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[Intervention Protocol]

Integrated community case management of childhood illness in low- and middle-income countries

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of the integrated community case management (iCCM) strategy for children younger than five years of age in low- and middle-income countries.

BACKGROUND

Description of the condition

In 2015 an estimated 5.9 million children died before reaching the age of five, mostly in low- and middle-income countries (LMICs) and particularly the regions of sub-Saharan Africa (SSA) (50% of deaths) and South Asia (31% of deaths) (You 2015). Cause of death estimates suggest that most under-five deaths are due to preventable or treatable conditions (Liu 2015). As of 2013

(the latest year for which data were available), 52% of under-five mortality globally was caused by infectious diseases including pneumonia (16%), diarrhoea (10%), and malaria (14%) (Liu 2015). In SSA 40% of under-five deaths were due to pneumonia, malaria, and diarrhoea and 34% were due to neonatal causes - a subset of which were also related to severe infections (Liu 2015). In South Asia, 54% of under-five deaths were due to neonatal causes, a subset of which were related to severe infections. Pneumonia and diarrhoea were also major causes, contributing 14% and 10% of the total respectively (Liu 2015).

Efficacious interventions for addressing the major causes of pre-

ventable under-five mortality exist (Darmstadt 2005; Jones 2003). In the mid-1990s the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and technical partners developed a strategy called the Integrated Management of Childhood Illness (IMCI) to reduce child mortality, illness and disability, and to promote improved growth and development among children younger than five years of age (Tulloch 1999; WHO 1997). IMCI includes three main components (Gera 2016; Tulloch 1999): 1) improvements in case-management skills of health staff through the provision of locally adapted guidelines on integrated management of childhood illness and activities to promote their use; 2) improvements in the health system required for effective management of childhood illnesses; and 3) improvements in family and community practices.

IMCI was designed to deliver treatment interventions of known efficacy for the main causes of under-five mortality through an integrated case management approach, recognizing that children presenting at health facilities often have multiple, overlapping signs and symptoms of these conditions (Fenn 2005; O'Dempsey 1993; Tulloch 1999; WHO 1997). A Cochrane Review of IMCI concluded with low certainty that IMCI may reduce child mortality, may reduce infant mortality (where interventions for the neonatal period are included), and may have mixed effects on care-seeking behaviour, morbidity and quality of care (Gera 2016).

In an earlier multi-country evaluation of IMCI, Bryce and colleagues found that "improving the quality of care in first-line government health facilities was not sufficient" to improve low utilization and population coverage; the components on health systems and family and community practices were slow to be implemented (if at all); and they concluded that "Delivery systems that rely solely on government health facilities must be expanded to include the full range of potential channels in a setting and strong community-based approaches...we must move beyond health facilities, and develop new and more effective ways of reaching children with proven interventions to prevent mortality. In most high-mortality settings, this means providing case management at community level, as well as focusing on prevention and reducing rates of undernutrition" (Bryce 2005).

Other researchers have also found accessibility of treatment services at government health facilities to be inadequate, particularly in SSA (Blanford 2012; Huerta Munoz 2012; Noor 2003; Noor 2006; Tsoka 2004).

Description of the intervention

In the 2000s the WHO and UNICEF, in collaboration with other development partners, developed an approach - now known as integrated community case management (iCCM) - to bring treatment services 'closer to home' and advocated for LMICs to adopt it (Bennett 2015; Diaz 2014; WHO/UNICEF 2012). The adoption of iCCM has been rapid, particularly in sub-Saharan Africa

where most countries have some form of written policy to enable implementation of iCCM (Rasanathan 2014).

Definition

iCCM is an extension of IMCI - providing treatment services outside of the healthcare facility at community level (Bennett 2015; Gera 2016); and c-IMCI - the original community-based component of IMCI which focused on promoting key family and community practices for improving child health (WHO 1997). iCCM is an approach to providing integrated case management services for two or more illnesses - including diarrhoea, pneumonia, or malaria (the latter in malaria-affected countries) - among children younger than five years of age at community level (i.e. outside of healthcare facilities) by lay health workers where there is limited access to health facility-based case management services (WHO/UNICEF 2012). Case management services as defined here include assessment, treatment, and referral services (WHO/UNICEF 2012), following locally adapted WHO/UNICEF guidelines (WHO 2011). In some contexts iCCM may also include case management services for acute malnutrition and newborn illness (Rasanathan 2014; WHO 2007). iCCM is considered an equity-focused approach in that it is primarily implemented in rural and hard-to-reach areas with limited access to facility-based case management services (WHO/UNICEF 2012).

Components of the intervention

There are three main components of iCCM (Diaz 2014; McGorman 2012; WHO/UNICEF 2012; Young 2012). Table 1 classifies the three main components of iCCM according to the Effective Practice and Organization of Care (EPOC) taxonomy of health systems interventions (EPOC 2015), providing a framework and common language for understanding and describing iCCM and its component interventions. The three main components of iCCM are summarized below:

1. Training and deployment component: interventions with the main purpose of increasing access to integrated case management services for children younger than five years of age by increasing the number of lay health workers trained on the generic or adapted WHO/UNICEF guidelines for integrated case management services and deployed where facility-based case management services are limited.
2. Systems component: interventions with the main purpose of improving implementation of iCCM by strengthening health systems' organization and management, including supplies, specifically related to iCCM.
3. Communication and community mobilization component: interventions with the main purpose of promoting good practices for health and nutrition and generating demand for case management services for ill children through communication and mobilization of communities and caregivers.

iCCM providers

iCCM providers may include any lay health workers (paid or voluntary) who:

- provide iCCM (integrated case management services for two or more illnesses among children younger than five years of age);
- are trained on iCCM, but have received no formal professional or paraprofessional certificate or tertiary education degree (adapted from [Lewin 2010](#)).

This definition includes iCCM providers who receive a certificate on completion of their iCCM training but excludes healthcare providers who receive pre-licensure or post-licensure training certified by a professional body, such as a nursing or midwifery council.

