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Study protocol for a core outcome set in paediatric sepsis in low middle-income countries

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034960
Article Type:	Protocol
Date Submitted by the Author:	12-Oct-2019
Complete List of Authors:	Wooldridge, Gavin; BC Children's Hospital, Pediatric Critical Care Murthy, Srinivas; University of British Columbia, Paediatrics Kisson, Niranjana; University of British Columbia, Department of Pediatrics
Keywords:	Paediatric infectious disease & immunisation < PAEDIATRICS, Community child health < PAEDIATRICS, Paediatric intensive & critical care < ANAESTHETICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE

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Study protocol for a core outcome set in paediatric sepsis in low middle-income countries

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ABSTRACT

Introduction

Despite only recently being declared a major global health issue, sepsis in children is the leading cause of death worldwide. New interventions and a concerted effort to enhance our understanding of sepsis are required to address the huge burden of disease, especially in low middle-income countries (LMIC) where it is highest. An opportunity therefore exists to ensure that ongoing research in this area is relevant to all stakeholders and is of consistently high quality. One method to address these issues is through the development of a core outcome set. (COS)

Methods and analysis

This study protocol outlines the phases in the development of a core outcome set for paediatric sepsis in LMIC. The first step involves performing a systematic review of all outcomes reported in the research of paediatric sepsis in low middle-income countries. A two-stage international e-Delphi survey will then invite a broad range of participants to rank each generated outcome for inclusion into the COS. Finally, a face to face consensus meeting will be held where each outcome will be reviewed, voted on and ratified for inclusion into the COS.

Ethics and dissemination

No core outcome sets exist for clinical trials in paediatric sepsis. This COS will serve to not only highlight the heavy burden of paediatric sepsis in this setting and aid collaboration and participation between all stakeholders, but to promote ongoing essential high quality and relevant research into the topic. A COS in paediatric sepsis in LMIC will advocate for a common language and facilitate interpretation of findings from a variety of settings.

Article Summary

Strengths and limitations of this study

- With the continued high burden of disease in low middle-income countries, a core outcome set (COS) for use in paediatric sepsis research in a resource-limited setting is required to focus efforts and improve research consistency, relevance and quality in this area.
- The protocol uses a well-established process involving a thorough systematic review and an all-encompassing 3 step Delphi survey involving clinicians, researchers, nurses, patients and parents/guardians
- The feasibility of an e-survey is limited in regions with poor internet access, so the use of a local facilitator will ensure patients and the parent/guardian have equal input into the COS development.

Keywords Paediatric sepsis, core outcome sets, low-middle income countries

INTRODUCTION

1
2
3 Sepsis is the leading cause of death in children, with the highest-burden in those countries least resourced
4 to address it. Now recognised as a major global health issue, in 2017 the WHO adopted a resolution with
5 the aim of reducing the human and economic burden of sepsis (1). Severe paediatric sepsis has a worldwide
6 prevalence of 8% (2) and a mortality of 9 -20% (3). Severe sepsis and septic shock has a mortality of 20 -
7 40% within developing countries (4)(5). It is thought to be the final common pathway to multi-organ failure
8 and death from a number of infectious diseases (6), including the top four causes of childhood mortality as
9 reported by the WHO.
10

11 With the high prevalence of disease, new interventions and treatments are essential, as is a concerted effort
12 to better understand the genesis of sepsis. Analysis and comparison of trials involving paediatric sepsis in
13 low middle-income countries (LMIC) are problematic however due to the significant heterogeneity and
14 inconsistency in reporting outcomes (7, 8). A standardised way to evaluate trial outcomes is therefore
15 imperative.
16

17
18 One method that is being increasingly used to address these issues is a minimum core outcome set (COS)
19 (7). These are defined as a minimum set of outcomes that should be consistently measured and reported in
20 clinical trials for a specific clinical area (7). All stakeholders have a role in developing the COS. The use
21 of COS not only aims to improve consistency across trials allowing accurate comparison, including
22 potential meta-analysis, but to limit selective reporting (9, 10) and improve the quality and relevance of
23 clinical research (11).
24

25 Limited funding and resources, a high sepsis burden of varying infectious aetiologies and a large proportion
26 of children with significant comorbidities determine the differences in outcomes seen in LMICs. These
27 factors are in contrast to HICs and hence necessitate a region-specific COS to better understand these
28 disparities and craft context-specific solutions. As an example total annual expenditure on health in many
29 parts of sub-Saharan Africa is under US \$25 per capita and often less than 3% of the GDP (12) and the
30 number of ICU beds as a percentage of hospital beds is approximately 1.5% in LMIC compared to 2.5 to
31 9% in HIC (13). Recognising the huge discrepancy in resources between regions is essential as is the
32 potential financial impact. In 2018, 11.7% of the world's population spent over 10% of their annual income
33 on healthcare, leaving an estimated 100 million people impoverished by out of pocket spending. (14) A
34 region-specific COS will ensure relevance and meaning to patients and clinicians alike. By advocating a
35 common language between stakeholders, interpretation of findings from a variety of diverse settings will
36 become simpler and attention can focus on research into the essential outcomes.
37
38

