneumonia and severe hypoxemia would have been missed without pulse oximetry at Malawian outpatient facilities using IMCI, and oximetry increased the referral of severely hypoxemic Malawian children with pneumonia at outpatient facilities using IMCI or by community health workers using iCCM.(8)

Frontline facility (IMCI) and community (iCCM) recommendation: Include oxygen saturation measurement in the IMCI and iCCM guidelines when assessing non-hospitalized children with a general danger sign and when assessing a non-hospitalized child with cough and/or difficult breathing (currently listed as footnote only in IMCI 2014 booklet, merits inclusion in primary cough or difficult breathing assessment for both IMCI and iCCM). Refer all children with a saturation <90%.

→ **Strength of recommendation: Recommended (strong)**

2) Include risk assessment scores in all guidelines

Current WHO guidelines use clinical signs associated with worse outcomes to classify pneumonia into categories of non-severe or severe disease. Within these categories patients are not additionally sub-classified according to any additional treatment failure or mortality risk. Objective risk assessment scores, or so-called severity of illness scores, have been successfully used for this purpose in many resource-rich settings,(9-11) and have been successfully implemented in several resource-constrained settings for adult care.(12, 13) Objective, easily measureable risk assessment scores have been proposed to further triage pediatric pneumonia patients in developing countries as well.(14, 15) Higher risk patients can be followed more closely in hospital or as outpatients in an effort to improve outcomes and better manage scant resources. Although several risk assessment scores have been developed and/or validated for hospitalized children with pneumonia in developing countries, to date none have been externally validated outside of their primary study settings or successfully implemented.(14, 16-20) There is ongoing work to externally validate a South African risk assessment score called RISC in Malawi (Carina King and Eric D. McCollum, personal communication). Despite significant effort no risk assessment scores appropriate for frontline lower-level health facilities or community health workers have yet been successfully developed or validated.(17)

Hospital (Pocketbook), frontline facility (IMCI), and community (iCCM) recommendation:

Currently there are no published data to support implementation of an externally validated risk assessment score and so none can be recommended as a generalizable tool. However, the RISC score is undergoing external validation in Malawi and appears to be a promising risk assessment score appropriate for children hospitalized with pneumonia in developing countries, but it will likely need to be adapted to local settings prior to implementation.

→ **Strength of recommendation: Not recommended (weak)**

3) Include bubble continuous positive airway pressure (bCPAP) in the Pocketbook guidelines

bCPAP is a low-cost modification of conventional CPAP that may be suitable for low-resource settings.(21) bCPAP is accepted as an effective neonatal treatment option, especially for premature infants with respiratory distress syndrome.(22) There is new data showing that bCPAP may also improve short-term respiratory physiology and mortality for non-neonates with pneumonia in developing settings. Multiple studies from Malawi,(23-25) Ghana,(26) and India(27, 28) have shown improvements in respiratory rate, oxygenation, and/or hypercarbia after bCPAP. In addition, a recent Bangladeshi randomized controlled trial at an urban referral hospital compared bCPAP to low and high flow oxygen in children 1-59 months old with hypoxemic pneumonia.(29) The study was controversially stopped early by the local DSMB due to lower mortality in the bCPAP arm, leaving final conclusions uncertain.(29) The controversy was discussed in a Lancet editorial.(30) Regardless, additional data demonstrating improved mortality in children with pneumonia from different settings, including those with higher rates of malaria, anemia, HIV, and malnutrition, will be needed. There is at least one study from Malawi (CPAP Improving Mortality for Pneumonia in African Children Trial (CPAP IMPACT), Eric D. McCollum, personal communication) that is powered for mortality and designed to provide this information. In addition, more data regarding appropriate patient selection for bCPAP, implementation feasibility and programmatic outcomes, and cost-effectiveness is needed from multiple settings in order to strengthen recommendations.

Hospital recommendation (Pocketbook): Include bCPAP treatment as an option for children with severe pneumonia and hypoxemia who have failed low flow oxygen treatment. Include a description of a low-cost bCPAP set-up with diagrams in the oxygen section of the Pocketbook along with clinical and nursing care requirements.

→ **Strength of recommendation: Recommended (weak)**

4) Do not treat fast breathing pneumonia with antibiotics in all guidelines

The WHO guidelines recommend amoxicillin treatment for children with fast breathing pneumonia. However, the majority of cases diagnosed as fast breathing pneumonia may not be from bacteria. There are many possible reasons for tachypnea in a child, many of which do not reflect bacterial respiratory disease(31-33) and recent research suggests that the majority of fast breathing pneumonia cases will resolve without antibiotic treatment.(34, 35) In the United States, clinical practice guidelines state that for outpatients, “antimicrobial therapy is not routinely required for preschool-aged children with CAP, because viral pathogens are responsible for the great majority of clinical disease (strong recommendation; high-quality evidence).”(36) In developing countries the management of fast breathing cases without antibiotics would likely reduce antibiotic resistance and treatment costs, simplify guidelines, and decrease the rates of adverse events from antibiotics.(37-39) However, due to methodological limitations, many of the studies in low-resource settings have not provided definitive answers to merit change in WHO guidelines.(35) There is a call for more research comparing antibiotics to no antibiotics in the management of fast breathing pneumonia in developing countries and several randomized trials are ongoing to evaluate this question.

Hospital (Pocketbook), frontline facility (IMCI), and community (iCCM) recommendation: No antibiotic treatment for fast breathing pneumonia in a child presenting with cough.

→ **Strength of recommendation: Not recommended (weak)**

5) Treating chest indrawing pneumonia with oral amoxicillin in the iCCM guidelines

At the facility level amoxicillin is recommended as first-line treatment based on studies showing oral amoxicillin is as effective as parenteral antibiotics for chest indrawing pneumonia treatment in children aged 2-59 months.(40) These studies used careful patient selection to exclude higher risk children with HIV-infection or –exposure, malnutrition, severe hypoxemia <90%, and other chronic illnesses. Presently, when identified at the community level, chest indrawing pneumonia is not treated

with oral amoxicillin and is instead referred to a facility. Unfortunately, many referrals are not completed resulting in inadequate treatment and poor outcomes. While there is increasing evidence (41-43) supporting home-based care of chest indrawing pneumonia and there are inherent theoretical advantages of simplified community management, there are potential drawbacks. Community health workers may not be able to adequately identify children with chest indrawing pneumonia that are higher risk in a programmatic setting due to restricted resources and limited training. For example, HIV testing, oxygen saturation measurement, and full nutritional assessment would be basic prerequisites for ensuring that home treatment of a patient with chest indrawing pneumonia would be safe and likely to be successful. Currently, these assessments are more readily available at facilities in most settings. Given these important risks and a lack of evidence demonstrating successful programmatic implementation in multiple settings we do not recommend community health worker amoxicillin treatment of chest indrawing pneumonia at this time. An ongoing multicountry randomized trial may address many of these questions.

Community recommendation (iCCM): At-home amoxicillin treatment of children aged 2-59 months with chest indrawing pneumonia.

→ **Strength of recommendation: Not recommended (weak)**

6) Management of children with pneumonia and wheezing in Pocketbook and IMCI guidelines

Current guidelines recommend a trial of a rapidly acting inhaled bronchodilator for children with wheezing and fast breathing or chest wall indrawing (44, 45). Age-based dosing and administration of multiple inhaled bronchodilator doses in rapid succession (when needed) is described in Pocketbook guidelines, while IMCI guidelines recommend 2 puffs of Salbutamol by metered dose inhaler (100 µg/puff) every 15 minutes for all children 2 months to 5 years of age regardless of weight (44, 45). In IMCI guidelines, children with wheezing are reclassified based on their response to bronchodilators, and it is recommended that children with continued fast breathing or chest wall indrawing receive antibiotics for pneumonia (45). Pocketbook guidelines recommend that children with wheezing and continued signs of hypoxemia (including chest wall indrawing) or fast breathing after a bronchodilator trial should be hospitalized, but it is not specified whether these children should be treated for pneumonia (44). Several studies investigated the outcomes of children with signs and symptoms of pneumonia who were administered a trial of inhaled bronchodilators (46-49). Notably, all of these studies included only children with wheezing and were conducted prior to pneumococcal conjugate vaccine introduction. In two of these studies, children who responded to bronchodilators (i.e., fast breathing and/or chest wall indrawing resolved) were not given antibiotics and were followed up for 5-7 days. Among children with fast breathing only and chest wall indrawing pneumonia, subsequent deterioration was observed in 6.5-14.9% and 12.6-37.9%, respectively (47, 48). There was significant variability in how these studies defined deterioration, and few additional details regarding the deteriorations were provided.

Hospital recommendations (Pocketbook):

a) Incorporate a bronchodilator trial into the Pocketbook management algorithm for all children, including those without wheezing, who have fast breathing or chest wall indrawing.

→ **Strength of recommendation: Not recommended (strong).**

b) To harmonize with IMCI guidelines, Pocketbook guidelines should more clearly include a reclassification of pneumonia severity following a trial of bronchodilator therapy for children with wheezing.

→ **Strength of recommendation: Recommended (weak).**

c) Pocketbook guidelines should specify that antibiotic treatment is warranted for children with wheezing who have continued fast breathing or chest wall indrawing after the bronchodilator trial.

- **Strength of recommendation: Recommended (weak).** Note: Further research on whether children with wheezing who respond to a trial of inhaled bronchodilator therapy can be safely managed without antibiotics would better inform Pocketbook and IMCI guidelines.

Frontline facility recommendations (IMCI):

- a) Incorporate a bronchodilator trial into the Pocketbook management algorithm for all children, including those *without* wheezing, who have fast breathing or chest wall indrawing.

→ **Strength of recommendation: Not recommended (strong).**

- b) IMCI guidelines should incorporate age-based dosing of inhaled salbutamol and describe administration of multiple doses in rapid succession (when needed) to harmonize with Pocketbook guidelines.

→ **Strength of recommendation: Not recommended (strong).**

- c) Incorporation of a diagram for construction of a spacer, as in current Pocketbook guidelines, may improve medication delivery at the frontline facility level.

→ **Strength of recommendation: Recommended (strong).**

7) Xpert MTB/RIF in Pocketbook guidelines

Establishing a diagnosis of tuberculosis (TB) in children is challenging because of difficulty in obtaining appropriate specimens for microbiological testing and paucibacillary disease. The Xpert MTB/RIF assay is a fully automated nucleic acid amplification test that enables rapid (<2 hours) detection of *Mycobacterium tuberculosis* and resistance to Rifampin. Current Pocketbook guidelines recommend Xpert MTB/RIF use is restricted to evaluating children with suspected multidrug-resistant TB or HIV-associated TB (44). However, since these guidelines were published, a growing body of literature supports routine use of Xpert MTB/RIF in children (50-53). A recent meta-analysis conducted by a WHO Steering Group concluded that Xpert MTB/RIF has a sensitivity of 66% from expectorated or induced sputum and 66% from gastric lavage or aspirate samples compared with culture for the diagnosis of pulmonary TB in children (54). Specificity was >98% for all specimen types compared with culture (54). Based on these data and on the recommendation of this Steering Group, a recent WHO policy update conditionally recommended use of Xpert MTB/RIF as an alternative to smear microscopy and culture for the diagnosis of pulmonary TB in children (54).

Hospital recommendation (Pocketbook): Include Xpert MTB/RIF as an alternative to smear microscopy and culture for the evaluation of all children with pneumonia and suspected TB in Pocketbook guidelines. This would harmonize Pocketbook guidelines with the recent WHO policy update and would be anticipated to improve the early detection of TB in children presenting with clinical pneumonia, albeit at some additional cost. National TB programs would still need to retain the capability to perform culture and smear microscopy given the sub-optimal sensitivity of Xpert MTB/RIF in children and the importance of smear microscopy to monitoring treatment response.

→ **Strength of recommendation: Recommended (weak)**

8) Amoxicillin Dispersible Tablets at all levels

The WHO has established child-friendly oral amoxicillin dispersible tablets (DT) as the optimal product formulation for first-line treatment of pneumonia in children less than 5 years of age at all levels, first-level referral hospital, frontline facility and within the community. This innovation in first-line antibiotic treatment—being flexible for dose adjustment while remaining within the effective therapeutic range—represents major life-, resource-, and cost-savings to families, health facilities, communities, and local governments. Oral amoxicillin DT can be easily administered by caregivers in the home, making treatment simpler. For many countries, this represents a shift from other commonly used formulations of amoxicillin, such as syrups and suspensions, and from other antibiotics. Despite it being a WHO-recommended lifesaving priority medicine, amoxicillin DT is frequently unavailable or underutilized.

Hospital (Pocketbook), frontline facility (IMCI), and community (iCCM) recommendation: Oral amoxicillin dispersible tablets for outpatient child pneumonia treatment at all health system levels.

→ **Strength of recommendation: Recommended (strong)**

Future considerations

Hospital, Frontline Facility: Several recent studies indicate that lung ultrasound has utility in childhood pneumonia diagnosis (55, 56). Most studies comparing performance to chest radiography have used experienced sonographers, with limited data available on use of this technology for pneumonia diagnosis by providers without formal ultrasonography training. A number of biomarkers, including C-reactive protein and procalcitonin, are currently being evaluated for their ability to distinguish viral and bacterial illnesses and predict pneumonia outcomes in children (57-59). In some of these studies, the addition of these biomarkers to clinical variables resulted in improved diagnostic accuracy (57, 59), but further research is needed before these measures can be routinely recommended and it is likely that point-of-care tests will need to be developed given limited laboratory capacity at most low-resource facilities. Thermal imaging systems also hold promise for the identification of children with bacterial pneumonia in hospital and front-line health facilities as an alternative to chest radiography and are an active area of research.

Community: Digital stethoscopes and auscultation, coupled with software programs capable of using these sounds to identify children with pneumonia, may facilitate pneumonia diagnosis by healthcare providers including community health workers, and is an area under investigation.(60)

B. Diarrhea and Dehydration Recommendations (8)

Based on survey responses and key informant interviews, five topics were selected for comprehensive literature review (ondansetron for vomiting, azithromycin for dysentery, probiotics for diarrhea, cryptosporidium diagnosis and treatment, and HIV diagnostic and treatment implications) and others for more brief review (prolonged diarrhea, shock, and rotavirus vaccine). Abbreviated risk-benefit tables are provided for the first three topics, in addition to online search terms for the five in-depth topics, in Appendix 2.

1) Ondansetron for vomiting

Several published systematic reviews of clinical trials in developed and developing countries evaluating oral ondansetron as an antiemetic for children with vomiting related to acute gastroenteritis (AGE) have reported statistically significant improvements in the cessation of vomiting, the need for intravenous fluid (IVF) rehydration, and hospitalizations, with a 2016 review reporting relative risk measures of 1.44 (95% CI 1.29-1.61), 0.41 (95% CI 0.29-0.59) and 0.40 (95% CI 0.19-0.83), respectively compared to placebo (61-63). A cost analysis of the use of oral ondansetron in children presenting to emergency departments in the U.S. and Canada estimated significant savings compared to a no-ondansetron policy(64). We were unable to obtain detailed pricing information for international markets, but prices quoted on Drugs.com (US pricing) were as low as \$1.88 per unit (for the 4mg disintegrating tab formulation)(65). Ondansetron is included in the WHO Model List of Essential Medicines for Children in injection, oral liquid, and oral tablet forms (but not the oral disintegrating tablet form) for children over one month of age(66). Limited data is available on the use of ondansetron in infants under six months, and the reported side effect profile includes rare QT prolongation(67). We did not find compelling evidence for the use of other antiemetics in children with vomiting and acute gastroenteritis.

Hospital recommendation (Pocketbook): Use of oral ondansetron for children greater than 6 months with vomiting due to gastroenteritis to reduce the need for IVF and continuation of breastfeeding when applicable.

→ ***Strength of recommendation: Recommended (weak)***

Frontline facility recommendation (IMCI): Use of oral ondansetron for children greater than 6 months with vomiting due to gastroenteritis to reduce the need for IVF and referral to hospital, improve tolerance of oral rehydration therapy (ORT) during high risk transfers to hospital, and continuation of breastfeeding when applicable.

→ ***Strength of recommendation: Recommended (weak)***

Community recommendation (iCCM): Not recommended as a community intervention at this time.

2) Azithromycin for dysentery

Currently ciprofloxacin is the only oral antibiotic mentioned specifically for treatment of dysentery in the WHO hospital pocketbook, while IMCI guidelines refer to use of first and second-line antibiotics based on local resistance patterns(68, 69). Knowing that in many settings the capacity to collect and disseminate local microbiological data to clinicians is limited, we considered mentioning azithromycin specifically as an oral treatment option. Azithromycin is included in the WHO Model List of Essential Medicines for Children in oral liquid and capsule forms, but only for treatment of trachoma(66). We were unable to obtain detailed pricing information for international markets, but prices quoted on Drugs.com (US pricing) were as low as \$1.32 per unit (for 250mg tabs)(70). A 2010 Cochrane systematic review on antibiotic therapy for *Shigella* dysentery that included adult and pediatric studies showed no statistically significant differences in fluoroquinolone versus macrolide therapy in terms of diarrhea or fever on follow up, time to cessation of blood in stool, bacteriologic failure, or other adverse events, with overall low to very low quality of evidence(71). *Campylobacter* is another not

infrequent infection causing dysentery (and non-bloody diarrhea) and macrolides have been recommended as first-line agents in children with this infection(72). IMCI guidelines recommend clinicians choose, when possible, a single antibiotic to treat various infections, and azithromycin has a better coverage profile than does ciprofloxacin for other frequent childhood bacterial infections including otitis media and pneumonia.

It should be noted that there are increasing reports of azithromycin-resistant *Shigella*, particularly in men who have sex with men(73-75), but also in children(76), so guidelines should clearly explain how to diagnose treatment failure and when to switch to an alternate drug.

Hospital recommendation (Pocketbook): Mention azithromycin as an oral treatment option for dysentery, particularly where local resistance data are not available, given its potential to treat *Shigella*, *Campylobacter*, and other bacterial infections.

→ **Strength of recommendation: Recommended (strong)**

Frontline facility recommendation (IMCI): Mention azithromycin as an oral treatment option for dysentery, particularly where local resistance data are not available, given its potential to treat *Shigella*, *Campylobacter*, and other bacterial infections.

→ **Strength of recommendation: Recommended (strong)**

Community recommendation (iCCM): Not recommended as a community intervention at this time.

3) Probiotics for diarrhea

A 2010 Cochrane systematic review of probiotics as treatment for acute diarrhea in adults and children included 56 pediatric studies with evidence that probiotics help shorten the duration and reduce stool frequency in acute infectious diarrhea(77). A more recent pediatric-focused systematic review for acute diarrhea included 8 studies and showed that probiotics reduced duration by 14.0% (95% CI 3.8-24.2%) and stool frequency on the second day of treatment by 13.1% (95% CI 0.8-25.3%), with no effect on hospitalization, but few studies were from low income settings, and none included concurrent zinc treatment(78). And a Cochrane systematic review in children with persistent diarrhea which included four trials showed that probiotics reduced duration by 4.02 days (95% CI 4.61-3.43), with one trial reporting a significantly shorter hospital stay with probiotic treatment(79). One small study from Thailand reported a non-significant reduction in overall estimated costs related to pediatric hospitalization for acute diarrhea with probiotic use(80). Overall there is low-moderate evidence of probiotic efficacy for the treatment of pediatric diarrhea but many studies have evaluated different strains and more data is needed on the optimal organism, dosing, treatment duration, as well as risks in specific populations including children with malnutrition and HIV(81).

Hospital recommendation (Pocketbook): Consider addition of probiotics as a treatment option for children admitted with diarrhea based on evidence of shorter hospital stays.

→ **Strength of recommendation: Recommended (weak)**

Frontline facility recommendation (IMCI): Consider addition of probiotics as an outpatient treatment option for children with diarrhea based on evidence of decreased stool frequency and duration.

→ **Strength of recommendation: Recommended (weak)**

Community recommendation (iCCM): Not recommended as a community intervention at this time.

4) Cryptosporidium diagnosis and treatment

GEMS was a multicenter prospective study to identify the etiology and population-level burden of diarrhea in children in developing world settings, and it identified *Cryptosporidium* as one of the top four causes of moderate-to-severe diarrhea with an increased risk of death in toddlers(82). Other studies from the developing world setting have also reported the high burden of *Cryptosporidium* diarrhea in children(83-85), and it is known to be an opportunistic diarrheal pathogen in children with HIV(86). PCR and rapid diagnostic tests for stool antigen offer increased sensitivity over microscopy, but widespread implementation is likely not possible at this time(83, 87). A 2013 literature review found that treatment with nitazoxanide resulted in significant reductions in clinical failure (RR 0.48, 95% CI 0.30-0.75) and parasitological failure (RR 0.62, 95% CI 0.46-0.83), but this therapy is less effective in HIV-infected patients and there is limited data on efficacy in infants(88, 89). We were unable to obtain detailed pricing information for nitazoxanide in international markets.

Hospital recommendation (Pocketbook): Perform stool microscopy for *Cryptosporidium* in children with persistent diarrhea in all locations, not just areas with high HIV prevalence, with specific mention of nitazoxanide as a treatment option when diagnostically confirmed.

→ **Strength of recommendation: Recommended (strong)**

Frontline facility recommendation (IMCI): No recommended changes.

Community recommendation (iCCM): No recommended changes.

5) HIV diagnostic and treatment implications

Children infected with HIV are likely to have more frequent or more severe episodes of diarrhea compared to HIV-uninfected children, and unexplained persistent diarrhea is a clinical stage 3 condition which should be a trigger for provider-initiated testing and counseling for HIV in high burden settings (WHO 2013 guidelines). *Cryptosporidium* diarrhea is more common in immune compromised children, but does not respond well to nitazoxanide treatment in this patient population(89). And while some studies have shown a higher burden of bacterial pathogens in HIV-infected adults and children(90, 91), we did not find enough evidence to support a different approach to antibiotic therapy for treatment of diarrhea for HIV-infected children.

Hospital recommendation (Pocketbook): Explicitly state that all children admitted with persistent diarrhea in countries with epidemic HIV should be offered HIV counseling and testing, with linkage to care if infected.

→ **Strength of recommendation: Recommended (strong)**

Frontline facility recommendation (IMCI): Explicitly state that all children with persistent diarrhea in countries with epidemic HIV should be offered HIV counseling and testing, with linkage to care if infected.

→ **Strength of recommendation: Recommended (strong)**

Community recommendation (iCCM): No recommended changes.

6) Prolonged diarrhea

The Persistent Diarrhea Working Group published research priorities in 2008 calling attention to the evidence gaps regarding prolonged diarrhea (7-14 days), its progression to persistent diarrhea, and its associated nutritional penalties(92). Subsequent studies have substantiated these findings(93), and some key respondents proposed a revision to WHO guidelines calling for referral of prolonged diarrhea as opposed to current community and IMCI recommendations for referring persistent diarrhea not responding to treatment, with potential stool testing and treatment for *Cryptosporidium*

(see above). This suggestion warrants further consideration, with more in-depth consideration of the longer-term nutritional implications.

7) Shock

Several respondents made suggestions about revisiting the treatment of shock based on the results of the FEAST trial from 2011(94). However, this study excluded patients with acute gastroenteritis, and we focused this literature review on hypovolemic shock related to fluid losses from acute diarrhea, not likely septic shock with fever. We did not find any compelling evidence to support a different approach to oral and parenteral volume expansion.

→ **Strength of recommendation: Not recommended (weak)**

8) Rotavirus vaccine

An area of interest identified for future research is how introduction of rotavirus vaccine in developing world countries will impact the etiology of childhood diarrhea, and whether there will be diagnostic or therapeutic implications. A large multisite study from developing countries reported differences in relative attributable fractions based on introduction of the vaccine(85), but at this time, there is insufficient longitudinal data from the developing world to recommend introduction of rotavirus immunization status into diagnostic or treatment algorithms at community, primary health facility, or hospital level.

→ **Strength of recommendation: Not recommended (weak)**

Future considerations

Other innovations mentioned by key respondents that are in research and development and may be considered in future guidelines revisions include the use of human milk oligosaccharides and hydrolyzed formulas for treatment of children who have weaned from breast milk(95, 96), amino acid-based ORT that may be beneficial over standard ORT for post-acute diarrheal weight gain, and molecular detection panels for identification of specific diarrheal pathogens at the referral hospital level(97).

C. Malaria Recommendations (1)

We identified one area for consideration in future guideline revision and two areas for further study prior to implementation. References and the risk-benefit summary table and literature search strategy are provided in Appendix 3.

1) Use of intravenous antibiotics in severe malaria

Among children with severe malaria, there is a high incidence of invasive bacterial infection (IBI), with non-typhoid salmonella the most common organism in areas of high-malaria prevalence (98-102). Incidence rates of bacteremia range from 4-19% and case fatality rate in severe malaria is higher when bacteremia is present (103-105). In one large study, mortality was 17% with IBI compared with 3.8% without IBI, and applying WHO criteria to guide antibiotic initiation demonstrated sensitivity and specificity of 60% and 53.3%, respectively. In addition, there are no identifiable clinical features which discriminate presence or absence of bacteremia among children with severe malaria (106, 107). Clinical features of impaired consciousness or respiratory distress identified 82% of fatal cases of severe malaria (108). With regard to malaria specifically, current pocketbook guidelines recommended antibiotics in the case of shock, or with suspicion of bacterial meningitis. Given the relative high incidence of IBI and difficulty identifying IBI clinically, hospital providers should be advised to consider intravenous antibiotic coverage with severe malaria, even without the presence of shock. Providers should be advised to obtain blood culture prior to initiating antibiotics, if laboratory capability exists. This recommendation should be further evaluated by prospective studies (1) validating clinical criteria to identify children with IBI and (2) evaluating recommended antibiotic regimens in areas without blood culture capability.