Package of services

iCCM providers deliver integrated case management services for two or more illnesses among children younger than five years of age ([WHO/UNICEF 2012](#); [Young 2012](#)), including:

- assessment and classification of the child's condition(s) using a simplified IMCI-adapted algorithm;
- referral of cases with general danger signs and other complicated cases;
- provision of treatment for the following conditions:
 - non-severe pneumonia with oral antibiotics;
 - non-severe diarrhoea with oral rehydration salts and zinc;
 - non-severe malaria with artemisinin-based combination therapy (in malaria-affected countries).

iCCM may also include assessment, classification and treatment of neonatal sepsis with oral antibiotics and referral as necessary; and assessment, classification and treatment of uncomplicated severe acute malnutrition (SAM) with ready-to-use therapeutic food and oral antibiotics, with referral as necessary ([Rasanathan 2014](#); [WHO 2007](#)).

How the intervention might work

Interventions in the training and deployment component target lay health workers to improve access to integrated case management services for children younger than five years of age at community level where facility-based case management services are limited. The logic of these interventions assumes that increasing the number of lay health workers trained to deliver integrated case management services based on locally adapted WHO/UNICEF guidelines ([WHO 2011](#)) for children younger than five years of age (who may present with multiple, overlapping symptoms), and deploying them to areas where facility-based case management services are limited, will improve the availability and geographic

accessibility of integrated case management services by bringing these services closer to caregivers ([Diaz 2014](#); [WHO/UNICEF 2012](#); [Young 2012](#)).

Interventions in the systems component aim to strengthen health systems components such as supply chain management, supervision, referral pathways, and health management information systems. The logic of these interventions assumes that effective iCCM implementation is dependent on a continuous supply of drugs and diagnostic tools, regular supervision, effective referral mechanisms, and a strong health management information system.

Interventions in the communication and community mobilization component target communities and caregivers with the main purpose of promoting good practices for health and nutrition and generating demand for case management services for ill children through communication and mobilization of communities and caregivers. The logic of these interventions assumes that effective iCCM implementation is dependent on effective communication and mobilization strategies, plans, materials, and messages around good health and nutrition practices as well as for increasing demand for case management services.

Why it is important to do this review

WHO and UNICEF have endorsed iCCM ([WHO/UNICEF 2012](#)); and the uptake of iCCM by national governments has been rapid ([Rasanathan 2014](#); [UNICEF 2005](#)). Evidence-based policy making is critical to health outcomes ([Bosch-Capblanch 2012](#); [Langlois 2015](#); [Lavis 2009](#); [Oliver 2014](#)). To date no systematic review of iCCM - that is, as an integrated approach for the management of diarrhoea, pneumonia, malaria (in malaria-affected areas), acute malnutrition, or newborn sepsis (or combinations of these conditions) at the community level by lay health workers - has been undertaken. This presents an important information gap relevant to evidence-based decision making of the general public, practitioners, policy makers, and researchers in low- and middle-income countries.

Systematic reviews have been undertaken and published on single-disease community case management (CCM) - that is CCM for diarrhoea ([Das 2013](#)), CCM for malaria ([Okwundu 2013](#); [Ruizendaal 2014](#); [Sazawal 2003](#)) and CCM for pneumonia ([Das 2013](#); [Druetz 2013](#); [Ruizendaal 2014](#); [Sazawal 2003](#)) - among children younger than five years of age in LMICs. The reviews that used the GRADE approach for assessing certainty of the evidence reported moderate-certainty evidence for the effectiveness of CCM on care-seeking behaviour ([Das 2013](#)), mostly moderate-certainty evidence for the effectiveness of CCM on appropriate treatment ([Das 2013](#); [Okwundu 2013](#)) and timeliness of treatment ([Okwundu 2013](#)), and mostly moderate-certainty evidence for effectiveness of CCM on mortality among children younger than five years of age ([Das 2013](#), [Okwundu 2013](#)). Two reviews ([Das 2013](#) and [Druetz 2013](#)) included studies on iCCM; however only [Das 2013](#) used GRADE and both were primarily focused on

the effects of CCM - not iCCM - and therefore did not address the objectives of this review.

A review of community-based management of pneumonia by Theodoratou 2010 included studies on CCM by lay health workers but did not report these results separately from the results of studies that included other types of healthcare workers such as nurses.

A systematic review assessed the evidence for the effect of integrating CCM for malaria with other interventions, including CCM for pneumonia, on outcomes for CCM for malaria - in particular quality of care and facilitators and barriers to high-quality CCM for malaria (Smith Paintain 2014). They found that integrating additional interventions with case management services at community level for malaria did not reduce the quality of the malaria services in contexts where training and supervision were maintained but quality of pneumonia case management was lower and variable (Smith Paintain 2014). This review did not use GRADE and was focused on the effects of iCCM on malaria outcomes, not outcomes across diseases as in this review.

A “scoping review” of the training, supervision and quality of care of iCCM that did not use GRADE reported evidence of positive effects on quality of care in large iCCM programmes where multifaceted interventions including training, supervision, and supply chain management were implemented (Bosch-Capblanch 2014). Amouzou and colleagues undertook a non-systematic review of the effect of iCCM on child mortality in sub-Saharan Africa and found that large heterogeneity of programme implementation and evaluation design precluded meta-analysis but revealed in six of eight studies a greater decline in mortality among children aged 2 to 59 months in intervention areas compared to comparison areas (Amouzou 2014).

Other systematic and non-systematic reviews have covered the effectiveness of lay health workers in terms of providing a range of maternal, newborn, and child health interventions (Christopher 2011; Hopkins 2007; Lewin 2010; Sanders 2007; Zaidi 2009).

The current review will build on previous reviews - which primarily focused on CCM or effects of iCCM on outcomes for a single disease - by focusing on the effects of iCCM as an integrated approach on outcomes across diseases using the rigorous Cochrane methodology, including the GRADE approach for assessing the certainty of the evidence.

OBJECTIVES

To assess the effects of the integrated community case management (iCCM) strategy for children younger than five years of age in low- and middle-income countries.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider types of studies for inclusion based on EPOC guidance (EPOC 2017a).

