Exploratory meeting to review new evidence for Integrated Management of Childhood Illness danger signs

Geneva, Switzerland, 4–5 September 2018
Exploratory meeting to review new evidence for Integrated Management of Childhood Illness (IMCI) danger signs

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Acronyms

IMCI Integrated Management of Childhood Illness
MCA Department of Maternal, Newborn, Child and Adolescent Health
MUAC mid-upper arm circumference
PICO P = Population/Problem; I = Intervention; C = Comparison; O = Outcome
RCT randomized controlled trial
SD standard deviation
SpO₂ peripheral capillary oxygen saturation
WAZ weight-for-age z score
WHZ weight-for-height z score
WHO World Health Organization
For children up to 5 years of age with common childhood illnesses, the World Health Organization's (WHO) Integrated Management of Childhood Illness (IMCI) strategy recommends using clinical signs for diagnosis, treatment and place-of-treatment decisions. In order to increase access to pneumonia treatment, in 2014 WHO revised the pneumonia management protocol within IMCI. It now recommends that lower chest indrawing, which previously required inpatient treatment with injectable penicillin, be treated with oral amoxicillin on an outpatient basis in settings with low HIV prevalence. However, recent retrospective analysis of data from hospitalized children in Kenya showed that mortality was high among children with mild to moderate palmar pallor, weight-for-age Z score (WAZ) less than -3 standard deviations (SD) and lower chest indrawing. This finding raised concerns that children with these signs should be treated on an inpatient basis, despite the revised guidelines.

In order to evaluate the implications of this new evidence and other data and to identify questions for future research, a two-day exploratory meeting of pneumonia research experts, epidemiologists and child health specialists/paediatricians from countries representing various levels of resources was held. The specific objectives of this meeting were to: i) review the evidence base on which chest indrawing was removed from the referral criteria; ii) review new evidence on risk factors for mortality in children with pneumonia; iii) review new evidence on the use of pulse oximetry for children with pneumonia; and iv) discuss implications of the new evidence on whether to initiate the process of revision of the current pneumonia management guidelines.

Data from both published and unpublished studies on risk factors for mortality and adverse outcomes were presented and critically reviewed by the experts. They concluded that there is a need for further evidence on four key questions: i) Should chest indrawing be reconsidered as a sign for referral to hospital?; ii) What are the risk factors for mortality in children with pneumonia?; iii) Where is the appropriate place of treatment for children with pneumonia who have other signs of illness?; and iv) Does use of pulse oximetry improve the outcome for children with pneumonia?
Background

For children up to 5 years of age with common childhood illnesses, WHO’s IMCI strategy (1) recommends using clinical signs for diagnosis, treatment and place-of-treatment decisions. In order to increase access to pneumonia treatment, in 2014 WHO revised pneumonia management guidance within IMCI. It now recommends that lower chest indrawing, which previously required hospitalization along with other referral clinical signs considered as danger signs for injectable antibiotics, be treated with oral amoxicillin on an outpatient basis in settings with low HIV prevalence. These danger signs include convulsions; unable to drink; unconscious or drowsy; vomiting everything; stiff neck; severe dehydration; stridor in a calm child; oedema on both feet; weight for height (WHZ) Z-score less than -3 SD or mid-upper arm circumference (MUAC) less than 115 mm; severe palmar pallor; clouding of the cornea in a child with measles, and tender swelling behind the ear in a child with an ear problem (1).

However, a recent retrospective analysis of data from hospitalized children in Kenya showed that mortality was high among children with mild to moderate palmar pallor, WAZ less than -3 SD and lower chest indrawing (2). This finding raised concerns that these children should be treated on an inpatient basis despite the revised guidelines. In order to evaluate the implications of this new evidence and other data and to identify questions for future research, a two-day exploratory meeting of pneumonia research experts, epidemiologists and child health specialists/paediatricians from a range of countries with varying resources was convened in Geneva, Switzerland, on 4–5 September 2018. See Annex 1 for the agenda of the meeting, and Annex 2 for the list of participants.
Objectives of the meeting

The objectives of the 2018 meeting were to:

1. review the evidence base on which chest indrawing was removed from the referral criteria;
2. review new evidence on risk factors for mortality in children with pneumonia;
3. review new evidence on the use of pulse oximetry for children with pneumonia;
4. discuss implications of the new evidence on whether to initiate the process of revision of the current pneumonia management guidelines.
Proceedings of the meeting

Objective 1: Review the evidence base on which chest indrawing was removed from the criteria for referral

Dr Rakesh Lodha presented an updated systematic review of four studies covering about 4000 under-5 children with chest indrawing pneumonia, to compare the efficacy of oral versus injectable antibiotics. The antibiotics used varied, but the comparison between routes of administration remained the same. The primary outcome measured was treatment failure as per the definition used in each study. Patients were excluded if there was a possibility of significant co-morbidities. Meta-analysis showed an odds ratio of 0.93 (95% confidence interval: 0.78, 1.12) in favour of oral rather than injectable antibiotics. The review concluded that children with chest indrawing pneumonia from low- and middle-income countries with low rates of HIV infection may be managed with oral antibiotics in the absence of danger signs or signs of very severe pneumonia (3).

