**Predictions/recommendations for future IMNCI taking into account mortality reductions and changing causes of death as well as etiologies within the major killers**

**From Eric Simoes and Sandy Gove, for the WHO IMNCI strategic review** 8 June 2016

Introduction

Reductions in pneumonia, malaria, and diarrhoea deaths were the main contributors to the large overall reduction in under five mortality between 2000 and 2010 of the global burden of under five deaths yet they remained the leading killers in 2010. Since then, malaria has continued its remarkable decline (60% decrease in global malaria mortality rates between 2000 and 2015) with malaria falling to fourth. Pneumonia and preterm birth complications are now the leading killers with the neonatal period accounting for most deaths overall (where the decline in mortality has been slower than in 1-59 month olds). Success in HIV PMTCT efforts has substantially reduced the childhood HIV burden.

IMNCI’s clinical management and prevention contributions to child survival strategies need to continue to emphasize the leading causes of child mortality, with attention focusing on infectious and neonatal causes and in particular on the most common causes of death- pneumonia and preterm birth complications.

Efforts to accelerate the decline in preventable deaths need to continue to focus on interventions known to save lives from the most important causes of death, especially in the few countries where most preventable deaths occur, while also addressing the need to modify interventions based on changing etiologies. Changing infectious etiologies of pneumonia, diarrhea and febrile illness impact both the few remaining high mortality countries but also countries which have significantly reduced mortality. At the same time, IMNCI should and can offer modified algorithms to address additional causes of death which begin to account for a great proportion of deaths as the overall mortality rate falls. The latter includes injury and chronic diseases.

There is a need to create a more flexible and modular system of WHO tools to support quality childcare that can build on iCCM, IMCI, first-level and referral care guidelines. This is driven by rapidly declining neonatal, infant and child mortality and the changing distribution of causes of mortality, and enabled by advancing evidence on effective interventions. Provision of quality care in this context, includes the preventive, promotive, therapeutic and developmental aspects of child health. The proposed approach, a more flexible and modular system:

* anticipates further changes in the epidemiology of childhood illness and in diagnostic tools, and available therapeutic and preventive interventions.
* provides a flexible approach to supporting improved care at various locations, aiming at equity in reaching children at greatest risk for death or disability. This involves:
  + progressively decentralizing certain interventions from the hospital to the first-level health facility and to community-based health workers; while at the same time improving hospital care, since further reducing mortality in the reasonable future will require more complex hospital-based care for some conditions [e.g. if facility-based deliveries becomes more universal, the management of the newborn, and subsequent reduction in early neonatal mortality, will be dependent on improved facility-based care]
  + supporting their modular evolution based on changing epidemiology and evidence, building on the existing approach to supporting assessment- differential diagnosis- treatment in the hospital book and the assess-classify- treatment algorithm in first-level IMCI.
  + making algorithm components more modular and amenable to change/progress and to variation between and within districts.
  + balanced and well-coordinated support for all three levels of care- the community, the first level facility and the hospital.
* allows these additional diagnostics and interventions to build on what has already been developed, synthesized and implemented, rather than starting over and requiring extensive retraining.

Given the differing understandings of what is included within IMCI and the greater likelihood of a fresh start with country and donor support, it would make sense to rebrand this with some name reflecting an integrated district approach for quality child care. However most country surveys suggest not changing the name and it could be retained for the first-level facility, within the broader 3 level package. At the same time, it would be important to clarify that this new modular approach to modifying components of the IMCI algorithm (such as the improving the management of cough or difficult breathing by the addition of pulse oximetry and, in health centres with difficult referral, oxygen) can be used in a “mix and match” way with the recent generic IMCI chart booklet or country adapted chart booklet. Equally important is the need to be able to use materials that could be modified for use in different methods of training and mentoring [preservice training, ICAAT, dIMCI, fIMCI, cIMCI etc]. A modular approach would suit this changing evolution of the provision of child health services.

Fortuitously the IMCI algorithm was designed in a way such that it can easily be modularized, with each main symptom using the same color-coded action approach to assess-classify-identify treatments, with a collection of treatment boxes linked to one or more classification tables. It was intended for flexible adaptation to country conditions. Over the years, changes to the generic chart booklet have been infrequent and “all at once.” Based on changes in epidemiology and anticipating the direction of changes and advances, we propose a number of likely modifications and additions to the hospital tools and a flexible set of modules for the first-level facility acute care algorithm, to reflect the variable technical resources that may become available to improve the management of pneumonia, diarrhoea, fever, and other conditions. The color-coded action approach is well ingrained in the minds of health workers working at the community and first level health facilities, since the CDD and ARI days, and expanded upon with IMCI. Currently, referral care guidelines are not widely utilized by physicians, and IMCI first level facility guidelines are viewed by them as too simplistic. Thus there is a disconnect, between community and first level of facility management guidelines and the referral care guidelines. This will have to be bridged, to enable seamless integration.

This allows for the production of alternative algorithm components – guidelines with tools to support on-site training- and suggested modifications to the hospital guidelines that can be more rapidly and flexibly disseminated, with appropriate variation depending on the background of the health worker.

We also are suggesting that the generic first-level facility chart booklet be shortened to only deliver acute care, screening, feeding advice and prevention, with the replacement of dangers signs with a ‘mini-ETAT’ including injury and the addition of Infection Prevention and Control (IPC) precautions and care for development. We would recommend moving chronic management of HIV care/ART to a separate chronic care module, sitting next to chronic care modules to support the management of obesity, malnutrition, asthma, sickle cell disease, and diabetes (see Chronic care, below). We recognize that childhood injuries will constitute an increasingly important part of child mortality over time. One can also predict that as neonatal mortality reduction begins to become apparent [sepsis management, prevention of asphyxia related neonatal mortality and management of the prematurely born infant], developmental delay, incompletely treated neonatal meningitis, and cerebral palsy, will result in a predictable increase in these conditions, necessitating guidelines for their management.