- Randomised trials, including cluster-randomised trials, with at least two intervention (iCCM) sites and at least two control sites (no iCCM).
- Non-randomised trials with at least two intervention (iCCM) sites and at least two control (no iCCM) sites and adjustment for baseline characteristics and confounders.
- Controlled before- after studies (CBAs) with at least two intervention (iCCM) sites and at least two control (no iCCM) sites in which allocation to different comparison groups was not made by study investigators, and outcomes were measured in both intervention and control groups at baseline and after the iCCM programme had been introduced.
- Interrupted time series studies with a clearly defined point in time when the intervention (iCCM) occurred and at least three data points before and three after the introduction of iCCM. We will use the EPOC standard criteria for assessing the methodological quality of ITS designs for inclusion.
- Repeated measures studies, specifically interrupted time series studies where measurements are made in the same individuals at each time point.

As a strategy, iCCM was intended to target areas within LMICs with poor geographic accessibility to facility-based case management services, and this review intends to provide evidence relevant to policy in these settings. For this reason, included studies will be restricted to LMICs as categorized by the World Bank using gross national income per capita in US dollars and the Atlas conversion factor (World Bank 2012). We will not restrict the inclusion of studies by language, publication status or date of publication. We will consider for inclusion full-text published studies, conference abstracts, and unpublished full-text studies, as well as unpublished data.

Types of participants

Types of recipients

Types of recipients will include children younger than five years of age and their caregivers in LMICs.

Types of healthcare providers

Types of healthcare providers will include any lay health workers (paid or voluntary) who

- provide iCCM (integrated case management services for two or more illnesses among children younger than five years of age);
- are trained on iCCM, but have received no formal professional or paraprofessional certificate or tertiary education degree (adapted from [Lewin 2010](#)).

Types of interventions

We will consider for inclusion studies on the implementation of generic WHO/UNICEF iCCM intervention (or local adaptation thereof) for at least two of the following iCCM diseases: diarrhoea, malaria (in endemic areas), pneumonia, severe acute malnutrition and newborn sepsis. We will also consider for inclusion studies with implementation of unbranded iCCM (i.e. where the intervention is not called by the name “iCCM” but where generic WHO/UNICEF iCCM for at least two iCCM diseases has been implemented). We recognize that iCCM in some contexts may include other childhood illnesses. We will consider studies of iCCM that include other childhood illnesses (e.g. antiretroviral therapy adherence for HIV, paediatric TB services) as long as they include at least two iCCM diseases.

To be considered for inclusion, a study must at minimum include training and deployment of lay health workers for iCCM as one component plus systems interventions to supply the necessary commodities and equipment with or without other systems interventions or interventions for community mobilisation and engagement. We recognize that iCCM may involve multiple health systems interventions and interventions for communication and community mobilization ([Table 1](#)) not all of which may be implemented in all contexts, in the same way or with the same strength. Since we expect there to be large variation between studies in the number and type of diseases being managed we anticipate not presenting one overall summary estimate but rather stratifying on two levels.

1) Two or more disease iCCM versus one disease CCM or standard facility-based care (case management for children younger than five years of age provided by nurses or doctors at first line facilities in LMICs).

2) three or more disease iCCM versus one disease CCM or standard facility-based care.

This will enable a comparison of two different levels of integrated case management services versus single disease case management services and standard facility care which is of policy relevance for countries considering establishing a community-based delivery platform for case management of childhood illnesses.

Comparison

We will include studies comparing programmes that implement the integrated community case management (iCCM) strategy with single disease community case management (CCM) and standard

facility care. We also suspect that effects will vary depending on a number of programme and contextual factors. These are summarized in [Subgroup analysis and investigation of heterogeneity](#) (below).

Types of outcome measures

Reporting of the outcomes listed here will not be an inclusion criterion for the review and we will include studies regardless of the assessed outcomes.

Primary outcomes

1. Coverage of appropriate treatment: the proportion of children younger than five years of age with one or more childhood illnesses (diarrhoea, malaria, pneumonia, severe acute malnutrition, or newborn sepsis) that receive appropriate treatment from an ‘appropriate provider’ of treatment services (trained, certified or otherwise qualified public or private provider, including iCCM providers). This could include oral rehydration therapy and zinc for diarrhoea, antimalarial drug prescription for fever, Ready-to-Use Therapeutic Foods (RUTF) for severe acute malnutrition, and antibiotics for newborn sepsis. Pneumonia treatment is not included due to the lack of a valid household survey indicator of pneumonia treatment ([Bryce 2013](#)). Pneumonia is included under the secondary outcome coverage of care seeking.

2. Quality of care assessed by adherence to standard/adapted WHO/UNICEF iCCM practice guidelines. This could include correct assessment (iCCM provider’s assessment matched a gold standard assessment); correct classification (iCCM provider’s classification matched a gold standard classification); and correct treatment (iCCM provider’s treatment matched a gold standard treatment). We will not exclude studies using other standards or indicators.

3. Case load or severity of illness at health facilities. This could include the proportion of facility case load made up by severe diarrhoea, severe malaria (in endemic settings), severe pneumonia, and cases with general danger signs or other complications.

4. Measures of mortality (neonatal, infant, under-five mortality and any mortality (neonatal + under-five mortality))

5. Adverse events

Secondary outcomes

1. Coverage of care-seeking to an ‘appropriate provider’ of treatment services. This could include care-seeking to a trained, certified or otherwise qualified public or private provider (including iCCM providers) for diarrhoea, fever, suspected pneumonia, malnutrition or newborn sepsis.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases for primary studies without any language or time limits:

- The Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, www.cochranelibrary.com, (including the Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register).
- MEDLINE, OvidSP.
- Embase, OvidSP.

To test whether or not to search Embase, we will search Embase and MEDLINE for the phrase 'integrated community case management' in title, abstract and keywords. We will screen all records that are unique to Embase, and will only do a systematic search of Embase if any of these records are eligible for inclusion.

See Appendix 1 for the MEDLINE strategy that has been peer reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist ([Sampson 2008](#)).

Searching other resources

Grey Literature

- Open Grey (www.opengrey.eu).
- Grey Literature Report (www.greylit.org).
- Any other relevant grey literature resources.

Trial Registries

- International Clinical Trials Registry Platform (ICTRP), World Health Organization (WHO) (www.who.int/ictrp).
- ClinicalTrials.gov, US National Institutes of Health (NIH) (ClinicalTrials.gov).