Dr Matthew Fox presented a review of predictors of treatment failure and mortality based on six studies: NO-SHOTS (4), APPIS (5), SPEAR (6), Agweyu and colleagues (7), MASS (8) and Atkinson and colleagues (9). The APPIS study (5) showed that among children 3–59 months of age hospitalized with chest indrawing pneumonia, oral treatment was as effective as injectable in many countries and contexts. However, this finding is not fully generalizable because the study was carried out in a hospital environment. Agweyu and colleagues (7) and the NO-SHOTS study (4) had similar findings in Kenya and Pakistan respectively. However, the studies were conducted only in these two countries and only in the context of hospital settings. The study by Atkinson and colleagues (9) also demonstrated that oral and intravenous antibiotics for the management of pneumonia in children gave equivalent results. Dr Fox reiterated that most of this research was carried out in a hospital environment, and emphasized that there were limited data to evaluate the benefits of hospitalization for children with pneumonia.

In conclusion, hospital versus home management of lower chest indrawing was evaluated in several studies presented and discussed in this session.
Objective 2: Review new evidence of risk factors for mortality in children with pneumonia

Dr Ambrose Agweyu presented data from a retrospective analysis of children aged 2–59 months admitted with pneumonia to 14 hospitals in Kenya (2). The objective of this study was to determine if a subset of the children categorized with WHO-defined pneumonia (presence of either fast breathing or lower chest indrawing) might be at increased risk of mortality and thus warranting hospitalization; and if so, what non-IMCI risk factors might be used to indicate referral. A total of 16 162 children with a discharge diagnosis of pneumonia and whose primary complaint was respiratory distress were studied. The overall mortality for this pneumonia subset was 2.7%, significantly higher than the 0.2–0.3% in the studies presented under Objective 1 (10). Within the group with pneumonia, WAZ between -2 and -3 SD (moderate malnutrition) or less than -3 SD (severe malnutrition), moderate to severe pallor and lower chest indrawing were recognized as the key risk factors for mortality.

Members of the panel discussed the selection criteria for the children included in this study. Data from hospitalized patients’ charts were collected retrospectively to identify a sample of children with WHO-defined pneumonia using the 2014 IMCI algorithm (1). Malaria, which might have contributed to an increase in mortality, was included by defining the hospitals as low or high malaria prevalence. Data were incomplete for HIV, MUAC and pulse oximetry assessment. Additionally, clinical assessments were completed by junior staff, which might have resulted in some errors due to subjectivity and limited clinical skills. However, in reality the IMCI criteria are not implemented as in controlled clinical trials, and most children are treated under these conditions.

Dr Anthony Scott presented data from PERCH (11), a case-control study of pneumonia aetiology. PERCH identified aetiology in 2440 under 5 children with lower chest indrawing pneumonia from seven sites in Asia and Africa. The objective was to identify risk factors for mortality in under-5 children with chest indrawing pneumonia. Mortality within seven days of discharge was 3.5%. Infants, female child, moderate malnutrition (WHZ < -2 or -3 SD), hypoxaemia (peripheral capillary oxygen saturation [SpO₂] < 92%) and duration of illness more than 5 days were associated with mortality.

The panel discussed using WAZ < -3 SD compared to WHZ < -3 SD, and suggested further analysis of the PERCH dataset to identify the predictive values of different respiratory signs.

Dr Yasir Bin Nisar presented data from the PREPARE project from 29 hospital and outpatient/community-based studies to identify risk factors for mortality in children 2–59 months of age (Yasir Bin Nisar on behalf of PREPARE project, WHO, Geneva, unpublished data, 4 September 2018). Pooled analysis showed that hospitalized children with pneumonia of any severity had substantially higher mortality rates than those who were identified at the outpatient/community level, with similar clinical signs of pneumonia of any severity. Younger age (2–11 months), female sex, very fast breathing (≥ 70 breaths per minute), WAZ
< - 3 SD and low haemoglobin levels (< 7 g/dL) were found to be risk factors for mortality in hospitalized children 2–59 months of age. Children with chest indrawing with or without fast breathing had higher mortality (4.8%) than those with fast breathing only (0.1%), while children identified in the community having chest indrawing with or without fast breathing had similar mortality (0.1%) as those having only fast breathing (0.1%).