39 AIMS AND OBJECTIVES

40 This study aims to develop a COS for use in clinical trials involving paediatric sepsis in LMICs. The specific
41 study objectives are to identify outcomes previously reported in trials of paediatric sepsis in LMIC and to
42 prioritise these outcomes using clinicians, researchers, patients and parents.
43

44 The protocol outlines our methods used to establish a COS and aims to raise awareness of paediatric sepsis
45 in LMIC and aid collaboration and participation between all stakeholders. A stepwise approach to COS
46 development will be undertaken as suggested by The Core Outcome Measures in Effectiveness Trials
47 (COMET) Initiative and the Outcome Measures in Rheumatology (OMERACT) Initiative (15).
48

49 METHODS AND ANALYSIS

50 Our COS development plan has been registered with the COMET initiative (www.comet-initiative.org). As
51 per published recommendations (16) and previous core outcome sets (11, 17 – 19), a three-step process will
52 be utilised to develop an international consensus for paediatric sepsis in low middle-countries COS:
53

- 54 1. Systematic review of outcomes currently reported in the research of paediatric sepsis in low
55 middle-income countries.
56
57
58
59

- 2.
3. Two round Delphi e-survey to prioritise outcomes
3. Consensus meeting of global experts, clinicians and nurses and e-survey participants to ratify COS

When complete, the Core Outcome Set Standards for Reporting (COS-STAR) (20) will be applied.

Scope of core outcome set

This COS will be purely focused on clinical outcomes in paediatric sepsis in LMIC, and not involve those outcomes that are specific to premature infants or certain conditions, such as meningococcal septicaemia.

Identification of existing knowledge

One prior systematic review in 2017 evaluated all paediatric randomised controlled trials of patients with septic shock. This however included high-income countries and was intensive care specific. Neonates were excluded. Mortality was the most frequent primary outcome whilst long term patient-centred outcomes were rarely used (4).

1. Systematic review

A systematic review will be performed to identify both morbidity and mortality outcomes reported in existing studies involving paediatric sepsis in low middle-income countries.

Types of studies, participants and interventions

All forms of published studies will be included. Subjects will children under the age of 18 with sepsis. Those involving a high proportion (>50%) of premature patients will be excluded. Studies undertaken in a low middle-income country, as defined by the World Bank, and those describing a clinical outcome that is measured systematically across the population studied will be included. Sepsis, severe sepsis or septic shock will be defined by either the International Consensus Conference on Pediatric Sepsis Definitions, American College of Chest Physicians/ Society of Critical Care Medicine consensus criteria, sepsis-relevant International Classification of Diseases (ICD)-9/ICD-10 codes), Integrated Management of Childhood Illness or clearly self- defined (e.g. positive blood culture with one or more symptoms). Only articles in English from 1994 to 2019 will be assessed.

Search methods for identification of studies and study eligibility

The search strategy will be applied to PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials and the World Health Organisation International Clinical Trials Platform (ICTRP). One review author (GW) will independently screen the abstracts returned from the search strategy and any studies not meeting inclusion criteria will be excluded. Assessment of methodological quality will not be undertaken as we are evaluating outcomes only. The electronic search strategy was developed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (21). Details are outlined in supplemental file 2.

Data extraction, analysis and presentation

One review author (GW) will perform data extraction using a standardised form. The following data will be retrieved: author details, year and journal of publication, sepsis definition, reported outcomes and outcome definition(s). The outcomes will then be listed and placed into broader outcome categories.

Records will be managed in EndNote X9 reference software (Clarivate Analytics, Boston, MA).

2. Delphi process

A two-round international Delphi process involving an electronic-based questionnaire populated by outcomes from the literature review will then be performed to rank the outcomes.

Selection of panel members

A minimum of 50 participants for the Delphi panel will be involved. Participants will be recruited from around the world, with an aim to have all from low middle-income countries. Experienced clinicians in paediatrics and critical care, nurses, researchers and previous patients and parents/ guardians will be invited to participate. These will be identified from prior research papers and previous collaborations with members of the research team.

Delphi Round 1

Participants will initially be asked to complete brief questions related to their profession and experience. A list of outcomes generated from the systematic review will then be presented, and the participants required to rank each one on a scale from 1 to 9 (22). A score of 1-3 indicates an unimportant outcome that should not be included, scores of 4-6 demonstrate an important but not critical outcome and scores of 7-9 imply an outcome that is essential to inclusion (17, 19, 20). A survey reminder will be sent out after 7 days and then again after 2 weeks. All outcomes will be carried on to the second round. There will be a free-text option for participants to suggest additional outcomes.