We will also

- search for relevant studies in the reference list of all included studies;
- conduct cited reference searches for all included studies using Web of Science, Thomson Reuters.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. At least two review authors (from among NO; DB; WO; KL; EJ; MK; TD; KD) will independently screen titles and abstracts for inclusion. We will code all the potentially eligible studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text study reports/publication and at least two review authors (from among NO; DB; WO; KL; EJ; MK; TD; KD) will independently screen the full text, identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third reviewer (one of the eight review authors who had not originally screened the particular title, abstract or full text). We will list in 'Characteristics of excluded studies', with reasons for their exclusion, studies that initially appear to meet the inclusion criteria but which we later rejected. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram ([Liberati 2009](#)); and a 'Characteristics of excluded studies' table.

Data extraction and management

We will use a standard data collection form, adapted from the EPOC Good Practice Data Collection Form ([EPOC 2017b](#)) and piloted on at least one study in the review, to gather study characteristics and outcome data. Two reviewers per study from among the eight reviewers (NO; DB; WO; KL; EJ; MK; TD; KD) will independently extract the following study characteristics from included studies.

1. Methods: study design, number of study centres and location, study setting, withdrawals, date of study, follow-up.
2. Participants: number, mean age of children, age range of children, sex of the child, socio-economic status (country baseline income level as defined by the HDI; household wealth defined as household assets or income), type of condition, diagnostic criteria, inclusion criteria, exclusion criteria, other relevant characteristics.
3. Interventions: intervention components, comparison, fidelity assessment; Where multiple trial arms are reported in a single trial, we will include only the relevant arms.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported. We will extract information separately for two of the PROGRESS groups specified for subanalysis ([O'Neill 2014](#)): socio-economic status (country baseline income level as defined by the HDI and household wealth defined as household assets or income); and sex of the child.
5. Notes: funding for trial, all stated conflicts of interest of trial authors, ethical approval.

Two reviewers - from among the eight reviewers - will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third reviewer (one of the eight review authors who had not originally extracted from the full text). NO will not be involved in data extraction for studies supported by UNICEF or the Global Fund to Fight AIDS, Tuberculosis, and Malaria (see '[Declarations of interest](#)' section)

Assessment of risk of bias in included studies

Two review authors (NO and TD) will independently assess risk of bias for each study using guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and EPOC (EPOC 2017c). NO will not be involved in risk of bias evaluation for studies supported by UNICEF or the Global Fund to Fight AIDS, Tuberculosis, and Malaria (see '[Declarations of interest](#)' section). NO and TD will resolve any disagreement by discussion or by involving a third assessor (KD). We will assess and present the risk of bias for studies with a separate control group (randomized trials, non-randomized trials, and controlled before- after studies) according to the nine standard criteria suggested by EPOC (EPOC 2017c).

1. Was the allocation sequence adequately generated?
2. Was the allocation adequately concealed?
3. Were baseline outcome measurements similar?
4. Were baseline characteristics similar?
5. Were incomplete outcome data adequately addressed?
6. Was knowledge of the allocated interventions adequately prevented during the study?
7. Was the study adequately protected against contamination?
8. Was the study free from selective outcome reporting?
9. Was the study free from other risks of bias?

We will assess and present the risk of bias for interrupted time series studies according to the seven standard criteria suggested by EPOC (EPOC 2017c).

1. Was the intervention independent of other changes?
2. Was the shape of the intervention effect pre-specified?
3. Was the intervention unlikely to affect data collection?
4. Was knowledge of the allocated interventions adequately prevented during the study?
5. Were incomplete outcome data adequately addressed?
6. Was the study free from selective outcome reporting?
7. Was the study free from other risks of bias?

Following EPOC guidance we will provide a summary assessment of the risk of bias for each important outcome (across domains), including all of the entries relevant to that outcome, within and across studies (EPOC 2017d). For each domain we will provide a judgement and a quotation in support of the judgement. The judgement for each outcome will assess the risk of bias as 'low risk' (low risk of bias for all key domains), as 'high risk' (high risk of

bias for one or more key domains), or as 'unclear risk' (unclear risk of bias for one or more key domains) (EPOC 2017d). We will interpret 'low risk' of bias to mean plausible bias that is unlikely to seriously alter the results; 'high risk of bias' to mean plausible bias that seriously weakens confidence in the results; and 'unclear risk' of bias to mean plausible bias that raises some doubt about the results (Table 2; EPOC 2017d). We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for mortality may be very different than for reported care-seeking). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will create plots of 'Risk of bias' assessments in Review Manager 5 (RevMan 5) (Review Manager 2014). Disagreements about risk of bias will be resolved by discussion between the authors assessing risk of bias or by group discussion, if necessary. We will not provide a summary assessment of the risk of bias for a study across outcomes because we cannot assume the risk of bias is the same for all outcomes in a study and generally a summary assessment of the risk of bias across outcomes is of little interest. We will not provide a summary assessment of the risk of bias for the review as a whole (across studies and outcomes) because this would require value judgements about which outcomes are critical to a decision: these judgements may vary across settings, and this review is intended to inform decisions across a variety of settings (Higgins 2011). When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

For RCTs, NRCTs and CBA studies, we will record outcomes in each comparison group. Where possible we will record or calculate risk ratios (RRs) and odds ratios (ORs) for dichotomous outcomes. If CBA studies do not provide an appropriate analysis or reporting of results but present the data for each district/region in the intervention and control groups respectively, for dichotomous outcomes we will re-analyse the data using a generalised linear model to calculate an adjusted RR.

If adjusted analyses are reported for dichotomous outcomes (adjusting for potential confounders in RCTs, NRCTs and CBAs), we will use estimates of effect from the primary analysis reported by the investigators and convert these to RRs, if possible. In the case where the adjusted analyses for dichotomous outcomes are

reported using ORs and not RRs then we will use RevMan 5 to convert ORs to RRs before we include the result in a meta-analysis (Review Manager 2014).

Continuous outcomes

For continuous outcomes, we will express the effect size as mean differences (MDs) with standard deviations (SDs) if outcomes are measured in the same way between studies. If some included studies report endpoint data and others report change from baseline data (with errors), we will combine these in the meta-analysis if the outcomes are reported using the same scale (Higgins 2011). We will use standardised mean differences (SMDs) with 95% confidence intervals (CIs) to combine data from trials that measure the same outcome but use different scales. We will standardise the data to their effect size by dividing the estimated MDs by their SDs. For CBA studies, we will use difference in differences between pre- and post-observation in intervention and control group. For time-to-event data we will report hazard ratios or similar measures such as risk ratios or survival rates.