The panel members expressed the opinion that a more accurate and weighted analysis could be performed after adjustment by site. Additionally, the experts suggested analysing data on WHZ, but Dr Nisar informed the experts that data for WHZ were missing from nearly 95% of the records.

Dr Salim Sadruddin presented findings from two unblinded RCTs conducted in Pakistan in children 2–59 months of age with lower chest indrawing pneumonia (12, 13). The objective was to compare clinical treatment failure rates among children with chest indrawing pneumonia in clusters receiving community treatment with oral amoxicillin versus children in the control clusters who received the standard of care (first dose of cotrimoxazole and referral). Treatment failure was defined as the presence of any of the following: IMCI danger signs; unwarranted changes in antibiotic treatment or death at any time; or persistence of fever and chest indrawing on day 3 of treatment. The intervention clusters (community-based treatment) had lower clinical treatment failure rates than the control clusters (referral). The study raised the question of how distance from home to outpatient care can affect mortality and treatment failure rates. No data were collected for anthropometry, pulse oximetry or anaemia/pallor in these studies. Members of the panel suggested that future research be done by comparing compliance with community treatment versus compliance with hospital treatment. The mortality in these RCTs was low (0.08%).

In conclusion, the panel pointed out that most studies to date have been completed only in hospitalized children. However, they noted that WAZ between - 2 and - 3 SD (moderate malnutrition) and less than - 3 SD (severe malnutrition) were significantly associated with high mortality. Further research is required in this field.
Objective 3: Review findings of new studies on the use of pulse oximetry for children with pneumonia

Dr Tim Colbourn presented a study conducted in Malawi comparing pulse oximetry and clinical signs as indicators for referral for children aged 2–59 months (n = 13 266) with pneumonia of any severity based on WHO criteria (14). The goal of this study was to improve the evidence base for outpatient pulse oximetry use at the community level by implementing pulse oximetry within the community case management of pneumonia and at the health facility level. The proportion of children with severe hypoxaemia as defined by the study (SpO₂ < 90%) was higher in health centres (first-level health facilities) than in the community, while the proportion of children with moderate hypoxaemia as defined by the study (SpO₂ 90%–92%) was similar (14). The IMCI chart booklet (1) and integrated community case management (iCCM) chart booklet (15) were applied retrospectively in order to determine the proportion of referrals that would have occurred had hypoxaemia been diagnosed and used for referral using two different threshold levels of SpO₂: < 90% and < 93%. Data showed that without pulse oximetry a considerable proportion of severely hypoxaemic children would be missed using IMCI chart booklet (1) signs for referral (42%) and the iCCM chart booklet (15) signs for referral (5.3%), whereas for moderate hypoxaemia the proportions were 61.5% and 30.9% respectively. Dr Colbourn suggested that in the absence of pulse oximetry, non-IMCI respiratory referral signs (grunting, nasal flaring, head nodding) should be used for referral of children receiving primary care.

The panel discussed how the danger signs which resulted in referral in this study were different and more common in the hospital than in the community or outpatient settings. Adjusting the hypoxaemia threshold for referral from SpO₂ < 90% to < 93% was also discussed. The higher threshold would allow for fewer missed referrals, but would increase the total number of referrals to hospital. Additional data linkage and analysis are needed to learn whether using SpO₂ < 93% was associated with reduced mortality. The panel considered the increase in the referral burden on hospitals, as such a change would increase sensitivity, while decreasing specificity of pneumonia diagnosis. The added value of a referral would be the availability of intravenous medicine, oxygen and other supportive treatment for the patients. A multi-country prospective study on implementation of pulse oximetry was suggested.

Dr Eric McCollum presented unpublished data from a sub-study of the pneumococcal conjugate vaccine effectiveness study in Sylhet, Bangladesh, with an emphasis on pulse oximetry in children 3–35 months with signs of possible lower respiratory tract infection (Eric McCollum on behalf of study team, Johns Hopkins Bloomberg School of Public Health, USA, unpublished data, 5 September 2018). The objectives of this sub-study were to evaluate the hypoxaemia threshold of SpO₂ of < 90% or < 93% and to objectively assess the value of adding pulse oximetry and respiratory danger signs to the current IMCI chart booklet (1). The study was conducted at Upazila Health Complexes (sub-district hospital level). Chest indrawing, fast breathing, grunting, nasal flaring, head nodding, tracheal tugging and crackles were positively associated with moderate (SpO₂ 90–92%)
and severe ($\text{SpO}_2 < 90\%$) hypoxaemia in Bangladesh. Wheezing was positively associated with moderate hypoxaemia and negatively associated with severe hypoxaemia. Panel members questioned whether this trend might support the conclusion that this population of moderately hypoxaemic patients was not very sick and that the added respiratory signs were not an accurate representation of hypoxaemia and mortality. The study demonstrated how $\text{SpO}_2 < 93\%$ increased the number of children eligible for referral by about 20% compared to the current IMCI criteria. Dr McCollum showed that among 179 children with $\text{SpO}_2 < 90\%$, IMCI identified 27 (15.0%) for referral with $\text{SpO}_2 < 90\%$, and identified only 82 (14.7%) among 556 children with $\text{SpO}_2 < 93\%$. He concluded that adding pulse oximetry and more respiratory danger signs could reduce the number of children with hypoxaemia not being referred.