**Future modifications for community, health centre and hospital algorithms and guidelines for quality child health.**

**ALRI case management**

**Changing etiology:** With improving economic conditions in most of Asia, and large parts of Africa, the bacterial components of acute lower respiratory tract infection will become far less important than the viral etiologies. (PERCH Study) Thus in most countries, infant mortality is already decreasing, and ARI deaths are becoming a smaller proportion of the overall infant mortality. (1) Most of these now are probably viral. (2, 3) In addition with the widespread use of the *Haemophilus influenzae* type B and pneumococcal vaccines, increasingly bacterial pneumonia will be staphylococcal or streptococcal, (4-6) as well as predictably resistant pneumococcus. (7) The reason for the latter is the current strategy of using amoxicillin for the treatment of severe and nonsevere pneumonia, that is now extended to the community.(8) The following issues will in all likelihood need to be dealt with for the management of acute lower respiratory tract infections

* Most severe and nonsevere pneumonia will be viral, respiratory syncytial virus, human metapneumovirus and parainfluenza virus. (2, 3)
* Pneumococcal vaccine will be in widespread use, and RSV vaccines will probably be implemented in the next 5 to 10 years. (9-11)
* Rhinovirus and other viruses will become increasingly important, for which there are no forseeable preventive methods, given the large numbers of different subtypes.(11)
* The pneumococcal vaccine, will lead to gradual serotype replacement, predictably with penicillin resistant strains, due to the overuse of amoxicillin at the community level. (7, 8)
* Bacteria causing pneumonia, will change from pneumococcus primarily to Staphylococcus and group A Streptococcus, for which bacteria vaccines are not being actively pursued for developing countries. (12)
* Hence it will always be necessary to use antibiotics for the management of pneumonia.
* The current simple algorithm may not be adequate, given the issue of overuse of amoxicillin for viral LRTI, and antibiotic resistance. Development of risk scoring systems for bacterial pneumonia, including possible use of RDT’s is a priority.
* Conversely, rapid diagnostic tests for pneumonia, will be available, but probably not be cost-effective, since most pneumonia will be viral.(13, 14)
* The management of hypoxemia and probably acidosis at first level facilities will be important. (15, 16)
* At the hospital level the management of hypoxemia and other supportive care, antibiotic resistant pneumonia and empyema, will become very important and will drive inpatient management regimens.(15-18)
* Pulse oximeters at all levels- iCCM, IMCI at health facility, hospital

GIS guided location of oxygen treatment, accompanied by additional training and deployment of more qualified health workers to these health centres where feasible.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| CHW | Health centre | Hospital |  |  |
| RR, clinical signs | RR, clinical signs,  severity score | RR, clinical signs, severity scores |  |  |
| Pulse oximeter | Pulse oximeter | Pulse oximeter |  |  |
|  | Antibiotics | First, second line antibiotics; antivirals as available |  |  |
|  | Oxygen if hospital referral distant (map locations) | Oxygen | Bubble CPAP | (Intubation, mechanical ventilation) |
|  | Severity score🡪refer | Severity score🡪more intensive care |  |  |
|  | Inhaled salbutamol | Inhaled salbutamol |  |  |

The risk of death from pneumonia or neonatal conditions is increased in the presence of hypoxemia. A substantial portion of children with pneumonia and severe hypoxemia would be missed without pulse oximetry in both first-level facilities and by CHWs using iCCM. Referral to hospital is still often difficult or substantially delayed in some rural areas, and most deaths still occur outside health facilities (an estimated 62% of children with severe ALRI are treated in hospitals while 81% of deaths happen outside hospitals; incidence of admissions for severe ALRI decreased with increasing distance from the hospital, consistent with previous reports access to hospital care is an important determinant of deaths from pneumonia in children in developing countries[[1]](#endnote-1)),(19) arguing for decentralized availability of oxygen to health centres where referral is difficult (with on-site training and prioritization in human resource support to make this feasible). These health centres should be located by geographic criteria based on referral time to a hospital and concentration of pneumonia deaths.

Pneumonia management is designed to serve endemic problems, while also contributing to preparation and response to epidemic problems. While SARI due to MERS and other novel viruses require a strong response, the main requirement for skilled respiratory care is for community-acquired pneumonias.

Case management still requires antibiotics, still empirically, although these progressively will not contribute to survival as most cases are viral and only benefit from supportive care. With further mortality reduction, improved nutrition and more data on safety, it may eventually be possible to treat fast breathing community-acquired pneumonia without antibiotics in some countries.

The proposed approach would provide a continuum of coherent care for severe ALRI at district level. Same simplified approach to managing respiratory distress in a child with pneumonia with assessment of severity, measurement of oxygen saturation then titrating the provision of oxygen. A simple training package that can be delivered on site by mentors is relevant for training at both health centre level and for health workers in the hospital emergency room and all staff on the inpatient ward. They all need to know how to identify severe disease requiring prompt upward referral. These improved clinical management tools must integrate adequate IPC, which have been missing from the generic IMNCI materials, although somewhat present in the child hospital guide and in country adaptations (particularly after the Ebola emergency).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Possible WHO modular approach to child health- integrated district approach to quality child care** | | | | | | |
| **Level of care** | **Community** | **First level/primary care** | | **Hospital care (district and large hospital)** | | **ICU in tertiary hospital ?** |
| A=Assess  Rx=Treat  Ref=Referral  D=country adaptation |  | **Health centres with referral** | **Health centre (or outpatient clinic) where referral to hospital is difficult** | **Emergency room** | **Inpatient care** | **ICU** |
| **Emergency triage assessment and treatment** |  |  | MiniETAT at start with immediate response  “ | ETAT- Update with new guidelines; include injury and IPC | --------------- | -------------- |
| **\*Cough or difficult breathing**:  -pneumonia | iCCM detect-treat pneumonia; addition of pulse oximeter with gismo to support counting respirations | A: RR, indraw, pulse ox  Rx: antibiotic options based on shift etiology  Ref: severe, sat<90/94; cough >14 days for possible TB, asthma | A: RR, indraw, pulse ox  Rx: antibiotic options based on shift etiology, oxygen based on sat<90/94, inhaled salbutamol.  Empirical Rx TB per algorithm; Xpert MTB/RIF test if available  Ref: very severe, cough>14 days | ETAT- if signs respiratory distress/sat <90/94, start oxygen.  Start and titrate oxygen based on saturation  Inhaled salbutamol | ETAT+: manage severe pneumonia per child hospital book with updates from oxygen manual/  2016 ETAT guidelines\* including bubble CPAP | ?SARI critical care course, updated |
|  |  |  | As above but start oxygen based on clinical signs |  |  |  |
|  |  |  | A: RR, indraw, pulse ox  Rx: antibiotic options based on shift etiology  Ref: severe, sat<90/94;cough>14 days |  |  |  |
| **Surveillance, dangerous pathogens** |  |  | IMCI classifications used in IDSR but no emphasis on clinician role in reporting.  Report suspected ILI, SARI |  |  |  |

**POCT:** Provide individual patient data once feasible and where this data will alter case management:

* Need feasible POCT for acidosis (not ABG)
* Need validated biomarkers to distinguish viral and bacterial illnesses and predict pneumonia outcomes in children
* Further POCTs to diagnose TB in children

**Modified small hospital guidelines, diagnostics, medicines and training tools**

* Bubble CPAP at hospital
* Improved support for on-site training in severe ALRI case management, oxygen delivery, salbutamol etc, divided by health worker cadre and as a clinical team as a whole.
* **Improved preparation of hospital clinical teams for management of patients presenting with dangerous pathogens with epidemic potential—both for IPC and clinical care.** 
  + Preparation to manage outbreaks of measles and SARI (reformulate measles case management - manage in isolation room)
  + Table on IPC precautions by pathogen; standard, droplet, contact, airborne precautions
  + Clinical team’s role in disease surveillance and response