Delphi Round 2

In the second phase of the electronic questionnaire, the first round scores for each outcome and number of prior respondents will be revealed to the participant. With this knowledge, each outcome will be rescored as described previously in Delphi round one.

At this point, patients and their parents or guardian will be identified by clinicians known to team members and approached after discharge. The questionnaire will be paper-based and outcome measures simplified into broad domains for the patients to rank with the use of a local facilitator.

Once again, a survey reminder will be sent out after 7 days and then again after 2 weeks.

Analysis of Outcomes

Descriptive statistics will be used to analyse the responses from both round one and two. Free text answers will be reviewed by the authorship team to evaluate for uncaptured outcomes in the first-round questionnaire and added if deemed appropriate to the second Delphi round questionnaire.

Our definition of consensus will follow that of previous COS publications (16). Analysis of the second round outcomes for which $\geq 70\%$ of panellists scored it 7-9 and fewer than 15% of panellists scored it 1-3 will have met criteria for inclusion in the consensus meeting discussion. Outcomes for which $\geq 70\%$ of panellists scored it 1-3, and fewer than 15% of panellists scored it 7-9 will be defined to have met consensus for exclusion. (16). Those outcomes not meeting criteria will be defined as lack of consensus.

3. Consensus Meeting

A face-to-face consensus meeting will be held after completion of the Delphi process to finalise the outcomes for inclusion in the COS. The exact final meeting format will depend upon the location and the number of participants able to attend. Invites will be sent to those that have completed both rounds of the Delphi survey. The outcomes from round two of the Delphi survey will be presented and discussed. Participants will then anonymously vote for each outcome for inclusion and exclusion in the finalised COS using a format similar to that of the Delphi survey. Consensus for inclusion will be as before: if $\geq 70\%$ of panellists vote in favour and fewer than 15% of panellists vote against. At this time, we will also enquire

of the participants as to the practicality, feasibility and cost-effectiveness of the finalised core outcome set and the ease as to which it could be implemented

Ethics

All participants involved will be asked for their consent before undertaking the Delphi survey, and all procedures will be conducted according to the Declaration of Helsinki. Involvement in the survey will be completely voluntary and the responses anonymised. A waiver for ethics approval has been granted by the authors' institution.

Implementation, dissemination and updating the COS

Upon completion of the consensus meeting, we will draft a COS guideline including an explanation of our methods using the COS-STAR template (20). It will be submitted to a high impact journal and presented at international meetings. We will seek endorsement and dissemination by major international societies and journals with an interest in paediatric sepsis and hope that it can be used as a standard in LMICs data sets for paediatric sepsis.

Discussion

At present, no core outcome sets exist for clinical trials in paediatric sepsis. Outcomes from HICs cannot be reliably extrapolated to LMICs (23). This region-specific COS aims to reduce heterogeneity that currently exists in this area, limit reporting bias and improve the quality and relevance of outcomes published. It will also hopefully serve to highlight the heavy burden of paediatric sepsis in this setting and aid collaboration and participation between all stakeholders, encouraging ongoing essential high-quality research into the topic and facilitate further understanding of this complex disease.

Author Contributions

GW and SM were involved in study conception. GW, SM AND NK were involved in manuscript drafting and editing.

Patient and Public Involvement

Patients will be approached during the second round of the Delphi Survey.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial or not for profit sectors.

Competing interests

All have no conflicts of interest to declare

Word Count 2969

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Supplemental File 2

Systematic Review Search Strategies

Criteria

- Inclusion:
 - Articles published in English
 - Peer Reviewed articles
 - Focus on paediatric patients with sepsis (those under 18 years of age)
 - Sepsis, severe sepsis or septic shock as defined by international consensus (International Consensus Conference on Pediatric Sepsis Definitions, American College of Chest Physicians/ Society of Critical Care Medicine consensus criteria, sepsis-relevant International Classification of Diseases (ICD)-9/ICD-10 codes), by IMCI and self-defined (e.g. positive blood culture with one or more symptoms)
 - Involve research in low - middle income countries
 - Describe a clinical outcome that is measured systematically across the population studied
 - Years : 1994 to 2019
- Exclusion
 - Adult studies (>18 yrs.)
 - Preterm Sepsis
 - Those performed in high resource countries (as defined by the World Bank)
 - No outcome data
 - Articles which are not peer reviewed
 - Duplicate references
 - Studies missing methods of data collection and eligibility criteria
 - Studies involving sepsis in specific subgroup population
 - Retrospective bacteremia