Hospital recommendation (Pocketbook): Consider addition of intravenous antibiotics in the treatment of severe malaria, considering local infection patterns and susceptibilities, especially in children with impaired consciousness and/or respiratory distress. Obtain blood culture prior to initiating antibiotics, where available.

→ **Strength of recommendation: *Recommend (weak)***; potential for antibiotic overuse exists if implemented without culture. Further study is needed.)

Frontline recommendation (IMCI): Not applicable, severe malaria is referred

Community recommendation (iCCM): Not applicable, severe malaria is referred

Future considerations

Use of mHealth and/or clinical algorithms to guide decisions on antibiotic treatment among children with fever who are malaria negative

There are higher rates of antibiotic prescription among febrile children who are malaria negative (109, 110) and high rates of antimalarial use persist even when diagnostic tests (RDT or smear) are negative (111, 112). There is a need for diagnostic tests and/or algorithms to guide the proper use of antibiotics/antimalarials and reduce unnecessary antibiotic prescriptions (113-115). An algorithm based on IMCI and utilizing mobile technology decreased unnecessary antibiotic prescriptions in community health centers (116). "Test-treat" packages compared with routine care also increase appropriate use of antimalarials and decrease unnecessary antibiotics (117). These interventions should be further studied and considered in future guidelines if validated.

Treatment of severe anemia in severe malaria

A recent study demonstrated that larger volume whole blood transfusion (30 mL/kg whole blood compared to 20 mL/kg) was safe in the treatment of severe anemia (Hb < 6) and resulted in a quicker hematological recovery and reduced need for subsequent transfusion (118). A multi-center study is underway evaluating liberal versus conservative transfusion strategies and their short- and long-term

mortality outcomes. The results of this trial will be critical in upcoming revisions of transfusion guidelines (119).

D. Malnutrition Recommendations (6)

Malnutrition Recommendations

We identified six malnutrition innovations for consideration in future guideline revisions. Particularly relevant to this section is WHO's December 2013 Guideline, "Updates on the Management of Severe Acute Malnutrition (SAM) in Infants and Children" (120). This was underpinned by eight systematic reviews, presented at a WHO Nutrition and Growth Advisory Group (NUGAG) meeting in February 2012(121). These included:

- Admission/discharge criteria for children who are 6–59 months of age with SAM;
- Where to manage children with SAM who have oedema;
- Use of antibiotics in SAM;
- Vitamin A supplementation in the treatment of SAM;
- Therapeutic feeding approaches in SAM;
- Fluid management in SAM;
- Management of HIV-infected children with SAM;
- Identifying and managing infants who are less than 6 months of age with SAM.

Due to the time lag between reviews and final guidelines being issued, we noted that the **2013 WHO SAM recommendations are not fully reflected in WHO 2013 Pocketbook; IMCI 2014 Chartbook; iCCM 2011 documents. The most urgent need therefore is to synchronize and align the various documents. It would be appropriate, given the malnutrition-specific expertise, to take the WHO 2013 SAM guidelines as 'gold standard'**. It is important however to note the paucity of evidence in this field: many WHO 2013 SAM recommendations were made on the basis of "weak" or "very weak" evidence. Evidence on SAM remains limited: there is all the greater need to consider the wider context and benefits/risks/costs of what little evidence there is. In this current review we have highlighted some issues which key informants and authors of this section believe are particularly discrepant or worthy of most immediate attention. Risk-benefit tables are provided as appendices for further detail. Please see appendix 5 for risk-benefit summary tables and references.

1) Diagnosis based on Mid Upper Arm Circumference (MUAC only)

Low MUAC is well established alongside low weight-for-length/height as an independent diagnostic criterion for wasting (<115mm= 'severe wasting'; 115 to<125mm = moderate wasting) (122, 123). WHO 2013 SAM guidelines recommend using MUAC in the community and MUAC or weight-for-height/length in primary health care facilities and hospitals (120). Characteristics making MUAC ideally suited to a wide variety of settings include simplicity, minimal cost, speed and ease of use (124). Other recent evidence includes that:

- MUAC it is more reliably measured (125), especially in younger infants (126)
- Mothers can also reliably assess MUAC (127)
- A 'click MUAC' plastic tool can be used by mothers in identifying low MUAC (128)
- A number-free coloured MUAC strap can be used by even illiterate/innumerate community workers (e.g. a small MUAC <115mm in the 'red zone', = 'SAM' (129))
- MUAC has superior performance in identifying those at high risk of mortality (130)
- MUAC changes in parallel to weight – making it a potential option for monitoring treatment/determining discharge from programmes as well as admission (131); further study and field testing is needed.

Many have argued for moving to MUAC-only case definitions of wasting (132),(133); others express concerns of excluding weight-for-length/height children that do not meet MUAC criteria (134, 135) and highlight that mortality is not the only outcome of concern in nutrition programmes (135) Though long and still debated (134, 135), evidence for potential benefit of MUAC only programming in contexts where community capacity and programme coverage is low, is now considerable(136). At very least, MUAC-only programming deserves much higher profile.

Hospital recommendation (Pocketbook): MUAC included already, but should be listed above weight-for-height (to better reflect mortality risk) and acknowledge more clearly as an independent criterion. Should also note MUAC criteria for moderate wasting (= 115mm to <125mm). New innovations like the colour-only tape and click-MUAC could also be noted.

→ **Strength of recommendation: Recommended (strong)**

Frontline facility recommendation (IMCI): As above, MUAC is already noted, though the potential benefit of MUAC-only programming to enable coverage and access to treatment is particularly great here in the community (136). Hence this should be considered as the default option. In some settings and populations, e.g. older children, weight-for-height should also be an option. **Strength of recommendation: Recommended (strong)**

Community recommendation (iCCM): Already focuses on MUAC alone. Particularly good that it highlights the use of the number-free MUAC strap. This could also be noted/acknowledged in Pocketbook/IMCI.

→ **Strength of recommendation: Recommended (strong)**

2) Focus on “Nutritionally Vulnerable” infants aged <6months

At present, wasting in infants < 6 months (infant <6m) is defined by low weight-for-length alone. Despite some promising studies in Kenya(126) and Gambia(137), more evidence is needed to finalize a global MUAC-based definition of infant wasting to complement the MUAC-defined wasting in older infants and children. This could come in the near future. Weight-for-age is also receiving renewed attention for this age group (138). For now, the limitations of weight-for-length are particularly notable in this age group: problems include poor reliability(126); practical challenges(139). As a result, infant malnutrition is rarely looked for in front-line practice(140). To further overcome these limitations in assessment, a wider definition of ‘nutritionally vulnerable’ infants is recognized as important(141). This involves feeding, clinical and social/ maternal assessment criteria as well as anthropometry(138)

Hospital recommendation (Pocketbook): This already lists some signs/symptoms of nutritional vulnerability, but it should be made clearer that these constitute independent reasons for support, irrespective of anthropometry.

→ **Strength of recommendation: Recommended (weak)**

Frontline facility recommendation (IMCI): (please also see treatment innovations below). Age cutoffs need to be changed. A peer-reviewed IMCI style

→ **Strength of recommendation: Recommended (weak)**

Community recommendation (iCCM): as for IMCI. Same (but more simply expressed) case criteria could be used.

→ **Strength of recommendation: Recommended (weak)**

3) Acute Malnutrition in Infants <6 months (including change to age cutoffs)

Acute malnutrition in infant<6m is not uncommon (142). WHO 2013 SAM guidelines recognize the need to align infant <6m SAM treatment with that of older children: differentiating “complicated”/“uncomplicated” SAM; including recommendations for outpatient (community-based) treatment for uncomplicated SAM (120). Intervention packages rather than single interventions are needed and include linking with other services and sectors including antenatal care, neonatal care, social care, mental health care – as well as clinical referrals and skilled breastfeeding support at all levels(143).

Hospital recommendation (Pocketbook): This already describes inpatient treatment of complicated infant SAM well. However, outpatient options, based on WHO 2013 SAM guidelines also need to be included as planning must begin early, once the main problem has stabilized. Interventions include emphasis on: Kangaroo care; community-based breastfeeding support; support for the mother/carer as part of infants’ treatment.

→ **Strength of recommendation: Recommended (strong)**

Frontline facility recommendation (IMCI): Current IMCI age cutoffs are unsuitable for nutrition. Rather than the <2month / >2 month distinction, nutritional assessment/ treatment should be divided

into <6 months age / 6 to 59 months. With the target diet for <6 month olds being exclusive breastfeeding there are very clear differences in management for the two age groups. Both are described in detail in WHO 2013 SAM guidelines. An peer-reviewed IMCI-style infant <6m guideline already exists(141).

→ **Strength of recommendation: Recommended (strong)**

Community recommendation (iCCM): Identification of SAM in infants<6m is not currently mentioned; it should be added. Options for treatment of uncomplicated SAM should be included. Follow up of discharged cases should be emphasised. Kangaroo mother care can be integrated with iCCM for nutrition.

→ **Strength of recommendation: Recommended (strong)**

4) Integrated treatment of SAM and MAM

Though both part of “Community Management of Acute Malnutrition” (CMAM), treatment for SAM and MAM (Moderate Acute Malnutrition) traditionally uses different nutritional products and is often even run by separate agencies in separate programmes. Globally, and in general. UNICEF has the mandate for SAM programmes that treat uncomplicated cases; WHO leads inpatient support for treatment of complicated SAM; WFP caters for MAM programmes. Given that SAM and MAM are a continuum rather than discrete conditions, it is plausible that management of uncomplicated cases can be combined. Bringing management closer together may also facilitate greater access to treatment for MAM children that are sick. Using one nutritional product at different doses has already been shown in one study to have similar clinical/nutritional outcomes, but programmatic advantages are reflected in superior coverage(144). Other studies are in the pipeline.

Hospital recommendation (Pocketbook): In the short term, there needs to be recognition and treatment of MAM. In the medium term, SAM and MAM treatment can be more directly integrated.

→ **Strength of recommendation: Recommended (weak)**

Frontline facility recommendation (IMCI): As for pocketbook. Include MAM treatment.

→ **Strength of recommendation: Recommended (weak)**

Community recommendation (iCCM): As for IMCI. Include MAM treatment ASAP

→ **Strength of recommendation: Recommended (weak)**

5) Post-discharge care and “thrive” interventions to improve long term outcomes

With the great success of new community-focused treatments of malnutrition reducing mortality (123), there is now increasing focus on longer term outcomes (145). Unfortunately, outcomes in some studies have been poor: high on-going mortality; persistent stunting; poor development; early indicators of future non-communicable disease(146),(147). It is not yet clear how post-discharge mortality might be reduced, but possibilities include antibiotic prophylaxis(148). No successful direct evidence in malnutrition yet exists. There is however well evidenced support for child development: The UNICEF Care for Child Development package http://www.unicef.org/earlychildhood/index_68195.html. This could be included as a key element of current guidelines.

Work is also needed on co-treatment of disability and SAM/MAM – this is a growing problem and presents numerous management challenges(149, 150).

Hospital recommendation (Pocketbook): Include links to Care for Child Development package

→ **Strength of recommendation: Recommended (weak)**

Frontline facility recommendation (IMCI): As for pocketbook

→ **Strength of recommendation: Recommended (weak)**

Community recommendation (iCCM): As for IMCI

→ **Strength of recommendation: Recommended (weak)**

6) Oedema and nutritional status assessment and monitoring using Bioelectrical Impedance Vector Analysis (BIVA).

Bioelectrical impedance analysis (BIA) is a non-invasive and rapid test done safely in clinical settings for quantifying total body water(151). BIA usually requires population-specific equations; but the reliability of such equations is low in individuals with body fluid imbalances, such as oedema in SAM (152). A novel method to assess body fluid variation know as Bioelectrical Impedance Vector Analysis (BIVA)(153), using BIA data, bypasses this limitation and enables a qualitative assessment of individual's hydration and cellular integrity. Unfortunately, most of the literature regarding BIA in children has conventionally focused on validating equations for the quantification of body water and only a small number of recent studies have investigated the utility of BIA in SAM(154).

Hospital recommendation (Pocketbook): Inclusion of BIVA to the diagnosis of SAM in children and to the monitoring of progress following care could provide a more comprehensive evaluation by assessing nutritional status, hydration and cellular integrity. It can be useful also to assess prognosis at admission for care.

→ **Strength of recommendation: Recommended (weak, future potential)**

Frontline facility recommendation (IMCI): If the method is further developed and simplified, BIVA could also help improve the diagnosis and monitoring of SAM.

→ **Strength of recommendation: Not recommended (weak)**

Community recommendation (iCCM): At present, BIA technology is not developed to a level that could be used by less technically trained personnel.

→ **Strength of recommendation: Not recommended (weak)**

E. Newborn Recommendations (9)

Newborn Disease

Based on survey responses and key informant interviews, nine newborn health innovations were identified for consideration in future guideline revisions and reviewed. Please see Appendix 5 for the newborn risk-benefit summary tables and references, future considerations, and additional innovation topics provided by key informants but not included in the main report.

Diagnostic innovations

1) Facility weight measurement and birth weight standards

Small for gestational age (SGA), defined as birth weight below 10th percentile for gestational age and gender (155), is a commonly used proxy for intrauterine growth restriction in low-resource settings. The global burden of both intrauterine growth restriction and preterm birth—the main drivers of low birthweight (<2,500 grams) remains exceedingly high.(156) Clinical assessment of SGA and newborn nutritional status in general is often challenging. A myriad of different size charts have been developed using dissimilar methodologies and based on heterogeneous populations. Customized size charts incorporating maternal characteristics have been used increasingly in practice but have not demonstrated utility over more simplistic population-based size charts in predicting neonatal morbidity or mortality. (157, 158)

More recently, the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) developed an international birth weight standard intended to complement the current WHO child growth standards (released in 2006). (159) Including newborns from eight different geographical locations (China, India, Italy, Kenya, Oman, UK and USA), these standards are derived strictly from pregnancies likely to have had healthy fetal growth. In doing so, the standards strive to capture the distribution of newborn weights at optimum pregnancy conditions, instead of merely the average distribution among a population. (160-163) INTERGROWTH-21st also established postnatal growth standards to monitor the growth of preterm infants. (164)

Currently, IMCI guidelines put forth by WHO fail to include the crucial first week of a newborn's life. Inclusion of INTERGROWTH-21st standards for birth weight and preterm follow-up within such a chapter, as well as within the Pocketbook, might be considered to facilitate identification of SGA newborns, who are at increased risk of morbidity and mortality. (165) Particularly in settings with reasonably accurate gestational dating methods, there is much potential benefit in using these new standards to identify high-risk infants and predict neonatal mortality risk. However, vast majority of women delivering in LIC does not know her first day of last menstruation and presumptive ultrasound diagnosis very seldom occurs. So in any case of gestational age insecurity, it is advisable to consider only birth weight, as a parameter. Moreover, in diagnostic and therapeutic terms, at present, there are no differences in management of SGA and LBW.

Hospital recommendation (Pocketbook): Include recommendations for point-of-care birth weight measurement for all hospital births, as well as comparison to INTERGROWTH-21st birth weight standards to guide the diagnosis of SGA babies and differentiate them from preterm babies; incorporate postnatal growth standards for preterm infants (<37 weeks' gestational age) into the Pocketbook to assess growth until 64 weeks' postmenstrual age, after which the WHO Child Growth Standards for term infants can be used.

Frontline facility recommendation (IMCI): Expand IMCI guidelines to include the crucial first week of life, when infants are at greatest risk and the vast majority of infant deaths occur. Include recommendations for point-of-care birth weight measurement for all facility births, as well as comparison to INTERGROWTH-21st birth weight standards to guide the diagnosis of SGA babies.

Community recommendation (iCCM): Not applicable.

2) Revise and harmonize danger signs for infants 0-59 days of life in the IMCI and iCCM guidelines

Health care providers in many countries rely on iCCM and IMCI guidelines for their first and often second line health facility contacts, neither of which provide guidelines on monitoring and care of neonates 0-6 days of life (when 75% of all neonatal deaths occur). (Dr. Hannah Blencowe) We recommend expanding IMCI guidelines to include the crucial first week of life, when infants are at greatest risk and the vast majority of infant deaths occur.

Typically, health workers providing immediate care in the community and primary health facilities have had as little as 2-3 weeks' instruction in the care of the sick newborn. Training health workers (CHWs and non-specialist physicians) to identify large numbers of signs or different sets of signs depending on the health care levels may threaten feasibility of implementation.(166) There is evidence for including a discrete list of *high yield* and prevalent danger signs and symptoms that can be recognized by non-specialist physicians (166-170) and CHWs (166 , 171, 172) to predict severe illness(166-168, 170, 172) or death.(166, 171) Inclusion, simplification, age-group expansion, and harmonization of the following danger signs and symptoms in IMCI and iCCM guidelines can efficiently and effectively identify young infants (including newborns 0-6 days of life) at risk of severe illness. It is notable that these signs are not specific for identifying the etiology of illness [i.e. prematurity vs. intrapartum related events vs. serious bacterial infection (SBI)] and that strength of association (ORs) varies significantly depending on the differences in the spectrum and prevalence of illness episodes.(166) In addition, stratifying newborns evaluated in the community to identify "high risk" infants might be used as an additional tool to improve triage and resource allocation to those at highest risk of mortality.(173)

Hospital recommendation (Pocketbook): Not applicable.

Frontline facility recommendation (IMCI): Include the Young Infant Study 7-sign algorithm (YIS7) for management of infants 0-59 days of life(DOL) concurrent with implementation and scaling up of community-based intervention strategies aimed at improving early healthcare seeking behavior.

→ **Strength of recommendation: Recommended (strong)**

Community recommendation (iCCM): Include YIS7 for management of infants 0-59 days of life (DOL), and consider introducing the topic of "high risk" infants who should receive more frequent visits or referral to a medical facility.(173)

→ **Strength of recommendation: Recommended (strong)** for YIS7 guidelines and weak for "high risk" infant category - while evidence for validity of CHW recognition of danger signs exists, benefits of stratifying infants to "high risk" groups has not been validated in other settings outside rural India.

3) Community weight measurement

Currently iCCM does not include community-based guidelines on the care of low birthweight (LBW) infants (weighing <2,500 grams at birth, due to either being born preterm or small for gestational age). Given that the rate of home births continues to be high in many developing country contexts, it is important to promote community-based mechanisms for the identification and special care of this vulnerable subset. Currently, most infants born outside of facilities are not weighed. It has been demonstrated that community workers can effectively accomplish this simple but important task during early home visits (preferably within 24 hours of birth).(174, 175) It has also been demonstrated that LBW infants who are identified might be managed effectively in the home setting by the mother and a trained health worker.(176)

A device with promising evidence for weighing infants in field settings is BIRTHweigh III,(177) a low-cost handheld spring scale with >90% sensitivity and specificity in making LBW classifications (as compared with the gold standard UNICEF Seca electronic scale). Field trials in Nepal and India have demonstrated high accuracy and community acceptability. (178-180) The color-coded weight categories presented by this scale bypass the issue of health workers being unable to read a conventional scale, but in doing so, fail to provide a numeric birth weight reading. Use of this or similar scales with clear referral guidelines for community health workers can aid in the timely identification and management of LBW infants, who contribute to the vast majority of infant deaths. Additional home-based care for these infants may include the points outlined in the joint WHO/UNICEF strategy: *Home visits for the newborn child*: increased attention to keeping the newborn warm, initiation of breastfeeding within the first hour of life, extra attention to hygienic practices, extra attention to neonatal danger signs and early care-seeking, and support for monitoring growth (see also “high risk” category in newborn innovations #2). (181)

Community recommendation (iCCM): Expand iCCM guidelines to include care of infants up to 2 months of age. Incorporate birth weight measurement by community health workers or skilled attendants into iCCM, as is outlined in WHO’s Facilitator Manual for *Caring for the newborn at home* (Session 20). Incorporate special care/referral guidelines for low birthweight infants born in home settings. These may reflect those presented in the joint WHO/UNICEF strategy *Home visits for the newborn child*: increased attention to keeping the newborn warm, initiation of breastfeeding within the first hour of life, extra attention to hygienic practices, extra attention to neonatal danger signs and early care-seeking, and support for monitoring growth.(181)

→ **Strength of recommendation: Recommended (strong).**

Treatment innovations

Hospital and frontline facility:

Health staff working at hospital level in low income countries (LIC) continue to await for recommendations on cost-effective, comprehensive neonatal care interventions. Specific evidence for the effectiveness of a package of hospital-based care for ill and preterm infants is scarce in low and middle-income countries (LMIC) since trials tend to focus on incremental gains of single interventions.(182) We identified a package of five interventions believed to leap forward hospital level newborn care.

4) Update neonatal resuscitation guidelines in pocketbook and include guidelines for neonatal resuscitation in IMCI

The Pocketbook neonatal resuscitation algorithm and chart (p46-49) need to be updated with new guidelines adapted for the LIC context. (183) These updated guidelines apply primarily to newly born infants, but are also applicable to neonates who have completed the newborn transition and require resuscitation during the first weeks after birth. Intensive (if any), subintensive rooms, delivery rooms, operating theaters must be in place with an equipped and ready neonatal resuscitation corner. Readiness for neonatal resuscitation requires assessment of perinatal risks, a system to assemble the appropriate personnel based on that risk, and an organized method for ensuring immediate access to supplies and equipment. A checklist (Appendix List 1) must be in place to ensure immediate access to the necessary equipment and must be checked before a neonate is in need of resuscitation, ideally before every delivery (184), including a list of the necessary equipment. (Appendix List 2 and Figure 1) Additional recommendations are provided based on a careful review of the current pocketbook guidelines and include recommendations from the new guidelines adapting these to the LIC context. (183) (Appendix List 3)

Hospital recommendation (Pocketbook): Review and revise the neonatal resuscitation procedure and algorithm and include the new recommendations (183) as discussed in the Appendix.

→ **Strength of recommendation: Recommended (strong)** for guideline update, coming from a wide consensus (ILCOR); conditional for acquisition of new equipment listed above.

Frontline facility recommendation (IMCI): Expand IMCI to include the first week of life, and include neonatal resuscitation within this chapter. Due to the extreme need of harmonization among publications, we suggest including the AAP Helping Babies Breathe (HBB) manual inside IMCI manual.(185)

→ **Strength of recommendation: Recommended (strong)**, it is an AAP validated tool, widely used.

5) Update Continuous positive airway pressure devices (CPAP) in hospital guidelines

Respiratory distress is the most common symptom in sick newborns, and remains one of the most common causes of neonatal deaths in LICs(186) while verbal autopsy in LICs may not differentiate between various causes of respiratory distress in term and preterm infants.(187) Currently, the pocketbook management of respiratory distress syndrome (RDS) is almost the same regardless of the etiology and includes (depending on maximum available support) provision of oxygen via nasal cannula, antibiotics, and aminophylline/caffeine. Evidence from high-quality studies including 2 Cochrane reviews (188, 189) (see appendix) suggests significant survival advantage in preterm neonates with moderate-severe respiratory distress managed with continue positive airways pressure devices (CPAP) as compared with those managed with oxygen alone. (190-192) In meconium aspiration syndrome (MAS), application of CPAP can be beneficial by resolving the atelectatic alveoli due to alveolar injury and secondary surfactant deficiency. (193)

The first report of CPAP devices in neonatal care in LICs dates back to 20 years ago. (194) More recent studies have assessed the use of CPAP versus no ventilation in South Africa,(195) Malawi, (196, 197) India,(194) South America, Fiji, and Vietnam (191, 198-200) with encouraging results. In LICs, there are NICUs with mechanical ventilators but without CPAP; also in these settings, use of CPAP is advantageous in reducing newborn mortality and the rate of intubation/mechanical ventilation. (201-203) Available evidence suggests that CPAP is a safe and effective mode of therapy in neonates with respiratory distress in LMICs and should be considered as an important strategy to treat newborns with respiratory insufficiency in LMICs. Moreover, in these settings bubble CPAP can be effectively and safely applied by nurses and other health workers after their initial training(203), and thus may improve neonatal survival and quality of neonatal care. Two Cochrane reviews, one updated in 2015, (189) conclude that CPAP has a role in nurseries where intensive care is not immediately available, which may include settings such as LICs without access to intensive care. It should be noted that advances in technology that most improve survival rates for infants with RDS would not significantly impact neonatal mortality without overall improvements in general neonatal care, including better methods of thermoregulation, feeding practices, intravenous nutrition, and regionalized perinatal care.(204)

Hospital recommendation (Pocketbook): Include guidelines in the Pocketbook for CPAP devices for newborns with respiratory distress.