**Diarrhoeal disease case management**

**Changing etiology:** Projecting forward, widespread availability of rotavirus vaccine will mean replacement of rotavirus with Norovirus and Campylobacter in the community. (20-24) Replacement pathogens are a substantial reality after rotavirus immunization although the ratio of severe disease with other pathogens is less. Severe diarrhoea causing mortality will likely be mostly due to Cryptosporidium species and stable toxin producing entertoxigenic E. coli (and, during outbreaks, cholera). (22) From the GEMS studies, most attributable cases of moderate-to-severe diarrhoea were due to four pathogens: rotavirus, Cryptosporidium, enterotoxigenic Escherichia coli producing heat-stable toxin (ST-ETEC; with or without co-expression of heat-labile enterotoxin), and Shigella. (22) Other pathogens were important in selected sites (eg, Aeromonas, Vibrio cholerae O1, Campylobacter jejuni). There was substantial variation in pathogens according to geography, diarrhoea severity, and season. Bloody diarrhoea was primarily associated with Campylobacter spp and Shigella spp, fever and vomiting with rotavirus, and vomiting with norovirus. Although capable of causing explosive outbreaks, norovirus usually causes less severe diarrhoea than rotavirus but can cause severe dehydration and death (21)

**Changing presentation:** Severe dehydrating diarrhoea seems to have become much less common today, outside of cholera outbreaks, and in fact is often not seen during district and regional level IMNCI training. Most ORT corners have closed. This probably reflects both changing etiology and widespread use of ORT. (25)

**Continue support for full package of interventions individually shown to have an impact on mortality and which can be implemented through community or facility-based IMCI**- ORS; zinc; antibiotics for dysentery; rotavirus vaccination; vitamin A supplementation; improved access to safe water, sanitation, and hygiene; and breastfeeding.[[2]](#footnote-1)

Health worker capacity in classifying dehydration and providing oral and IV hydration will remain necessary, while severe dehydration will be less common but its management still important in managing outbreaks of cholera and individual cases of Cryptosporidium. All health facilities should be able to provide IV fluids or at least ORS by NG tube. Hospital clinical teams should be supported in their capacity to manage HUS and prepared to respond to cholera outbreaks.

**Modified first-level facility algorithm components will be needed to:**

To further reduce diarrhoea mortality, provide national/subnational data (not individual patient data) to modify the treatment recommendations on:

* Antibiotic resistance for Shigella and salmonella species- these need to be taken into account for antibiotic recommendations
* For bloody diarrhoea, availability of etiological information is important to improve the algorithm (beyond Shigella and amoeba) and present options, to avoid antibiotic treatment for some Shiga-toxin producing E. coli (0157; EHEC), for which retrospective and prospective observational studies have reported an increased risk of HUS with the administration of antibiotics during the bloody diarrhea phase. EHEC *E. coli* outbreaks have need reported from Africa.(26) Whereas early administration of effective antibiotics to persons infected with *S. dysenteriae* type 1 infected is associated with decreased Shiga toxin concentrations in stool and a low risk of developing HUS.(27)

Either sentinel surveillance and/or data from outbreaks on both etiology/subtype and antimicrobial sensitivity should be able to be disseminated to front line health workers (with various mHealth tools including eIDSR), to inform empirical antibiotic treatment or whether to withhold antibiotics.

**POCT:** Provide individual patient data once feasible and where this data will alter case management:

* For profuse and prolonged watery diarrhoea, rapid diagnostic tests to diagnose Campylobacter (as stool microscopy seems unlikely to be successful peripherally) in order to provide specific treatment with nitazoxanide. (With modified algorithm component to reflect this.)
* rapid diagnostic tests in the stool for detection of other bacterial pathogens may become available such as for some Shiga-toxin producing E. coli (0157; EHEC). (With modified algorithm component to reflect this.)

**Other modifications to first-level facility algorithm to consider:**

* Dividing the age ranges given the differential severity of both watery diarrhea and bloody diarrhea in the very young infants compared to older children (if also make sense for other conditions).
* Fluid plans A, B and C remain important for diarrhoea with dehydration but should clarify fluid management of severely malnourished children, as done in the hospital guidelines, to clearly distinguish this fluid resuscitation from that appropriate in malaria, sepsis, etc (according to the updated ETAT guidelines).
* Specify IPC precautions for management of diarrhoeal diseases, especially important for Shigella, cholera and Norovirus.
* To reduce morbidity (days of diarrhoea, hospitals stays)- further research then addition of probiotics.
* Once proven, further nutritional and other interventions to address the malabsorption and malnutrition from subclinical infections and persistent diarrhoea.
* Consider moving instructions on the management of persistent diarrhoea and severe malnutrition to a IMNCI chronic care module (or set of modules, as children with these conditions benefit from longitudinal follow-up and tracking (see Chronic care, below).

**Modified small hospital guidelines, diagnostics, medicines and training tools**

* **Support for on-site training for management of diarrhoeal disease supported by an updated hospital book**, divided by health worker cadre and some for the clinical team as a whole.
* **Improved preparation of hospital clinical teams for management of patients presenting with dangerous pathogens with epidemic potential—both for IPC and clinical care.**

Reinforce preparation to manage outbreaks of bloody diarrhoea and cholera

Table on IPC precautions by pathogen; standard, droplet, contact, airborne precautions

Some attention to clinical team’s role in disease surveillance and response

**Fever case management**

Global warming, and travel is increasing the spread of mosquitoes and mosquito borne illnesses across continents and into increasingly higher altitudes. Thus the traditional areas for defining malaria or dengue risk are becoming increasingly diffuse. RDT's for malaria are already available in some areas but not in others, even within countries. In those countries, there may be overlapping areas of dengue and malaria, no risk malaria areas etc. so the fever algorithm may need to be adaptable even within country.(28, 29)

The use of RDT's will become increasingly important. Despite substantial success in malaria control, primary care IMNCI needs to continue to include a fever algorithm that addresses malaria case management based on mRDT ‘test and treat’ in countries which have not eliminated malaria, with outreach using iCCM in communities without facility access and rectal artesunate while being referred for hospitalization for severe malaria. Management guidelines are going to become increasingly complex as artemisin resistance develops. (30-32)

The fever algorithm needs to be strengthened to adequately address malaria RDT-negative fevers, supported as possible by a few RDTs focused on nationally common and important causes of fever, or backed up by national/subnational data from panels of tests. There is a continued need to have more data on the distribution of the causes of fever in various geographical areas and on treatment of febrile illnesses, to identify which children would benefit from antibiotic treatment. (33, 34)