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('sepsis'/exp OR sepsis:ti,ab,kw OR septic:ti,ab,kw OR pyemia*:ti,ab,kw OR pyohemia*:ti,ab,kw OR pyaemia*:ti,ab,kw OR septicemia*:ti,ab,kw OR 'blood poisoning':ti,ab,kw) AND ('newborn'/exp OR 'pediatrics'/exp OR 'child'/exp OR 'adolescent'/exp OR infant*:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw OR pediatric:ti,ab OR paediatric:ti,ab OR child:ti,ab,kw OR children:ti,ab,kw OR toddler*:ti,ab,kw OR adolescen*:ti,ab,kw OR teen*:ti,ab,kw OR youth*:ti,ab,kw OR boy:ti,ab,kw OR boys:ti,ab,kw OR girl*:ti,ab,kw OR juvenile*:ti,ab,kw) AND ('developing country'/exp OR 'low income country'/exp OR 'middle income country'/exp OR 'afghanistan'/exp OR 'albania'/exp OR 'algeria'/exp OR 'american samoa'/exp OR 'angola'/exp OR 'armenia'/exp OR 'azerbaijan'/exp OR 'bangladesh'/exp OR 'belarus'/exp OR 'belize'/exp OR 'benin'/exp OR 'bhutan'/exp OR 'bolivia'/exp OR 'bosnia and herzegovina'/exp OR 'botswana'/exp OR 'brazil'/exp OR 'bulgaria'/exp OR 'burkina faso'/exp OR 'burundi'/exp OR 'cape verde'/exp OR 'cambodia'/exp OR 'cameroon'/exp OR 'central african republic'/exp OR 'chad'/exp OR 'china'/exp OR 'colombia'/exp OR 'comoros'/exp OR 'democratic republic congo'/exp OR 'congo'/exp OR 'costa rica'/exp OR 'cote d'ivoire'/exp OR 'cuba'/exp OR 'djibouti'/exp OR 'dominica'/exp OR 'dominican republic'/exp OR 'ecuador'/exp OR 'egypt'/exp OR 'el salvador'/exp OR 'eritrea'/exp OR 'ethiopia'/exp OR 'equatorial guinea'/exp OR