→ **Strength of recommendation: Recommended (strong)**- need for large high-quality studies regarding safety, and cost effectiveness of CPAP in LICs. Further research is needed before wide-scale implementation in LMICs. (205)

6) Umbilical venous catheter (UVC) in hospital guidelines

Health care providers in high-income countries (HIC) utilize umbilical venous catheters (UVCs) routinely for management of ill preterm and term newborns. This procedure provides a secure, fast, and relatively easy vascular access during the first week of life, preserving the delicate peripheral

veins, and can be performed in the delivery room (emergently) or in the NICU. Inclusion of UVC placement guidelines in the pocketbook should be considered as part of a comprehensive package of neonatal interventions. The advantages of UVC placement in comparison to peripheral vein catheters in neonates include: possibility of intravenous nutrition, safe drug and blood product administration, elimination of stress and pain related to repeated venipuncture attempts, emergency vascular access in the delivery room, blood draws, and access for exchange blood transfusion (for instances in cases of severe hyperbilirubinemia). (206-212) The procedure is short and does not require anesthesia. The use of UVC was first reported in 1947 (213) and among 549 surveyed US NICUs, 99% reported standard placement of UVCs in ill preterm and term newborns.(214) WHO suggests that UVC placement in LIC hospitals is indicated when the need for IV access is urgent, but a peripheral IV line cannot be quickly established (215); nonetheless the procedure is not mentioned in the Pocketbook. When surveyed, both nurses (who can also performed the procedure if trained) and doctors from HICs and LICs consider UVCs as an important treatment tool for patient care. (216, 217) Additional references to relevant studies are included in the appendix.

Hospital recommendation (Pocketbook): Include in the Pocketbook guidelines for the UVC procedure as currently included in “Managing newborn problems: a guide for doctors, nurses, and midwives, World Health Organization 2003”.

→ **Strength of recommendation: Recommended (strong)** - more data needed but large magnitude impact likely).

7) Role of Pulse oximetry in pocketbook guidelines for newborns

Despite its importance in virtually all types of acute severe illness, hypoxemia is often not well recognized or managed in settings where resources are limited, especially in developing countries.(218) A child must be recognized as hypoxemic, either by a trained health care provider on the basis of clinical signs or with a pulse oximeter.(219) Pulse oximetry is commonly used to assist clinicians in assessment and management of newborns in the delivery room (DR). In many DRs, pulse oximetry is now the standard of care for managing high risk infants, enabling immediate and dynamic assessment of oxygenation and heart rate.(220) Used to measure the percentage of oxygenated hemoglobin in arterial blood (SpO₂), pulse oximetry is the most accurate non-invasive method for detecting hypoxemia. The technology is robust and cost-effective for district hospitals. Pulse oximeters can be used to both detect and monitor hypoxemia, make more efficient use of oxygen supplies, and improve patient monitoring.(221, 222) Pulse oximetry correctly identified hypoxemia in 20–30% more children than with signs alone.(223) The systematic use of pulse oximetry to monitor and treat newborns and children in resource-poor developing countries, when coupled with a reliable oxygen supply, improves quality of care and reduces mortality.(224) Routine pulse oximetry screening test is also effective in identifying newborns with critical congenital heart defects (CCHD) and other hypoxemic illnesses in various settings.(225-227)

Hospital recommendation (Pocketbook):

Include pulse oximetry in the Pocketbook not only for use in neonatal departments but also, specifically, as a device for neonatal resuscitation in neonatal resuscitation corners and as a device useful in the diagnosis of critical congenital cardiac diseases.

→ **Strength of recommendation: Recommended (strong)** (Use of pulse oximetry to better monitor and to better choose treatment in newborns in resource-poor developing countries, improves quality of care and reduces mortality)

8) Facility thermal care

Low birthweight and preterm infants are at high risk of hypothermia due to impaired body temperature regulation—a large problem particularly in low-resource settings lacking incubators and access to neonatal intensive care. Kangaroo mother care (KMC) is a package of interventions including early and continuous skin-to-skin contact with the mother, frequent and exclusive breastfeeding, and early

discharge from the facility. For newborns weighing <2,000 grams in hospital-based settings, the benefits of KMC after stabilization are well-established.(228-231) A recent Cochrane review demonstrated a 40% reduced risk of mortality before discharge, 55% reduced risk of nosocomial infection/sepsis, and 66% reduced risk of hypothermia.(232) An even more recent review found the risk in mortality reduction to be 36%.(233) The cost-effective intervention has also been linked with improved breastfeeding and long-term growth outcomes, and is important for mother-infant attachment.(232, 234) Even so, widespread adoption has not yet been achieved. Including KMC in IMCI guidelines for the care of stabilized low birthweight infants in hospital and frontline facilities, in harmony with other relevant WHO materials, may help improve uptake of this important intervention.

Hospital recommendation (Pocketbook) AND Frontline facility recommendation (IMCI):

Incorporate Kangaroo Mother Care (KMC) into all facility-based care for *low birthweight infants* (<2,500 grams) regardless of gestational age after stabilization. KMC includes a package of interventions: early and continuous skin-to-skin contact with the mother, frequent and exclusive breastfeeding, and early discharge from the facility with follow-up. Promote early skin-to-skin contact (SSC) in facility-based care (within hospital and frontline facilities) for *healthy normal weight infants*. Early SSC involves placing the naked baby on the mother's chest in prone position with a dry cap on the head and warm blanket across the back, ideally immediately following birth.(235)

Community health worker:

9) Community thermal care/Kangaroo Mother Care

While the utility of facility-based Kangaroo Mother Care (KMC) in improving neonatal outcomes particularly for low birthweight infants (weighing <2,500 grams at birth) is well-established, community-based KMC has much less evidence.(232, 233) Community KMC includes skin-to-skin contact immediately following birth for all infants, and breastfeeding support.(236) The sole randomized-controlled trial concluded insufficient justification for community KMC due to potential bias from missing birthweight data. However, for infants modeled to be low birthweight, neonatal mortality rate was 9.5% in the intervention arm vs. 22.5% in the control arm (adjusted OR 0.37, 95% CI 0.16 to 0.86).(237) A secondary analysis on this cohort found that implementation factors may play a large role in effectiveness of community KMC, as impact on survival was exclusively for those newborns held in skin-to-skin contact for at least seven hours per day in the first two days of life.(238) As such, community KMC remains a promising yet unproven intervention. More work must be done on tackling perceived barriers to practicing continuous KMC and strategies for gaining widespread community support.(239, 240) However, it is reasonable to include thermal care of infants within iCCM and incorporate post-discharge KMC practices into IMCI guidelines to guide mothers for the home setting.

Hospital recommendation (Pocketbook) AND Frontline facility recommendation (IMCI):

Incorporate post-discharge Kangaroo Mother Care (KMC) guidelines into the Pocketbook and IMCI for low birthweight infants born in facilities. Continuation of KMC at home following initiation in the hospital or frontline facility includes: early and continuous skin-to-skin contact with the mother (emphasizing importance of contact several hours per day), as well as frequent and exclusive breastfeeding.

Community recommendation (iCCM): Expand iCCM guidelines to include care of infants less than 2 months of age. Include thermal care of all infants within this section, for implementation by community health workers in partnership with mothers and families.

WHO Child Health Guideline Innovation Working Group Key Informants (110)

Himali de Silva	Eric Houpt	Gerda Pohl
Maya Asir	Elizabeth Cristofalo	Jane E. Lucas
Peter Kazembe	Carl Bose	Abedallattif Khalloof
Jane E. Harding	Daniel Feikin	Linus Olson
Esther Babirekere-Iriso	Himali de Silva	Victoria Lima
Helen Nabwera	Casie Tesfai	Uduak Okomo
Louise Tina Day	Everlyn Matiri	Carlos A. Delgado
Helen S. Doss	Raj Kumar Gupta	Simon Pius
Gulam Muhammed Al Kibria	Christopher Gill	Ebru Ergenekon
Tanya Khara	Terrence Forrester	Ronan Mac Loughlin
Bernard E. Ebruke	Martha Mwangome	Jane Hirst
Laura Hammitt	Ma. Corazon Bernabe	Carlo Bellieni
Daniel Martinez Garcia	Sean R. Moore	Jose Luis Alvarez Moran
S. van der Kam	Safaa	Chloe Puett
Emma Sacks	Malgorzata Grzemska	Alexandra Rutishauser-Perera
James Colborn	Malcolm Molyneux	Chepkorir Langat Purity
Zein A Karrar	Henry C. Baggett	Naor Bar-Zeev
Beena D Kamath-Rayne	Jennifer Verani	Hedwig Deconinck
Lanyero Betty	Polly Walker	Emmalita M Manalac
Himani Pandya	Joseph Okebe	Mark Myatt
Nicolette Nabukeera Barungi	Archana Patel	Abhay Bang
Fyezah Jehan	Deborah Vandyke	Saradha Suresh
Martina Oneko	Ann Ashworth	Anthony P. Calibo
A.S.M. Nawshad Uddin Ahmed	Richard Wennberg	Mark Neuman
Trevor Duke	Andi L. Shane	Deborah Harris
Arturo Abdelnour	Michele Usuelli	Michele Monroy
Luis Martinez Arroyo	Jennifer Yourkavitch	Geert Tom Heikens
Hamish Graham	Akash Bang	Indi Trehan
Donald Thea	Jesper Kjærgaard	Sudha Basnet
Yolanda Barbera Lainez	Zaeem Haq	Grant Mackenzie
Jeanette Bailey	Sayed Khedr Selim	Tahmeed Ahmed
Susan Niermeyer	Natasha Lelijveld	Steve Graham
Sanjay Sinho	Hannah Blencowe	Bradford D. Gessner
Steve Wall	Annemieke Brands	Kathryn Maitland
M Monir Hossain	Per Ashorn	Mike English
Alain Labrique	David Brewster	Mark Manary
Kevin Sztam	Shihab Ibrahim	

Johns Hopkins University Informational Specialists (3)

Katie Lobner
Carrie Price
Maria Trusky

Appendix 1.

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Risk-benefit summary table for including pulse oximetry in IMCI and iCCM guidelines

Existing recommendation / practice

Pocketbook hospital guidelines include pulse oximetry in the assessment of the child with cough and/or difficult breathing. Pocketbook guidelines classify those children with an oxygen saturation <90% (i.e., severe hypoxemia) as having severe pneumonia requiring hospitalization for parenteral antibiotic and oxygen treatment.

Proposed recommendation / practice

- Include oxygen saturation measurement in the IMCI guidelines when assessing non-hospitalized children with a general danger sign and when assessing a non-hospitalized child with cough and/or difficult breathing. Refer all children with an oxygen saturation <90% to the nearest facility for oxygen treatment.
- Include oxygen saturation measurement in the iCCM guidelines when assessing non-hospitalized children with a general danger sign and when assessing a non-hospitalized child with cough and/or difficult breathing. Refer all children with an oxygen saturation <90% to the nearest facility for oxygen treatment.

Quality of evidence

(for outcomes deemed critical)

LOW

There is one unpublished observational study from Malawi (Eric D. McCollum, personal communication, manuscript under review, (1)) that demonstrates an increased referral of children with hypoxemic pneumonia at frontline outpatient facilities and with community health workers using pulse oximeters. This study also showed that a large proportion of hypoxemic pneumonia cases at frontline outpatient facilities would not have been referred without pulse oximetry, and to a lesser extent the same with community health workers. Another unpublished study from Malawi (Carina King, personal communication, manuscript under review (2)) shows that an oxygen saturation of 90-94% in children 2-59 months old with fast breathing measured by community health workers predicts treatment failure. Additional evidence from non-hospitalized children most relevant to IMCI and iCCM guidelines needs to be generated from other settings and referral outcomes need to be included in future study designs. Program-based cost effectiveness data with pulse oximeter use at frontline outpatient health facilities and with community health workers is needed.

Benefits/desired effects

Improve the identification and referral of non-hospitalized children with hypoxemic pneumonia <90% at lower level health facilities and receiving care from non-traditional community health workers.

Risks/ undesired effects

The cost and maintenance of quality pulse oximeters appropriate for children is still high and investment in these devices at frontline outpatient facilities and with community health workers may not be cost effective in actual practice. Full implementation of oximeters at outpatient facilities may be unaffordable for national programs in developing countries.

Values/ Acceptability

- There is a strong demand to include pulse oximetry at these outpatient health system levels by content experts.
- Some carers and healthcare providers may value a non-invasive diagnostic test at lower level health facilities and with community health workers.
- Some carers and healthcare providers may not value an additional test on their child and may not accept the results.

Costs

High quality pulse oximeters appropriate for children of all ages cost at least \$200 USD with an age-appropriate probe.

Feasibility

National program capacity to invest and maintain pulse oximeter devices at outpatient facilities or with community health workers

	without significant cost reductions and/or subsidies is questionable.
Final recommendation	Include oxygen saturation measurement in the IMCI and iCCM guidelines when assessing non-hospitalized children with a general danger sign and when assessing a child with cough and/or difficult breathing. Refer all children with an oxygen saturation <90%.
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak</i> CONDITIONAL (unknown whether pulse oximetry increases successful referral of children with hypoxemic pneumonia and if it is cost-effective in actual practice)
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Low
Comments justifying recommendation	Hypoxemic pneumonia is a driver of child pneumonia mortality and the inclusion of oxygen saturation more prominently in the IMCI and iCCM guidelines will demonstrate collective support for pulse oximetry. This may help to further create momentum to reduce oximetry costs and encourage innovation to make oximetry feasible for wider scale up at the outpatient care level.
Gaps, research needs, comments	Threshold for inpatient facility referral may need to be higher than 89% (current threshold) given that many children with oxygen saturations 90-92% have signs of respiratory distress that are associated with treatment failure. These children would likely benefit from closer observation in hospital as well as parenteral antibiotics.

PubMed literature search criteria for pulse oximetry at frontline facilities or community health workers during child pneumonia care outside of hospitals (search conducted May 8, 2016):

("Oximetry"[Mesh] OR "oximetry"[tiab] OR "Oximeter"[tiab] OR "oximeters"[tiab] OR "oxygen saturation"[tiab]) AND ("Pneumonia"[Mesh] OR "Pneumonia, Bacterial"[Mesh] OR "acute chest syndrome"[tiab] OR "aspiration pneumonia" [tiab] OR "bacterial pneumonia"[tiab] OR "bronchiolitis obliterans organizing pneumonia"[tiab] OR "Bronchopneumonia"[tiab] OR "bronchopneumonia"[tiab] OR "community acquired pneumonia"[tiab] OR "Experimental Lung Inflammation"[tiab] OR "health care associated pneumonia"[tiab] OR "hospital acquired pneumonia"[tiab] OR "inflammatory lung disease"[tiab] OR "legionnaire disease"[tiab] OR "lobitis"[tiab] OR "lung infiltrate"[tiab] OR "lung inflammation"[tiab] OR "lung inflammations"[tiab] OR "peripneumonia"[tiab] OR "pleuritis"[tiab] OR "pleuropneumonia"[tiab] OR "pneumonia"[tiab] OR "pneumonias"[tiab] OR "pneumonic lung"[tiab] OR "pneumonitides"[tiab] OR "pulmonary candidiasis"[tiab] OR "Pulmonary Inflammation"[tiab] OR "pulmonary inflammation"[tiab] OR "Pulmonary Inflammations"[tiab] OR "severe acute respiratory syndrome"[tiab] OR "ventilator associated pneumonia"[tiab]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Child, Preschool"[mesh] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab]) AND Cochrane LMIC Filter

***88 manuscript titles, 13 abstracts, 4 full manuscripts reviewed, 2 manuscripts cited.**

1. McCollum ED, King C, Deula R, Zadutsa B, Mankhambo L, Nambiar B, et al. Pulse oximetry implementation with rural frontline health workers during three years of child pneumonia care in two central Malawi districts: a prospective observational study. 2016.

2. King C, Colbourn T, Mankhambo L, Beard J, Hay Burgess D, Costello A, et al. Non-treatment of children with community health worker-diagnosed fast-breathing pneumonia in rural Malawi – sub-analysis of a prospective cohort study. 2016.

Risk-benefit summary table for including bubble continuous positive airway pressure (bCPAP) in Pocketbook guidelines

Existing recommendation / practice

Pocketbook hospital guidelines do not formally include bCPAP in the treatment of the child with severe pneumonia and hypoxemia. CPAP is referenced in one sentence of section 4.5.1 (p96) for children with bronchiolitis and respiratory failure, who also would meet severe pneumonia criteria.

Proposed recommendation / practice

- Include bCPAP treatment as an option for children with severe pneumonia and hypoxemia who have failed low flow oxygen treatment.
- Include a description of a low-cost bCPAP set-up with diagrams in the oxygen section of the Pocketbook along with associated clinical and nursing care.

Quality of evidence

(for outcomes deemed critical)

LOW

bCPAP improves short-term respiratory physiology outcomes in children with severe pneumonia. Multiple studies from Malawi,(1-3) Ghana,(4) and India(5, 6) have shown improvements in respiratory rate, oxygenation, and/or hypercarbia after bCPAP.

One Bangladeshi randomized controlled trial at an urban referral hospital compared nasal bCPAP to low and high flow nasal oxygen in children 1-59 months old with hypoxemic pneumonia.(7) The study was controversially stopped early by the local DSMB due to lower mortality in the bCPAP arm, leaving final conclusions uncertain.(7)

Patient selection for bCPAP likely important for optimizing outcomes and resources but limited data to date, cost-effectiveness data absent and limited implementation data. Mortality data from multiple settings needed.

Benefits/desired effects

Reduce mortality in children with severe pneumonia and hypoxemia.

Risks/ undesired effects

The ongoing costs including maintenance of bCPAP equipment is unknown and may ultimately not be affordable for national pneumonia programs. The current flow driver for bCPAP is likely to be an oxygen concentrator and one bCPAP set-up typically uses one oxygen concentrator (since 5-10 liters per minute of flow is generally required). In comparison, one oxygen concentrator can deliver low flow oxygen to five or more patients at once. Therefore, mortality benefit of bCPAP, compared to low flow oxygen, and appropriate patient selection criteria are of paramount importance. bCPAP tends to require more intensive nursing care with higher nurse-to-patient ratios to maintain the nasal interface on the child so that maximum benefit can be achieved. It is likely that only certain settings will be able to achieve this higher level of supportive care needed to achieve benefit in a programmatic setting.

Values/ Acceptability

- Some carers and healthcare providers may value and accept bCPAP at first level referral hospitals.
- Some carers and healthcare providers may not value and accept bCPAP at first level referral hospitals, especially since weaning off of bCPAP often fails initially and requires the child to restart bCPAP. This may not be acceptable to many carers.

Costs

Full bCPAP set-ups can cost \$2,000-\$3,000 when including the oxygen concentrator that can provide up to 10 liters per minute flow and a reliable nasal interface (mask or prongs). A separate humidification unit can further increase costs but some

	concentrator designs are now incorporating a modified humidifier into the device at lower costs.
Feasibility	National program capacity to invest and maintain bCPAP devices and oxygen concentrators without significant cost reductions and/or subsidies is questionable.
Final recommendation	Include bCPAP treatment as an option for children with severe pneumonia and hypoxemia who have failed low flow oxygen treatment. Include a section on bCPAP set-up with diagrams in the oxygen section of the Pocketbook along with associated clinical and nursing care.
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak QUALIFIED</i> (more data needed from a variety of high-burden settings to include mortality outcomes, implementation feasibility, and cost-effectiveness)
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Low
Comments justifying recommendation	More data is needed from a variety of high-burden settings to include mortality outcomes, implementation feasibility, and cost-effectiveness.
Gaps, research needs, comments	Additional data demonstrating improved mortality in children with pneumonia from different settings, including those with higher rates of malaria, anemia, HIV, and malnutrition, will be needed. Further, more data regarding appropriate patient selection for bCPAP, implementation feasibility and programmatic outcomes, and cost-effectiveness is needed from multiple settings.

PubMed literature search criteria 2005-2016, search conducted on May 8, 2016.

("Pneumonia"[Mesh] OR "Pneumonia, Bacterial"[Mesh] OR "acute chest syndrome"[tiab] OR "aspiration pneumonia"[tiab] OR "bacterial pneumonia"[tiab] OR "bronchiolitis obliterans organizing pneumonia"[tiab] OR "Bronchopneumonia"[tiab] OR "bronchopneumonia"[tiab] OR "community acquired pneumonia"[tiab] OR "Experimental Lung Inflammation"[tiab] OR "Experimental Lung Inflammations"[tiab] OR "health care associated pneumonia"[tiab] OR "hospital acquired pneumonia" [tiab] OR "inflammatory lung disease"[tiab] OR "legionnaire disease"[tiab] OR "lobitis"[tiab] OR "lung infiltrate"[tiab] OR "lung inflammation"[tiab] OR "lung inflammations"[tiab] OR "nonspecific inflammatory lung disease"[tiab] OR "organizing pneumonia"[tiab] OR "peripneumonia"[tiab] OR "pleuritis"[tiab] OR "pleuropneumonia"[tiab] OR "pneumonia"[tiab] OR "pneumonias"[tiab] OR "pneumonic lung"[tiab] OR "pneumonic pleurisy"[tiab] OR "pneumonic pleuritis"[tiab] OR "pneumonitides"[tiab] OR "pulmonal inflammation"[tiab] OR "pulmonal inflammations"[tiab] OR "pulmonary candidiasis"[tiab] OR "Pulmonary Inflammation"[tiab] OR "pulmonary inflammation"[tiab] OR "pulmonary inflammations"[tiab] OR "pulmonic inflammation"[tiab] OR "pulmonic inflammations" [tiab] OR "severe acute respiratory syndrome"[tiab] OR "ventilator associated pneumonia"[tiab]) AND (("Continuous Positive Airway Pressure"[Mesh] AND "bubble"[tiab]) OR "bubble CPAP"[tiab] OR ("bubble" AND ("continuous positive airway pressure"[tiab] OR "bcpap"[tiab]))) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies" [tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths" [tiab])

***87 manuscript titles, 9 abstracts, 8 full manuscripts reviewed, 7 manuscripts cited.**

1. Walk J, Dinga P, Banda C, Msiska T, Chitsamba E, Chiwayula N, et al. Non-invasive ventilation with bubble CPAP is feasible and improves respiratory physiology in hospitalised Malawian children with acute respiratory failure. *Paediatrics and international child health*. 2016;36(1):28-33.
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3. McCollum ED, Smith A, Golitko CL. Bubble continuous positive airway pressure in a human immunodeficiency virus-infected infant. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2011;15(4):562-4.
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7. Chisti MJ, Salam MA, Smith JH, Ahmed T, Pietroni MA, Shahunja KM, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. *Lancet*. 2015;386(9998):1057-65.

Risk-benefit summary table for incorporation of inhaled bronchodilator trial into pneumonia management algorithms

Existing recommendation / practice

In current **IMCI** and **Pocketbook guidelines**, a trial of a rapid acting inhaled bronchodilator is given to children with fast breathing or chest indrawing only if there is wheezing on examination. Age-based dosing and administration of multiple inhaled bronchodilator doses in rapid succession (when needed) is described in **Pocketbook guidelines**, while **IMCI guidelines** recommend 2 puffs of Salbutamol given via metered dose inhaler (100 µg/puff) every 15 minutes for all children 2 months to 5 years of age. In **IMCI guidelines**, children with wheezing are reclassified based on their response to this bronchodilator trial, and children with continued fast breathing or chest wall indrawing receive antibiotic treatment for pneumonia. **Pocketbook guidelines** recommend that children with wheezing and continued signs of hypoxia (including chest wall indrawing) or fast breathing after a bronchodilator trial should be admitted to the hospital, but it is not specified whether these children should be treated according to the pneumonia management algorithm.

Proposed recommendation / practice

- Incorporate routine use of a rapidly acting inhaled bronchodilator into management algorithms for all children 2 months to 5 years of age with fast breathing or chest indrawing, regardless of whether wheezing is present or not.
- Incorporate age-based dosing of inhaled salbutamol and describe administration of multiple doses in rapid succession (when needed) in IMCI guidelines for consistency with Pocketbook guidelines.
- Harmonize the IMCI and Pocketbook guidelines to include reclassification of disease status (severe pneumonia, pneumonia, no pneumonia) after bronchodilator trial in children with wheezing and fast breathing or chest wall indrawing.

Quality of evidence

(for outcomes deemed critical)

VERY LOW

We identified no studies that examined a management algorithm that included a trial of a rapidly acting inhaled bronchodilator for all children, including those without wheeze, who have fast breathing or chest wall indrawing.

There are limited data from downgraded observational studies that response to bronchodilators may be used as a criterion to identify children with fast breathing or chest wall indrawing who do not require antibiotics.

Benefits/desired effects

- 1) Reduced antibiotic exposure would be anticipated to lead to fewer antibiotic-related adverse effects and lessen the development of antibiotic resistance.
- 2) Potential to reduce hospital referrals and admissions for children with bronchodilator-responsive symptoms – most of whom would be anticipated to have viral illnesses.

Risks/ undesired effects

- 1) A trial of bronchodilators could delay receipt of antibiotic therapy in children with bacterial pneumonia, which has the potential to worsen outcomes of these children. Some children with bacterial pneumonia who require antibiotics may have improvement in their symptoms with the bronchodilator trial.
- 2) Routine administration of a rapidly acting inhaled bronchodilator would require additional time for health care providers to administer.
- 3) Chest auscultation has low inter-observer agreement, and additional training would be warranted to train providers to accurately detect wheezing.

Values/ Acceptability

- The majority of hospital and front-line health facilities are anticipated to have providers with experience in chest auscultation and availability of inhaled bronchodilators.