New point-of-care tests to detect pathogens or host biomarkers are needed, but only integrated into the first- level fever algorithm and the hospital guidelines after being tested for evidence of clinical benefit rather than simply on their availability or their diagnostic performance.(35) Health workers should be provided with guidance on whom to test and response to test results. An emphasis in the algorithm revisions and local adaptations should be to support reduction of antibiotic use/development of antibiotic resistance. (33, 35)

Within all age groups beyond the first month, most fever is predominantly due to viral infections, with a predominance of acute respiratory infections. In RDT-negative fever, health workers should be supported to consider other causes of fever within the algorithm such as pneumonia and dysentery and to consider locally important infections such as rickettsial diseases and leptospirosis.(36, 37)

Typhoid fever, will increasingly become more important in the Asian subcontinent and its management in acute febrile fever algorithms is already probably necessary.(38)

The mortality of UTI was as high as 20 percent in the pre-antibiotic era. In contrast, when UTI are appropriately treated with antibiotics, acute complications (eg, renal abscess, death) are uncommon. Diagnosis of UTI by dipstick urinalysis is already available and its addition to the fever algorithm should be explored.(39) (34)

Making RDTs available to overcome reluctance to report suspected dangerous pathogens causing febrile illness such as Ebola (where there is substantial overlap in clinical signs with other febrile illnesses) can improve surveillance and rapid response to cases. (40)

* Artemisin resistance will mean that the use of expensive antimalarials, if available, will need malaria diagnosis to be very accurate. (41)
* Dengue vaccines are already available, and have been introduced into Philippines already, despite the fact that long-term studies on the safety, are lacking. There is also theoretical, and actual data that suggests enhanced disease, could occur as vaccine immunity wanes. (42, 43) Currently however these vaccines are not used in the current IMCI age group. Although there are no specific treatments, skilled supportive care for dengue hemorrhagic fever and dengue shock syndrome can reduce mortality (44).
* Fever from especially dangerous pathogens with epidemic potential includes measles, meningococcal meningitis, and viral haemorrhagic fevers. Measles should now be addressed as a dangerous pathogen with periodic outbreaks—its management does not need to remain in the main algorithm under fever, rather as a surveillance trigger—leading to ring vaccinations and isolation with appropriate IPC and case management.

**Neonatal care**

It can be predicted that with increasing use of facilities for maternal deliveries and the use of skilled birth attendants at deliveries, the following changes to newborn care will be needed in the next 10 to 20 years:

* Neonatal sepsis related deaths will decrease
* neonatal sepsis will need to be treated with drugs for antibiotic resistant gram-negative organisms
* the stillbirth rate will fall, but there will be an increase in preterm delivery
* facility-based management of preterm babies will go beyond kangaroo care and breast-feeding, as birth weights go below 1000 g
* the management of and prevention of low birth weight will become increasingly important as survival increases
* the management of minor and major congenital malformations will become increasingly important
* babies with birth asphyxia will survive, and predictably there will be an increased burden for the management of developmentally disabled babies
* with increasing improvements in social economic status, there will be a larger number of infants of diabetic mothers
* the emphasis on neonatal survival will change from survival only to the management of chronic conditions such as: developmental disability, chronic lung disease of prematurity, low birth weight

Bhutto et al have estimated that he maximum effect on neonatal deaths is through interventions

delivered during labour and birth, including for obstetric complications (41%), followed by care of small and ill

newborn babies (30%). (45). To rapidly reduce the stillbirth and neonatal mortality rates, a higher proportions of deliveries need to take place in well-equipped facilities with high quality of care.

For those not planning or able to deliver in a facility, a systematic approach needs to assure that a birth attendant/TBA/CHW able to deliver essential newborn care including newborn resuscitation if needed at home is linked with the pregnant woman. Approaches to support interventions across the woman’s continuum of care (preconception, antenatal, intrapartum, immediate postnatal period, and after) and good linkages between community care, first-level facilities and hospital, using various phone and other technical aids, will be increasingly possible to achieve.

Provide appropriate level guidelines and training to the right health workers according to their contact with the neonate by days of life in the first week and each week after that: “Almost all asphyxia-related and the majority of prematurity- and malformation-related deaths occurred in the first week of life (98%, 83% and 78%, respectively). Only one-half of sepsis-related deaths occurred in the first week while one-quarter occurred in each of the second and third to fourth weeks of life. The distribution of both overall and cause-specific mortality did not differ greatly between Asia and Africa. The first 3 days after birth account for about 30% of under-five child deaths. The first week of life accounts for most of asphyxia-, prematurity- and malformation-related mortality and one-half of sepsis-related deaths.”(46)

All health workers (including TBAs, CHWs) present at births need neonatal resuscitation/asphyxia management skills and supplies. The same basic guidelines should be provided as guidelines and job aids, using standardized (and available) equipment then taught consistently, whether this dissemination happens from the maternal or child health side, including those delivering babies and those providing newborn care. A more modular approach to algorithm components and their dissemination would allow the identical guideline/algorithm component to be available within IMNCI with the provision (in cooperation with those responsible for maternal care) of on-site training for newborn resuscitation and other immediate newborn care- for both midwives, other skilled birth attendants and all other health workers who may encounter newborns.

Emphasis should be placed on supporting a coordinated chain of interventions between the 3 levels to assure timely provision of antibiotics for neonatal pneumonia/sepsis and referral to hospital for full supportive care, with data review/expert consensus suggesting greater impact of injectable than oral antibiotics and greater mortality reduction from hospital management. (47) The first-level IMNCI guidelines already recommend pre-referral intramuscular antibiotics. Home- based newborn care by CHWs with pre-referral injectable antibiotic treatment has been shown to reduce neonatal sepsis mortality and overall neonatal mortality.(48) Training TBAs to perform newborn resuscitation and to recognize possible sepsis in the first month and give pre-referral antibiotics in Zambia resulted in a 45% reduction in mortality in the intervention area compared to the control.(49)

In 2008, the IMCI chart booklet was updated to include the first week of life with the exception of immediate newborn care and resuscitation/management of asphyxia which remained in the IMPAC guidelines and training materials (these can be provided from IMPAC or the hospital book when relevant). (Note that the first week was withdrawn from the original IMCI chart booklet as several conditions were considered by the separate Reproductive health/maternal department to be within their province- management of asphyxia, sepsis from PROM or other intrauterine infections, immature lungs, and birth trauma; these guidelines appeared instead in the IMPAC PCPNC.) The current components of the first-level algorithm and how they might be strengthened over time as new technologies become available:

* neonatal sepsis
* the current IMCI algorithm already has been simplified to 7 signs (the addition of additional, uncommon signs with a high odds ratio made no difference to sensitivity and specificity of the overall algorithm: grunting, cyanosis, capillary refill, stiff limbs). Further data may result in an even better set of signs.
* Additional use of pulse oximetry is likely to identify additional neonates with hypoxaemia not detected by clinical signs.
* For health workers with more capacity or able to use an electronic aid, more complex risk scoring could be substituted once validated.
* jaundice
* possible adaptations/advances including adding lower cost transcutaneous bilirubin testing devices; Phototherapy devices such as a portable “bilibed” to provide both phototherapy treatment and heat (50)
* diarrhoeal disease
* management of low birthweight infants

The IMCI hospital book (2013) includes newborn care and resuscitation, management of sepsis and other neonatal complications, and preterm and low birth-weight infants. These need to be operationalized through on-site training and mentoring.