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38 OR cambodia*:ti,ab,kw OR khmer:ti,ab,kw OR cameroon*:ti,ab,kw OR cameroun:ti,ab,kw OR
39 'central african republic':ti,ab,kw OR 'centrafrican republic':ti,ab,kw OR 'chad':ti,ab,kw OR
40 tchad:ti,ab,kw OR chadian:ti,ab,kw OR china:ti,ab,kw OR chinese:ti,ab,kw OR
41 colombia*:ti,ab,kw OR comoros:ti,ab,kw OR 'comoro islands':ti,ab,kw OR comorian:ti,ab,kw OR
42 'democratic republic of the congo':ti,ab,kw OR 'democratic republic congo':ti,ab,kw OR
43 congo*:ti,ab,kw OR 'costa rica':ti,ab,kw OR 'costa rican':ti,ab,kw OR 'cote d ivoire':ti,ab,kw OR
44 'ivory coast':ti,ab,kw OR ivorian:ti,ab,kw OR cuba*:ti,ab,kw OR djibouti*:ti,ab,kw OR
45 dominica*:ti,ab,kw OR 'dominican republic':ti,ab,kw OR 'french sudan':ti,ab,kw OR
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3 ecuador*:ti,ab,kw OR egypt*:ti,ab,kw OR 'united arab republic':ti,ab,kw OR 'el salvador':ti,ab,kw
4 OR salvador*:ti,ab,kw OR eritrea*:ti,ab,kw OR ethiopia*:ti,ab,kw OR 'equatorial guinea':ti,ab,kw
5 OR equatoguinean:ti,ab,kw OR fiji*:ti,ab,kw OR gabon*:ti,ab,kw OR gaboon:ti,ab,kw OR
6 gambia*:ti,ab,kw OR 'republic of georgia':ti,ab,kw OR 'georgia republic':ti,ab,kw OR 'georgia
7 ssr':ti,ab,kw OR ghana*:ti,ab,kw OR grenada:ti,ab,kw OR grenadian:ti,ab,kw OR
8 guinea*:ti,ab,kw OR 'guinea-bissau':ti,ab,kw OR 'portuguese guinea':ti,ab,kw OR 'bissau-
9 guinean':ti,ab,kw OR guatemala*:ti,ab,kw OR guyana:ti,ab,kw OR guyanese:ti,ab,kw OR
10 haiti*:ti,ab,kw OR hondura*:ti,ab,kw OR india:ti,ab,kw OR 'indian union':ti,ab,kw OR
11 indonesia*:ti,ab,kw OR 'netherlands east indies':ti,ab,kw OR 'east indies':ti,ab,kw OR 'west
12 irian':ti,ab,kw OR 'west new guinea':ti,ab,kw OR timor:ti,ab,kw OR java:ti,ab,kw OR 'irian
13 jaya':ti,ab,kw OR bali:ti,ab,kw OR sumatra:ti,ab,kw OR celebes:ti,ab,kw OR sulawesi:ti,ab,kw
14 OR 'malay archipelago':ti,ab,kw OR madoera:ti,ab,kw OR madura:ti,ab,kw OR iran*:ti,ab,kw OR
15 iraq*:ti,ab,kw OR jamaica*:ti,ab,kw OR jordan*:ti,ab,kw OR kazakhstan*:ti,ab,kw OR
16 kazakh:ti,ab,kw OR kenya*:ti,ab,kw OR kiribati*:ti,ab,kw OR 'democratic peoples republic of
17 korea':ti,ab,kw OR 'north korea':ti,ab,kw OR 'north korean':ti,ab,kw OR kosovo:ti,ab,kw OR
18 kosovar:ti,ab,kw OR kosovan:ti,ab,kw OR kyrgyzstan*:ti,ab,kw OR kirghizia:ti,ab,kw OR 'kyrgyz
19 republic':ti,ab,kw OR 'kirghiz ssr':ti,ab,kw OR kirgizstan:ti,ab,kw OR kyrgyzs:ti,ab,kw OR
20 lao*:ti,ab,kw OR laotian*:ti,ab,kw OR lebanon:ti,ab,kw OR lebanese:ti,ab,kw OR
21 lesotho*:ti,ab,kw OR basutoland:ti,ab,kw OR liberia*:ti,ab,kw OR libya*:ti,ab,kw OR
22 macedonia*:ti,ab,kw OR madagascar:ti,ab,kw OR malagasy:ti,ab,kw OR malawi*:ti,ab,kw OR