Costs

Costs would be anticipated to be somewhat lower based on the reduced need for referral and hospitalization and reduced use of

	antibiotics.
Feasibility	The systems and expertise needed to incorporate a trial of inhaled bronchodilator into the management algorithms are already in place at the hospital and frontline facility levels.
Final recommendation	There are insufficient data to expand use of a trial of rapidly acting inhaled bronchodilator to all children, including those without recognized wheeze, who have fast breathing and/or chest indrawing in the IMCI and Hospital Care for Children pneumonia management guidelines. IMCI guidelines should incorporate age-based dosing of inhaled salbutamol and describe administration of multiple doses in rapid succession (when needed) to harmonize with Pocketbook guidelines. Pocketbook guidelines should more clearly include a reclassification of pneumonia severity following the trial of bronchodilator therapy for children with wheezing, and specify that antibiotic treatment is warranted for children who have continued fast breathing or chest wall indrawing.
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak</i> CONDITIONAL
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> VERY LOW
Comments justifying recommendation	There are insufficient data to support incorporation of a bronchodilator trial into pneumonia management algorithms for children in the absence of wheezing. Such a modification would expose a large number of children to inhaled bronchodilator therapy without evidence suggesting benefit, and could delay receipt of antibiotic therapy in children with bacterial pneumonia.
Gaps, research needs, comments	Further research is needed to determine whether children whose fast breathing or chest wall indrawing resolve with bronchodilator therapy can be safely managed without antibiotics.

PubMed literature search criteria for management of wheezing in hospital and front-line facilities (search conducted May 8, 2016):

("Pneumonia"[Mesh] OR "pneumonia"[tiab] OR "pneumonias"[tiab]) AND ("Respiratory Sounds"[Mesh] OR "respiratory sound"[tiab] OR "respiratory sounds"[tiab] OR wheez*[tiab]) AND (inciden*[tiab] OR prevalen*[tiab] OR association*[tiab]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Child, Preschool"[mesh] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab])

102 manuscript titles, 16 abstracts, 3 full-text manuscripts reviewed in this literature search; 6 additional manuscript titles identified based on citations from reviewed full-text manuscripts, and additional 3 full-text manuscripts reviewed; 4 manuscripts cited

1. Hazir T, Qazi S, Nisar YB, Ansari S, Maqbool S, Randhawa S, et al. Assessment and management of children aged 1-59 months presenting with wheeze, fast breathing, and/or lower chest indrawing; results of a multicentre descriptive study in Pakistan. Archives of disease in childhood. 2004;89(11):1049-54.
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3. Alves da Cunha AJ, Alves Galvao MG, Santos M. Wheezing and respiratory infections in Brazilian children: does a standard management work? Journal of tropical pediatrics. 2009;55(3):198-201.

4. Lochindarat S, Qazi SA, Bunnag T, Nisar YB, Jatanachai P. Are we adequately managing children with wheeze using the standard case management guidelines? Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2008;91 Suppl 3:S60-8.

Risk-benefit summary table for use of Xpert MTB/RIF assay in the diagnosis of pulmonary tuberculosis in children

Existing recommendation / practice

Current **Pocketbook guidelines** recommend obtaining specimens for smear microscopy and culture from most children with suspected pulmonary tuberculosis (TB). Xpert MTB/RIF is recommended as the initial diagnostic test for children suspected of having multidrug-resistant or HIV-associated TB. The document "Xpert MTB/RIF: WHO Policy update and Implementation manual" (WHO, 2013) reasserts this latter recommendation and offers a conditional recommendation that Xpert MTB/RIF may be used rather than smear microscopy and culture for all children suspected of having pulmonary TB.

Proposed recommendation / practice

- Include Xpert MTB/RIF as an alternative to smear microscopy and culture as the initial diagnostic test for all children with pneumonia and suspected pulmonary TB.

Quality of evidence

LOW

Benefits/desired effects

1) Xpert MTB/RIF has improved sensitivity for the diagnosis of pulmonary TB in children compared with smear microscopy. Xpert MTB/RIF provides more rapid results than culture. Routine use of Xpert MTB/RIF would be anticipated to improve the early identification of children with pulmonary TB.
2) The detection of isoniazid resistance could improve outcomes of children with multidrug-resistant TB.

Risks/ undesired effects

1) While the sensitivity of the Xpert MTB/RIF assay for the diagnosis of pulmonary TB is superior to smear microscopy, it is sub-optimal compared to culture. Thus, children with suspected pulmonary TB and a negative Xpert MTB/RIF still require further evaluation (including culture).
2) Performance of smear microscopy would remain an important component of national TB programs given its importance in monitoring response to treatment.

Values/ Acceptability

- Routine use of Xpert MTB/RIF would have substantial financial and operational implications for national TB programs, and this would likely need to be phased in gradually.

Costs

Expanded use of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children with pneumonia would be anticipated to increase costs. The Xpert MTB/RIF cartridges are available at a discounted price (<US\$10-15) for low- and middle-income countries. The GeneXpert device costs approximately US\$17,000.

Feasibility

The Xpert MTB/RIF assay is most commonly performed on specimens (expectorated or induced sputum, gastric aspirates) that can be collected in most hospital settings. The GeneXpert platform is increasingly available in low- and middle-income countries, largely through the support of public and private organizations. TB Xpert - a partnership between UNITAID and the WHO - will deliver 220 GeneXpert systems and >1 million cartridges to 21 countries in Africa, Asia, and Eastern Europe.

Final recommendation

Pocketbook guidelines should be updated to harmonize with a recent WHO policy update that conditionally recommended Xpert MTB/RIF as an alternative initial diagnostic test for all children with pneumonia and suspected pulmonary TB.

Strength of recommendation

Strong OR Conditional OR Qualified OR Weak
CONDITIONAL

Quality of evidence

High / Moderate / Low / Very Low

**that informs
recommendation**

LOW

**Comments justifying
recommendation**

Diagnosis of TB in children is challenging because of difficulty in obtaining appropriate specimens and paucibacillary disease. Expanded use of Xpert MTB/RIF would improve capabilities for TB diagnosis in children.

**Gaps, research needs,
comments**

- Nearly all of the available studies were conducted in referral or major hospital settings. Further data are needed on the feasibility and associated costs of expanding use of this technology to front-line health care facilities.

PubMed literature search criteria for not treating fast breathing pneumonia with antibiotics, search conducted May 5, 2016 with the limits of 2005 – 2016 and English

("Pneumonia"[Mesh] OR "pneumonia"[tiab] OR "pneumonias"[tiab]) AND (nonsevere [tiab] OR non severe [tiab] OR fast breathing [tiab] OR "world health organization"[tw]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn" [mesh] OR "Child, Preschool"[mesh] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics" [tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab]) AND (antibiotic*[tiab] OR anti biotic*[tw] OR amoxicillin*[tw] OR amoxycillin*[tw] OR "anti-bacterial agents"[mesh] OR placebo*[tw] OR pharmacolog*[tw] OR nonpharmacolog*[tw] OR drug therapy [sh] OR alternative*[tw] OR complementar*[tw]) AND (comparison*[tw] OR comparative*[tw] OR compared[tw] OR treatment*[tw] OR management*[tw] OR intervention*[tw] OR course*[tw])

*126 results returned

PubMed literature search criteria for oral amoxicillin treatment of chest indrawing pneumonia by community health workers, search conducted May 5, 2016 with the limits of 2005 – 2016 and English

("Pneumonia"[Mesh] OR "pneumonia"[tiab] OR "pneumonias"[tiab]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Child, Preschool"[mesh] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab]) AND ("Amoxicillin" [Mesh] OR "amoxicillin"[tiab] OR "amoxycillin"[tiab]) AND ("cct"[tw] OR "ccts"[tw] OR "clinical trial"[publication type] OR "clinical trial"[tw] OR "clinical trials as topic"[mesh] OR "clinical trials"[tw] OR "clinical trials, phase i as topic"[mesh] OR "clinical trials, phase ii as topic"[mesh] OR "clinical trials, phase iii as topic"[mesh] OR "clinical trials, phase iv as topic" [mesh] OR "cohort studies"[mesh:noexp] OR "cohort"[tw] OR "cohorts"[tw] OR "concurrent"[tw] OR "controlled clinical trial"[pt] OR "controlled clinical trials as topic"[mesh] OR "controlled trial"[tw] OR "controlled trials"[tw] OR "follow up" [tw] OR "follow-up studies"[mesh] OR "followup"[tw] OR "incidence"[tw] OR "long term"[tw] OR "longitudinal studies" [mesh] OR "longitudinal"[tw] OR "longterm"[tw] OR "multi center"[tw] OR "multi centre"[tw] OR "multicenter studies as topic"[mesh] OR "multicenter"[tw] OR "multicentre"[tw] OR "non experimental"[tw] OR "nonexperimental"[tw] OR "observational studies as topic"[mesh] OR "observational study"[pt] OR "phase 1"[tw] OR "phase 2"[tw] OR "phase 3" [tw] OR "phase 4"[tw] OR "phase four"[tw] OR "phase i"[tw] OR "phase ii"[tw] OR "phase iii"[tw] OR "phase iv"[tw] OR "phase one"[tw] OR "phase three"[tw] OR "phase two"[tw] OR "phase four"[tw] OR "placebo" [tw] OR "placebos" [tw] OR "prospective studies"[mesh] OR "randomisation"[tw] OR "randomization"[tw] OR "randomized" [tw] OR "randomised"[tiab] OR "randomly" [tw] OR "random"[tw] OR "rct"[tw] OR "rct"[tw] OR "rcts"[tw] OR "studies"[ti] OR "study"[ti] OR drug therapy[sh] OR groups [tw] OR observation*[tw] OR placebo [tw] OR prospective*[tw] OR randomized[tw] OR randomly[tw] OR systematic*[tw] OR trial* [ti] OR "meta analysis"[tw] OR "metaanalysis"[tw] OR "meta analyses"[tw] OR "metaanalyses"[tw])

*151 results returned

PubMed literature search criteria for severity of illness scores in children with pneumonia, search conducted May 5, 2016

("Severity of Illness Index"[Mesh] OR "severity of illness"[tiab] OR "risk score"[tiab] OR "risk scores"[tiab] OR "prognostic score"[tiab] OR "prognostic scores"[tiab]) AND ("Pneumonia"[Mesh] OR "Pneumonia, Bacterial"[Mesh] OR "acute chest syndrome"[tiab] OR "aspiration pneumonia"[tiab] OR "bacterial pneumonia"[tiab] OR "bronchiolitis obliterans organizing pneumonia"[tiab] OR "Bronchopneumonia"[tiab] OR "bronchopneumonia"[tiab] OR "community acquired pneumonia"[tiab] OR "Experimental Lung Inflammation"[tiab] OR "health care associated pneumonia"[tiab] OR "hospital acquired pneumonia"[tiab] OR "inflammatory lung disease"[tiab] OR "legionnaire disease"[tiab] OR "lobitis"[tiab] OR "lung infiltrate"[tiab] OR "lung inflammation"[tiab] OR "lung inflammations"[tiab] OR "peripneumonia" [tiab] OR "pleuritis"[tiab] OR "pleuropneumonia"[tiab] OR "pneumonia"[tiab] OR "pneumonias"[tiab] OR "pneumonic lung"[tiab] OR "pneumonitides"[tiab] OR "pulmonary candidiasis"[tiab] OR "Pulmonary Inflammation"[tiab] OR "pulmonary inflammation"[tiab] OR "Pulmonary Inflammations"[tiab] OR "severe acute respiratory syndrome"[tiab] OR "ventilator associated pneumonia"[tiab]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent" [tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood" [tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric" [tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab])

AND Cochrane LMIC Filter

*189 results returned

Appendix 2.

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Abbreviated risk-benefit summary table for ondansetron for the treatment of vomiting to guidelines, (see text for additional details and references)

Existing recommendation/practice

Current IMCI and WHO hospital guidelines specifically recommend to not use any antiemetics in children with vomiting and diarrhea.

Proposed recommendation/practice

Include the use of oral ondansetron for children with vomiting secondary to acute gastroenteritis at primary health facilities and referral hospitals.

Quality of evidence
(for outcomes deemed critical)

Moderate-high, including randomized controlled trials from developed and developing world countries, and systematic reviews.

Benefits/desired effects

Reduce vomiting to increase the likelihood of successful oral rehydration, with decreased need for intravenous fluids and referrals for hospital care. Quicker return to breastfeeding for children not yet weaned.

Risks/undesired effects

Side effect profile includes potentially serious complications including rare reports of serotonin syndrome when used with other serotonergic medications, and prolongation of the QT segment which can lead to unstable cardiac rhythm and death.

Values/Acceptability

Ondansetron is already on the WHO Model List of Essential Medicines for Children, and both caregivers and providers may value a treatment that reduces vomiting in children with acute gastroenteritis. The side effect profile with rare, but potentially serious adverse reactions, however, may not be acceptable to caregivers and providers.

Costs

We were unable to obtain detailed pricing information for international markets, but prices quoted on Drugs.com (US pricing) were as low as \$1.88 per unit (for the 4mg disintegrating tab formulation).

Feasibility

Could be incorporated into existing national drug distribution channels.

Final recommendation

Include oral ondansetron in IMCI and Hospital guidelines for children >6 months with vomiting secondary to acute gastroenteritis.

Strength of recommendation

Recommended (weak)

Quality of evidence that informs recommendation

Moderate-high

Comments justifying recommendation

See text

Gaps, research needs, comments

More pediatric studies on the use of oral ondansetron from developing world countries.

PubMed literature search criteria, divided into two searches conducted May 5, 2016:

("Ondansetron"[Mesh] OR "ondansetron"[tw] OR "selective 5 ht3 receptor antagonist"[tw] OR "selective 5 ht3 receptor antagonists"[tw] OR "GR38032F"[tw] OR "GR-38032F"[tw] OR "GR 38032F"[tw] OR "Zofran"[tw] OR "SN-307"[tw] OR "SN 307"[tw] OR "SN307"[tw] OR "cedantron"[tw])

OR "ceramos"[tw] OR "emeset"[tw] OR "gr 38032"[tw] OR "gr 38032f"[tw] OR "gr c507 75"[tw] OR "gr38032"[tw] OR "gr38032f"[tw] OR "modifical"[tw] OR "narfoz"[tw] OR "onsia"[tw] OR "sakisozin"[tw] OR "sn 307"[tw] OR "vomceran"[tw] OR "zetron"[tw] OR "zofran"[tw] OR "zofrene"[tw] OR "zofron"[tw] OR "zophran"[tw] OR "zophren"[tw] OR "zuplenz"[tw]) AND ("Gastroenteritis"[Mesh] OR gastroenteriti*[tw]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "young adult"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab] OR "young adult"[tiab] OR "young adults"[tiab])

("Antiemetics"[Mesh] OR anti emetic*[tw] OR antiemetic*[tw]) AND ("Gastroenteritis"[Mesh] OR gastroenteriti*[tw]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "young adult"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab] OR "young adult"[tiab] OR "young adults"[tiab]) NOT ondansetron*[tw]

*113 results returned

Abbreviated risk-benefit summary table for azithromycin for the treatment of dysentery to guidelines, (see text for additional details and references)

Existing recommendation/practice

Currently ciprofloxacin is the only oral antibiotic mentioned specifically for treatment of dysentery in the WHO hospital pocketbook, while IMCI guidelines refer to use of first and second-line antibiotics based on local resistance patterns.

Proposed recommendation/practice

Specifically mention azithromycin as a treatment option for pediatric dysentery.

Quality of evidence (for outcomes deemed critical)	Moderate, including randomized controlled trials from developed and developing world countries, and a systematic review.
Benefits/desired effects	Successfully treat <i>Shigella</i> and <i>Campylobacter</i> dysentery. Treat other concurrent bacterial infections per IMCI recommendations.
Risks/undesired effects	Treatment failure due to azithromycin-resistant <i>Shigella</i> , drug side effects.
Values/Acceptability	Azithromycin is already on the WHO Model List of Essential Medicines for Children for treatment of trachoma, and both caregivers and providers may value a treatment that treats dysentery and other common pediatric bacterial infections. It has a generally safe side effect profile, but it may not be acceptable to some caregivers and providers.
Costs	We were unable to obtain detailed pricing information for international markets, but prices quoted on Drugs.com (US pricing) were as low as \$1.32 per unit (for the 250mg tabs).
Feasibility	Could be incorporated into existing national drug distribution channels.
Final recommendation	Strong recommendation to mention azithromycin as an oral treatment option for dysentery in IMCI and hospital guidelines, particularly where local resistance data are not available, given its potential to treat <i>Shigella</i> , <i>Campylobacter</i> , and other bacterial infections.
Strength of recommendation	Recommended (strong)
Quality of evidence that informs recommendation	Moderate
Comments justifying recommendation	See text
Gaps, research needs, comments	Additional antibiotic resistance data for <i>Shigella</i> from developing world countries.

PubMed literature search criteria, search conducted May 5, 2016:

("Dysentery"[Mesh] OR "dysentery"[tw] OR infectious diarrhea*[tw]) AND ("Azithromycin"[Mesh] OR "azadose"[tw] OR "azitrocin"[tw] OR "azythromycin"[tw] OR "cp 62993"[tw] OR "cp62993"[tw] OR "cp-62993"[tw] OR "goxal"[tw] OR "sumamed"[tw] OR "toraseptol"[tw] OR "ultreon"[tw] OR "vinzam"[tw] OR "zentavion"[tw] OR "zithromax"[tw] OR "zitromax"[tw])

*23 results returned

Abbreviated risk-benefit summary table for probiotics for the treatment of diarrhea to guidelines, (see text for additional details and references)

Existing recommendation/practice

Currently no mention of probiotics in community, IMCI, or hospital guidelines.

Proposed recommendation/practice

Include probiotics as a recommended treatment for pediatric acute and/or persistent diarrhea.

Quality of evidence
(for outcomes deemed critical)

Low-moderate, includes randomized controlled trials from developed and developing world countries, and systematic reviews, but not all evaluating same strains, doses, durations.

Benefits/desired effects

Decreased stool frequency, duration of illness, and duration of hospitalizations.

Risks/undesired effects

Disseminated infections in immunocompromised patients including children with HIV.

Values/Acceptability

Treatment with live strains of probiotics may be a novel concept for caregivers and providers and may encounter acceptability issues not commonly seen with other more traditional medications.

Costs

We were unable to obtain detailed pricing information for international markets.

Feasibility

Could be incorporated into existing national drug distribution channels.

Final recommendation

Weak recommendation to consider addition of probiotics as a treatment option for children admitted with diarrhea based on evidence of shorter hospital stays, and as an outpatient treatment option based on evidence of decreased stool frequency and duration.

Strength of recommendation

Recommended (weak)

Quality of evidence that informs recommendation

Low-moderate

Comments justifying recommendation

See text

Gaps, research needs, comments

Standardized studies in terms of strain used, dose, duration, etc.

PubMed literature search criteria, search conducted May 5, 2016:

("Diarrhea"[Mesh] OR diarrhea*[tiab] OR diarrhoea*[tiab]) AND ("Probiotics"[Mesh] OR probiotic*[tw] OR pro biotic*[tw]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "young adult"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab] OR "young adult"[tiab] OR "young adults"[tiab])

*85 results returned

PubMed literature search criteria for diagnosis and treatment of *Cryptosporidium*, search conducted May 5, 2016, (see text for additional details and references)

("Cryptosporidium"[Mesh] OR cryptosporidium*[tw]) AND ("Diarrhea"[Mesh] OR diarrhea*[tiab] OR diarrhoea*[tiab]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab]) AND (diagnos*[tw] OR "exam"[tw] OR "exams"[tw] OR "examination"[tw] OR "test"[tw] OR "tests"[tw] OR "testing"[tw] OR "assay"[tw] OR "blood"[tw] OR "serum"[tw] OR "marker"[tw] OR "markers"[tw] OR "mass screening"[mesh] OR screen*[tw] OR misdiagnos*[tw] OR "accuracy"[tw] OR "finding"[tw] OR "findings"[tw] OR treatment*[tw] OR "course"[tw] OR antibiotic*[tw] OR intervention*[tw] OR detection*[tw]) NOT ("animals"[mesh] NOT ("animals"[mesh] AND "humans"[mesh]))

*173 results returned

PubMed literature search criteria for HIV diagnostic and treatment implications, divided into two searches conducted May 5, 2016, (see text for additional details and references)

("Diarrhea"[Mesh] OR diarrhea*[tiab] OR diarrhoea*[tw]) AND ("HIV"[mh] OR "HIV-1"[mh] OR "HIV-2"[mh] OR "HIV Infections"[mh] OR "HIV"[tw] OR "HIV-1"[tw] OR "HIV-2"[tw] OR "HIV"[tiab] OR "human immunodeficiency virus"[tw] OR "human immunodeficiency virus 1"[tw] OR "human immunodeficiency virus 2"[tw] OR "human immunodeficiency viruses"[tw] OR "HTLV-III"[tw] OR "human T cell lymphotropic virus type III"[tw] OR "human T lymphotropic Virus type III"[tw] OR "human t-cell leukemia virus type III"[tw] OR "human t cell leukemia virus type III"[tw] OR "human t-cell lymphotropic virus type III"[tw] OR "human t-lymphotropic virus type III"[tw] OR "LAV-HTLV-III"[tw] OR "lymphadenopathy-associated virus"[tw] OR "lymphadenopathy associated virus"[tw] OR "lymphadenopathy-associated viruses"[tw] OR "lymphadenopathy associated virus"[tw] OR "Acquired Immunodeficiency Syndrome"[mh] OR "acquired immunodeficiency syndrome"[tw] OR "AIDS"[tw] OR "acquired immunologic deficiency syndrome"[tw] OR "acquired immune deficiency syndrome"[tw] OR "acquired immuno-deficiency syndrome"[tw] OR "acquired immuno deficiency syndrome"[tw] OR "acquired immuno-deficiency syndromes"[tw] OR "acquired immuno deficiency syndromes"[tw] OR "acquired immunodeficiency syndromes"[tw]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab]) AND ("Reproducibility of Results"[Mesh] OR algorithm*[tw] OR sensitivit*[tw] OR specificit*[tw] OR valid*[tw] OR "reproducibility"[tiab] OR "test retest"[tiab] OR detection*[tw] OR assessment*[tw])

("Diarrhea"[Mesh] OR diarrhea*[tiab] OR diarrhoea*[tw]) AND ("HIV"[mh] OR "HIV-1"[mh] OR "HIV-2"[mh] OR "HIV Infections"[mh] OR "HIV"[tw] OR "HIV-1"[tw] OR "HIV-2"[tw] OR "HIV"[tiab] OR "human immunodeficiency virus"[tw] OR "human immunodeficiency virus 1"[tw] OR "human immunodeficiency virus 2"[tw] OR "human immunodeficiency viruses"[tw] OR "HTLV-III"[tw] OR "human T cell lymphotropic virus type III"[tw] OR "human T lymphotropic Virus type III"[tw] OR "human t-cell leukemia virus type III"[tw] OR "human t cell leukemia virus type III"[tw] OR "human t-cell lymphotropic virus type III"[tw] OR "human t-lymphotropic virus type III"[tw] OR "LAV-HTLV-III"[tw] OR "lymphadenopathy-associated virus"[tw] OR "lymphadenopathy associated virus"[tw] OR "lymphadenopathy-associated viruses"[tw] OR "lymphadenopathy associated virus"[tw] OR "Acquired Immunodeficiency Syndrome"[mh] OR "acquired immunodeficiency syndrome"[tw] OR "AIDS"[tw] OR "acquired immunologic deficiency syndrome"[tw] OR "acquired immune deficiency syndrome"[tw] OR "acquired immuno-deficiency syndrome"[tw] OR "acquired immuno deficiency syndrome"[tw] OR "acquired immuno-deficiency syndromes"[tw] OR "acquired immuno deficiency syndromes"[tw] OR "acquired immunodeficiency syndromes"[tw]) AND ("Child"[mesh] OR "Infant"[mesh] OR "Infant, Newborn"[mesh] OR "Adolescent"[mesh] OR "Child, Preschool"[mesh] OR "adolescence"[tiab] OR "adolescence"[tiab] OR "adolescent"[tiab] OR "adolescents"[tiab] OR "babies"[tiab] OR "baby"[tiab] OR "child"[tiab] OR "childhood"[tiab] OR "child hood"[tiab] OR "children"[tiab] OR "infant"[tiab] OR "infants"[tiab] OR "juvenile"[tiab] OR "juveniles"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "paediatric"[tiab] OR "paediatrics"[tiab] OR "pediatric"[tiab] OR "pediatrics"[tiab] OR "preschool child"[tiab] OR "teen"[tiab] OR "teenager"[tiab] OR "teenagers"[tiab] OR "teens"[tiab] OR "toddler"[tiab] OR "toddlers"[tiab] OR "youth"[tiab] OR "youths"[tiab]) AND (pathogen*[tw] OR "treatment outcome"[tw] OR "treatment outcomes"[tw] OR "outcome assessment"[tw] OR "outcome assessments"[tw] OR "outcomes assessment"[tw])

*225 results returned

Appendix 3.

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Risk-benefit summary table for antibiotics in the treatment of severe malaria in the pocketbook

Existing recommendation / practice

Pocketbook hospital guidelines recommend intravenous antibiotics in severe malaria in cases of shock or suspected bacterial meningitis.