Panel members raised multiple points about Dr McCollum’s presentation, including whether there could be a large cost of increasing referrals associated with a decrease in specificity of the pneumonia algorithm, leading to hospital overflow. Also, there were missing data in terms of causation between missed hypoxaemic referrals and poor outcomes in those patients. In terms of deciding the appropriate hypoxaemia threshold, pooling different datasets could help find an appropriate cut-off. Lastly, the experts indicated that it would be useful to compare the mortality rate among hypoxaemic children who had $\text{SpO}_2$ between 90% and 92% with those who had $\text{SpO}_2 < 90\%$ and those with $\text{SpO}_2 \geq 93\%$. This could help establish the additive value of pulse oximeters and how they would identify children who are likely to die in the community.

In conclusion, the panel agreed that pulse oximetry should be added to the WHO IMCI chart booklet (1) as a mandatory assessment for children with signs and symptoms suggestive of pneumonia, with further research on the implementation and feasibility of pulse oximetry in programme settings. Further research is also needed to analyse the effect of $\text{SpO}_2 < 93\%$ pulse oximetry assessment on patient outcomes to review the cut-off.
Objective 4: Discuss implications of the new evidence on whether to initiate the process of revision of the current pneumonia management guidelines

Panel members discussed the implications of the potential need to initiate the process of revision of the current pneumonia management guidelines (16) with respect to the following aspects:

i. Should chest indrawing be reconsidered as a sign for referral to hospital?

ii. Should pulse oximetry become a mandatory part of the guidelines?

iii. Should children with respiratory signs and moderate malnutrition be referred to hospital?

iv. Should other respiratory signs such as, but not limited to, head nodding, nasal flaring, or grunting be added to the guidelines?

v. Should the exact diagnostic criteria be adjusted with age such that there is a stratification in the guidelines?

vi. General comments about revisions to the WHO pneumonia guidelines.

i. Should chest indrawing be reconsidered as a sign for referral to hospital?

While this issue was discussed during the meeting, in addition a post-meeting written communication was conducted with all the participants to obtain further clarity due to the variance in the opinions of the participants. The WHO Secretariat sought written feedback from each one of the experts on the following two options:

- Option 1: In view of currently available evidence, initiation of the review process for potential revision of the WHO pneumonia guidelines (16) for this issue is not required at this time. It should be initiated when more data are available.

- Option 2: The review process for potential revision of the WHO pneumonia guidelines (16) for this issue should be initiated now using existing data.

About 60% of the experts present chose Option 1, while others either selected Option 2 or did not opt for either option.

Those who chose Option 1 supported their selection based on the following criteria:

- The new evidence (2) presented in the meeting on the outcomes of children 2–59 months old with lower chest indrawing raised the following issues:
  - Methodological weaknesses were observed, such as the retrospective hospital-based observational study design used.
  - Interpretation of study findings was incomplete as the case fatality rate was reported for only those children with lower chest indrawing who
were hospitalized, but not for those who were not hospitalized and were treated at home as per the current WHO pneumonia guidelines (16).

- Two risks factors, severe anaemia and severe malnutrition, identified in this study are already part of the referral signs in the IMCI chart booklet published in 2014 (1).

- Data from randomized controlled trials (RCTs) (4, 5, 9) on which guidelines for management of children 2–59 months old with lower chest indrawing (16) were robust and showed equivalence between oral and injectable therapies.