Interrupted time series (ITS) studies

For ITS studies that meet the criteria for inclusion according to EPOC 2017e we will record changes in level and in slope. If papers with ITS design do not provide an appropriate analysis or reporting of results but present the data points in a graph or in a table that we can scan, we will re-analyse the data using the methods described in Ramsay 2003.

Studies reporting multiple measures of the same outcome

When a single study uses two separate methods to measure the same outcome (e.g. two measures of quality of care) or measures two different outcomes that we could consider part of the same outcome category (e.g. two different measures of access to treatment services), we will adopt the approach to measures of treatment effect outlined in Brennan 2009, Flodgren 2011 and Giguère 2012. We will select the primary outcome identified by the study authors that correlates to our stated outcomes of interest. If the study authors do not specify any primary outcomes, we will select the one specified in the sample size calculation. If no sample size calculations are reported, we will rank the reported effect estimates and select the outcome with the median effect estimate. When there is an even number of outcomes, we will include the outcome whose effect estimate is ranked $n/2$, where n is the number of outcomes.

Unit of analysis issues

For cluster randomised studies which do not adequately account for clustering in their analysis, we will adjust the analysis for clustering if the following information can be extracted.

- The number of clusters (or groups) randomised or allocated to each intervention group, or the average (mean) size of each cluster.
- The outcome data ignoring the cluster design for the total number of individuals included in the study (for example, number or proportion of individuals with events, or means and standard deviations).
- An estimate of the intracluster (or intraclass) correlation coefficient (ICC). Where no information on the ICC is reported, we will extrapolate the ICC from other included cluster randomised studies, if available. If this is not possible, we will not combine the findings of these studies in a meta-analysis, but will present the results in an additional table.

We will use inflated variances to adjust appropriately for clustering (Higgins 2011). For cluster RCTs where study authors do not take clustering into account in the original analysis and where reanalysis is not possible, we will only report the estimate of effect (and not the P value or CIs - the P value may be too small and the CIs too narrow).

For area level analysis (e.g. districts as the unit of analysis) we will not make inferences about the individuals based on the area to which they belong, to avoid ecological fallacy.

Dealing with missing data

We will contact trial investigators and authors in order to verify key study characteristics and obtain missing outcome data where possible (e.g. when a study is identified as abstract only). We will investigate causes of missing data and attrition rates and critically appraise imputation methods used. If a study does not report means and SDs for continuous outcomes and study authors have failed to provide the needed information, then we will use the medians, ranges and sample size to estimate the same. In some cases, the pooled baseline SD will be used for follow-up data measurements. We will assess the impact of imputations on meta-analysis as part of sensitivity analyses.

If this is not possible we will report the data as missing and report this in the 'Risk of bias' tables and will not attempt to impute values.

For all outcomes we will carry out analysis, as far as possible, on an intention-to-treat (ITT) basis of available cases. We will attempt to include all participants or clusters randomised to each group in the analyses, and analyse data according to initial group allocation irrespective of whether or not participants received, or complied with, the planned intervention. When assessing adverse events, adhering to the principle of ITT may be misleading and we will therefore relate the results to the treatment received. This means that for adverse effects we will base the analyses on the participants who actually received the intervention and the number of adverse events that are reported in the studies.

For studies reporting per protocol analysis, we will ask the authors to provide a full breakdown of information for all subjects - including those that withdrew from, or did not comply with, the protocol.

Assessment of heterogeneity

We will first make a qualitative assessment of the extent to which the included studies are similar to each other. This will include an assessment of the settings, the interventions, the participants and outcomes. We will also examine the forest plots from the meta-analyses, visually assessing the levels of heterogeneity (in terms of the size or direction of treatment effect and by looking at the overlap between CIs around the treatment effect estimate for each included study). We will compute the I^2 statistic and use the χ^2 test ($P < 0.10$) to assess the presence or absence of heterogeneity of effects beyond chance alone. When observed intervention effects are more different from each other than one would expect due to chance alone, we will assume that the studies have 'clinical' or statistical heterogeneity or both.

If we find a sufficient number of studies for a pre-specified outcome we will conduct a meta-analysis. We will use the I^2 statistic to quantify the level of statistical heterogeneity among the trials in each analysis. If we identify substantial or considerable heterogeneity (approximately an I^2 statistic value of 50% to 100%) we will not undertake pooled estimates; we will note this in the text, and we will explore this heterogeneity through the prespecified subgroup analyses. We will interpret with caution results from meta-analyses with high levels of unexplained heterogeneity.

Assessment of reporting biases

We will attempt to be as comprehensive as possible in our search strategy so as to find and include all relevant studies and to reduce any possible publication bias. This will include a search of published studies, grey literature, registers of prospective trials and discussions with colleagues (Higgins 2011).

We will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis.

We will use funnel plots to make a visual assessment of whether there is asymmetry, which may signal the presence of reporting bias, even if it is not a definitive indicator of such bias. If we find more than 10 studies that report similar outcomes, we will create and examine a funnel plot to explore possible publication biases, interpreting the results with caution (Sterne 2011).

For continuous outcomes with intervention effects measured as mean differences, we will use the test proposed in Egger 1997 to test for funnel plot asymmetry. For dichotomous outcomes with intervention effects measured as RRs or ORs, and continuous

outcomes with intervention effects measured as SMDs, we will not consider funnel plot calculations because funnel plots using risk differences are seldom of interest (Egger 1997). We will interpret the results of tests for funnel plot asymmetry in the light of visual inspection of the funnel plot, as the statistical results may not be representative if there are small-study effects.

Data synthesis

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges. When we encounter this we will note that the data is skewed and consider the implication of this. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. intervention A versus usual care and intervention B versus usual care) must be entered into the same meta-analysis, we will halve the control group to avoid double counting.