Proposed recommendation / practice

Include recommendation to consider intravenous antibiotics for cases of severe malaria, especially in children with impaired consciousness or respiratory distress. Obtain blood culture prior to antibiotic initiation, if possible.

Quality of evidence

(for outcomes deemed critical)

WEAK

Evidence exists that invasive bacterial infection (IBI) is common in severe malaria, and clinical features do not discriminate children with and without IBI. Case fatality is higher among children with IBI. Impaired consciousness and respiratory distress are strong predictors of mortality among children with severe malaria.

Benefits/desired effects

Treat IBI appropriately and reduce risk of mortality among children with severe malaria.

Risks/ undesired effects

Risk of inappropriate antibiotic use and development of antibiotic resistance. Risk of guideline application to children who do not have severe malaria.

Values/ Acceptability

Likely to be acceptable to most providers. Aligns with WHO recommendations for management of severe pneumonia and shock, but allows for clinical judgment to ensure that IBI coverage is considered for children at high risk of death.

Costs

Cost of intravenous antibiotics and blood culture, if available, and potential for extended length of hospitalization.

Feasibility

High level of feasibility given that these children are admitted to hospital and receiving parenteral antimalarials

Final recommendation

Healthcare providers should consider addition of intravenous antibiotics in children with severe malaria, especially in children with impaired consciousness or respiratory distress. Blood culture should be obtained, if possible, prior to initiating antibiotics.

Strength of recommendation

WEAK

(no randomized controlled trials assessing mortality benefit in treatment of severe malaria with IBI)

Quality of evidence that informs recommendation

Low

Comments justifying recommendation

Case fatality is highest in children with severe malaria and IBI. Hospital-level providers should be advised to consider appropriate antibiotic coverage to treat IBI in order to decrease mortality.

Gaps, research needs, comments

Further research should focus on specific recommendations for which children are most likely to benefit from intravenous antibiotics and make recommendations for duration of therapy when blood culture capability does not exist.

PubMed literature search criteria for intravenous antibiotics/bacteremia and severe malaria:

("malaria"[tiab] OR "severe malaria"[tiab]) AND ("antibiotics"[tiab] OR "bacteremia"[tiab]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) AND ("2011/05/15"[PDat] : "2016/05/12"[PDat])

***68 manuscript titles, 29 abstracts, 15 full manuscripts reviewed, 11 manuscripts cited.**

Appendix 4.

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Diagnosis based on Mid Upper Arm Circumference (MUAC only)

Existing recommendation / practice

Both pocketbook and IMCI guidelines focus on severe wasting alone and both highlight weight-for-length alongside MUAC in diagnosis of wasting.

Proposed recommendation / practice

- Include definition and treatment of moderate wasting

- Prioritise MUAC case definitions

Quality of evidence <i>(for outcomes deemed critical)</i>	LOW See main text
Benefits/desired effects	<ul style="list-style-type: none">- Children with MAM get treated. Though the relative risks of mortality/morbidity are less than for SAM, greater numbers mean that population impact of treatment is potentially large.- Improved identification of wasted children → a key feature towards improved programme coverage- Improved identification of malnourished children with higher risk of mortality
Risks/ undesired effects	<ul style="list-style-type: none">- The risks of treating MAM are negligible- MUAC only programmes bias younger infants. Older children who may also be vulnerable are not enrolled to nutrition treatment programmes- Nutritionally vulnerable children identified using WHZ may be excluded
Values/ Acceptability	<ul style="list-style-type: none">- The treatment of MAM is already acceptable and would likely be valued by carers / communities- MUAC-based assessment is considerably easier both for patients and healthcare workers doing the assessment.
Costs	<ul style="list-style-type: none">- Treating MAM would add extra costs to programmes. There is however little data on cost-effectiveness.- Using MUAC-only would save significant equipment costs but might increase programme costs
Feasibility	Both are feasible
Final recommendation	<ul style="list-style-type: none">- MAM should be proactively identified and treated- MUAC should be given greater prominence in all guidelines and MUAC-only programming should be considered as a default option where coverage/access to treatment is sub-optimal. WHZ remains an option in some settings and populations.

Strength of recommendation

Strong OR Conditional OR Qualified OR Weak

STRONG

(good risk/benefit balance likely)

Quality of evidence that informs recommendation

High / Moderate / Low / Very Low

Moderate

Comments justifying recommendation

See in-text references for published discussion of this issue.

Gaps, research needs, comments

There is further need to confirm mortality/morbidity risks of a) children who meet WHZ criteria but not MUAC criteria for SAM or MAM and b) older children who may not be treated using MUAC-only admissions. In addition,, the role of changed (increased) MUAC thresholds could be explored – these would improve sensitivity.

Focus on “Nutritionally Vulnerable Infants aged <6 months

Existing recommendation / practice

Infants <6 month wasting is currently defined by low weight-for-length alone

Proposed recommendation / practice

a) Widen the case definition to include feeding problems, clinical vulnerability (e.g. not gaining or losing weight) and maternal factors

b) Consider a MUAC-based cutoff (evidence for this likely available over the next year)

(NB Substantial progress towards this has already been made in a peer-reviewed “C-MAMI” (Community Management of Acute Malnutrition in Infants) tool

<http://www.enonline.net/c-mami>

Quality of evidence <i>(for outcomes deemed critical)</i>	LOW (see main text)
Benefits/desired effects	a) Infants get identified more proactively and at an earlier stage when outcomes are likely to be better and before they have developed more severe anthropometric growth failure b) In the same way as it has enhanced case detection for older children, infant MUAC is likely to facilitate significant improvements in case-identification and programme coverage: both individual and public health benefits
Risks/ undesired effects	a) Before efforts are made to scale up identification of nutritionally-vulnerable infants, it is important to have outpatient based treatment options in place. Many current national SAM guidelines recommend only inpatient-based care: the risks of this (nosocomial infection; opportunity costs of time away from home; maternal anxiety which might interrupt breastfeeding in a small but clinically stable/growing infant(1)) might outweigh

	<p>any benefits.</p> <p>b) Optimal MUAC cutoffs for infants are not yet known. These are likely to apply only to infants 1 to <6 months age. It would be important to get a good balance between sensitivity and specificity</p>
Values/ Acceptability	- No problems anticipated
Costs	- Both the proposed changes are likely to result in increased programme costs since more infants would be recruited into programme. Balancing that, the current costs of not identifying/not treating are likely paid in terms of excess mortality/morbidity.
Feasibility	Both are feasible
Final recommendation	<p>a) Emphasize a wider case definition of nutritional vulnerability in infants – to take into account feeding and clinical issues as well as anthropometry. This is ready for inclusion into protocols now.</p> <p>b) More research into optimal MUAC cut-offs before adopting this into recommendations (though likely to come soon)</p>
Strength of recommendation	<p><i>Strong OR Conditional OR Qualified OR Weak</i></p> <p>a) STRONG</p> <p>(good risk/benefit balance likely)</p> <p>b) n/a - not recommended now, but review next year</p>
Quality of evidence that informs recommendation	<p><i>High / Moderate / Low / Very Low</i></p> <p>a) Low</p>
Comments justifying recommendation	See in-text references for published discussion of this issue.
Gaps, research needs, comments	More research is needed on how new case definitions (including MUAC-based definitions) work in field

settings. Further research on weight-for-age to identify risk in this age group is also required.

Acute Malnutrition in Infants <6 months (including change to age cutoffs)

Existing recommendation / practice

Both pocketbook and IMCI describe the care of infants aged <6months but focus on inpatient options alone

IMCI uses <2 month / >2 months age cutoff

Proposed recommendation / practice

- Align pocketbook/ IMCI/ iCCM with WHO 2013 infant SAM guidelines. This should include description of outpatient based care options for uncomplicated infant SAM

- For nutrition assessment, in IMCI/iCCM, have separate sections for infants aged <6months, infants/children 6 to 59 months.

(NB A peer-reviewed version of the <6m guideline has already been developed, the “c-MAMI tool” - <http://www.enonline.net/c-mami>)

Quality of evidence <i>(for outcomes deemed critical)</i>	LOW See main text
Benefits/desired effects	<ul style="list-style-type: none">- Infants with SAM/MAM get treatment and excess mortality / morbidity is avoided- 6 months makes lots more sense as a nutrition cutoff since infants below this age should be exclusively breastfed. Their treatment options are hence very different to those for older infants/children. Guidelines which are clearer about this are likely to be better followed and hence more effective
Risks/ undesired effects	<ul style="list-style-type: none">- As noted in previous section, before efforts are made to scale up identification of nutritionally-vulnerable infants, it is important to have effective outpatient based treatment options in place. Many current

	<p>national SAM guidelines recommend only inpatient-based care: the risks of this (nosocomial infection; opportunity costs of time away from home; maternal anxiety which might interrupt breastfeeding in a small but clinically stable/growing infant(1)) might outweigh any benefits.</p>
<p>Values/ Acceptability</p>	<ul style="list-style-type: none"> - As for older children, community/outpatient based treatment options for infants are very likely to be well received by both communities and healthcare workers (whose scarce inpatient beds will not be overloaded by infants). - The revised age cutoff is already well understood for nutritional interventions so would be well accepted.
<p>Costs</p>	<ul style="list-style-type: none"> - Treating infant SAM/MAM would increase programme costs since many current programmes do not actively look for or treat this group. - Again however, the cost of NOT treating is far greater – it results in avoidable mortality/morbidity
<p>Feasibility</p>	<p>Though not yet formally tested, C-MAMI guidelines are all based on adapted existing tool and guidelines and thus feasibility of highly promising</p>
<p>Final recommendation</p>	<ul style="list-style-type: none"> - Incorporate WHO 2013 infant SAM guidelines into pocketbook/IMCI/iCCM. As part of this, include outpatient care options - Change age cu
<p>Strength of recommendation</p>	<p><i>Strong OR Conditional OR Qualified OR Weak</i></p> <p>STRONG</p> <p>(good risk/benefit balance likely / already recommended by WHO 2013 and classed as “strong” there.)</p>
<p>Quality of evidence that informs recommendation</p>	<p><i>High / Moderate / Low / Very Low</i></p> <p>Very low</p>
<p>Comments justifying</p>	<p>See in-text references for published discussion of this</p>

recommendation

issue.

**Gaps, research
needs, comments**

There is need to formally test c-MAMI guidelines and discover ways to optimized treatment. See here for full related research priorities(2).

Integrated treatment of SAM and MAM

Existing recommendation / practice

Pocketbook, IMCI and iCCM guidelines focus on SAM alone.

Proposed recommendation / practice

- a. Include definition and treatment of moderate wasting
- b. Integrate the treatment of SAM and MAM in one programme using one nutritional product at varied dose

Quality of evidence

(for outcomes deemed critical)

LOW

See main text

Benefits/desired effects

- a. Children with MAM get treated. Though the relative risks of mortality/morbidity are less than for SAM, greater numbers mean that population impact of treatment is potentially large.
- b. Integrated programme is cheaper and simpler to run since requires only one set of staff/logistics/M&E. Coverage and public health impact is increased

Risks/ undesired effects

- a. The risks of treating MAM are negligible
- b. More evidence is needed to ensure a combined programme is safe and effective. Risks could include poorer weight gain and poorer nutritional recovery if the amount of food prescribed at each stage is suboptimal.
Given this is a big change to current practice, there could however be a short term period of uncertainty whilst it is determined who should run / be responsible for programmes in the new landscape.

Values/

- a. The treatment of MAM is already acceptable and
-

Acceptability	<p>would likely be valued by carers / communities</p> <p>b. A combined programme is much simpler to run and understand and is likely to be well accepted by local communities and healthcare workers. A more challenging task is for international organizations to reframe their areas of responsibility / operations.</p>
Costs	<p>a. Treating MAM would add extra costs to programmes. There is however little data on cost-effectiveness.</p> <p>b. A combined programme will share key infrastructure and resources and is highly likely to be more cost-effective than separate SAM/MAM care.</p>
Feasibility	Both are feasible
Final recommendation	<p>a. MAM should be proactively identified and treated</p> <p>b. More evidence is needed before integrated care can be recommended – but this is currently in-progress so a re-review on this topic is needed in 1-2 years</p>
Strength of recommendation	<p><i>Strong OR Conditional OR Qualified OR Weak</i></p> <p>STRONG (for MAM treatment)</p> <p><i>n/a for integrated care</i></p>
Quality of evidence that informs recommendation	<p><i>High / Moderate / Low / Very Low</i></p> <p>Low</p>
Comments justifying recommendation	See in-text references for published discussion of this issue.
Gaps, research needs, comments	<p>Research on integrated SAM/MAM care is currently in progress. (COMPASS / MANGO projects)</p> <p>https://ciff.org/grant-portfolio/reinventing-community-management-acute-malnutrition/</p>

Post-discharge care and “thrive” interventions to improve long term outcomes

Existing recommendation / practice

Pocketbook, IMCI and iCCM focus on short term outcomes following SAM treatment, notably mortality.

Proposed recommendation / practice

- Include more details of / reference to child development packages e.g. **UNICEF Care for Child Development package**
http://www.unicef.org/earlychildhood/index_68195.html
- Include more details of disability/nutrition interactions in guidelines

Quality of evidence <i>(for outcomes deemed critical)</i>	LOW See main text
Benefits/desired effects	- More focus on long term and developmental outcomes as well as child survival: the “thrive, not just survive” child health agenda.
Risks/ undesired effects	- Resources are already limited and spreading focus too thinly means that, at best, development/disability/thrive work will be poorly done; at worst, it will distract from core ‘survive’ interventions
Values/ Acceptability	- No problems foreseen with acceptability, but in busy programmes with limited staff finding adequate time/resources could be challenging.
Costs	- Long term, anything which improves child development /improves disability-related problems is likely to be cost-effective. A bigger challenge however will be how to fund short term costs of greater developmental focus in nutrition treatment

	programmes.
Feasibility	Yes
Final recommendation	<ul style="list-style-type: none"> - More focus on child development using a recognized package such as the UNIEF Care for Child Development wherever possible. - Include more focus on disability and disability/nutrition interactions and possible solutions e.g. http://disabilitycentre.lshtm.ac.uk/getting-to-know-cerebral-palsy/
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak</i> Weak
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Low
Comments justifying recommendation	Whilst of great potential value, more research is needed on cost-effectiveness in a population of malnourished children. Risks are low, but costs are potentially large.
Gaps, research needs, comments	As well as optimizing child development post-malnutrition, work is needed on how to reduce later deaths following initial cure from SAM/MAM.

Risk-benefit summary table for including Bioelectrical Impedance Vector Analysis (BIVA) in Pocketbook and IMCI guidelines

Existing recommendation / practice

At present, BIVA is not included in the Pocketbook hospital or IMCI guidelines.

Proposed recommendation / practice

- Continue research work to understand if inclusion of BIVA for the diagnosis of SAM improves our assessment of treatment prognosis and survival.
- Continue research work to understand if inclusion of BIVA in the monitoring of SAM treatment improves our assessment of treatment prognosis and survival

Quality of evidence

LOW

(for outcomes deemed critical)

There are 2 studies, one published and one not^{1,2}, with observational data using BIVA for assessing changes in hydration status in SAM children treated at a clinic:

(1) BIVA parameters differ between healthy controls, SAM children with oedema and SAM children without oedema;

(2) BIVA data, mean vectors, during SAM treatment changed differently between the two SAM groups, indexing fluid loss among those with oedema and mass accretion among those without oedema; and

(3) that BIA data at admission was different between children that survived or died.

There is also one study with observational data that used BIA data in critically ill children in Brazil³. The study showed that BIA data could help discern between

¹ Girma T, Kæstel P, Workeneh N, Mølgaard C, Eaton S, Andersen GS, Michaelsen KF, Friis H, Wells JC. Bioimpedance index for measurement of total body water in severely malnourished children: Assessing the effect of nutritional oedema. Clin Nutr. 2016 Jun;35(3):713-7

² Girma T. Bioimpedance in severely malnourished children. An emerging method for monitoring hydration of children with severe acute malnutrition. 2014. PhD Thesis University of Copenhagen.

³ Azevedo ZM, Moore DC, de Matos FA, Fonseca VM, Peixoto MV, Gaspar-Elsas MI, Santinoni E, Dos Anjos LA, Ramos EG. Bioelectrical impedance parameters in critically ill children: importance of reactance and resistance. Clin Nutr. 2013 Oct;32(5):824-9

	<p>children that recovered and those whose health deteriorated and died.</p> <p>Additional evidence from hospitalised and non-hospitalised children most relevant to Pocketbook hospital and IMCI guidelines needs to be generated from other settings.</p>
Benefits/desired effects	Improve the identification of SAM at admission and the monitoring of treatment response in children.
Risks/ undesired effects	The economic and technical costs of BIA machines for children, as well as its consumables, are still high. Scaling up the usage of this technology at frontline settings may not be affordable or cost-effective.
Values/ Acceptability	<ul style="list-style-type: none"> - Acceptability of the usage of this technology by health personnel or patients for the assessment of acute malnutrition is still unknown - If the method becomes simplified, it may become valued by healthcare providers to better allocate care resources. - Some carers and healthcare providers may not value the additional test on their child and may not accept the results.
Costs	A good quality BIA machine appropriate for children of all ages cost about \$2,500 USD. The cost of the consumables per test is about \$0.80
Feasibility	National program capacity to invest and maintain BIA devices at hospital or outpatient facilities is unknown.
Final recommendation	Further research work is needed to fully understand the potential of BIVA for an improved diagnostic and monitoring of SAM in hospital or frontline settings.
Strength of recommendation	<p><i>Strong OR Conditional OR Qualified OR Weak</i></p> <p>CONDITIONAL</p> <p>(unknown whether BIA will improve diagnosis of</p>

	monitoring of children with SAM
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Low
Comments	
Gaps, research needs, comments	

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Appendix 5

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Risk-benefit summary table for point of care testing for bilirubin (transcutaneous bilirubin screening) in the Pocketbook and IMCI guidelines

Existing recommendation / practice

- Pocketbook hospital guidelines recommend all newborns should be monitored for development of jaundice, which should be confirmed by a bilirubin measurement, when possible, among high-risk infants. Treatment recommendations including phototherapy and exchange transfusion (when possible) are based on serum bilirubin levels and stratified by newborn age and preterm status.
- IMCI guidelines do not provide guidance regarding screening for jaundice or bilirubin monitoring (currently begins at one week of age).

Proposed recommendation / practice

- Do not currently recommend TcB POC device. Include high-risk and danger signs for testing and access to phototherapy.

Checklists for

- a. High-risk signs (that should lead to serial bilirubin testing)
 - a. Maternal Blood type Rh negative
 - b. Maternal Blood type O group
 - c. Low birthweight or premature baby
 - d. Jaundice within 24 hours of birth
 - e. Progression of jaundice within 72 hours
 - f. Persistence of jaundice > 1 week of age
- b. Danger signs (imminent acute bilirubin encephalopathy) that need urgent

access to phototherapy

- a. Bilirubin level >5, >10 and >15 mg/dL at age 24, 48, and 72 hours, respectively
- b. Sleepiness or lethargy
- c. Poor breast milk intake (decreased suck)
- d. Shrill or inconsolable cry
- e. Limp (hypotonia) or stiff with handling (hypertonia)
- f. Abnormal movements (seizures, tremors, etc)
- g. Fever.

(Checklist provided by Dr. Vinod K Bhutani, personal communication)

- Do not currently recommend TcB POC device. Consider including high-risk and danger signs for testing and access to phototherapy. Reexamine the value of clinical screening for non-physiologic jaundice during the first 7 days of life as part of danger signs in iCCM guidelines
- Reexamine the value of clinical screening for non-physiologic jaundice during the first 7 days of life as part of danger signs in iCCM guidelines. {Olusanya, 2014 #4544; Slusher, 2011 #4524}

Quality of evidence
(for outcomes deemed critical)

WEAK for Hospitals and VERY WEAK for Frontline facilities. Multiple studies from LMIC hospitals {Hemmati, 2013 #4539; Morgan, 2016 #4536; Rylance, 2014 #4531} demonstrate acceptability, and feasibility of using TcB screening to identify infants who need evaluation. Studies from frontline facilities are limited. {Lam, 2008 #4535}

Benefits/desired effects

Improve identification and timely treatment of newborns with severe jaundice, especially in settings with limited availability of TsB for initiation or continuation of phototherapy.

Risks/ undesired effects

- 1) Phototherapy might adversely affect the correlation between TcB and TsB measurements due to bleaching effects on the skin. {Rylance, 2014 #4531} {Maisels, 2009 #4545}
- 2) Transcutaneous bilirubinometers is not always reliable babies with pigmented skin and among those exposed to sunlight. {Maisels, 2009 #4545} {Rylance, 2014 #4531}
- 3) There is insufficient evidence to recommend an optimal single or multiple sites of TcB based on current devices. {Rylance, 2014 #4531}
- 4) As with any point- of-care test, regular monitoring for appropriate quality assurance by comparison with TsB measurements is necessary. Significant variation can

occur among instruments, and the use of a new instrument should be compared with hospital laboratory measurements to ensure that the instrument is working properly; such checks should be performed periodically. {Maisels, 2009 #4545}

Values/ Acceptability	<ol style="list-style-type: none">1) Current overreliance by hospital personnel on visual assessment of the cephalocaudal progression or ominous signs of acute bilirubin encephalopathy/kernicterus particularly among out-born infants might prohibit its acceptability. {Olusanya, 2014 #4544}2) It is anticipated that poor knowledge of the risks and dangers inherent in severe newborn jaundice, the temptation from prior experience to presume that all jaundice is physiological, or inappropriate advice from health workers will account for continued delay in prompt care seeking or accepting the necessary treatment. {Olusanya, 2014 #4544}
Costs	<ol style="list-style-type: none">1) The transcutaneous bilirubinometer is prohibitively expensive for most hospitals in the low-resource setting, costing approximately 3000 Euros. {Rylance, 2014 #4531}2) Additional cost includes the disposable cartridges (also expensive) which along with the service contract costs should be considered as part of the necessary financial commitment.3) Transcutaneous bilirubinometer is very fragile and for repair needs to be sent back to the manufacturer (often located in the US), further adding to the potential cost.4) The cost per case, however, highly depends on the incidence of kernicterus as well as its potential reduction resulting from the intervention.
Feasibility	National program capacity to invest and maintain TcB monitoring devices at hospitals or outpatient facilities without significant cost reductions and/or subsidies is highly questionable.
Final recommendation	Do not recommend inclusion of TcB device for pocketbook or IMCI. Include high-risk and danger signs for testing and access to phototherapy in the pocketbook and potentially IMCI.
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak Weak</i>
Quality of evidence that	<i>High / Moderate / Low / Very Low Low/Very low</i>

**informs
recommendation**

**Comments
justifying
recommendation**

- High cost, in the absence of proven benefit for this setting, specially for the management of neonates with hemolytic jaundice who are at the highest risk of adverse consequences. Can only be effective in conjunction with a package of interventions including access to effective phototherapy and clear guidelines on levels that prompt treatment or referral

**Gaps, research
needs,
comments**

- Most important gap in knowledge is when neither TcB nor TsB is accessible, should a health care worker implement phototherapy
- “Explore inclusion of conjunctival icterus as an easy sign of moderate to severe hyperbilirubinemia in the iCCM and IMCI physical diagnosis/danger signs, potentially reflecting a serum bilirubin requiring or justifying phototherapy.” (Dr. Richard Wennberg)
- Need to explore other non-invasive bilirubin monitoring such as exhaled carbon monoxide measurement to assess the risk for hyperbilirubinemia (Dr. Ebru Ergenekon) or the use of Bilistick {Coda Zabetta, 2013 #4529}
- Need to develop low-cost devices for effective phototherapy that do not require continuous electricity, including sunlight filters, solar-powered devices, and battery-operated devices. {Slusher, 2011 #4524}
- Need for better screening for G6PD and/or of ABO incompatibility. An estimated 200-400 million people worldwide are G6PD deficient and 7.5% of the global population carry 1 or 2 genes for the condition. G6PD deficiency independently increased the risk of kernicterus many fold (OR 28.2, 95% CI 2.6-307.7) and advanced diagnosis might help to identify newborns at highest risk of severe jaundice and ABE/kernicterus. {Slusher, 2011 #4524}

PubMed literature search criteria for “(“Bilirubin”[Mesh] OR “bilirubin”) AND “transcutaneous” AND (“Jaundice, Neonatal/diagnosis”[mh] OR “jaundice”) using the Cochrane LMIC filter available on <http://epoc.cochrane.org/lmic-filters>”
40 manuscript titles, 14 abstracts, 9 full manuscripts reviewed (including one systematic review), 13 manuscripts cited [including 4 abstracts]

(additional references provided by Dr. Vinod Bhutani are available upon request)

Risk-benefit summary table for inclusion of facility-based weight measurement and birth weight standards for newborns in the Pocketbook and IMCI guidelines

Existing recommendation / practice

Facility-based birth weight measurement and additional care for newborns identified to be low birthweight or small for gestational age (SGA) is not included in existing WHO IMCI guidelines, which begin at 1 week of age.