While these experts did not express a wish to have any change in the current WHO pneumonia guidelines at this stage, they proposed continuing to collect data on outcomes of children 2–59 months old with lower chest indrawing to facilitate a future revision process. They emphasized the importance of including evidence from the recently-concluded WHO-coordinated community-based trial which evaluated the effectiveness of home-based management with oral amoxicillin by community health workers in resource-limited communities of two African (Ethiopia and Malawi) and two Asian (Bangladesh and India) countries versus facility referral in children 2–59 months old with lower chest indrawing (EMPIC study).\(^1\)

Those who favoured Option 2 supported their selection based on the following criteria:

- The new evidence (2) presented in the meeting on outcomes of children 2–59 months old with lower chest indrawing, which raised several concerns about the current WHO pneumonia guidelines (16), had the following key aspects:
  - Information on study outcomes of children with pneumonia of any severity was collected from 14 hospitals across Kenya in real-life settings.
  - The case fatality rate was 2.7% among children 2–59 months old with lower chest indrawing, which is realistic for children with this sign in Africa.
  - Additional risk factors, such as mild to moderate anaemia and mild to moderate malnutrition, were identified which are not included in the current list of referral signs in the IMCI chart booklet (1).

- Data from RCTs (4, 5, 9) on which guidelines for management of children 2–59 months old with lower chest indrawing (16) were based have the following issues:
  - Enrolled children were less sick than those presenting to health facilities in real-life settings. This was based on two observations: i) a low case fatality rate among enrolled children; and ii) a high prevalence of wheezing.
  - Definition of treatment failure was based on subjective signs. Appearance of any danger sign or death at any time during treatment were objective signs of failure, whereas other criteria, such as persistence of signs, were subjective.

In addition to suggesting a revision of the current WHO pneumonia guidelines (16), the experts expressed the need for more evidence from high-mortality settings where the current pneumonia guidelines (16) are being implemented.

A few experts who did not explicitly support either Option 1 or Option 2 proposed no revision of current WHO pneumonia guidelines (16). However, they suggested adaptation of these guidelines at country level in such a way that the decision be left to health care providers, after consultation with parents, on place of treatment for oral amoxicillin (inpatient or outpatient) for the management of children with lower chest indrawing without any general danger signs, until more evidence from real-life settings is available. One expert suggested a regional stratification of these guidelines (16), based on the severity of risk of mortality (low versus high). For example, it was suggested that high mortality risk countries should use the previous WHO IMCI chart booklet for pneumonia management (17) until more evidence is available to initiate the guidelines revision process.

**Way forward**

Though the opinion of the experts on this issue was divided, the WHO Secretariat decided that it would be prudent to initiate the process of updating the current WHO pneumonia guidelines (16), while collecting additional evidence and conducting analysis on existing data.

The first step in this process will be to scope the updating and synthesize currently available evidence through systematic reviews. At the same time, WHO will undertake:

- Short-term prospective observational/cohort studies to collect outcome data for children 2–59 months old with lower chest indrawing in real-life settings where the current WHO pneumonia guidelines (16) are being implemented.

- Re-analysis of existing and available RCT data using a revised treatment failure definition, which will include deterioration (appearance of any general danger sign) or death any time during treatment. A stratified analysis of enrolled children with and without wheeze and their outcome will also be carried out. WHO has access to datasets from four trials (4, 5, 12, 13).

**ii. Should pulse oximetry become a mandatory part of the guidelines?**

The WHO guidelines (18) recommend pulse oximetry to determine the presence of hypoxaemia and to guide administration of oxygen therapy in infants and children with hypoxaemia. Two derivative documents from the WHO guidelines, i.e. the *Pocket book of hospital care for children* (18) and *Oxygen therapy for children* (19) both recommend measuring oxygen saturation with pulse oximetry in all children suspected of having pneumonia and giving oxygen if SpO$_2$ is < 90%. However, the current WHO IMCI chart booklet (1) states in a footnote on the assessment for respiratory infection “If pulse oximeter is available, determine oxygen saturation and refer if < 90%”. The panel was in favour of adding pulse oximetry to the WHO IMCI criteria as a mandatory assessment. Strong physiological evidence exists for the inclusion into the IMCI criteria of this objective measurement as part of routine assessment. It would provide health workers at first-level health facilities
with more tools, and help them to stratify risk. However, pulse oximetry data should be analysed in the context of danger signs and used as a supplement to IMCI criteria in order to ensure that there is no over-referral. The panel also discussed how technological innovations could have unintended consequences, such as replacement of discharged/flat batteries; and management of broken and non-functional instruments. A bigger issue could be the difficulty of obtaining accurate SpO$_2$ readings. This problem could arise because: i) inexpensive pulse oximeter models can be erratic, with a tendency to produce a reading before the signal has stabilized, leading to false low recordings with obvious consequences; and ii) lack of training and skills of health workers. Both situations could lead to errors in over-reporting hypoxaemia.