If there is no evidence of heterogeneity we will carry out a meta-analysis using a fixed-effect model to provide an overall estimate of treatment effect when more than one study examines similar interventions provided that studies use similar methods; studies are similar regarding setting; and studies measure the same outcome in similar ways in comparable populations. Given the complexity of the intervention and varying contexts of implementation, we are likely to find evidence of heterogeneity. If this is the case we will use a random-effects meta-analysis. For continuous variables we will use the inverse-variance method. For dichotomous variables we will use the method proposed by Mantel 1959. If cluster RCTs meet the inclusion criteria, we will use the generic inverse-variance method. We will carry out all statistical analysis using Stata v14 (StataCorp 2015).

For ITS and repeated measures studies, the preferred analysis method is either a regression analysis with time trends before and after the intervention, adjusted for autocorrelation and any periodic changes; or auto-regressive integrated moving average (ARIMA) analysis. We will attempt to present the results for outcomes as changes along two dimensions: change in level and change in slope. Since the interpretation of change in slope can be difficult, we will present the long-term effects similarly to the way we plan to calculate and present the immediate effects. We will use the generic inverse-variance method for combining the data in a meta-analysis for each NRCT study design (ITS and CBA studies) separately.

We will report the results of the meta-analysis as part of a structured synthesis and will include forest plots where appropriate (EPOC 2017g). We will not combine results from RCTs and NRCTs together in meta-analysis, nor will we present pooled estimates for NRCTs with different types of study designs. Evidence on different interventions may be available from different types of studies

(for example, it is likely that interventions implemented at the national level will have been evaluated in NRCTs rather than randomised trials). Where there is evidence on a particular outcome from both RCTs and NRCTs, we will use the evidence from trials that are at lower risk of bias to estimate treatment effect.

We will create a 'Summary of findings' table using the following outcomes.

1. Coverage of appropriate treatment.
2. Quality of care as measured by adherence to recommended iCCM practice or guidelines.
3. Measures of mortality (neonatal, infant, under-five mortality and any mortality (neonatal + under-five mortality)).
4. Case load or severity of illness at health facilities.
5. Coverage of care-seeking to an 'appropriate provider' of treatment services.

We will use the considerations recommended in the EPOC GRADE worksheets (design, risk of bias, inconsistency, indirectness, imprecision, and other) to assess the certainty of evidence across studies as it relates to the main outcomes (EPOC 2017g). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the EPOC GRADE worksheets (EPOC 2017g), and using GRADEpro software (GRADEpro GDT 2015). We will express the results as one of four levels of quality (high, moderate, low or very low). We will justify all decisions to down- or up-grade the quality of studies using footnotes and make comments to aid readers' understanding of the review where necessary. We will consider whether there is any additional outcome information that could not be incorporated into meta-analyses and note this in the comments and state if it supports or contradicts the information from the meta-analyses. If it is not possible to meta-analyse the data we will summarise the results in the text using a structured synthesis (EPOC 2017f). This structured synthesis may include reporting on interquartile ranges and ranges of effects for relevant outcomes and we will include a summary of the findings in the review text. Guided by the framework presented in Table 1 and text in the sections 'Description of the intervention' and 'How the intervention might work' (above), this structured analysis may also include a description of the intervention mechanisms described across the studies. We will include information from the structured synthesis in the 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We will consider sub-analyses for a number of groups as we assume that the effects of iCCM on our outcomes of interest may vary according to context (Bennett 2015; Bosch-Capblanch 2014; Haines 2007; Kok 2014).

We plan to carry out the following subgroup analyses.

1. Country baseline income level (low income, middle income) as defined by the Human Development Index. We

hypothesize that effects may be greater for low-income countries because the gap in access to care is greater in the former; additionally the effects may be greater in low-income countries because the share of under-five mortality (i.e. the target group for iCCM) is greater in low-income countries compared to middle-income countries, where neonatal mortality makes up a greater share of under-five mortality (Liu 2015; You 2015).

2. Household wealth as defined as household assets or income: poorer households may have less access to, and choice of, providers and therefore may benefit more from iCCM (Geldsetzer 2014).

3. Gender of child (male/female): we hypothesize that in some contexts social norms may influence preferential care-seeking behaviour for male children (Geldsetzer 2014; Treleven 2016).

4. Ratio of iCCM providers per population (higher ratio/lower ratio): although the evidence is unclear on whether the ratio of iCCM providers affects outcomes (Oliphant 2014; Amouzou 2016), we hypothesize that higher ratios of iCCM providers per population may have greater effects due to greater exposure to iCCM providers.

5. Active case-finding compared to passive case-finding: although the evidence is unclear on whether the choice of case-finding approach (active or passive) affects outcomes (Oliphant 2014), we hypothesize that iCCM providers that do passive case-finding (i.e. work from a fixed site and wait for care-seekers) may have a greater effect than iCCM providers conducting active case-finding because mothers may know better where to find the iCCM providers and - in large populations - iCCM providers may not be able to reach all children in need through active case-finding.

The following outcomes will be used in subgroup analysis.

1. Coverage of appropriate treatment.
2. Quality of care as measured by adherence to recommended iCCM practice or guidelines.
3. Measures of mortality (neonatal, infant, under-five mortality and any mortality (neonatal + under-five mortality)).
4. Case load or severity of illness at health facilities.
5. Coverage of care-seeking to an 'appropriate provider' of treatment services.

Subgroup analyses will check for variation in the intervention effect across different populations, interventions or setting characteristics. We will use meta-regression analysis to test for subgroup interactions. Using the Stata v14 command "metan" we will investigate differences between two or more subgroups (Borenstein 2008; StataCorp 2015). We will be using the standard Bonferroni correction where the usual 0.050 criterion for statistical significance will be divided by 25 (5 subgroups * 5 outcomes) to yield the Bonferroni critical value of 0.002 (0.05/25), so a comparison would need to have P less than 0.002 to be significant. Alternatively, we will control for multiple testing by adjusting the false discovery rate using the more powerful Benjamini-Hochberg procedure (Benjamini 1995).

Sensitivity analysis

We are aware that overall risk estimates from any meta-analysis can be susceptible to outlying effect sizes, impacting on a change in statistical significance and clinical relevance and even a reversal of effectiveness of an intervention. Therefore, we will perform sensitivity analysis defined a priori to assess the robustness of our findings. We will conduct the following sensitivity analyses.