CPAP is mentioned in the hospital book. The recent oxygen guidelines (51) support use of bubble CPAP for premature babies with RDS in hospital. These could be made available with modular training. (Adaptations/advances: lower-cost robust CPAP equipment with standardised settings and neonatal intensive care context specific “kits” may become available; surfactant if more stable, at lower cost.) (50) It will be important for the WHO department within their program management materials to provide guidance on stepwise augmentation of more intensive newborn care in limited resource settings, to assure an effective balance of community, first-level and hospital care which is planned according to estimated impact (45) and cost.

**Emergency care and management of injury and abuse**

Injury is growing in importance as a contributor to mortality and disability as other causes decline in under fives, even though the proportion of mortality from injury is much higher in older children and adults. Burns and falls are often more important than road traffic accidents in under fives.

**Evolve the ETAT algorithm and training to more thoroughly include injury**

* Further integrate trauma/injury into the ETAT algorithm and add training/mentoring tools to better support management of burns, wounds and other injuries. (With the decline in severe dehydration, consider changing D from dehydration to Disability, making it more consistent with ILCOR and other international triage algorithms.)
* Work with other Departments and efforts in improving emergency care, to be sure there is quality and consistency with the child health resuscitation and other care guidelines and tools as well as an approach that continues to support compatible approaches for pregnant women, older children, adolescents and adults.

Many countries are now starting emergency programs. Such guidance, and preparatory training, are needed both for national staff and emergency response teams to war casualties, earthquakes, tsunamis, building collapse, etc. More support for injury management within the ETAT and hospital training/mentoring program would assure quality approaches that are consistent with the other recommendations for resuscitation and ongoing care for infectious diseases.

* Careful approaches to recognize and respond to child abuse are needed (for country adaptation) (see section on Child development below)

**Extract a “mini-ETAT” to replace dangers signs at the start of the IMNCI algorithm**

This would support immediate lifesaving interventions at health centre level for medical conditions as well as burns and other injuries. Preparing health centre health workers for first-response to trauma can help save lives, while their ability to definitively manage minor injuries can decongest hospital emergency services.

**Child development**

**Assure a continuum of support for care for development** and response to developmental delays at all three levels—community, first-level facilities and hospitals.

* Counsellors and aids at first-level facilities can be trained to help implement care for development, to not overload the clinical health workers, but this should be integrated within acute care visits.
* The current tools are, appropriately, predominantly preventive. Guidelines and tools on developmental milestones and interventions when there is delayed development are needed. Although developmental milestones are mentioned within several disease management guidelines, they should be presented in the hospital guidelines. Currrently only age-specific toys are included.

**Explore modifiable contributors to developmental delay** in addition to prematurity, serious infections and malnutrition

* There is some evidence that nonaccidental trauma may be an important cause of post- neonatal developmental delay in India and likely other countries.(52) The role child abuse and interventions need much further work.

**Nutrition**

It is clear that malnutrition makes a very large contribution to mortality (both indirect and direct) which warrants support for broad implementation of multiple interventions to improve nutrition. IMNCI now provides a relatively complex algorithm for detecting and managing acute malnutrition, yet at first level facilities in most countries (in the absence of uncontrolled HIV in children), health workers will uncommonly see children with severe acute malnutrition. At the same time, as will be demonstrated in Ethiopia, Nigeria and the Democratic Republic of Congo using DHS data, and GIS mapping [review by Elizabeth Root and Eric Simoes] it can be seen that the areas of highest infant and under five mortality, don't often overlap with those with the highest degrees of acute or chronic malnutrition. Rather those areas appear to be related more to food insecurity.

This would imply that in the field of nutrition, perhaps IMCI should focus as much on the effective promotion of good nutrition as on the classification and management of acute malnutrition. In addition to the continued strong promotion of exclusive breastfeeding and vitamin A (and zinc in diarrhoea), providing support for complementary feeding after 6 months is reliant on good counselling using well adapted feeding recommendations that can be effectively discussed with mothers and to solve problems with feeding in the context of available foods. This requires ethnographic knowledge of local food availability and food customs (57) and the ability to estimate the energy density and micronutrients of traditional complementary foods which mothers have access to. (58) Where there is significant food insecurity, child health programmes at district level need to work with the nutrition program and WFP on solutions. Adaptation of the feeding recommendations may have been deemphasized in the IMCI adaptation process (these adaptations were not listed in Eva Kudlova’s adaptation reviews in 2002 or 2016 but perhaps are cataloged elsewhere).

In 2015, stunting rates were dropping but 159 million children around the world were still affected. (59) Attention to early infant feeding and care practices and reducing morbidity from disease in the first 2 years of life are essential to further reduce stunting. The range of child interventions that can have an impact on linear growth are diverse and deserve further attention both in implementation and research (linear growth meeting draft).

At the same time, there were 41 million overweight children in the world; about 10 million more than there were 2 decades ago. (59) In urban areas, even in developing countries, childhood obesity with all its attendant problems is increasingly an issue. The current IMNCI guidelines focused on the recognition of acute malnutrition and on standardized age-specific feeding recommendations. While the health worker is trained to recognize Z scores, there is no guidance as to the management of obesity. This should be added. Increasingly the disconnect between severe acute malnutrition in rural areas and obesity in urban areas, means the training for urban and rural healthcare workers may of necessity have to be different, once again emphasizing that going forward, a modular approach is needed that can readily be adapted at the regional or district level. Good cooperation between an integrated child health programme and the nutrition program, especially at the district level will become increasingly important.

**Chronic care**

IMNCI needs to prepare for increasing numbers of children surviving with chronic conditions. As more preterm newborns survive, many will require skilled chronic care for developmental disabilities, cerebral palsy, chronic lung disease of prematurity, etc.

Asthma, epilepsy, sickle cell disease, congenital heart disease, rheumatic heart disease (in older children), sequelae of prematurity and birth injuries, developmental delays, congenital malformations, undernutrition and obesity, persistent diarrhoea and even children recently discharged from hospital after a severe illness—all benefit from regular tracking to assure recovery or optimally manage a chronic condition which cannot be cured. Together these represent a substantial burden of disease.