Further research is needed on feasibility and implementation of introducing pulse oximetry in routine outpatient practice, acceptability by health workers, training requirements for health workers; and its effect on patient outcomes in terms of referrals, appropriate management of hypoxaemia and survival.

iii. **Should children with respiratory signs and moderate malnutrition be referred to hospital?**

The panel agreed that further research is required for the inclusion of moderate malnutrition as a potential sign for referral into WHO pneumonia guidelines (16). The panel discussed how MUAC is a promising measure as a risk factor, and additional analysis of existing data should be carried out to consider its inclusion into future guidelines. However, there is a potential for over-referral and a need for more data about risk for a malnourished child assessed through MUAC. In addition, MUAC is not currently recommended to be used under 6 months of age.

iv. **Should other respiratory signs such as, but not limited to, head nodding, nasal flaring or grunting be added to the guidelines?**

The panel recommended against the inclusion of other respiratory signs into the WHO IMCI (1) criteria for outpatient management. These signs are very specific but not very sensitive, and difficult to teach to primary health care workers. The panel also discussed whether these signs could add significant diagnostic and prognostic value to the current IMCI criteria (1). Hence, it was decided not to consider other respiratory signs at present. However, the panel proposed conducting further research in this area to see if the addition of these signs increased the sensitivity of pneumonia diagnosis beyond the currently-included danger signs.

v. **Should the exact diagnostic criteria be adjusted with age such that there is stratification in the guidelines?**

The panel recommended against the inclusion of further age categories into the WHO IMCI criteria (1), even though younger age has been shown to be a high risk factor for mortality. However, modifying the fast breathing criteria by raising the respiratory rate threshold to 50 breaths per minute in children 12–59 months of age should be considered.
vi. General comments about revisions to the WHO guidelines

The WHO pneumonia guidelines could be regionally stratified, particularly for Africa, but to do so would be challenging in terms of both practice and implementation. However, it was suggested that a differentiation should be made between the presence of multiple danger signs, which is clinically different from the presence of only one danger sign. There was general consensus among panellists that more studies regarding risk factors associated with pneumonia should be carried out at the community/outpatient level as opposed to the hospital level, and also in routine real-world settings instead of in carefully controlled trials.
Future research agenda

1. What are the risk factors for mortality in children with pneumonia?

   i. Further analyses of already-collected data

   a. PREPARE dataset – as mentioned above, WHO’s Department of Maternal, Newborn, Child and Adolescent Health (MCA) under the PREPARE project gathered 41 pneumonia datasets from studies in various countries. A preliminary analysis identified various risk factors for mortality in children with pneumonia, as presented during the meeting. The panel suggested that the risk factor analysis should be run again, adjusted by site.

   Specific research question (in PICO² format)

   - Among children under 5 years of age with WHO-defined pneumonia managed by appropriate therapy (P), does the presence of specific socio-demographic factors (I), versus the absence of these factors (C), increase the risk of mortality (O)? If yes, by how much?

   b. Further analysis of the PERCH dataset should be conducted to understand the predictive values of different respiratory signs for poor outcomes.

   Specific research question

   - Among children under 5 years of age with WHO-defined pneumonia managed by appropriate therapy (P), does the presence of specific respiratory and other clinical features (I), versus the absence of these clinical features (C), increase the risk of poor outcomes in terms of therapy failure and mortality (O)?

   ii. Further data collection

   a. Preliminary analysis of existing community-level data show that there is limited information on risk factors for mortality in children with pneumonia. Therefore, more research on risk factors associated with pneumonia outcomes should be carried out at the community and outpatient levels as opposed to the hospital level.

² P = Population; I = Intervention; C = Comparison; O = Outcome.
Specific research question

- Among children under 5 years of age with WHO-defined pneumonia managed at community level in resource-limited settings (P), does the presence of specific socio-demographic, and/or respiratory or other clinical factors (I), versus the absence of these factors (C), increase the risk of mortality (O)?

2. Where is the appropriate place of treatment for children with pneumonia who have other signs of illness?

   a. The panel discussed the possibility of implementing a study to evaluate the optimal place for treatment (outpatient or inpatient) of pneumonia in children with moderate malnutrition and/or moderate pallor/anaemia. Moderate malnutrition would be defined as either WAZ - 2 to - 3 SD, MUAC 115 to 125 cm, or WHZ - 2 to - 3 SD.

   Specific research questions

   - Among children under 5 years of age with WHO-defined pneumonia who have moderate malnutrition (P), does standard treatment in hospital (I), versus outpatient treatment (C), reduce the risk of mortality or therapy failure (O)?
   
   - Among children under 5 years of age with WHO-defined pneumonia who have moderate pallor/anaemia (P), does standard treatment in hospital (I), versus outpatient treatment (C), reduce the risk of mortality or therapy failure (O)?

   b. Similarly, new evidence should be generated on children less than 5 years of age with WHO-defined pneumonia who have signs of respiratory and/or other danger signs rather than IMCI general danger signs (I) by conducting further research.