1. Restricting the analysis to published studies.
2. Restricting the analysis for each outcome to studies with a low risk of bias for the particular outcome. For the prespecified outcomes in this review, the most important risk of bias domains are: a) baseline outcomes and characteristics; and b) completeness of outcome data.
3. Restricting analysis to studies with four or more illnesses; (although we will stratify analysis as two or more illnesses and three or more illnesses, the right number may be four or more illnesses, or this may not matter at all).

We will perform additional meta-analyses and generate forest plots by omitting studies that were unpublished (for 1) or with extreme risk of bias (for 2) or sparse levels of illnesses (for 3) to assess their impact on results of the main meta-analysis. We will also do a number of additional meta-analyses where a priori identified studies will be omitted one at a time (and using the remaining $N - 1$ studies) where N is the number of included studies in the main meta-analysis.

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. iCCM components categorized by the EPOC taxonomy of health systems interventions

EPOC Category	EPOC Sub-category	Target	Intervention	iCCM Component and Purpose
Who provides care and how the healthcare workforce is managed	Role expansion or task shifting Recruitment and retention strategies for underserved areas	Health workers	Interventions to recruit, train and retain lay health workers to provide iCCM	Training and deployment component: interventions with the main purpose of increasing access to integrated case management services for children younger than five years of age by increasing the number of lay health workers trained on the generic or adapted WHO/UNICEF guidelines for integrated case management services and deployed where facility-based case management services are limited
Interventions targeted at health workers	Clinical practice guidelines	Health workers	Implementation of simplified IMCI-adapted clinical guidelines for iCCM providers	
Mechanisms for the payment of health services	Payment methods for health workers	Health workers	Interventions for the payment of iCCM providers such as salary, fees for service, capitation	
Coordination of care and management of care processes	Referral systems	Health system	Interventions to improve systems for referral of patients between community and facility levels	Systems component: interventions with the main purpose of improving implementation of iCCM by strengthening health systems organiza-

Table 1. iCCM components categorized by the EPOC taxonomy of health systems interventions (Continued)

	Procurement and distribution of supplies: systems for procuring and distributing drugs or other supplies		Interventions to improve the supply of iCCM drugs and equipment	tion and management, including supplies, specifications, and training
Information and communication technology (ICT)	Health information systems The use of information and communication technology	Health system	Interventions to improve health information systems and use of information communication technology for iCCM	
Interventions targeted at health workers	Monitoring the performance of the delivery of healthcare	Health workers, supervisors, managers, policy makers	Interventions to improve monitoring, evaluation, and research for iCCM	
	Managerial supervision	Supervisors, managers	Interventions to improve managerial supervision of iCCM providers	
Authority and accountability for health policies	Community mobilization	Communities and caregivers	Interventions to promote good practices for health and nutrition and generate demand for use of iCCM providers when children are ill	Communication and community mobilization component: interventions with the main purpose of promoting good practices for health and nutrition and generating demand for case management services for ill children through communication and mobilization of communities and caregivers

Based on [EPOC 2015](#)

Table 2. Approach for summary assessments of the risk of bias for each outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results.	Low risk of bias for all key domains.	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results.	Unclear risk of bias for one or more key domains.	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

From [Higgins 2011](#)

APPENDICES

Appendix I. MEDLINE Search Strategy

MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE 1946 to Present, Ovid

#	Searches	Results
1	integrated community case management of childhood illness*. ti,ab,kf	34
2	Community Health Workers/	4523
3	Allied Health Personnel/	11304
4	Volunteers/	9086
5	exp Peer Group/	18630
6	Home Nursing/	8784
7	Midwifery/	18126
8	Delivery of health Care, Integrated/	10982

(Continued)

9	integrated management.ti,ab,kf.	1351
10	iccm.ti,ab,kf.	162
11	(community worker? or community health* worker? or community health care worker?).ti,ab,kf	4030
12	(community level worker? or community level health* worker? or community level health care worker?).ti,ab,kf	33
13	(community health* provider? or community health care provider? or community health* aide? or community health care aide? or community health* agent? or community health care agent? or community health* assistant? or community health care assistant? or community health* promoter? or community health care promoter? or community health* distributor? or community health care distributor? or community health* surveyor? or community health care surveyor?).ti,ab,kf	513
14	(community based health* provider? or community based health care provider? or community based health* aide? or community based health care aide? or community based health* agent? or community based health care agent? or community based health* assistant? or community based health care assistant? or community based health* promoter? or community based health care promoter? or community based health* distributor? or community based health care distributor? or community based health* surveyor? or community based health care surveyor?).ti,ab,kf	52
15	(community volunteer? or community health* volunteer? or community health care volunteer?).ti,ab,kf	884
16	(community health* educator? or community health care educator?).ti,ab,kf	60
17	health promoter?.ti,ab,kf.	511
18	(allied health personnel or allied health* worker? or allied health care worker?).ti,ab,kf	363
19	(health assistant? or welfare assistant?).ti,ab,kf.	223
20	(voluntary worker? or voluntary health* worker? or voluntary health care worker? or volunteer worker? or volunteer health* worker? or volunteer health care worker?).ti,ab,kf	410

(Continued)

21	(voluntary team? or voluntary health* team? or voluntary health care team? or volunteer team? or volunteer health* team? or volunteer health care team? or voluneer collaborator?).ti,ab,kf	29
22	(health* auxiliary or health* auxilliary or health care auxiliary or health care auxilliary or health* auxiliaries or health* auxilliaries or health care auxiliaries or health care auxilliaries or auxiliary nurse? or auxilliary nurse?).ti,ab,kf	390
23	(village health* worker? or village health care worker? or village health* volunteer? or village health care volunteer?).ti,ab,kf	433
24	(lay worker? or lay health* worker? or lay health care worker?).ti,ab,kf	391
25	(lay personnel or lay health* personnel or lay health care personnel).ti,ab,kf	57
26	(lay advisor? or lay health* advisor? or lay health care advisor? or lay counselor? or lay health* counselor? or lay health care counselor? or lay counsellor? or lay health* counsellor? or lay health care counsellor? or adherence counselor? or adherence counsellor?).ti,ab,kf	385
27	(lay volunteer? or lay health* volunteer? or lay health care volunteer?).ti,ab,kf	121
28	(peer educator? or peer counselor? or peer counsellor?).ti,ab,kf	915
29	lady health*.ti,ab,kf.	140
30	(child health* worker? or child health care worker? or maternal health* worker? or maternal health care worker?).ti,ab,kf	65
31	(traditional midwife or traditional midwives or traditional birth attendant? or doula? or skilled birth attendant?).ti,ab,kf	2152
32	(health* extension worker? or health care extension worker?).ti,ab,kf	192
33	(paramedics or paramedical personnel).ti,ab,kf.	4312
34	(drug seller? or drug distributor? or drug vendor?).ti,ab,kf	261
35	(medicin* seller? or medicin* distributor? or medicin* vendor?).ti,ab,kf	99
36	licensed chemical seller?.ti,ab,kf.	8