23 nyasaland:ti,ab,kw OR malaysia*:ti,ab,kw OR malaya*:ti,ab,kw OR maldives:ti,ab,kw OR
24 maldivian:ti,ab,kw OR mali:ti,ab,kw OR Malian:ti,ab,kw OR 'marshall islands':ti,ab,kw OR
25 mauritania*:ti,ab,kw OR mauretania:ti,ab,kw OR mauritius:ti,ab,kw OR mauritian:ti,ab,kw OR
26 mexico:ti,ab,kw OR mexican*:ti,ab,kw OR micronesia*:ti,ab,kw OR moldova*:ti,ab,kw OR
27 moldavia*:ti,ab,kw OR mongolia*:ti,ab,kw OR montenegro:ti,ab,kw OR montenegrin:ti,ab,kw
28 OR morocco:ti,ab,kw OR ifni:ti,ab,kw OR moroccan:ti,ab,kw OR mozambique:ti,ab,kw OR
29 'portuguese east africa':ti,ab,kw OR mocambique:ti,ab,kw OR mozambican:ti,ab,kw OR
30 myanmar:ti,ab,kw OR burma:ti,ab,kw OR myanma:ti,ab,kw OR burmese:ti,ab,kw OR
31 namibia*:ti,ab,kw OR nauru*:ti,ab,kw OR nepal*:ti,ab,kw OR nicaragua*:ti,ab,kw OR
32 niger*:ti,ab,kw OR nigeria*:ti,ab,kw OR pakistan*:ti,ab,kw OR 'papua new guinea':ti,ab,kw OR
33 'east new guinea':ti,ab,kw OR paraguay*:ti,ab,kw OR peru*:ti,ab,kw OR philippines:ti,ab,kw OR
34 phillipines:ti,ab,kw OR filipino*:ti,ab,kw OR romania*:ti,ab,kw OR rumania*:ti,ab,kw OR
35 roumania*:ti,ab,kw OR russia*:ti,ab,kw OR rwanda*:ti,ab,kw OR ruanda:ti,ab,kw OR
36 samoa*:ti,ab,kw OR 'navigator islands':ti,ab,kw OR 'sao tome principe':ti,ab,kw OR
37 santomean:ti,ab,kw OR senegal*:ti,ab,kw OR serbia*:ti,ab,kw OR 'sierra leone':ti,ab,kw OR
38 'sierra leonean':ti,ab,kw OR 'solomon islands':ti,ab,kw OR 'solomon islander':ti,ab,kw OR
39 somali*:ti,ab,kw OR 'south africa':ti,ab,kw OR 'south african':ti,ab,kw OR 'south sudan':ti,ab,kw
40 OR 'south sudanese':ti,ab,kw OR 'sri lanka':ti,ab,kw OR 'sri lankan':ti,ab,kw OR ceylon:ti,ab,kw
41 OR 'saint lucia':ti,ab,kw OR 'st. lucia':ti,ab,kw OR 'saint lucian':ti,ab,kw OR 'saint vincent':ti,ab,kw
42 OR 'st. vincent':ti,ab,kw OR grenadines:ti,ab,kw OR sudan*:ti,ab,kw OR surinam*:ti,ab,kw OR
43 swaziland:ti,ab,kw OR 'swazi':ti,ab,kw OR eswatini:ti,ab,kw OR syria*:ti,ab,kw OR
44 tajikistan*:ti,ab,kw OR tadjikistan*:ti,ab,kw OR tadhik:ti,ab,kw OR tanzania*:ti,ab,kw OR
45 tanganyika:ti,ab,kw OR thai*:ti,ab,kw OR 'timor-leste':ti,ab,kw OR 'east timor':ti,ab,kw OR
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3 togo*:ti,ab,kw OR tonga*:ti,ab,kw OR tunisia*:ti,ab,kw OR tunesia:ti,ab,kw OR turkey:ti,ab,kw
4 OR turkish:ti,ab,kw OR turkmenistan:ti,ab,kw OR turkmen*:ti,ab,kw OR tuvalu*:ti,ab,kw OR
5 uganda*:ti,ab,kw OR ukraine:ti,ab,kw OR ukrainian:ti,ab,kw OR ukraine:ti,ab,kw OR
6 uzbekistan*:ti,ab,kw OR uzbek:ti,ab,kw OR vanuatu*:ti,ab,kw OR venezuela*:ti,ab,kw OR
7 vietnam*:ti,ab,kw OR 'viet nam':ti,ab,kw OR 'west bank':ti,ab,kw OR 'gaza':ti,ab,kw OR
8 yemen*:ti,ab,kw OR zambia*:ti,ab,kw OR zimbabwe*:ti,ab,kw)
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13 PubMed