   Specific research question

   - Among children under 5 years of age with WHO-defined pneumonia (P), does the presence of respiratory signs (crepitations, nasal flaring, grunting, head nodding, etc.) apart from respiratory rate and lower chest indrawing (I), versus the absence of these signs (C), improve decision-making for place of therapy and consequently clinical outcome (O)?

   c. Further community-based studies are required in children who are diagnosed in outpatient settings and then either referred to a higher-level health facility or receive treatment on an outpatient basis with close monitoring of compliance with treatment and acceptance of referral advice to identify the care-seeking behaviour of the community.

   Specific research question

   - Among children under 5 years of age with WHO-defined pneumonia (P), does referral to a higher-level facility with close monitoring of compliance with referral acceptance and treatment (I) versus
outpatient treatment with oral antibiotics (C), reduce the risk of treatment failure (O)?

3. Does use of pulse oximetry improve management of pneumonia in children?
   
i. **Further analysis of already-collected data**

   For the Malawi (14) and Bangladesh (Eric McCollum on behalf of study team, Johns Hopkins Bloomberg School of Public Health, USA, unpublished data, 5 September 2018) pulse oximetry studies, additional linkage to other available datasets is needed to determine whether increased referral of children with a higher SpO\(_2\) cut-off is associated with better outcomes. The PREPARE database could also be used to carry out a similar analysis where pulse oximetry results are available.

   **Specific research questions**

   - Among children under 5 years of age with WHO-defined pneumonia (P), does referral after use of pulse oximetry (I), versus referral without the use of pulse oximetry (C), reduce the risk of mortality and other adverse outcomes (O)?
   
   - Among children under 5 years of age with WHO-defined pneumonia (P), does SpO\(_2\) < 93% using pulse oximetry (I), versus those with SpO\(_2\) ≥ 93% (C), reduce the risk of mortality and other adverse outcomes (O)?

   

   ii. **Further data collection**

   To evaluate the feasibility, acceptability and effect of the implementation of pulse oximetry assessment at the primary health care level through implementation research, oxygen should be available at the next level of health care when a referral is made after assessment. The study should provide insights on the following: cost of implementation, cost-effectiveness, programmatic feasibility, design of step-wise introduction, effects of implementation on health systems and patients, outcome data (pre- and post-introduction), and results for varying thresholds for hypoxaemia. Results would be more generalizable if the research were conducted as a multicentre multi-country study, with enough power to interpret the results for each country separately. Sites should be selected with varying altitudes, since SpO\(_2\) is lower in children living at high altitude because of lower partial oxygen pressure.

   **Specific research questions**

   - Among children under 5 years of age with WHO-defined pneumonia (P), does assessment of hypoxaemia by primary-level health care workers with a pulse oximeter (I), versus no pulse oximeter assessment (C), improve the rate of referral to a higher-level health care facility where oxygen is available to reduce the risk of poor outcomes in terms of treatment failure/mortality (O)?
Among children under 5 years of age with WHO-defined pneumonia with or without general danger signs (P), is hypoxaemia identified by pulse oximeter used by primary-level health care workers and referral to hospital for oxygen therapy (I), versus referral without the use of pulse oximeters (C), cost-effective for preventing adverse outcomes including death (O)?

Along with studying the above-mentioned specific questions, other programme issues should be assessed, such as:

- whether primary-level health care workers using a pulse oximeter adhere to the IMCI algorithm and correctly assess and classify children under 5 years of age with pneumonia and make correct decisions for referral;
- documenting the feasibility and acceptability of primary-level health care workers’ experience using pulse oximetry in a sick child consultation (qualitative studies in various sites will be required to collect this information).
References


## Annex 1.

### Agenda of exploratory meeting

### DAY 1: TUESDAY, 4 SEPTEMBER 2018

#### Section I: Introduction

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>09:00–09:10</td>
<td>Welcome (Rajiv Bahl)</td>
</tr>
<tr>
<td>09:10–09:30</td>
<td>Objectives of meeting (Yasir Bin Nisar)</td>
</tr>
<tr>
<td>09:30–09:45</td>
<td>Overview of IMCI danger signs and pneumonia case management (Wilson M Were)</td>
</tr>
<tr>
<td>09:45–10:00</td>
<td>Discussion – initial thoughts</td>
</tr>
<tr>
<td>10:00–10:30</td>
<td>Coffee break</td>
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</tbody>
</table>