Proposed recommendation / practice

- Expand IMCI guidelines to include the crucial first week of life, when infants are at greatest risk and the vast majority of infant deaths occur.
- Emphasize birth weight measurement for all infants born in facilities.
- Incorporate immediate and long-term follow up care of low birthweight infants (<2,500 grams) into IMCI guidelines. Improve differentiation and diagnosis of preterm infants vs. small for gestational age (SGA) by including birthweight standards (those developed by INTERGROWTH-21st) in the guidelines for use in hospitals and frontline facilities.
- Incorporate postnatal growth standards for preterm infants (<37 weeks' gestational age) into IMCI guidelines to assess growth until 64 weeks' postmenstrual age, after which the WHO Child Growth Standards for term infants can be used.
- Promote appropriate thermal care for infants identified to be low birthweight (see recommendation on facility-based thermal care).

Quality of evidence
(for outcomes deemed critical)

Conditional
INTERGROWTH-21st international birthweight standards, released in 2014, have demonstrated utility and wide applicability. Developed using only women at low risk of impaired fetal growth from 8 different geographical locations consisting of multi-ethnic populations, they are intended to represent the standard of optimum fetal growth. Given they were recently developed, however, there are still important barriers to implementation. {Kozuki, 2015 #7; Villar, 2013 #4; Villar, 2014 #3; Villar, 2014 #1}

Benefits/desired effects

- 1) Draw attention to this extremely vulnerable subset of infants in need of additional care within IMCI guidelines
- 2) Reinforce importance of the diagnosis and management of low birthweight infants
- 3) Establish a useful standard to use in diagnosing term-SGA and preterm-SGA (one developed based on optimum fetal growth); identify infants who are not low

	<p>birthweight but still at increased risk due to being SGA {Villar, 2015 #2}</p> <p>4) Complement current WHO child growth standards (released in 2006) with newborn standards {de Onis, 2009 #10}^{Error! Bookmark not defined.}</p>
Risks/ undesired effects	<p>1) Continued inaccurate diagnosis of SGA due to unreliable gestational age dating methods</p> <p>2) Overtreatment of infants who are SGA due to constitutionally small size rather than fetal growth restriction</p>
Values/ Acceptability	<p>In general, the newborn health community has been reluctant to adopt a single set of birthweight standards; many different standards have been developed using dissimilar methodologies and based on heterogeneous populations.</p>
Costs	<p>Minimal costs associated with adoption of standards since facilities should already have equipment for weight measurement, although additional care for newly identified high-risk infants may be costly</p>
Feasibility	<p>Implementation may be facilitated by integration of these standards into existing complementary frameworks (WHO Child Growth Standards).¹ Maximum uptake will require support of policy makers, programmers, and local champions.{de Onis, 2012 #9}</p> <p>Simpler to use in resource-limited clinical settings than customized birth weight charts, which have not demonstrated increased utility. {Chatfield, 2013 #11}</p> <p>Increased feasibility in settings with greater proportions of women using more accurate methods of gestational dating</p>
Final recommendation	<p>Include facility birthweight measurement and standards based on INTERGROWTH-21st in IMCI guidelines to facilitate diagnosis of low birthweight and SGA, as well as to monitor the growth of preterm infants</p>
Strength of recommendation	<p><i>Strong OR Conditional OR Qualified OR Weak Conditional</i></p>
Quality of evidence that informs recommendation	<p><i>High / Moderate / Low / Very Low Low to moderate</i></p>
Comments justifying recommendation	

Gaps, research needs, comments

- More research is needed on effective follow-up methods and long-term management of SGA infants to prevent harmful later sequelae
- More research is needed on validation and implementation of INTERGROWTH-21st birthweight standards

PubMed Search Criteria Used:

Search #1: "intergrowth"[tw] AND ("small for gestational age"[tiab] OR "birth weight"[tiab] OR "IUGR"[tiab] OR "intrauterine growth restriction"[tiab])

**12 manuscript titles, 6 abstracts reviewed; 3 manuscripts cited

Search #2: ("weight measurement"[tw] OR "weight measurements"[tw] OR "growth charts"[mesh] OR "growth chart"[tw] OR "growth chart"[tw]) AND ("fetal growth"[tw] OR "fetal development"[tw] OR "intrauterine growth"[tw] OR "gestational age"[tw] OR "low birth weight"[tw]) AND ("at birth"[tw] OR "newborn"[tw] OR "newborns"[tw] OR neonat*[tw]) AND ("cct"[tw] OR "ccts"[tw] OR "clinical trial"[publication type] OR "clinical trial"[tw] OR "clinical trials as topic"[mesh] OR "clinical trials"[tw] OR "clinical trials, phase i as topic"[mesh] OR "clinical trials, phase ii as topic"[mesh] OR "clinical trials, phase iii as topic"[mesh] OR "clinical trials, phase iv as topic"[mesh] OR "cohort studies"[mesh:noexp] OR "cohort"[tw] OR "cohorts"[tw] OR "concurrent"[tw] OR "controlled clinical trial" [pt] OR "controlled clinical trials as topic"[mesh] OR "controlled trial"[tw] OR "controlled trials"[tw] OR "follow up"[tw] OR "follow-up studies"[mesh] OR "followup"[tw] OR "incidence"[tw] OR "long term"[tw] OR "longitudinal studies"[mesh] OR "longitudinal"[tw] OR "longterm"[tw] OR "multi center"[tw] OR "multi centre"[tw] OR "multicenter studies as topic"[mesh] OR "multicenter"[tw] OR "multicentre"[tw] OR "non experimental"[tw] OR "nonexperimental"[tw] OR "observational studies as topic"[mesh] OR "observational study"[pt] OR "phase 1"[tw] OR "phase 2"[tw] OR "phase 3"[tw] OR "phase 4"[tw] OR "phase four"[tw] OR "phase i"[tw] OR "phase ii"[tw] OR "phase iii"[tw] OR "phase iv"[tw] OR "phase one"[tw] OR "phase three"[tw] OR "phase two"[tw] OR "phase four"[tw] OR "placebo" [tw] OR "placebos" [tw] OR "prospective studies"[mesh] OR "randomisation"[tw] OR "randomization"[tw] OR "randomized" [tw] OR "randomised"[tiab] OR "randomly" [tw] OR "random"[tw] OR "rct"[tw] OR "rct"[tw] OR "rcts"[tw] OR "studies"[ti] OR "study"[ti] OR drug therapy[sh] OR groups [tw] OR observation*[tw] OR placebo [tw] OR prospective*[tw] OR randomized[tw] OR randomly[tw] OR systematic*[tw] OR trial* [ti] OR "meta analysis"[tw] OR "metaanalysis"[tw] OR "meta analyses"[tw] OR "metaanalyses"[tw])

**105 manuscript titles, 29 abstracts reviewed; 11 manuscripts cited

Risk-benefit summary table for expansion and uniformity of including danger signs for infants 0-59 days of life at risk of severe illness or sepsis in iCCM and IMCI guidelines

Existing recommendation / practice

Current IMCI guidelines do not provide guidance on the care of newborns 0-6 days of life (DOL). Assessment of young infants 7-59 days of life includes an assessment for the presence of 12 danger signs including 1) History of convulsions; 2) Fast breathing; 3) Severe chest indrawing; 4) Nasal flaring; 5) Grunting; 6) Bulging fontanelle; 7) Pus draining from ear; 8) Umbilical redness extending to the skin; 9) Fever (37.5°C or above axillary or feels hot) or low body temperature (35.4°C or lower axillary or feels cold); 10) Many or severe skin pustules; 11) Lethargy or unconscious; 12) Less than normal movement. Of note, the revised IMCI chart booklet recommends the use of Young Infant Study 7-sign algorithm (YIS7) {Group, 2008 #4522} which differs from the current guidelines.

While the iCCM guidelines do not provide guidance on the care of infants 0-59 days of life, the “Caring for the newborn at home” booklet provides a list of 9 danger signs including: 1) Inability to feed ; 2) Convulsions; 3) Tachypnea; 4) Chest indrawing; 5) High temperature : 37.5°C or more axillary; 6) Very low temperature: 35.4°C or less axillary ; 7) Severe jaundice 8) Lethargy 9) Signs of local infection including umbilicus, conjunctivitis, or cellulitis. The presence of any of the danger signs is an indication for referral or hospital-level care.

Proposed recommendation / practice

- Expand to include infants 0-59 days of age, simplify, and harmonize the iCCM and IMCI guidelines based on YIS7: 1) History of convulsion; 2) Respiratory rate $\geq 60/\text{min}$; 3) Severe chest in-drawing present ; 4) History of difficulty feeding; 5) History of convulsions; 6) Movement only when stimulated, 7) Axillary temperature of 37.5°C or more or below 35.5° .
- Consider adding non-physiologic jaundice (including visible jaundice on the first day of life) as a danger sign for infants 0-6 days of life.
- Where possible, this guidance based on clinical signs should be accompanied by point of care testing at the facility level, as this list is not specific to differentiate between various etiologies of illness including serious bacterial infection (SBI), intrapartum related events (birth asphyxia), or prematurity. With emerging innovations for management of various illnesses (i.e. therapeutic hypothermia for asphyxia) and increasing awareness of unanticipated consequences of potentially unnecessary treatments (i.e. empiric antibiotics for presumed SBI), there is an increasing need for development of point of care testing at the facility level to improve specificity of the current diagnostic approach.
-
- Consider Introducing the topic of “high risk” neonate who can be identified on the day of birth using the following three criteria: 1) birth weight $<2,000\text{ g}$, 2)

preterm birth (<37 weeks) or 3) baby not taking feeds; and mother's report that baby's feeding has decreased or stopped at any time during day of life 2 to 28. These high risk neonates should receive more visits by health workers and early treatment for any identified sickness. Alternatively, they can be referred to a medical facility where more evaluation and/or management can be provided. {Reddy, 2005 #3353}

Quality of evidence <i>(for outcomes deemed critical)</i>	Moderate
Benefits/desired effects	<ol style="list-style-type: none"> 1) Expansion of the current guidelines can serve to improve case management and improve outcomes and referrals as required 2) The high-risk criteria can identify the 20-25% of neonates among whom 80-95% of neonatal deaths are expected to occur
Risks/ undesired effects	<ol style="list-style-type: none"> 1) This algorithm which is based on the presence of a single danger sign, identifies nearly 25% neonates in the community for referral, which is too high and leads to significant over diagnosis. (Dr. Abhay Bang, personal communication) It is possible that changing the criteria to the presence of two signs can improve specificity, but will also impact the sensitivity. {Bang, 2005 #3351;Group, 2008 #4522} 2) Current IMCI guidelines were introduced without field trials and subsequent evidence showed no or poor effectiveness. It is possible that inclusion of newborns in iCCM and IMCI guidelines will not decrease the rate of neonatal deaths. (Dr. Abhay Bang and Dr. Mike English, personal communication)
Values/ Acceptability	Despite improved sensitivity and specificity, it is likely that appropriate referral will continue to be low due to unwillingness, inability or delay in care seeking by families.
Costs	While uniform training and a potentially shorter list of danger signs might decrease the cost of health provider training, identification and referral of additional young infants at risk for severe illness are anticipated to increase the total cost.
Feasibility	It is anticipated that introduction and training the same algorithm to be used in the community and facility level will be simpler, lower cost and more feasible.

Final recommendation	Expand the age group, simplify, and harmonize the young infant (0-59 DOL) danger signs in iCCM and IMCI guidelines
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak Conditional</i>
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low Low to Moderate</i>
Comments justifying recommendation	There is evidence that with proper training, frontline health providers can recognize young infants with severe illness, including among newborns (0-6 DOL) who account for 75% neonatal deaths. Inclusion of danger signs which have been validated in various settings is anticipated to improve timely recognition, referral and/or “closer to home” management of sick infants.
Gaps, research needs, comments	- Further research is needed to examine the potential utility of a different set of danger signs for newborns 0-6 days of life which is based on unique signs and symptoms that might primarily present soon after birth (i.e. apnea or jaundice) and reexamine the role of isolated findings reflective of normal transitional physiology (i.e. 4-6 hours of life for fast breathing OR hypothermia immediately following birth) in prompting referral or hospitalization (Dr. Carl Bose)

PubMed literature search criteria for “Diagnosis of neonatal sepsis by community health workers using "danger signs" up to 2 months of age”.

("neonatal sepsis" OR ("sepsis" AND "neonatal") OR "neonatal septicemia" OR ("neonatal" AND "severe disease") OR ("neonatal" and "Bacteremia") OR ("infant" AND "Bacteremia") OR ("blood poisoning" AND "infant") OR ("blood poisoning" AND "neonate") OR ("neonate" AND "septic") OR ("neonate" AND "sepsis") OR ("neonate" AND "septic shock") OR ("newborn" AND "sepsis") OR ("infant" AND "sepsis") OR ("neonate" AND "fungemia") OR ("infant" AND "fungemia") OR ("newborn" AND "fungemia") OR ("newborn" AND "septic shock") OR ("newborn" and "bacteremia") OR ("newborn" AND "blood poisoning") OR ("infant" AND "blood infection") OR ("newborn" AND "blood infection") OR ("neonate" AND "blood infection")) AND ("diagnosis" OR "danger signs" OR "identification" OR "algorithm" OR "detection" OR "diagnoses") AND ("community health worker" OR "community health" OR "Community health workers" OR "birth attendant" OR "birth attendants" OR "midwife" OR "midwives" OR "village health" OR "rural health" OR "barefoot doctor" "" "infant sepsis" OR "infant septicemia" OR ("infant" AND "severe disease") OR ("infant" AND "Bacteremia") OR ("blood poisoning" AND "infant") OR ("infant" AND "septic") OR ("infant" AND "sepsis") OR ("infant" AND "fungemia") OR ("infant" AND "blood infection") OR ("infant" AND "septic

shock") OR ("baby " AND "severe disease") OR ("baby" AND "Bacteremia") OR ("blood poisoning" AND "baby") OR ("baby"AND "septic") OR ("baby " AND "sepsis") OR ("baby" AND "fungemia") OR ("baby " AND "blood infection") OR ("baby" AND "septic shock" "infant sepsis" OR "infant septicemia" OR ("infant" AND "severe disease") OR ("infant" AND "Bacteremia") OR ("blood poisoning" AND "infant") OR ("infant" AND "septic") OR ("infant" AND "sepsis") OR ("infant" AND "fungemia") OR ("infant" AND "blood infection") OR ("infant" AND "septic shock") OR ("baby " AND "severe disease") OR ("baby" AND "Bacteremia") OR ("blood poisoning" AND "baby") OR ("baby"AND "septic") OR ("baby " AND "sepsis") OR ("baby" AND "fungemia") OR ("baby " AND "blood infection") OR ("baby" AND "septic shock")

****63 manuscript titles, 17 abstracts, 7 full manuscripts reviewed (including one systematic review), 9 manuscripts cited** [including 3 abstracts {Weber, 2003 #4514;English, 2004 #4515;Duke, 2005 #4513}],

Risk-benefit summary table for inclusion of community-based birth weight measurement of newborns in iCCM guidelines

Existing recommendation / practice

Community-based birth weight measurement or the care of low birthweight infants (due to either being born preterm or small for gestational age) is not included in existing WHO iCCM guidelines, which begin at 2 months of age. Currently, most babies born outside of facility settings are not weighed.

Proposed recommendation / practice

- Expand iCCM guidelines to include care of infants less than 2 months of age.
- Incorporate birth weight measurement by community health workers or skilled attendants into iCCM, as is outlined in WHO's Facilitator Manual for *Caring for the newborn at home*.
- Incorporate special care/referral guidelines for low birthweight infants born in home settings. These may reflect those presented in the joint WHO/UNICEF strategy *Home visits for the newborn child*: increased attention to keeping the newborn warm, initiation of breastfeeding within the first hour of life, extra attention to hygienic practices, extra attention to neonatal danger signs and early care-seeking, and support for monitoring growth.{UNICEF, 2009 #54}
- Provide charts to record/trend birth weight or at minimum, weight category: normal weight (>2,500 g), low birthweight (<2,500 g), very low birthweight (<1,500 g) that women may present at frontline facility or hospital if referral is made.
- Promote research further evaluating various scale prototypes for use by community health workers in field settings with high rates of home births. A promising option is BIRTHweigh III, a low-cost spring scale developed by PATH that performs birth weight categorization.

Quality of evidence
(for outcomes deemed critical)

QUALIFIED

While field trials have demonstrated accuracy and community acceptability of low-cost portable scales such as BIRTHweigh III,{Darmstadt, 2007 #19;Harrison G, #22;Mullany, 2006 #23} impacts on newborn outcomes and overcoming implementation barriers remain to be explored.

Benefits/desired effects

- 1) Draw attention to the identification and management of this extremely vulnerable subset of infants in need of additional care or timely referral within iCCM guidelines
- 2) Utilize community health workers to perform the simple, yet valuable task of obtaining birth weight measurements at first contact (ideally within 24 hours of birth)
- 3) Improve the management of babies born at home, a high

	proportion of which are low birthweight and therefore have increased risk of morbidity and mortality
Risks/undesired effects	<ol style="list-style-type: none"> 1) Will add to the workload for community health workers, although many are already conducting home visits within the first few days of birth and this is not a time-intensive task 2) Increase in referral of low birthweight infants born at home may add to already crowded and resource-scarce facilities
Values/ Acceptability	<ul style="list-style-type: none"> - Negative newborn weight-related beliefs have been reported in community trials, as early weight measurements may conflict with traditional customs and low levels of knowledge exist regarding rationale for taking these measurements{Darmstadt, 2008 #20} - Generally high levels of acceptability by community health workers, varying by scale (color-coded nature of BIRTHweigh III helpful for non-literate, lighter weight vs. UNICEF Seca); motivation and adherence to time-sensitive protocols must be addressed{2008 #14;Charlton, 2009 #18} - Global newborn health community generally views birth weight measurement as very important to evaluating risk
Costs	Training and materials (including scales) to support community health workers are main costs; cost of scales may be a barrier (BIRTHweigh III model costs \$5 each)
Feasibility	Particularly those scale designs not requiring literacy likely to be feasible, but community perceptions surrounding the importance of birth weight must be explored further and addressed
Final recommendation	Include identification and management of low birthweight infants born at home within iCCM guidelines
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak Qualified</i>
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Low
Comments justifying recommendation	Identification of low birthweight infants in community settings known to be very important but need more evidence of effectiveness of community-based weight measurement from field trials

Gaps, research needs, comments

- Need more research on best-suited scales for various contexts
- Although existing research suggests community health workers able to effectively categorize weight, capacity of facilities to care for infants needing additional care or health outcomes has not been determined

PubMed Search Criteria Used:

((("Body Weights and Measures/instrumentation"[Mesh] OR "Body Weights and Measures/methods"[Mesh] OR "Body Weights and Measures/mortality"[Mesh] OR "Body Weights and Measures/prevention and control"[Mesh] OR "Body Weights and Measures/standards"[Mesh] OR "Body Weights and Measures/trends"[Mesh]) OR "body measures"[All Fields] OR "body measure"[All Fields] OR ("body weights and measures"[MeSH Terms] OR ("body"[All Fields] AND "weights"[All Fields] AND "measures"[All Fields]) OR "body weights and measures"[All Fields] OR ("measure"[All Fields] AND "body"[All Fields])) OR "measures, body"[All Fields] OR "birth weight"[MeSH Terms] OR ("birth"[All Fields] AND "weight"[All Fields]) OR "birth weight"[All Fields] OR "neonatal measurement"[tiab] OR "neonatal weight"[tiab] OR "Neonatal Screening/instrumentation"[Mesh] OR "Neonatal Screening/methods"[Mesh] OR "Neonatal Screening/standards"[Mesh] OR "Neonatal Screening/trends"[Mesh]) AND ("health auxiliary"[tw] OR "frontline health workers"[tw] OR "frontline health worker"[tw] OR "midwife"[tw] OR "Midwifery"[tiab] OR "midwives"[tw] OR "Birth Attendant"[tw] OR "Midwives"[tw] OR "outreach worker"[tw] OR "outreach workers"[tw] OR "lay health worker"[tw] OR "lay health workers"[tw] OR "promotora"[tw] OR "promotoras"[tw] OR "village health worker"[All Fields] OR "village health workers"[tw] OR "volunteer health worker"[tw] OR "volunteer health workers"[tw] OR "voluntary health workers"[tw] OR "voluntary health worker"[tw] OR "community health agent"[tw] OR "community health agents"[tw] OR "health promoter"[tw] OR "health promoters"[tw] OR "Community Health Workers"[Mesh] OR "community health worker"[tw] OR "community health workers"[tw] OR "community health aide"[tw] OR "community health aides"[tw] OR "community health nursing"[tw] OR "community health nurses"[tw] OR "community health nurse"[tw] OR "community health officers"[tw] OR "community health officer"[tw] OR "community health volunteer"[tw] OR "community health volunteers"[tw] OR "community health assistants"[tw] OR "community health promoters"[tw] OR "community health promoters"[tw] OR "community IMCI"[tw] OR "community volunteer"[tw] OR "community volunteers"[tw] OR "health extension workers"[tw] OR "health extension worker"[tw] OR "village health volunteer"[tw] OR "village health volunteers"[tw] OR "Community Health Nursing"[Mesh] OR "close-to-community provider"[tw] OR "close-to-community providers"[tw] OR "community-based practitioners"[tw] OR "lady Health worker"[tw] OR "lady Health workers"[tw] OR "barefoot doctor"[tw] OR "Community Practitioners"[tw] OR "Community Practitioner"[tw] OR "community-based practitioners"[tw] OR "promotoras de salud"[tw] OR "traditional birth attendants"[tw] OR "traditional birth attendant"[tw] OR "Anganwadi"[tw] OR "Barangay health workers"[tw] OR "Basic health worker"[tw] OR "Basic health

workers"[tw] OR "Brigadista"[tw] OR "Community drug distributors"[tw] OR "Community health agent"[tw] OR "Community health agents"[tw] OR "Community health promoter"[tw] OR "Community health promoters"[tw] OR "Community health representative"[tw] OR "Community health representatives"[tw] OR "Community health volunteer"[tw] OR "Community health volunteers"[tw] OR "Health promoter"[tw] OR "Health promoters"[tw] OR "Kader"[tw] OR "Outreach educators"[tw] OR "Promotora"[tw] OR "Sevika"[tw] OR "Accompagnateur"[tw] OR "Accredited Social Health Activist"[tw] OR "Animator"[tw] OR "ASHA"[tw] OR "Auxiliary Nurse"[tw] OR "Auxiliary Nurse-midwife"[tw] OR "Behvarz"[tw] OR "Care Group"[tw] OR "Care Groups"[tw] OR "Community Health Agent"[tw] OR "Community Health Agents"[tw] OR "Community Health Care Provider"[tw] OR "Community Health Care Providers"[tw] OR "Community HealthCare Providers"[tw] OR "Community Health Extension Worker"[tw] OR "Community Health Extension Workers"[tw] OR "Community Health Officer"[tw] OR "Community Health Officers"[tw] OR "Family Health Worker"[tw] OR "Family Health Workers"[tw] OR "Family Welfare Assistants"[tw] OR "Female Community Health Volunteer"[tw] OR "Female Community Health Volunteers"[tw] OR "Health Agent"[tw] OR "Health Agents"[tw] OR "Health Assistant"[tw] OR "Health Assistants"[tw] OR "Health Extension Worker"[tw] OR "Health Extension Workers"[tw] OR "Health Surveillance Assistants"[tw] OR "Kader"[tw] OR "Malaria Agent"[tw] OR "Malaria Agents"[tw] OR "Nutrition Counselor"[tw] OR "Nutrition Counselors"[tw] OR "Peer Educator"[tw] OR "Peer Educators"[tw]) AND ("Infant, Newborn"[mesh] OR "Infant, Low Birth Weight"[mesh] OR "Infant, Small for Gestational Age"[mesh] OR "Infant, Very Low Birth Weight"[mesh] OR "Infant, Postmature"[mesh] OR "Infant, Premature"[mesh] OR "Infant, Extremely Premature"[mesh] OR "Infant, Extremely Low Birth Weight"[mesh] OR "low birth weight"[tiab] OR "low birth weights"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "newborns"[tiab] OR "post mature infant"[tiab] OR "post mature infants"[tiab] OR "postmature infant"[tiab] OR "postmature infants"[tiab] OR "pre mature infants"[tiab] OR "pre term infant"[tiab] OR "pre term infant"[tiab] OR "premature infant"[tiab] OR "premature infants"[tiab] OR "preterm infant"[tiab] OR "preterm infants"[tiab])

Risk-benefit summary table for updating neonatal resuscitation guidelines in pocketbook and including guidelines for neonatal resuscitation in IMCI

Existing recommendation / practice

Pocketbook hospital guidelines include a comprehensive neonatal resuscitation session for newborns management. Procedure and equipment are defined, but need to be updated. {al, 2015 #2}

There is no mention in the IMCI booklet regarding the first week of life, when most neonatal deaths occur.

Proposed recommendation / practice

- To update the Pocketbook neonatal resuscitation algorithm and guidelines {al, 2015 #2}, including the definition and equipment for neonatal resuscitation corner, and the equipment checklist procedure before every delivery.
- Include the need chest x-ray in case of persistent severe respiratory distress to rule out or manage pneumothorax (access to this diagnostic modality will also be beneficial for umbilical vein catheterization, another newborn care innovation).
- Include the need for pulse oximetry at the neonatal resuscitation corner (see other newborn innovations), plastic wraps for VLBW infants, and intubation sets.
- A paragraph for comprehensive neonatal care in delivery room for those departments aiming to scale up neonatal care (including additional equipment such as intubation sets).
- There is no mention in the IMCI booklet regarding the first week of life, when most neonatal deaths occur. Neonatal resuscitation has to be included. Due to the extreme need for harmonization within relevant publications, we suggest including, as it is, the Helping Babies Breath (HBB) manual {Elk Grove Village, 2011 #9} inside the IMCI manual.