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15 ("Sepsis" [Mesh] OR sepsis[tiab] OR septic[tiab] OR pyemia*[tiab] OR pyohemia*[tiab] OR
16 pyaemia*[tiab] OR septicemia*[tiab] OR "blood poisoning"[tiab]) AND ("Infant,
17 Newborn"[Mesh] OR "Pediatrics"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR
18 infant[tiab] OR infants[tiab] OR baby[tiab] OR babies[tiab] OR newborn[tiab] OR newborns[tiab]
19 OR neonate[tiab] OR neonates[tiab] OR pediatric [tiab] OR paediatric[tiab] OR child[tiab] OR
20 children[tiab] OR toddler[tiab] OR toddlers[tiab] OR adolescent[tiab] OR adolescence[tiab] OR
21 teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR youth[tiab] OR boy[tiab] OR
22 boys[tiab] OR girl[tiab] OR girls[tiab] OR juvenile[tiab] OR juveniles[tiab]) AND ("Developing
23 Countries"[Mesh] OR "Afghanistan"[Mesh] OR "Albania"[Mesh] OR "Algeria"[Mesh] OR
24 "American Samoa"[Mesh] OR "Angola"[Mesh] OR "Armenia"[Mesh] OR "Azerbaijan"[Mesh]
25 OR "Bangladesh"[Mesh] OR "Republic of Belarus"[Mesh] OR "Belize"[Mesh] OR
26 "Benin"[Mesh] OR "Bhutan"[Mesh] OR "Bolivia"[Mesh] OR "Bosnia and Herzegovina"[Mesh]
27 OR "Botswana"[Mesh] OR "Brazil"[Mesh] OR "Bulgaria"[Mesh] OR "Burkina Faso"[Mesh] OR
28 "Burundi"[Mesh] OR "Cabo Verde"[Mesh] OR "Cambodia"[Mesh] OR "Cameroon"[Mesh] OR
29 "Central African Republic"[Mesh] OR "Chad"[Mesh] OR "China"[Mesh:NoExp] OR
30 "Colombia"[Mesh] OR "Comoros"[Mesh] OR "Democratic Republic of the Congo"[Mesh] OR
31 "Congo"[Mesh] OR "Costa Rica"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Cuba"[Mesh] OR
32 "Djibouti"[Mesh] OR "Dominica"[Mesh] OR "Dominican Republic"[Mesh] OR "Ecuador"[Mesh]
33 OR "Egypt"[Mesh] OR "El Salvador"[Mesh] OR "Eritrea"[Mesh] OR "Ethiopia"[Mesh] OR
34 "Equatorial Guinea"[Mesh] OR "Fiji"[Mesh] OR "Gabon"[Mesh] OR "Gambia"[Mesh] OR
35 "Georgia (Republic)"[Mesh] OR "Ghana"[Mesh] OR "Grenada"[Mesh] OR "Guinea"[Mesh] OR
36 "Guinea-Bissau"[Mesh] OR "Guatemala"[Mesh] OR "Guyana"[Mesh] OR "Haiti"[Mesh] OR
37 "Honduras"[Mesh] OR "India"[Mesh] OR "Indonesia"[Mesh] OR "Iran"[Mesh] OR "Iraq"[Mesh]
38 OR "Jamaica"[Mesh] OR "Jordan"[Mesh] OR "Kazakhstan"[Mesh] OR "Kenya"[Mesh] OR
39 "Democratic People's Republic of Korea"[Mesh] OR "Kosovo"[Mesh] OR "Kyrgyzstan"[Mesh]
40 OR "Laos"[Mesh] OR "Lebanon"[Mesh] OR "Lesotho"[Mesh] OR "Liberia"[Mesh] OR
41 "Libya"[Mesh] OR "Macedonia (Republic)"[Mesh] OR "Madagascar"[Mesh] OR
42 "Malawi"[Mesh] OR "Malaysia"[Mesh] OR "Mali"[Mesh] OR "Mauritania"[Mesh] OR
43 "Mauritius"[Mesh] OR "Mexico"[Mesh] OR "Micronesia"[Mesh] OR "Moldova"[Mesh] OR
44 "Mongolia"[Mesh] OR "Montenegro"[Mesh] OR "Morocco"[Mesh] OR "Mozambique"[Mesh]
45 OR "Myanmar"[Mesh] OR "Namibia"[Mesh] OR "Nepal"[Mesh] OR "Nicaragua"[Mesh] OR
46 "Niger"[Mesh] OR "Nigeria"[Mesh] OR "Pakistan"[Mesh] OR "Papua New Guinea"[Mesh] OR
47 "Paraguay"[Mesh] OR "Peru"[Mesh] OR "Philippines"[Mesh] OR "Romania"[Mesh] OR
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3 "Russia"[Mesh] OR "Rwanda"[Mesh] OR "Samoa"[Mesh] OR "Sao Tome and Principe"[Mesh]
4 OR "Senegal"[Mesh] OR "Serbia"[Mesh] OR "Sierra Leone"[Mesh] OR "Somalia"[Mesh] OR
5 "South Africa"[Mesh] OR "South Sudan"[Mesh] OR "Sri Lanka"[Mesh] OR "Saint Lucia"[Mesh]
6 OR "Saint Vincent and the Grenadines"[Mesh] OR "Sudan"[Mesh] OR "Suriname"[Mesh] OR
7 "Swaziland"[Mesh] OR "Syria"[Mesh] OR "Tajikistan"[Mesh] OR "Tanzania"[Mesh] OR
8 "Thailand"[Mesh] OR "Timor-Leste"[Mesh] OR "Togo"[Mesh] OR "Tonga"[Mesh] OR
9 "Tunisia"[Mesh] OR "Turkey"[Mesh] OR "Turkmenistan"[Mesh] OR "Uganda"[Mesh] OR
10 "Ukraine"[Mesh] OR "Uzbekistan"[Mesh] OR "Vanuatu"[Mesh] OR "Venezuela"[Mesh] OR
11 "Vietnam"[Mesh] OR "Yemen"[Mesh] OR "Zambia"[Mesh] OR "Zimbabwe"[Mesh] OR
12 “developing country” OR “developing countries” OR “developing economy” OR “under
13 developed country” OR “under developed countries” OR “third world” OR “low income country”
14 OR “low income economy” OR “low income nation” OR “lower income country” OR “lower
15 middle income country” OR “middle income country” OR “middle income economy” OR “middle
16 income nation” OR “poor country” OR “poor countries” OR “LAMI country” OR “LAMI
17 countries” OR Afghanistan[tiab] OR Afghani*[tiab] OR Albania*[tiab] OR Algeria*[tiab] OR