#### Section II: New evidence for pneumonia guidelines

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>10:30–11:30</td>
<td>Kenya district hospital retrospective data analysis (Ambrose Agweyu)</td>
</tr>
<tr>
<td>11:30–12:00</td>
<td>Discussion</td>
</tr>
<tr>
<td>12:00–13:00</td>
<td>Lunch</td>
</tr>
</tbody>
</table>

#### Section III: Evidence/rationale for updated pneumonia guidelines

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:00–13:30</td>
<td>Oral amoxicillin for chest indrawing pneumonia – systematic review (Rakesh Lodha)</td>
</tr>
<tr>
<td>13:30–14:00</td>
<td>Field studies – NOSHOTS, APPIS, SPEAR, and MASS risk factor analysis (Matthew Fox)</td>
</tr>
<tr>
<td>14:00–14:15</td>
<td>Discussion</td>
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</tbody>
</table>

#### Section IV: New analysis on risk factors for pneumonia mortality/poor outcome

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>14:15–14:45</td>
<td>PERCH study risk factors for mortality/poor outcome (Anthony Scott)</td>
</tr>
<tr>
<td>14:45–15:15</td>
<td>PREPARE risk factors for mortality in hospitalized and outpatient children (Yasir Bin Nisar)</td>
</tr>
<tr>
<td>15:15–15:30</td>
<td>Coffee break</td>
</tr>
<tr>
<td>15:30–16:00</td>
<td>Haripur and Hala risk factors for mortality/poor outcome in community (Salim Sadruddin)</td>
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<tr>
<td>16:00–17:00</td>
<td>Discussion</td>
</tr>
</tbody>
</table>
### DAY 2: WEDNESDAY, 5 SEPTEMBER 2018

**Section I: Use of pulse oximetry**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>09:00–09:30</td>
<td>Use of pulse oximetry in Malawi (Tim Colbourn)</td>
</tr>
<tr>
<td>09:30–10:00</td>
<td>Use of pulse oximetry in Bangladesh (Eric McCollum)</td>
</tr>
<tr>
<td>10:00–10:30</td>
<td>Discussion</td>
</tr>
<tr>
<td>10:30–11:00</td>
<td>Coffee break</td>
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</table>

**Section II: Should there be a change in criteria for referral?**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>11:00–12:00</td>
<td>Discussion</td>
</tr>
<tr>
<td>12:00–13:00</td>
<td>Lunch</td>
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</tbody>
</table>

**Section III: Is further research/evidence synthesis required?**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>13:00–15:00</td>
<td>Discussion</td>
</tr>
<tr>
<td>15:00–15:30</td>
<td>Coffee break</td>
</tr>
</tbody>
</table>

**Section IV: Next steps**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>15:30–16:30</td>
<td>Discussion</td>
</tr>
</tbody>
</table>
## Annex 2.

### List of participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samira Aboubaker</td>
<td>Bellevue, Switzerland</td>
</tr>
<tr>
<td>Ambrose Agweyu</td>
<td>KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya</td>
</tr>
<tr>
<td>Tim Colbourn</td>
<td>UCL Institute for Global Health, London, United Kingdom</td>
</tr>
<tr>
<td>Mike English</td>
<td>KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya</td>
</tr>
<tr>
<td>Matthew Fox</td>
<td>Boston University, Boston, MA, USA</td>
</tr>
<tr>
<td>Brad Gessner</td>
<td>Pfizer Vaccines, Agence de Médecine Préventive, University of Maryland, Baltimore, MD, USA (via Skype)</td>
</tr>
<tr>
<td>Fyezah Jehan</td>
<td>Aga Khan University, Karachi, Pakistan</td>
</tr>
<tr>
<td>Rakesh Lodha</td>
<td>All India Institute of Medical Sciences, New Delhi, India</td>
</tr>
<tr>
<td>Eric McCollum</td>
<td>Department of Pediatrics, John Hopkins School of Medicine, Baltimore, MD, USA</td>
</tr>
<tr>
<td>Kim Mulholland</td>
<td>University of Melbourne, Melbourne, Australia</td>
</tr>
<tr>
<td>Shamim Qazi</td>
<td>Cointrin, Switzerland</td>
</tr>
<tr>
<td>Anthony Scott</td>
<td>London School of Hygiene and Tropical Medicine, London, United Kingdom</td>
</tr>
</tbody>
</table>

### Secretariat

- Rajiv Bahl        | MCA, WHO headquarters                                                  |
- Yasir Bin Nisar   | MCA, WHO headquarters                                                  |
- Nigel Rollins     | MCA, WHO headquarters                                                  |
- Salim Sadruddin   | Global Malaria Programme, WHO headquarters                             |
- Wilson Were       | MCA, WHO headquarters                                                  |
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