(Continued)

37	(pharmaceutical seller? or pharmaceutical distributor? or pharmaceutical vendor?).ti,ab,kf	14
38	(community management or community based management or community case management or community based case management).ti,ab,kf	782
39	(home based management or home nursing or home based nursing or home based carer?).ti,ab,kf	1578
40	(barefoot doctor? or traditional healer? or link worker? or front line worker? or front line health* worker? or front line health care worker? or family planning personnel or family planning worker?).ti,ab,kf	3374
41	(health surveillance assistant? or relais or accredited social health activist? or anganwadi worker? or agentes polivalentes elementares or shasthya shebika or promotoras or keshatan or gizi or health development army or therapy supporter or behvarz or brigadista?).ti,ab,kf	500
42	or/2-41 [Community Health Workers]	96307
43	Disease Management/	30902
44	exp Malaria/	64206
45	exp Diarrhea/	51460
46	exp Malnutrition/	118905
47	exp Infant, Newborn, Diseases/	171305
48	exp Sepsis/	115868
49	exp Respiratory Tract Infections/	346880
50	Dehydration/	12703
51	exp Fever/	41978
52	disease management.ti,ab,kf.	12832
53	(malaria or paludism or diarrhea or diarrhoea or diarrheal disease? or diarrhoeal disease? or pneumonia or malnutrition or mal nutrition or malnourished or mal nurished or respiratory infection? or respiratory tract infection? or sepsis or severe in-	590676

(Continued)

	fection? or fever or dehydration or dehydrated or danger sign? .ti,ab,kf	
54	((newborn? or new born? or neonat* or neo nat* or perinatal or peri natal or childhood) adj3 (disease? or illness*)).ti,ab,kf	30525
55	or/43-54 [Conditions to be managed]	1276234
56	Developing Countries.sh,kf.	84665
57	(Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,kf,ti,ab,cp	246675
58	(Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorus- sia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiri- bati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauri- tania or Mauritius or Agalega Islands or Mexico or Microne- sia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or	3335437

(Continued)

	Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadjhikistan or Tadjikistan or Tadjhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,kf,ti,ab,cp	
59	((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab,kf	114585
60	((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab,kf	447
61	(low* adj (gdp or gnp or gross domestic or gross national)).ti,ab,kf	217
62	(low adj3 middle adj3 countr*).ti,ab,kf.	10450
63	(lmic or lmics or third world or lami countr*).ti,ab,kf.	5637
64	transitional countr*.ti,ab,kf.	153
65	or/56-64 [LMICs]	3476023
66	randomized controlled trial.pt.	496470
67	controlled clinical trial.pt.	99235
68	multicenter study.pt.	248570
69	pragmatic clinical trial.pt.	731
70	non-randomized controlled trials as topic/	247

(Continued)

71	interrupted time series analysis/	360
72	controlled before-after studies/	297
73	(randomis* or randomiz* or randomly).ti,ab.	804311
74	groups.ab.	1844027
75	(trial or multicenter or multi center or multicentre or multi centre).ti	229718
76	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or repeated measur*).ti, ab	8684216
77	or/66-76	9701626
78	exp Animals/	22477984
79	Humans/	17802402
80	78 not (78 and 79)	4675582
81	review.pt.	2440369
82	meta analysis.pt.	91502
83	news.pt.	188730
84	comment.pt.	723964
85	editorial.pt.	461089
86	cochrane database of systematic reviews.jn.	14513
87	comment on.cm.	723962
88	(systematic review or literature review).ti.	108531
89	or/80-88	8177064
90	77 not 89 [Methods filter]	6777056

(Continued)

91	1 or (42 and 55 and 65 and 90) [Community health workers AND Conditions to be managed AND LMICs AND Methods filter]	1982
92	remove duplicates from 91	1780

WHAT'S NEW

Date	Event	Description
28 November 2017	Amended	Protocol republished with a new citation to correct an error in spelling of author's name

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: NPO, KD, KL, DB, EWJ, SM, TD, WAO, MK.

Designing the protocol: NPO, KD, KL, DB, EWJ, SM, TD, WAO, MK.

Coordinating the protocol: NPO, TD.

Designing search strategies: MJ, NPO, KD, KL, DB, EWJ, SM, TD, WAO, MK.

Writing the protocol: NPO, KD, KL, DB, EWJ, SM, TD, WAO, MK.

Providing general advice on the protocol: NPO, KD, KL, DB, EWJ, SM, TD, WAO, MK.

Securing funding for the protocol: NPO.

Performing previous work that was the foundation of the current study: KD, EWJ.

DECLARATIONS OF INTEREST

NPO has worked as a Health Specialist for UNICEF at its headquarters in New York, USA. UNICEF was involved in the development of iCCM with WHO; UNICEF has advocated for countries to adopt iCCM; and UNICEF has provided funding and technical support in numerous countries for iCCM implementation, monitoring, evaluation and research. NPO was involved in providing technical support in numerous countries for iCCM monitoring, evaluation, and implementation research. NPO works as a Health Specialist - Public Health and M&E - for the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) in Geneva, Switzerland. GFATM has funded the implementation of iCCM and CCM in numerous countries.

KD: none known

KL: none known

DB: none known

EWJ: none known

SM: none known

WAO: none known

MK: none known

MJ: none known

TD: none known

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Internal sources

- No sources of support supplied

External sources

- Bill and Melinda Gates Foundation, USA.

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- National Research Foundation, South Africa.

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- South African Medical Research Council, South Africa.

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- Alliance for Health Policy and Systems Research, Switzerland.

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