The same general principles of chronic care apply (53) including the need for care as close to home as feasible, with care decentralized to primary care facilities, under the periodic direction of the hospital clinical team or specialist team. All require longitudinal patient monitoring so fit better in a chronic care module (or set of modules) than in acute care.

Within a primary care facility or hospital outpatient, It may be useful organize the chronic care together for children with various diagnoses, drawing on the experience of HIV care/ART which in most countries has developed defaulter tracking, medical records appropriate for an ongoing condition (such as the HIV patient monitoring card and longitudinal register), patient counseling, referral networks, and linkages to pharmacy and laboratory services, all critical for continuity of care.(54) Many rely on assistance in the clinic on lay provides and in the community by CHWs.

It is important for the child health team to actively collaborate with the NCD team (at the several levels of WHO but also within partner agencies), who are currently developing and implementing operationalized asthma and diabetes guideline modules, training tools, and approaches to mentoring and quality improvement.

For HIV, the substantial success in PMTCT with declining HIV infected children suggests the guidelines for their care in the IMNCI chart booklet (“Treat the HIV-infected child” (pages 22 to 27); the recording forms (ART initiation steps” and HIV on ART follow-up steps” (pages 62-64)) be moved to a separate chronic care module, while retaining HIV testing.

**Cancer:** As an example, in Brazil, mortality in children younger than age five years decreased from 129 per 1,000 live births in 1970 to 59 per 1,000 in 1990, and to 19 per 1,000 in 2010; cancer now leads the causes of non- accidental death in that country (as it does in high income countries).(55) A large proportion of cancers affecting children and young adults are now highly curable in high-income countries, in particular leukemia and lymphomas, retinoblastoma, and testicular cancer. 90 percent of children with leukemia in high-income countries can be cured, but 90 percent of those with that disease in the world’s twenty-five poorest countries die from it.(56) Childhood cancer treatment requires specialized diagnostic and therapeutic capabilities, the ability to manage complications, but can be done without expensive, high- technology equipment. The few cancer hospitals in LMICs predominantly serve adults. It is important to assure appropriately sized equipment for children and paediatric expertise. An effective model is twinning between established cancer centers and cancer hospitals in LMICs, aiming to improve survival amongst children with cancer. In many of these hospitals, supportive care capabilities lag behind those in high income counties, making it dangerous to directly transfer treatment protocols, which may result in higher treatment-related mortality due to these deficiencies in supportive care.

Pediatric leukemia may present with a variety of nonspecific symptoms, such as fever, anemia, malaise, or hemorrhage; many of the symptoms are also associated with infections, and leukemia appears to be seriously underdiagnosed. The underdiagnosis of childhood brain tumors is likely even greater, with many regions reporting few or no incident cases of pediatric central nervous system malignancies. (48)

In some countries, IMNCI should begin to support a district approach to identification then referral to a tertiary cancer hospital capable of diagnosing pediatric malignancies (and entering them into cancer registries) and providing treatment.

**Comments on mHealth tools to support health worker use of updated IMNCI algorithms and the hospital care guidelines**

Given the ongoing changes described above, more flexible and nimble tools are needed. Digital tools can potentially make the first-level IMNCI algorithm and the hospital guidelines more easy to adapt and update and disseminate, as well as provide the locally relevant data on pathogens and their antimicrobial resistance. The opportunity for adoption of such tools continues to grow, as telecommunications networks improve and an increasing proportion of health workers in LMICs acquire smartphones with adequate screens. Some progress has already been made. The WHO child hospital book and the paediatric (and adult) guidelines within the *Clinical management of viral haemorrhagic fever*s pocket guide (60) are all now available through mobile apps. Use of the D-Tree digital version of IMCI led to improvements in adherence to IMCI protocols.

More needs to be learned about how digital tools can complement other IMNCI interventions to improve case management. It is important that the content within digital tools be able to be presented and understood on paper, given the range of circumstances and capacities of health workers. Digital tools, when thoughtfully incorporated into care delivery systems, have the potential to improve case management through mass dissemination of care guidelines, decision-support for providers, front-line data collection for quality improvement, and support for on-site learning with mentoring visits and for distance learning. Such tools will not replace the need to train, mentor, and support health-workers, but they have the potential to reduce costs and increase accountability.

**References:**

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, Cousens S, Mathers C, Black RE. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015; 385: 430-440.

2. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, O'Brien KL, Roca A, Wright PF, Bruce N, Chandran A, Theodoratou E, Sutanto A, Sedyaningsih ER, Ngama M, Munywoki PK, Kartasasmita C, Simoes EA, Rudan I, Weber MW, Campbell H. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010; 375: 1545-1555.

3. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, Simmerman JM, Gordon A, Sato M, Howie S, Krishnan A, Ope M, Lindblade KA, Carosone-Link P, Lucero M, Ochieng W, Kamimoto L, Dueger E, Bhat N, Vong S, Theodoratou E, Chittaganpitch M, Chimah O, Balmaseda A, Buchy P, Harris E, Evans V, Katayose M, Gaur B, O'Callaghan-Gordo C, Goswami D, Arvelo W, Venter M, Briese T, Tokarz R, Widdowson MA, Mounts AW, Breiman RF, Feikin DR, Klugman KP, Olsen SJ, Gessner BD, Wright PF, Rudan I, Broor S, Simoes EA, Campbell H. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; 378: 1917-1930.

4. Deceuninck G, Quach C, Panagopoulos M, Thibeault R, Cote-Boileau T, Tapiero B, Coic L, De Wals P, Ovetchkine P. Pediatric Pleural Empyema in the Province of Quebec: Analysis of a 10-Fold Increase Between 1990 and 2007. *Journal of the Pediatric Infectious Diseases Society* 2014; 3: 119-126.

5. Reiss-Mandel A, Regev-Yochay G. Staphylococcus aureus and Streptococcus pneumoniae interaction and response to pneumococcal vaccination: Myth or reality? *Hum Vaccin Immunother* 2016; 12: 351-357.

6. Ebruke C, Dione MM, Walter B, Worwui A, Adegbola RA, Roca A, Antonio M. High genetic diversity of Staphylococcus aureus strains colonising the nasopharynx of Gambian villagers before widespread use of pneumococcal conjugate vaccines. *BMC Microbiol* 2016; 16: 38.

7. Kim L, McGee L, Tomczyk S, Beall B. Biological and Epidemiological Features of Antibiotic-Resistant Streptococcus pneumoniae in Pre- and Post-Conjugate Vaccine Eras: a United States Perspective. *Clin Microbiol Rev* 2016; 29: 525-552.