Quality of evidence *(for outcomes deemed critical)*

Strong for recommendations coming from Circulation. 2015;132 [suppl 2]:S543–S560 and co-published in Pediatrics; Neonatal Resuscitation 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.

Strong for Neonatal resuscitation to be included in IMCI, the AAP Helping Babies Breath (HBB) manual is already validated and widely used. {Elk Grove Village, 2011 #9}

Conditional re the inclusion of a paragraph named “hospitals aiming to scale up comprehensive neonatal care”

Benefits/desired effects	To reduce neonatal mortality and neonatal asphyxia through an up to date management of neonatal resuscitation
Risks/ undesired effects	In case of endotracheal intubation inclusion, cases must be well defined and selected, to avoid unnecessary intubations.
Values/ Acceptability	- training for updated resuscitation is needed at the hospital and frontline level
Costs	<p>Affordable for updating neonatal resuscitation at the hospital level (basic equipment if not currently in place, and the need for updated training).</p> <p>Cost-effective for including HBB manual in IMCI (equipment and training) if national programs aim to scale up neonatal resuscitation at frontline facilities (basic equipment if not currently in place, and training).</p> <p>Relatively high, but Cost-effective for including comprehensive neonatal care at the hospital level, if national programs aim to scale up neonatal care at hospital level, comprehensive equipment when not yet in place, and training: pulse oximetry, portable x ray machines (readily available for the neonatal unit), umbilical venous catheter sets, nasal CPAP, endotracheal intubation sets, and plastic wraps.</p>
Feasibility	<p>National program aiming to scale up neonatal care at hospital and frontline facilities can include these procedures and equipment, starting from national and regional departments. WHO to take the lead in a standardized road map for early expansion of comprehensive neonatal care at hospital levels in LIC and inclusion of basic neonatal resuscitation at frontline facilities.</p> <p>One of the greatest challenges in promoting care development is to ensure that it occurs in a organized and coordinated manner. WHO could work with interested MoH to approve the procedure, develop training material and support staff training, procedures for patient consent must be put in place, submit the results to the MoH for consideration. Then procedures can be used in regular clinical care, starting from tertiary level health facilities, regional, and national hospitals. Ensuring the necessary</p>

	<p>staff (numbers, skills, medical and nursing, biomedical, radiology) are available to manage higher number of procedures. Ensuring staff are sufficiently skilled through training and ongoing competency checks.</p>
<p>Final recommendation</p>	<p>To update the Pocketbook Neonatal resuscitation algorithm and guidelines, including definition and equipment for neonatal resuscitation corner, equipment checklist procedure before every delivery.</p> <p>A paragraph for comprehensive neonatal care in delivery room for those departments aiming to scale up neonatal care (including additional equipment). To include, as it is, the HBB manual inside IMCI manual</p>
<p>Strength of recommendation</p>	<p><i>Strong OR Conditional OR Qualified OR Weak</i> CONDITIONAL (unknown whether UVC contributes to reducing mortality in VLBW in LIC)</p>
<p>Quality of evidence that informs recommendation</p>	<p><i>High / Moderate / Low / Very Low</i> POCKETBOOK: Strong for guideline update, coming from wide consensus (ILCOR); conditional for comprehensive neonatal care and additional equipment listed</p> <p>FRONTLINE FACILITY RECOMMENDATION (IMCI): strong for including, as it is, the AAP HBB manual inside IMCI manual{Elk Grove Village, 2011 #9}. It is an already AAP validated tool, widely used.</p>
<p>Comments justifying recommendation</p>	<p>Improvements of neonatal resuscitation at every level is considered the most cost-effective interventions for reduction of neonatal mortality and morbidity in LICs. According to WHO estimates, around 3% of the 120 million babies born each year in developing countries develop birth asphyxia and require resuscitation. It is estimated that some 900,000 of these newborns die as the result of asphyxia. {Organisation, 1998 #4}</p>
<p>Gaps, research needs, comments</p>	<p>-The required nurse-patient ratio in neonatal units scaling up comprehensive neonatal care must be defined in agreement with ministries of health. - Implementation research in departments already fulfilling basic neonatal care in countries aiming to scale up neonatal care, starting from tertiary level hospitals is needed.</p>

**PubMed literature search criteria for neonatal resuscitation at hospital level in LIC
(search conducted May 9, 2016): 36 publications**

(neonatal[All Fields] AND ("resuscitation"[MeSH Terms] OR "resuscitation"[All Fields]))
AND (("poverty"[MeSH Terms] OR "poverty"[All Fields] OR ("low"[All Fields] AND
"income"[All Fields]) OR "low income"[All Fields]) AND countries[All Fields]) Among
these, relevant were:

**PubMed literature search criteria for neonatal resuscitation 2016 guidelines
(search conducted May 9, 2016): 23 publications**

neonatal[All Fields] AND ("resuscitation"[MeSH Terms] OR "resuscitation"[All Fields])
AND 2016[All Fields] AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH
Terms] OR "guidelines"[All Fields])

List 1

1. Resuscitation equipment be checked before and after every birth by a professional in charge of this task.
2. The health workers must know how to take apart pieces and reassemble the equipment (after use).
3. Resuscitation equipment must be checked and ALWAYS be in working condition.
4. The equipment must be disinfected after each use.

List 2

Equipment is listed as follows {Organisation, 1998 #4}, {resuscitation., 2012 #5}, {Neonatal Resuscitation Program Textbook, 2010 #6}:

1. Aarm room (at least 25°C)
2. A (wall) thermometer
3. Good light
4. Draught-free, (wall) clock with a seconds hand
5. warm dry towels and blankets
6. Flat surface for resuscitation under radiant heater or resuscitation table
7. Sterile gloves
8. Sterile kit to cut the cord
9. Appropriate hand washing for all the staff (HIGHLY NEEDED)
10. Self-inflating bags (to have available in two sizes with a volume of 250 and 400 ml with relief valve and reservoir)
11. Two masks sizes 0 and 1
12. Suction device: bulb, catheter, or mucus extractor
13. Electric or pump suction machine
14. Stethoscope
15. Source of oxygen (ideally oxygen concentrator) with a connecting tube to the bag
16. Pulse oximetry and probes (see other newborn innovation)
17. Adrenaline
18. Normal saline (for volume resuscitation)

Additional equipment, not essential but to be included in the equipment list for hospitals aiming to scale up comprehensive neonatal care include:

1. Intubation equipment: laryngoscope with appropriate blades
2. Endotracheal tubes of appropriate sizes (2.5, 3, 3.5)
3. Megill forceps
4. Umbilical vein catheters (see other newborn innovation)



Figure 1 – “Respiratory equipment on a stick” - Using a simple IV pole, the resuscitation equipment can be assembled and maintained together, and readily available to be taken to the delivery suite, or the bedside where it is needed. (Photo courtesy of Swedish Medical Center, Seattle, WA. Photo borrowed from Dr. Myra Wycoff with permission).

List 3

These have to be included in the updated algorithm:

- In section A chart 12, In addition to “look for *Breathing or crying? *Good muscle tone...”, a third question must be added: “*Term gestation?”. If the answer to any of these assessment questions is “no,” then the infant should be moved to the resuscitation area, including a radiant warmer to receive assistance. The need to transfer the infant to the resuscitation area should be added to the current flowchart before “*stimulate by rubbing the back 2 to 3 times...”
- in section A chart 12, in the box recommending stimulating and suctioning there should also be a sentence to dry the baby to prevent heat loss.
- For the same box, proper thermal care interventions for immediate care of preterm newborns (< 32 weeks gestation) must include immediate placement inside a transparent plastic wraps, which when combined with other environmental heat sources, is very effective in reducing hypothermia in preterm babies during stabilization and transfer within the hospital. {al, 2015 #2} {Zulfi qar

A Bhutta, 2014 #1}. Additional thermal care practices includes delayed bathing, to prevent excess heat loss. {Zulfi qar A Bhutta, 2014 #1}.

- The pocketbook recommends that the hospital must have measurement of oxygen saturation included in the equipment, but inclusion of a pulse oximetry is not specifically mentioned in the essential hospital equipment list, even though it is very important, specially in the neonatal resuscitation corner (see other newborn innovation). Neonatal staff in LIC, should be well aware that during resuscitation of a newborn, achieving an oxygen saturation of 100% should not be the target, and goal saturations should be based on a simplified oxygen target table included in the book (and should also be posted on the resuscitation corners walls. {OD., 2005 #7}, {Dawson JA, 2007 #8}:

Pre-ductal SpO2

2 min.:	60 %
3 min.:	70 %
4 min.:	80 %
5 min.:	85 %
10 min.:	90 %

- In section B chart 12, only check heart rate if chest is moving adequately. If chest not moving adequately, corrective steps should be done before HR check. The picture on Page 48--baby should not get chest compressions without ventilation.
- In section C chart 12, addition of "Ventilation Corrective Steps" in the text for Neonatal Resuscitation. Ventilation is the most important step in the neonatal resuscitation. The chart on page no 47 mentions "Take ventilation corrective steps" if HR is between 60-10. However the text does not explain what all corrective steps need to be taken. Also, these corrective steps (MRSOP) should also be performed when the ventilation is initiated but chest rise is not there. This instruction is missing from the chart as well as the text. The chart/text just say "make sure the chest is moving well." But what to do if it is not moving, should also be a part of the text/chart.
- In section C chart 12, if the heart rate < 60/min despite adequate ventilation, administered oxygen must be 100% (FiO2 1) and not "give higher oxygen".
- in section C chart 12, if the heart rate < 60/min despite adequate ventilation with 100% oxygen and chest compressions, the flow chart mentions "other ventilatory support", but this is not further specified and it is not further clarified. It probably aims to mean endotracheal intubation. We suggest to remove this from the algorithm or to add an asterisk and clearly mention the procedure of endotracheal intubation, in a separate paragraph titled "Hospitals aiming to scale up comprehensive neonatal care". This paragraph should discuss indications for endotracheal intubation. Alternatively, the algorithm should state: if the staff is familiar with the procedure of endotracheal intubation, intubate and continue ventilating with bag and endotracheal tube especially if nasal CPAP is available in the neonatal unit.

- In section C chart 12, administration of epinephrine (adrenaline) or volume resuscitation, or both is indicated, while the pocketbook only mentions administration of adrenaline. Hypovolemia is an important cause of refractory circulatory failure and an indication for prompt volume expansion especially when blood loss is known or suspected (pale skin, poor perfusion, weak pulse, history of placental abruption) and the infant's heart rate has not responded adequately to other resuscitative measures. Normal saline solution (or blood) may be considered for volume expansion in the delivery room with the recommended dose of 10 mL/kg, which may need to be repeated. In these cases, a peripheral intravenous line or (preferably) an umbilical catheter must be promptly inserted and consideration of a fluid bolus should be added to the current flow chart.
- Meconium-stained amniotic fluid (MSAF)/suspected meconium aspiration syndrome: This frequent and life threatening condition needs to be specified in the pocketbook with a dedicated paragraph as it is in every resuscitation manual. {Neonatal Resuscitation Program Textbook, 2010 #6} The new guidelines {al, 2015 #2} indicate a new approach that fits well for hospitals in LIC, especially when health staff is not well familiar with endotracheal intubation. If an infant born through MSAF presents with poor muscle tone and inadequate breathing effort, the initial resuscitation steps should be completed under the radiant warmer (chart 12, column 1, box 2). If the staff is familiar with endotracheal intubation, it is advised (and should be included in the pocketbook) to intubate before stimulation, perform endotracheal aspiration while extubating and reassess. This procedure can be repeated without delaying positive pressure ventilation. Without the possibility of mechanical ventilation in the NICU, this is the only case in which endotracheal intubation can be recommended, if nasal CPAP is not available (see other newborn innovation). If staff is not familiar with the procedure, it is useless to attempt and might delay bag-mask ventilation(BVM) of the lung. Therefore Positive Pressure Ventilation should be initiated if the infant is not breathing or the heart rate < 100/min after the initial steps are completed. In making this suggested change, greater value has been placed on harm avoidance (i.e., delays in providing bag-mask ventilation (BVM), potential harm of the procedure) over unknown benefit of routine endotracheal intubation and suctioning below the cord. {al, 2015 #2}

Risk-benefit summary table for including Continue positive airways pressure devices (CPAP) in hospital guidelines (pocketbook)

Existing recommendation / practice

Pocketbook hospital guidelines does not mention the use of continue positive airways pressure devices (CPAP) in the management of ill premature and term newborns with respiratory distress. At present, the maximum level of support for newborn with any kind of respiratory distress includes provision of oxygen via nasal cannula, antibiotics, and aminophylline/caffeine.

Proposed recommendation / practice

- To include in the Pocketbook hospital guidelines CPAP devices for all newborns with moderate to severe respiratory distress, where mechanical ventilation is not available.
-
- To include in the Pocketbook hospital guidelines CPAP devices for all newborns with moderate to severe respiratory distress, where mechanical ventilation is available, before shifting to mechanical ventilation.
- To include in the Pocketbook hospital guidelines access to portable x-ray machines, and pulse oximetry as diagnostic tools to better manage newborns in need of CPAP

Quality of evidence *(for outcomes deemed critical)*

High

A 2002 Cochrane Meta-analysis {Ho JJ, 2002 #5} evaluating CPAP against oxygen (at present the standard care in LIC) showed that CPAP use reduced the overall rate of mortality [RR 0.52 (95% CI 0.32, 0.87)] and CPAP in spontaneously breathing preterm infants with respiratory distress syndrome reduces both intensive care admissions (by 53%) and mortality (48%). The 2015 updated Cochrane review {Ho JJ, 2015 #6}, conclude that CPAP has a role in nurseries where intensive care is not immediately available, which may include settings such as low income countries with no access to intensive care. CPAP has now become a standard of care for all preterm neonates with respiratory distress. Evidence from high-quality studies suggests significant survival advantage in preterm neonates with severe respiratory distress and managed with CPAP as compared with those managed with oxygen alone. {Ho JJ, 2002 #5}, {Ho JJ, 2015 #6}, {Narendran V, 2003 #7}, {Pieper CH, 2003 #8}, {A Thukral, 2016 #9}

In LICs, there are NICUs with mechanical ventilators but

without CPAP. Three publications, one in Nicaragua {al., 2015 #18}, and two systematic reviews {A Thukral, 2016 #9}, {Martin S, 2014 #20}, one published in 2016 conclude that systematic use of a nasal CPAP (nCPAP) device reduces newborn mortality, and the rate of intubation/mechanical ventilation. Better outcomes were seen in neonates with a birth weight >1000 g than neonates <1000 g, and in those with mild to moderate respiratory distress compared to neonates with more severe disease. {Martin S, 2014 #20}

Benefits/desired effects

NCPAP interventions applied widely in LICs, with appropriate supportive infrastructure and general newborn care, will have a significant impact on reducing neonatal mortality. {Beena D. Kamath, 2011 #2}

Risks/undesired effects

Studies on safety of CPAP therapy in LIC {A Thukral, 2016 #9} suggested a very-low risk of pneumothorax (0 to 7.2%). Access to bedside (portable) X-ray machines for newborns with worsening RDS in spite of CPAP treatment could minimize the already low risks of pneumothorax complications.

Dependence on imported CPAP devices, choice of appropriate interface, lack of awareness and expertise among doctors and inadequately trained nursing staff are major challenges. {Gupta, 2015 #21}

Factors like cost and availability of consumables and additional equipment like humidifier and availability of skilled staff can limit the upscaling of CPAP therapy. In addition, the use of CPAP also requires regular training of staff for optimal delivery of CPAP.

Values/Acceptability

Our review shows that methods for CPAP therapy are currently available, simple to use, safe and relatively inexpensive. {Duke, 2014 #22}

When accessing higher technology, a “learning curve” exists for the medical staff to be able to appropriately care for sick newborns. In addition, although the technology can be available, the inability to quickly replace faulty machines may contribute to proper implementation. {Bhutta Z, 1997 #3}, {Beena D. Kamath, 2011 #2} The use of CPAP would be problematic without trained personnel, a supporting infrastructure, and innovative designs for resource-poor

settings. {Beena D. Kamath, 2011 #2} However, it has been shown that nurses can institute CPAP easily after 1 to 2 months of training {Koyamaibole L, 2006 #17}

Costs

Relatively inexpensive methods of delivering CPAP are now available and warrant trials in moderate-sized hospitals in LICs. {Duke, 2005 #23}, {Duke, 2014 #22}

Even the low-cost indigenously designed CPAP systems have been shown to be effective in reducing the mortality and up-transfers among term and preterm neonates with respiratory distress in LMIC. {Daga S, 2014 #24}, {Hendriks H, 2014 #25} There are several devices to deliver bubble CPAP which range from commercial machines to 'homemade' devices. {Duke, 2014 #22} Stand-alone CPAP devices need to have the air compressor incorporated in the machine and only need electricity to work. All circuits and patient interfaces have to be reusable. {J Brown, #26}

The more widespread availability of the basic interventions of oxygen and CPAP would have the greatest impact on decreasing RDS-specific mortality rates around the world. Much work is already being done to make these interventions more easily adaptable and economical in low-resource settings. {Dibiasi RM, 2010 #27}, {Mokuolu OA, 2002 #28}, {Koyamaibole L, 2006 #17}

Feasibility

It is time for WHO to take the lead in a standardized the road map of early expansion of CPAP implementation in LICs for the care of newborns with respiratory distress (regardless etiology) within the cost-effective comprehensive neonatal care in LICs. The device should be included in the pocketbook. One of the greatest challenges in promoting care development is to ensure that it occurs in an organized and coordinated manner: WHO should promote discussion with MoHs interested in scaling up neonatal care at hospital level in LICs to plan interventiona at the national level, including: machines approved for use by the MoH, staff properly trained on use and maintenance, standard procedures for patient consent, and submission of results to the MoH for consideration. Then the machine can be used in regular clinical care, starting from tertiary level health facilities, regional and national hospitals.

Ensuring that the necessary staff (numbers, skills, medical and nursing, biomedical, radiology) are available to care for

	<p>infants placed on CPAP. Ensuring staff are sufficiently skilled through training and ongoing competency checks. Ensuring the hospital has written policies and procedures for safe use of CPAP, outlining how, when, and where it will be used. Ensuring the availability of the necessary equipment and supplies to run CPAP. Ensuring access to biomedical support for CPAP. Access to medical staff with 24 hour in-house coverage who are trained and competent in using CPAP, including recognizing and managing complications. Minimum nurse:patient ratio must be defined and the maintenance system should be readily available</p>
Final recommendation	<p>Include CPAP devices, pulse oximeter and bedside x-ray machines in the hospital guidelines within a defined cost-effective, comprehensive hospital level neonatal care at LIC.</p>
Strength of recommendation	<p><i>Strong OR Conditional OR Qualified OR Weak</i> CONDITIONAL</p>
Quality of evidence that informs recommendation	<p><i>High / Moderate / Low / Very Low</i> High</p>
Comments justifying recommendation	<p>Evidence is high, at least as a rescue strategy, especially considering that at present, oxygen support is the maximum treatment that is offered. Strength of recommendation is conditional for feasibility reasons in LIC due to financial, human resources, and organizational issues.</p> <p>CPAP are well accepted by staff, have been used for decades in high income country NICUs and have been a cornerstone for management of sick newborn with respiratory distress.</p>
Gaps, research needs, comments	<p>-Nurse-patient ratio in neonatal unit using CPAP and in general scaling up comprehensive neonatal care must be defined in agreement with MoHs.</p> <p>- Implementation research in departments already fulfilling basic neonatal care in countries aiming to scale up neonatal care, starting from tertiary level hospitals is needed.</p>

PubMed literature search criteria for continue positive airway pressure devices (CPAP) in LIC (search conducted May 8, 2016): 58

(continue[All Fields] AND positive[All Fields] AND airways[All Fields] AND ("pressure"[MeSH Terms] OR "pressure"[All Fields]) AND ("instrumentation"[Subheading] OR "instrumentation"[All Fields] OR "devices"[All Fields] OR "equipment and supplies"[MeSH Terms] OR ("equipment"[All Fields] AND "supplies"[All Fields]) OR "equipment and supplies"[All Fields])) OR CPAP[All Fields] AND ("developing countries"[MeSH Terms] OR ("developing"[All Fields] AND "countries"[All Fields]) OR "developing countries"[All Fields]) Among these, relevant were:

Risk-benefit summary table for including umbilical vein catheterization (UVC) in pocketbook guidelines

Existing recommendation / practice

Pocketbook guidelines do not include information regarding UVC placement for management of ill preterm and term newborns. WHO suggest that UVC in low income countries hospitals is indicated when the need for IV access is urgent, but a peripheral IV line cannot be established quickly.

In “Managing newborn problems: a guide for doctors, nurses, and midwives, World Health Organization 2003”, the procedure and equipment are defined, but the guidelines do not mention the importance of having a bedside x-ray machine to confirm proper positioning. {Organization, 2003 #11}

Proposed recommendation / practice

Include in the Pocketbook guidelines, the UVC procedure as indicated in “Managing newborn problems: a guide for doctors, nurses, and midwives, World Health Organization 2003”. Indications include:

- In the delivery room when the need for IV access is urgent (suspected hypovolemia by due to conditions such as placenta abruption) and when the heart rate remains below 60 despite proper ventilator support and chest compression.
- For management of unstable or very low birth weight (VLBW; <1,500 grams at birth) infants.
- For gradual transition from total parenteral nutrition to full enteral feeding.
- For newborns with feeding intolerance.
- For newborns in need of blood exchange transfusion.
- Additional drug/equipment to scale up comprehensive neonatal care includes parenteral nutrition (amino acid intravenous solution - available in many hospital with a surgical department) and syringe pumps.
- Include portable x-ray machines as an essential equipment to scale up hospital level neonatal care at in LIC. This will also benefit the management of pneumothorax.

Quality of evidence
(for outcomes deemed critical)

Moderate

Four studies compared UVCs vs peripheral venous access (the only possible alternative at present in LIC) in the management of sick newborns. One retrospective analysis

on VLBW infants showed that those with an UVC combined with PICC had a markedly higher weight gain and shorter length of hospital stay and showed a declining trend in the rates of nosocomial infection. {Yang ZM, 2013 #14} A second prospective, randomized study evaluated UVC risks and benefits compared with peripheral intravenous lines up to 14 days of life. Infants with an UVC had significantly fewer venipunctures and peripheral intravenous lines placed during their first 2 weeks of life; less time and money were spent obtaining peripheral line access in the UVC group and the incidence rates of sepsis and complications were not higher in the treated patients compared to controls, concluding that UVC placement during the first 2 weeks of life is a relatively safe, less stressful, and cost-effective means of providing intravenous therapy to neonates. {Loisel DB, 1996 #15} In a third study, the efficacy and safety of using UVCs compared to peripheral venous catheters was studied in 129 critically ill premature infants during the first three weeks of life. Infants who received parenteral nutrition by umbilical venous catheter had greater parenteral caloric intake, lower physiologic weight loss and greater weight gain during the study as compared to infants who received parenteral nutrition by peripheral vein, while the overall incidence of sepsis was comparable in both groups .(19% vs 19.7%) {Pereira GR, 1992 #16} Eventually, a 1979 study from Benin indicates that UVC placement should be restricted to a carefully selected group of patients and it should be placed under strict aseptic technique. {Omene JA, 1979 #17} A 2015 Cochrane analyzed percutaneous central venous catheters (PICC) versus peripheral catheters for delivery of parenteral nutrition in neonates: data from one small trial suggest that use of PICC to deliver parenteral nutrition increases nutrient input; three trials suggest that PICC placement decreases the number of catheters needed to deliver nutrition and no evidence suggests that PICC increases risks of adverse events, particularly invasive infection. Obviously PICC and UVC are different, but it is somehow significant as the Cochrane review highlighting the positive role of central catheters compared with peripheral lines. {Ainsworth S, 2015 #18} In addition, among 549 USA NICUs, 80% believed that it is safe to provide more complete enteral nutrition to newborns with UVCs in place with a gradual transition from total parenteral nutrition to full enteral feeding. {Tiffany KF, 2003 #10}

Benefits/desired effects

- Provide a secure, fast, and relatively easy vascular access during the first week of life, preserving peripheral veins, both in the delivery room and later in NICU
- Possibility of intravenous nutrition
- Safe drug and blood product administration
- Elimination of stress and pain related to repeated venipuncture attempts
- Emergency vascular access in the delivery room
- Blood draws
- Access for exchange blood transfusion

Risks/undesired effects

All known risk factors related to UVC malposition can be minimized by obtaining an x-ray at the patient's bedside. This equipment must be in place as a precondition to set up this procedure.

Other risks related to UVC placement, like increased catheter related infections (CRBSI) are well studied and not proven {Butler-O'Hara M, 2006 #19}, {Naomi P. O'Grady, 2011 #20}, {Seguin J, 1994 . #21}, {Loisel DB, 1996 #22}, {Landers S, 1991 #23}, especially proper aseptic procedures are followed.

CDC guidelines indicate that UVC should be removed as soon as possible when no longer needed, but can be used up to 14 days if managed aseptically {Naomi P. O'Grady, 2011 #20}.

An association between umbilical vein catheters with CRBSI is reported in 3%–8% of cases {Landers S, 1991 #23}.

Values/Acceptability

- The material for surgical set is already available in the surgical department of the hospital with cleaning procedures already in place.
- The catheter for the UVC is relatively inexpensive
- The procedure is easy to learn by different cadres and is considered important by the staff. {Sánchez Del Hierro G,

	2014 #12}, {Cordero L, 2013 #13}, {Chan LC, 2006 #24}
Costs	The catheter is about 5 US dollars each
Feasibility	National programs aiming to scale up neonatal care can include this procedure, starting from the national, and regional departments. Availability of portable x-ray machines is a precondition. WHO to take the lead in a standardized road map of early expansion of comprehensive neonatal care at the hospital level in LIC. One of the greatest challenges in promoting care development is to ensure that it occurs in an organized and coordinated manner. WHO could work with interested MoH to approve the procedure, develop training material, support staff training, procedures for patient consent must be put in place, submit the results to the MoH for consideration. Then the procedure can be used in regular clinical care, starting from tertiary level health facilities, regional and national hospitals. Ensuring the necessary staff (numbers, skills, medical and nursing, biomedical, radiology) are available to care for the infants with a UVC. Ensuring that staff are sufficiently skilled through training and ongoing competency checks. Ensuring that the hospital has a written policies and procedures for safe use of UVC, outlining how, when and where it will be used. Ensuring the availability of the necessary equipment and supplies to place and use the UVC.
Final recommendation	Include UVC and portable x-ray machines in the hospital guidelines for delivery room and neonatal departments, as indicated in “Managing newborn problems: a guide for doctors, nurses, and midwives, World Health Organization 2003”, within a defined cost-effective, comprehensive neonatal care at hospital level in LIC.
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak</i> CONDITIONAL (unknown whether UVC contribute reducing mortality in VLBW in LIC)
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Moderate
Comments justifying recommendation	Easy, affordable, well accepted, used for several decades in western NICUs; a cornerstone for sick newborns

management in the first week of life, and important especially where other catheters (e.g. PICC) are not present due to cost.

Gaps, research needs, comments

-Nurse-patient ratio in neonatal unit using UVC, and in general scaling up comprehensive neonatal care must be defined in an agreement with MoHs.

- Implementation research in departments already fulfilling basic neonatal care in countries aiming to scale up neonatal care, starting from tertiary level hospitals is needed.

PubMed literature search criteria for Umbilical venous catheter (UVC) at hospital level in LIC (search conducted May 8, 2016):

Here is the search that I used in PubMed, both with and without a filter for LMIC 74 :

```
((("Umbilical Veins"[Mesh] OR "umbilical vein"[tiab] OR "umbilical veins"[tiab]) AND ("catheterization"[mesh] OR catheter*[tiab] OR cannulation*[tiab])) OR umbilical vein catheter*[tiab] OR "UVC"[tiab] OR "umbilical catheter"[tiab] OR "umbilical catheters"[tiab] OR "umbilical catheterization"[tiab] OR "umbilical catheterization"[tiab]) AND ("Infant, Newborn"[mesh] OR "Infant, Low Birth Weight"[mesh] OR "Infant, Small for Gestational Age"[mesh] OR "Infant, Very Low Birth Weight"[mesh] OR "Infant, Postmature"[mesh] OR "Infant, Premature"[mesh] OR "Infant, Extremely Premature"[mesh] OR "Infant, Extremely Low Birth Weight"[mesh] OR "low birth weight"[tiab] OR "low birth weights"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "newborns"[tiab] OR "post mature infant"[tiab] OR "post mature infants"[tiab] OR "postmature infant"[tiab] OR "postmature infants"[tiab] OR "pre mature infant"[tiab] OR "pre mature infants"[tiab] OR "pre term infant"[tiab] OR "pre term infant"[tiab] OR "premature infant"[tiab] OR "premature infants"[tiab] OR "preterm infant"[tiab] OR "preterm infants"[tiab])
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Risk-benefit summary table for including Pulse oximetry in pocketbook guidelines

Existing recommendation / practice

Pocketbook hospital guidelines mention pulse oximetry in the management of ill premature and term newborns with respiratory distress.

Proposed recommendation / practice

- To include in the Pocketbook hospital guidelines pulse oximetry in neonatal resuscitation corners and as a useful device to help in diagnosis of critical congenital heart diseases (CCHD).

Quality of evidence (for outcomes deemed critical)	High pulse oximetry is the standard of care for management of all sick patients in neonatal units, and at birth.
Benefits/desired effects	Extension of use of pulse oximeters at hospitals level is cost-effective
Risks/ undesired effects	Device already included at hospital level. No risk in extending the use.
Values/ Acceptability	Pulse oximetry is noninvasive, easy to do and does not require any special skills.
Costs	The technology is robust, and the price of pulse oximeters is now lower than the past.
Feasibility	It is time for WHO to take the lead in a standardized road map of early expansion of cost-effective comprehensive neonatal care in LICs. The device should be included in the pocket book with extended use. The machine can be used in routine clinical care, and in every provincial hospital. If not enough machines are available for neonatal care, it is advisable to keep 1 in the delivery room and 1 rotating to all sick newborns in the neonatal unit, to be used along with checking vital signs.
Final recommendation	Extend use of pulse oximetry at hospital level to maximize its cost effectiveness.
Strength of	<i>Strong OR Conditional OR Qualified OR Weak</i>

recommendation	<i>strong</i>
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> High
Comments justifying recommendation	Pulse oximetry is now the standard of care for managing high risk infants, enabling immediate and dynamic assessment of oxygenation and heart rate
Gaps, research needs, comments	

PubMed literature search criteria for oxypulsimete in LIC(search conducted May 8, 2016): 83

Here is the search she used in combination with a Cochrane LMIC search filter: ("Oximetry"[Mesh] OR "oximetry"[tiab] OR "Oximeter"[tiab] OR "oxypulsimeter"[tiab]) AND ("Infant, Newborn"[mesh] OR "Infant, Low Birth Weight"[mesh] OR "Infant, Small for Gestational Age"[mesh] OR "Infant, Very Low Birth Weight"[mesh] OR "Infant, Postmature"[mesh] OR "Infant, Premature"[mesh] OR "Infant, Extremely Premature"[mesh] OR "Infant, Extremely Low Birth Weight"[mesh] OR "low birth weight"[tiab] OR "low birth weights"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "newborns"[tiab] OR "post mature infant"[tiab] OR "post mature infants"[tiab] OR "postmature infant"[tiab] OR "postmature infants"[tiab] OR "pre mature infant"[tiab] OR "pre mature infants"[tiab] OR "pre term infant"[tiab] OR "pre term infant"[tiab] OR "premature infant"[tiab] OR "premature infants"[tiab] OR "preterm infant"[tiab] OR "preterm infants"[tiab])Among these, relevant were:

Risk-benefit summary table for inclusion of facility thermal care in Pocketbook and IMCI guidelines

Existing recommendation / practice

- Facility-based thermal care for newborns is not included in existing WHO IMCI guidelines, which begin at 1 week of age.
- Currently a section titled “Teach the mother how to keep the low weight infant warm at home” under the counseling guidelines for mothers in the 2014 Pocketbook that advises keeping room warm, avoiding bathing, providing skin to skin contact on the mother’s chest, among other things.

Proposed recommendation / practice

- Expand IMCI guidelines to include the crucial first week of life, when infants are at greatest risk and the vast majority of infant deaths occur.
- Incorporate Kangaroo Mother Care (KMC) into facility-based care for *low birthweight infants* (<2,500 grams) regardless of gestational age after stabilization. KMC includes a package of interventions: early and continuous skin-to-skin contact with the mother, frequent and exclusive breastfeeding, and early discharge from the facility with follow-up. KMC can be initiated in the hospital (ideally as soon after birth as possible) and continued in the home setting.
- Promote early skin-to-skin contact (SSC) in facility-based care (within hospital and frontline facilities) for *healthy normal weight infants*. Early SSC involves placing the naked baby on the mother’s chest in prone position with a dry cap on the head and warm blanket across the back, ideally immediately following birth.

Quality of evidence
(for outcomes deemed critical)

STRONG

The benefits of Kangaroo Mother Care for low birthweight newborns after stabilization are well-established (most recent 2014 Cochrane review demonstrating 40% reduced risk of mortality at discharge, 55% reduced risk of nosocomial infection/sepsis, 66% reduced risk of hypothermia, reduced hospital stay, and improved breastfeeding and weight gain).{Conde-Agudelo, 2014 #29} Another recent systematic review found a 36% reduced risk of mortality associated with KMC compared to conventional care.{Boundy, 2016 #30} Much literature also addresses the implementation and scale-up aspects of KMC.{Bergh, 2016 #34;Bergh, 2014 #33;Bergh, 2012 #35;Blencowe, 2009 #36;Vesel, 2015 #37} WHO has produced separate documents promoting KMC.{Organization, 2003 #38}

The benefits of early skin-to-skin contact for healthy newborns are well-established by a recent Cochrane review.{Moore, 2012 #32}

Benefits/desired effects

- 1) Draw attention to this extremely vulnerable subset of infants in need of additional care within IMCI guidelines, and harmonize IMCI with other WHO guidelines addressing postnatal care
- 2) Improve the management of low birthweight and preterm neonates to decrease risk of hypothermia, infection/sepsis, and death
- 3) Allow for systematic and consistent adoption of KMC, increasing awareness and trust of the practice among health care workers and families
- 4) Promote KMC as more than an alternative to incubator care, a valuable option to be used beyond only those newborns in settings with insufficient technology and/or skilled staff
- 5) Empower mothers and other caregivers as crucial components in the care of their infants, helping to meet both physical and emotional needs

Risks/ undesired effects

- 1) By promoting KMC as an effective intervention, providers and caregivers alike may be overly reassured and less sensitively assessing infant for danger signs
- 2) Use during stabilization period has not been properly evaluated for safety and effectiveness
- 3) Demands time and energy from mothers recovering from arduous labor processes and may have many other familial obligations
- 4) Conflict with traditional customs

Values/ Acceptability

- Generally accepted by mothers and families particularly if they are informed about its benefits and if fathers are also involved; low knowledge of KMC at onset{Nguah, 2011 #39}
- Health care workers sometimes reluctant due to lack of belief in utility of KMC{Chan, 2016 #40}
- Consensus statement by newborn health stakeholders

	(2013) urges for accelerated KMC implementation{Engmann, 2013 #42}
Costs	<ul style="list-style-type: none"> - Less costly than incubator care, but families still struggle with transportation issues - Low resources for newborn-care services can be a barrier to implementation{Chan, 2016 #40;Seidman, 2015 #41}
Feasibility	Relatively simple and feasible intervention likely to be widely generalizable, but in need of implementation support in the form of context-specific materials adapted to local factors and sociocultural norms, as well as commitment to consistently high quality{Dickson, 2015 #44;Kadam, 2005 #43}
Final recommendation	Include Kangaroo Mother Care in IMCI guidelines for stabilized low birthweight infants within hospitals and frontline facilities
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak</i> Strong
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> High
Comments justifying recommendation	Over three decades of research have confirmed KMC as a valuable intervention and it is important to promote it throughout all relevant WHO materials.
Gaps, research needs, comments	<ul style="list-style-type: none"> - More research is needed on safety and effectiveness of early onset continuous KMC in <i>unstabilized</i> or <i>relatively stabilized</i> LBW infants.{Conde-Agudelo, 2014 #29} - The vast majority of research been done in low and middle-income settings and more trials on intermittent and continuous KMC are needed in <i>high-income</i> settings.{Conde-Agudelo, 2014 #29}

PubMed Search Strategy:

("Kangaroo-Mother Care Method"[Mesh] OR "kangaroo mother care"[tiab] OR "kangaroo care"[tiab] OR "skin to skin"[tiab] OR "Body Temperature Regulation"[Mesh] OR "thermal care"[tiab] OR "temperature regulation"[tiab] OR "temperature control"[tiab] OR "heat loss"[tiab] OR "heat losses"[tiab] OR "thermoregulation"[tiab] OR "thermoregulations"[tiab] OR "heat regulation"[tiab] OR hypotherm*[tw] OR hypertherm*[tw]) AND ("Infant, Newborn"[mesh] OR "Infant, Low Birth Weight"[mesh] OR "Infant, Small for Gestational Age"[mesh] OR "Infant, Very Low Birth Weight"[mesh] OR "Infant, Postmature"[mesh] OR "Infant, Premature"[mesh] OR "Infant, Extremely

Premature"[mesh] OR "Infant, Extremely Low Birth Weight"[mesh] OR "low birth weight"[tiab] OR "low birth weights"[tiab] OR "neonatal"[tiab] OR "neonate"[tiab] OR "neonates"[tiab] OR "newborn"[tiab] OR "newborns"[tiab] OR "post mature infant"[tiab] OR "post mature infants"[tiab] OR "postmature infant"[tiab] OR "postmature infants"[tiab] OR "pre mature infant"[tiab] OR "pre mature infants"[tiab] OR "pre term infant"[tiab] OR "pre term infant"[tiab] OR "premature infant"[tiab] OR "premature infants"[tiab] OR "preterm infant"[tiab] OR "preterm infants"[tiab]) AND ("cct"[tw] OR "ccts"[tw] OR "clinical trial"[publication type] OR "clinical trial"[tw] OR "clinical trials as topic"[mesh] OR "clinical trials"[tw] OR "clinical trials, phase i as topic"[mesh] OR "clinical trials, phase ii as topic"[mesh] OR "clinical trials, phase iii as topic"[mesh] OR "clinical trials, phase iv as topic"[mesh] OR "cohort studies"[mesh:noexp] OR "cohort"[tw] OR "cohorts"[tw] OR "concurrent"[tw] OR "controlled clinical trial" [pt] OR "controlled clinical trials as topic"[mesh] OR "controlled trial"[tw] OR "controlled trials"[tw] OR "follow up"[tw] OR "follow-up studies"[mesh] OR "followup"[tw] OR "incidence"[tw] OR "long term"[tw] OR "longitudinal studies"[mesh] OR "longitudinal"[tw] OR "longterm"[tw] OR "multi center"[tw] OR "multi centre"[tw] OR "multicenter studies as topic"[mesh] OR "multicenter"[tw] OR "multicentre"[tw] OR "non experimental"[tw] OR "nonexperimental"[tw] OR "observational studies as topic"[mesh] OR "observational study"[pt] OR "phase 1"[tw] OR "phase 2"[tw] OR "phase 3"[tw] OR "phase 4"[tw] OR "phase four"[tw] OR "phase i"[tw] OR "phase ii"[tw] OR "phase iii"[tw] OR "phase iv"[tw] OR "phase one"[tw] OR "phase three"[tw] OR "phase two"[tw] OR "phase four"[tw] OR "placebo" [tw] OR "placebos" [tw] OR "prospective studies"[mesh] OR "randomisation"[tw] OR "randomization"[tw] OR "randomized" [tw] OR "randomised"[tiab] OR "randomly" [tw] OR "random"[tw] OR "rct"[tw] OR "rct"[tw] OR "rcts"[tw] OR "studies"[ti] OR "study"[ti] OR drug therapy[sh] OR groups [tw] OR observation*[tw] OR placebo [tw] OR prospective*[tw] OR randomized[tw] OR randomly[tw] OR systematic*[tw] OR trial* [ti] OR "meta analysis"[tw] OR "metaanalysis"[tw] OR "meta analyses"[tw] OR "metaanalyses"[tw]) AND (hospital*[tw] OR "clinic"[tw] OR "clinics"[tw] OR office*[tw] OR center*[tw] OR facility*[tw] OR unit*[tw] OR ward*[tw]) AND Cochrane LMIC Filter

169 results, evidence filter, Cochrane LMIC filter, 1/1/2005 - 5/3/2016, English

Risk-benefit summary table for inclusion of community-based thermal care in IMCI and iCCM guidelines

Existing recommendation / practice

- Community-based thermal care for newborns is not included in existing WHO iCCM guidelines, which begin at 2 months of age.
- Section titled “Teach the mother how to keep the low weight infant warm at home” under the counseling guidelines for mothers in the 2014 Chart Booklet that advises keeping room warm, avoiding bathing, providing skin to skin contact on the mother’s chest, among other things.

Proposed recommendation / practice

- Expand iCCM guidelines to include care of infants less than 2 months of age. Include thermal care of all infants within this section, for implementation by community health workers in partnership with mothers and families.
- Incorporate post-discharge Kangaroo Mother Care (KMC) guidelines into IMCI for low birthweight infants born in facilities. Continuation of KMC at home following initiation in the hospital includes: early and continuous skin-to-skin contact with the mother (emphasizing importance of contact several hours per day), as well as frequent and exclusive breastfeeding.
- Promote research evaluating the safety and effectiveness of community-based Kangaroo Mother Care (KMC) immediately after birth for all newborns. This would be implemented by community health workers in settings with high rates of home births.

Quality of evidence (for outcomes deemed critical)

CONDITIONAL

The benefits of community-based Kangaroo Mother Care for newborns have only been evaluated through one randomized control trial in 2008, which concluded insufficient justification for community KMC due to potential bias from missing birthweight data. However, for infants modeled to be LBW, neonatal mortality rate was 9.5% in the intervention arm vs. 22.5% in the control arm (adjusted OR 0.37, 95% CI 0.16 to 0.86).{Sloan, 2008 #46}

A secondary analysis on this cohort found that implementation factors may play a large role in effectiveness of community KMC, as impact on survival was exclusively for those newborns held in skin-to-skin contact for at least seven hours per day in the first two days of life. {Ahmed, 2011 #47}

Other home visit trials evaluating the promotion of skin-to-skin contact in the community setting have also yielded

encouraging results.{Vesel, 2013 #50}

Benefits/desired effects

- 1) Draw attention to this extremely vulnerable subset of infants in need of additional care within iCCM and IMCI guidelines
- 2) Emphasize proper implementation (ideally >20 h/day) of community KMC as a promising option for thermal care in settings in which incubators are not available or too scarce to meet local needs
- 3) Improve the management of babies born at home, a high proportion of which are low birthweight and/or preterm and therefore have increased risk of morbidity and mortality
- 4) Establish mothers as crucial components in the care of their infants

Risks/ undesired effects

- 1) By promoting KMC as an effective intervention, mothers and community health workers alike may be overly reassured and less sensitively assessing infant for danger signs
- 2) Mistaken use of KMC as alternative to facility referral for unstable infants may have poor consequences
- 3) Demands time and energy from mothers recovering from arduous labor processes and may have many other familial obligations
- 4) Conflict with traditional customs

Values/Acceptability

- Requires strong focus on tackling perceived barriers; highly acceptable by communities when presented through appropriate cultural paradigms{Bazzano, 2012 #51}
- Health workers sometimes reluctant due to lack of belief in utility of KMC stemming from poor training{Lunze, 2012 #52}
- Global newborn health community generally views community KMC as promising intervention in need of more evidence

Costs

Training and materials to support community health workers are main costs; overall much less costly than transporting to facility and ensuring incubator care

Feasibility

Relatively simple intervention likely to be widely generalizable, but in need of implementation support in the form of context-specific materials adapted to local factors and sociocultural norms{Darmstadt, 2006 #49;Hunter, 2014 #48}

Final recommendation	Include thermal care of infants within iCCM and incorporate post-discharge KMC practices into IMCI guidelines to guide mothers in the home setting
Strength of recommendation	<i>Strong OR Conditional OR Qualified OR Weak Conditional</i>
Quality of evidence that informs recommendation	<i>High / Moderate / Low / Very Low</i> Low
Comments justifying recommendation	Highly promising but needs more evidence of benefit in community settings
Gaps, research needs, comments	<ul style="list-style-type: none">- More large, well-conducted trials needed to evaluate effectiveness of community-based KMC as currently there is only one RCT- Need more research on approaches for introduction into community settings, which will differ from hospital-based implementation

Future Considerations

Hospital:

- Need for low cost incubators that can be maintained and repaired at the local level.
- Equipment for determining if bag-mask ventilation is effective (Laerdal) (Dr. Beena D Kamath-Rayne)
- *New diagnostics to help with gestational age dating (low cost ultrasound?)*
- PCR technologies for POC diagnosis
- *Near infrared spectroscopy to assess tissue oxygenation*
- *Aerosol-mediated delivery of exogenous surfactants*
- We do not have it yet but we need a rapid diagnostic for CSF to ascertain if there is meningitis/encephalitis

Frontline facility:

- Phototherapy - low-cost devices that do not require continuous electricity, including sunlight filters, solar-powered devices, and battery-operated devices.
- Phase changing material norm temperature mattresses for transport - Transport of ill children that need treatment start with in 6 h can be done by using this device
- First Breath Trigger device <http://www.grandchallenges.ca/grantee-stars/0690-01-10/>
- Exhaled carbonmonoxide measurement to assess the risk for hyperbilirubinemia
- Aerosol mediated delivery of vaccines and antibiotics
- 40 % dextrose gel for treatment of hypoglycemia. This treatment is safe, inexpensive and potentially life saving, while breast feeding is being established in resource poor communities

Community health worker:

- mHealth Apps that collect data and provide decision support - Although they may not be quite ready we should be thinking about how we can integrate decision support with data collection and data analysis at community level - we need to start learning from the data about the consequences of decisions made at community level to slowly improve decision making at scale. There will also be benefits in terms of understanding needs and access - but this will require a big uplift in the data collation and analytic capacity.

Hospital:

- Improved guidance on length of antibiotic treatment, as guided by blood cultures
- Nasogastric tube feeding and cup feeding protocols for feeding breastmilk (fresh or stored/banked);
- Importance of glucose monitoring. Hypoglycemia (specially among small/preterm infant) is a major cause of morbidity and mortality.

Frontline facility:

- Medication dosing for < 4 kg
- Safe oxygen use, specially for preterm infants
- Telemedicine for remote locations to support management of severe cases.
- Sun filter phototherapy or battery supported phototherapy - Sun filters do not require power and are effective in treating mid level jaundice. Local treatment will improve compliance of parents and CHEWs to treat jaundice appropriately.
- Avoid all creams and ointments that contain hemolytic agents for G6PD deficient babies. Do not use antibiotics, herbs, sunlight treatment. These habits are major causes of hemolysis and kernicterus in G6PD def. babies and inappropriate frontline treatment is a major cause of delayed care seeking.

Community health worker:

- point of care bilirubin assay (e.g., Bilistick)
- Current practice of first placing baby on breast, if not sucking, then cup feeding places baby at high risk of unsafe swallow and subsequent respiratory illnesses which can be preventable. Infants with disabilities, weak or too ill to suck and swallow need to be assessed for readiness for safe feeding. A simple method using a sterile gauze strip has been trialed successfully in several hospital facilities. This method allows the health care staff to assess if aaw can suck. If they cannot, the same method can be a treatment to enable a baby to suck safely and learn to coordinate suck, swallow and breathing. They are then able to breastfeed within a day or at most, a couple of days depending on degree of illness and disability. It helps reduce fatigue and respiratory effort and increase success at breastfeeding. Improved weight gain and early hospital discharge needs to be trialed via a randomised clinical trial as this has yet not been done.
- Disposable preloaded single dose injectable antibiotics for pre-referral sepsis management, for trained CHWs with appropriate remote support. In places such as the Sahel, CAR, northern Kenya, access to a facility with injectable antibiotics for managing sepsis in the newborn can take 2-3 days to find and access

transport. In such settings the risks of not providing antibiotics is higher than the risks that CHWs cannot adequately manage the case. Current standards of CHWs training and education is considerably higher than 5-10 years ago, and thus with remote support they can conduct this treatment.

- learning platform including interactive video - I think the most important action at this time is to create more accessible learning platforms for health workers so they can better use information already in existence and proven to work. We create simple, relevant teaching videos on many of these topics used worldwide by 1000's of organizations. Can you imagine the power of video to show mothers danger signs in newborns, or the before and after of hydrating a child with diarrhea. They will never forget. I am pulling in the recent quote from Neil Pakenham -Walsh: "The single biggest piece of unfinished business' of the 20th century is to extend the basic benefits of modern science and medicine ... The most urgent task before us is to get medical and health knowledge to those most in need of that knowledge. Of the approximately 50 million people who were dying each year in the late 1980s, fully two thirds could have been saved through the application of that knowledge." Grant J. Opening Session, World Summit on Medical Education, Edinburgh 1993. Medical Education 1994; 28 (supplement 1): 11. Children continue to die from common childhood killers (pneumonia, diarrhea, malaria...) primarily because they do not receive basic life-saving interventions - interventions that are not only well established but are also often locally available, such as antibiotics and oral rehydration solution. Major contributing factors include failure to recognize danger signs and consequent delays in taking appropriate action. With respect to 'local availability' I think we can be fairly sure that almost every family, even the most disadvantaged, has access locally to the means to save life in the case of acute diarrhea. For pneumonia, we do not have data, but it would indeed be interesting to know how many children die from pneumonia despite local availability of oral amoxicillin (local availability being defined perhaps by the presence of this inexpensive, lifesaving drug within 10 miles of the home).
 - Co-trimoxazole can be safely used in neonates for treating pneumonia and sepsis. A global literature review showed no case of co-trimoxazole induced aggravation of jaundice or kernicterus. 2) Co-trimoxazole has been safely used in nearly 2000 neonates with infections by SEARCH, Gadchiroli. No early or long term neurological sequelae.
-