8. Soofi S, Ahmed S, Fox MP, MacLeod WB, Thea DM, Qazi SA, Bhutta ZA. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2012; 379: 729-737.

9. Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23-24 March 2015. *Vaccine* 2016; 34: 190-197.

10. Jorquera PA, Anderson L, Tripp RA. Understanding respiratory syncytial virus (RSV) vaccine development and aspects of disease pathogenesis. *Expert review of vaccines* 2016; 15: 173-187.

11. Royston L, Tapparel C. Rhinoviruses and Respiratory Enteroviruses: Not as Simple as ABC. *Viruses* 2016; 8.

12. Giersing BK, Modjarrad K, Kaslow DC, Okwo-Bele JM, Moorthy VS. The 2016 Vaccine Development Pipeline: A special issue from the World Health Organization Product Development for Vaccine Advisory Committee (PDVAC). *Vaccine* 2016; 34: 2863-2864.

13. Basnayake TL, Waterer GW. Rapid diagnostic tests for defining the cause of community-acquired pneumonia. *Curr Opin Infect Dis* 2015; 28: 185-192.

14. Kunze N, Moerer O, Steinmetz N, Schulze MH, Quintel M, Perl T. Point-of-care multiplex PCR promises short turnaround times for microbial testing in hospital-acquired pneumonia--an observational pilot study in critical ill patients. *Ann Clin Microbiol Antimicrob* 2015; 14: 33.

15. Ramakrishna B, Graham SM, Phiri A, Mankhambo L, Duke T. Lactate as a predictor of mortality in Malawian children with WHO-defined pneumonia. *Arch Dis Child* 2012; 97: 336-342.

16. Chisti MJ, Salam MA, Smith JH, Ahmed T, Pietroni MA, Shahunja KM, Shahid AS, Faruque AS, Ashraf H, Bardhan PK, Sharifuzzaman, Graham SM, Duke T. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. *Lancet* 2015; 386: 1057-1065.

17. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis* 2013; 13: 1057-1098.

18. Kelesidis T, Braykov N, Uslan DZ, Morgan DJ, Gandra S, Johannsson B, Schweizer ML, Weisenberg SA, Young H, Cantey J, Perencevich E, Septimus E, Srinivasan A, Laxminarayan R. Indications and Types of Antibiotic Agents Used in 6 Acute Care Hospitals, 2009-2010: A Pragmatic Retrospective Observational Study. *Infect Control Hosp Epidemiol* 2016; 37: 70-79.

19. Nair H, Simoes EA, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JS, Feikin DR, Mackenzie GA, Moisi JC, Roca A, Baggett HC, Zaman SM, Singleton RJ, Lucero MG, Chandran A, Gentile A, Cohen C, Krishnan A, Bhutta ZA, Arguedas A, Clara AW, Andrade AL, Ope M, Ruvinsky RO, Hortal M, McCracken JP, Madhi SA, Bruce N, Qazi SA, Morris SS, El Arifeen S, Weber MW, Scott JA, Brooks WA, Breiman RF, Campbell H. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013; 381: 1380-1390.

20. Baehner F, Bogaerts H, Goodwin R. Vaccines against norovirus: state of the art trials in children and adults. *Clin Microbiol Infect* 2016.

21. Hall AJ, Glass RI, Parashar UD. New insights into the global burden of noroviruses and opportunities for prevention. *Expert review of vaccines* 2016: 1-3.

22. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, Wu Y, Sow SO, Sur D, Breiman RF, Faruque AS, Zaidi AK, Saha D, Alonso PL, Tamboura B, Sanogo D, Onwuchekwa U, Manna B, Ramamurthy T, Kanungo S, Ochieng JB, Omore R, Oundo JO, Hossain A, Das SK, Ahmed S, Qureshi S, Quadri F, Adegbola RA, Antonio M, Hossain MJ, Akinsola A, Mandomando I, Nhampossa T, Acacio S, Biswas K, O'Reilly CE, Mintz ED, Berkeley LY, Muhsen K, Sommerfelt H, Robins-Browne RM, Levine MM. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013; 382: 209-222.

23. Lopman BA, Steele D, Kirkwood CD, Parashar UD. The Vast and Varied Global Burden of Norovirus: Prospects for Prevention and Control. *PLoS Med* 2016; 13: e1001999.

24. Platts-Mills JA, Babji S, Bodhidatta L, Gratz J, Haque R, Havt A, McCormick BJ, McGrath M, Olortegui MP, Samie A, Shakoor S, Mondal D, Lima IF, Hariraju D, Rayamajhi BB, Qureshi S, Kabir F, Yori PP, Mufamadi B, Amour C, Carreon JD, Richard SA, Lang D, Bessong P, Mduma E, Ahmed T, Lima AA, Mason CJ, Zaidi AK, Bhutta ZA, Kosek M, Guerrant RL, Gottlieb M, Miller M, Kang G, Houpt ER. Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). *The Lancet Global health* 2015; 3: e564-575.

25. Munos MK, Walker CL, Black RE. The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. *Int J Epidemiol* 2010; 39 Suppl 1: i75-87.

26. Okeke IN. Diarrheagenic Escherichia coli in sub-Saharan Africa: status, uncertainties and necessities. *Journal of infection in developing countries* 2009; 3: 817-842.

27. Bennish ML, Khan WA, Begum M, Bridges EA, Ahmed S, Saha D, Salam MA, Acheson D, Ryan ET. Low risk of hemolytic uremic syndrome after early effective antimicrobial therapy for Shigella dysenteriae type 1 infection in Bangladesh. *Clin Infect Dis* 2006; 42: 356-362.

28. Sewe M, Rocklov J, Williamson J, Hamel M, Nyaguara A, Odhiambo F, Laserson K. The association of weather variability and under five malaria mortality in KEMRI/CDC HDSS in Western Kenya 2003 to 2008: a time series analysis. *Int J Environ Res Public Health* 2015; 12: 1983-1997.

29. Upadhyayula SM, Mutheneni SR, Chenna S, Parasaram V, Kadiri MR. Climate drivers on malaria transmission in Arunachal Pradesh, India. *PLoS One* 2015; 10: e0119514.

30. Phyo AP, Nkhoma S, Stepniewska K, Ashley EA, Nair S, McGready R, ler Moo C, Al-Saai S, Dondorp AM, Lwin KM, Singhasivanon P, Day NP, White NJ, Anderson TJ, Nosten F. Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. *Lancet* 2012; 379: 1960-1966.

31. Price RN, von Seidlein L, Valecha N, Nosten F, Baird JK, White NJ. Global extent of chloroquine-resistant Plasmodium vivax: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; 14: 982-991.

32. Tun KM, Imwong M, Lwin KM, Win AA, Hlaing TM, Hlaing T, Lin K, Kyaw MP, Plewes K, Faiz MA, Dhorda M, Cheah PY, Pukrittayakamee S, Ashley EA, Anderson TJ, Nair S, McDew-White M, Flegg JA, Grist EP, Guerin P, Maude RJ, Smithuis F, Dondorp AM, Day NP, Nosten F, White NJ, Woodrow CJ. Spread of artemisinin-resistant Plasmodium falciparum in Myanmar: a cross-sectional survey of the K13 molecular marker. *Lancet Infect Dis* 2015; 15: 415-421.

33. Rambaud-Althaus C, Shao AF, Kahama-Maro J, Genton B, d'Acremont V. Managing the Sick Child in the Era of Declining Malaria Transmission: Development of ALMANACH, an Electronic Algorithm for Appropriate Use of Antimicrobials. *PLoS One* 2015; 10: e0127674.

34. Shao AF, Rambaud-Althaus C, Samaka J, Faustine AF, Perri-Moore S, Swai N, Kahama-Maro J, Mitchell M, Genton B, D'Acremont V. New Algorithm for Managing Childhood Illness Using Mobile Technology (ALMANACH): A Controlled Non-Inferiority Study on Clinical Outcome and Antibiotic Use in Tanzania. *PLoS One* 2015; 10: e0132316.

35. World Health Organization. WHO Informal Consultation on Fever Management in Peripheral Health Care Settings: A Global Review of Evidence and Practice. 2013. Geneva.

36. Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, Stein C, Abela-Ridder B, Ko AI. Global Morbidity and Mortality of Leptospirosis: A Systematic Review. *PLoS Negl Trop Dis* 2015; 9: e0003898.

37. Allan KJ, Biggs HM, Halliday JE, Kazwala RR, Maro VP, Cleaveland S, Crump JA. Epidemiology of Leptospirosis in Africa: A Systematic Review of a Neglected Zoonosis and a Paradigm for 'One Health' in Africa. *PLoS Negl Trop Dis* 2015; 9: e0003899.

38. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. *Lancet* 2015; 385: 1136-1145.

39. World Health Organization. Urinary Tract Infections in Infants and Children in Developing Countries in the Context of IMCI. 2005. Geneva.

40. Walker NF, Brown CS, Youkee D, Baker P, Williams N, Kalawa A, Russell K, Samba AF, Bentley N, Koroma F, King MB, Parker BE, Thompson M, Boyles T, Healey B, Kargbo B, Bash-Taqi D, Simpson AJ, Kamara A, Kamara TB, Lado M, Johnson O, Brooks T. Evaluation of a point-of-care blood test for identification of Ebola virus disease at Ebola holding units, Western Area, Sierra Leone, January to February 2015. *Euro Surveill* 2015; 20.

41. White NJ. Can new treatment developments combat resistance in malaria? *Expert Opin Pharmacother* 2016: 1-5.

42. Simmons CP. A Candidate Dengue Vaccine Walks a Tightrope. *N Engl J Med* 2015; 373: 1263-1264.

43. Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, Muhammad Ismail HI, Reynales H, Limkittikul K, Rivera-Medina DM, Tran HN, Bouckenooghe A, Chansinghakul D, Cortes M, Fanouillere K, Forrat R, Frago C, Gailhardou S, Jackson N, Noriega F, Plennevaux E, Wartel TA, Zambrano B, Saville M. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med* 2015; 373: 1195-1206.

44. Horstick O, Farrar J, Lum L, Martinez E, San Martin JL, Ehrenberg J, Velayudhan R, Kroeger A. Reviewing the development, evidence base, and application of the revised dengue case classification. *Pathogens and global health* 2012; 106: 94-101.

45. Bhutta ZA DJ, Bahl R, Lawn JE, Salam RA, Paul VK, Sankar MH, Blencowe H, Rizvi A, Chou VB, Walker N. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *The Lancet Global health* 2014; 384: 347-370.

46. Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A, Paul VK. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. *J Perinatol* 2016; 36 Suppl 1: S1-s11.

47. Zaidi AG, HA; Syed, S; Cousens, S; Lee, ACC; Black, R; Bhutta, ZA; Lawn, JE. Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health* 2011; 11(Suppl 3).

48. Bang AT, Reddy HM, Deshmukh MD, Baitule SB, Bang RA. Neonatal and infant mortality in the ten years (1993 to 2003) of the Gadchiroli field trial: effect of home-based neonatal care. *J Perinatol* 2005; 25 Suppl 1: S92-107.

49. Gill CJ, MacLeod WB, Phiri-Mazala G, Guerina NG, Mirochnick M, Knapp AB, Hamer DH. Can traditional birth attendants be trained to accurately identify septic infants, initiate antibiotics, and refer in a rural African setting? *Global health, science and practice* 2014; 2: 318-327.

50. Lawn JE DR, Paul VK, von Xyander S, Johnson JdG, Costello A, Kinney MV, Segre J, Moluneux L. Born too soon, care for the pre-term baby. *Reproductive Health* 2013; 10(Suppl 1).

51. World Health Organization. Oxygen Therapy for Children. 2016. Geneva.

52. Runyan DK, Shankar V, Hassan F, Hunter WM, Jain D, Paula CS, Bangdiwala SI, Ramiro LS, Munoz SR, Vizcarra B, Bordin IA. International variations in harsh child discipline. *Pediatrics* 2010; 126: e701-711.

53. World Health Organization. General Principles of Good Chronic Care. 2004. Geneva.

54. Rabkin M, Nishtar S. Scaling up chronic care systems: leveraging HIV programs to support noncommunicable disease services. *J Acquir Immune Defic Syndr* 2011; 57 Suppl 2: S87-90.

55. Gelband H, Jha P, Sankaranarayanan R, Gauvreau CL, Horton S. Summary. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: Disease Control Priorities, Third Edition (Volume 3). Washington (DC): The International Bank for Reconstruction and Development / The World Bank. 2015.

56. The good news about cancer in developing countries. *Lancet* 2011; 378: 1605.

57. World Health Organization. IMCI Adaptation Guide. 2002. Geneva.

58. Dewey KG A-AS. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Maternal and Child Nutrition* 2008; 4: 24-85.

59. UNICEF-WHO-World Bank. Levels and trends in child malnutrition. UNICEF-WHO-World bank joint child malnutrition estimates: Key findings of the 2015 edition. 2015.

60. World Health Organization. Clinical management of patients with viral haemorrhagic fever: A pocket guide for front-line health workers. 2016. Geneva.

1. [↑](#endnote-ref-1)
2. estimate a reduction in diarrhoe mortality of 54 percent to 78 percent if implemented to a feasible level, and by 92 percent to 95 percent if universally applied (Bhutta and others 2013; Fischer Walker and others 2011] [↑](#footnote-ref-1)