18 "American Samoa"[tiab] OR Samoan*[tiab] OR Angola[tiab] OR Angolan*[tiab] OR
19 Armenia*[tiab] OR Azerbaijan*[tiab] OR Bangladesh[tiab] OR Bengali*[tiab] OR Belarus*[tiab]
20 OR Byelorussian[tiab] OR Byelarus[tiab] OR Belorussia[tiab] OR Belize*[tiab] OR Benin*[tiab]
21 OR Bhutan*[tiab] OR Bolivia*[tiab] OR Bosnia*[tiab] OR Herzegovina[tiab] OR
22 Botswana*[tiab] OR Bechuanaland[tiab] OR Batswana[tiab] OR Motswana[tiab] OR Brazil*[tiab]
23 OR Bulgaria*[tiab] OR "Burkina Faso"[tiab] OR Burkinabé[tiab] OR Burundi*[tiab] OR "Cabo
24 Verde"[tiab] OR “Cape Verde”[tiab] OR “Cape Verdean”[tiab] OR Cambodia*[tiab] OR
25 Khmer[tiab] OR Cameroon*[tiab] OR Cameroun[tiab] OR "Central African Republic"[tiab] OR
26 “Centrafrican Republic”[tiab] OR "Chad"[tiab] OR Tchad [tiab] OR Chadian[tiab] OR China[tiab]
27 OR Chinese[tiab] OR Colombia*[tiab] OR Comoros[tiab] OR “Comoro Islands”[tiab] OR
28 Comorian[tiab] OR “Democratic Republic of the Congo”[tiab] OR “Democratic Republic
29 Congo”[tiab] OR Congo*[tiab] OR "Costa Rica"[tiab] OR “Costa Rican”[tiab] OR "Cote
30 d'Ivoire"[tiab] OR “Ivory Coast”[tiab] OR Ivorian[tiab] OR Cuba*[tiab] OR Djibouti*[tiab] OR
31 Dominica*[tiab] OR "Dominican Republic"[tiab] OR “French Sudan”[tiab] OR Ecuador*[tiab]
32 OR Egypt*[tiab] OR “United Arab Republic”[tiab] OR "El Salvador"[tiab] OR Salvador*[tiab]
33 OR Eritrea*[tiab] OR Ethiopia*[tiab] OR "Equatorial Guinea"[tiab] OR Equatoguinean[tiab] OR
34 Fiji*[tiab] OR Gabon*[tiab] OR Gaboon[tiab] OR Gambia*[tiab] OR “Republic of Georgia”[tiab]
35 OR “Georgia SSR”[tiab] OR Ghana*[tiab] OR Grenada[tiab] OR Grenadian[tiab] OR
36 Guinea*[tiab] OR "Guinea-Bissau"[tiab] OR “Portuguese Guinea”[tiab] OR Guatemala*[tiab] OR
37 Guyana[tiab] OR Guyanese[tiab] OR Haiti*[tiab] OR Hondura*[tiab] OR India[tiab] OR “Indian
38 Union”[tiab] OR Indonesia*[tiab] OR “Netherlands East Indies”[tiab] OR “East Indies”[tiab] OR
39 “West Irian”[tiab] OR “West New Guinea”[tiab] OR Timor[tiab] OR “Java”[tiab] OR “Irian
40 Jaya”[tiab] OR Bali[tiab] OR Sumatra[tiab] OR Celebes[tiab] OR Sulawesi[tiab] OR “Malay
41 Archipelago”[tiab] OR Madura[tiab] OR Iran*[tiab] OR Iraq*[tiab] OR Jamaica*[tiab] OR
42 Jordan*[tiab] OR Kazakhstan*[tiab] OR Kazakh[tiab] OR Kenya*[tiab] OR Kiribati*[tiab] OR
43 “Democratic People’s Republic of Korea”[tiab] OR “North Korea”[tiab] OR “North Korean”[tiab]
44 OR Kosovo[tiab] OR Kosovar[tiab] OR Kosovan[tiab] OR Kyrgyzstan*[tiab] OR Kirghizia[tiab]
45 OR “Kyrgyz Republic”[tiab] OR “Kirghiz SSR”[tiab] OR Kirgizstan[tiab] OR Kyrgyzs[tiab] OR
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Lao[tiab] OR Laos[tiab] OR Laotian*[tiab] OR Lebanon[tiab] OR Lebanese[tiab] OR
Lesotho*[tiab] OR Basutoland[tiab] OR Liberia*[tiab] OR Libya*[tiab] OR Macedonia*[tiab] OR
Madagascar[tiab] OR Malagasy[tiab] OR Malawi*[tiab] OR Nyasaland[tiab] OR Malaysia*[tiab]
OR Malaya*[tiab] OR Maldives[tiab] OR Maldivian[tiab] OR Mali[tiab] OR Malian[tiab] OR
“Marshall Islands”[tiab] OR Mauritania*[tiab] OR Mauretania[tiab] OR Mauritius[tiab] OR
Mauritian[tiab] OR Mexico[tiab] OR Mexican*[tiab] OR Micronesia*[tiab] OR Moldova*[tiab]
OR Moldavia*[tiab] OR Mongolia*[tiab] OR Montenegro[tiab] OR Montenegrin[tiab] OR
Morocco[tiab] OR Ifni[tiab] OR Moroccan[tiab] OR Mozambique[tiab] OR “Portuguese East
Africa”[tiab] OR Mocambique[tiab] OR Mozambican[tiab] OR Myanmar[tiab] OR Burma[tiab]
OR Myanma[tiab] OR Burmese[tiab] OR Namibia*[tiab] OR Nauru*[tiab] OR Nepal*[tiab] OR
Nicaragua*[tiab] OR Niger*[tiab] OR Nigeria*[tiab] OR Pakistan*[tiab] OR “Papua New
Guinea”[tiab] OR “East New Guinea” [tiab] OR Paraguay*[tiab] OR Peru*[tiab] OR
Philippines[tiab] OR Phillipines[tiab] OR Filipino*[tiab] OR Romania*[tiab] OR
Rumania*[tiab] OR Roumania*[tiab] OR Russia*[tiab] OR Rwanda*[tiab] OR Ruanda[tiab]
OR Samoa*[tiab] OR “Sao Tome”[tiab] OR Senegal*[tiab] OR Serbia*[tiab] OR “Sierra
Leone”[tiab] OR “Sierra Leonean” [tiab] OR “Solomon Islands” [tiab] OR “Solomon Islander”
[tiab] OR Somali*[tiab] OR “South Africa”[tiab] OR “South African” [tiab] OR “South
Sudan”[tiab] OR “South Sudanese” [tiab] OR “Sri Lanka”[tiab] OR “Sri Lankan” [tiab] OR
Ceylon[tiab] OR “Saint Lucia”[tiab] OR “St. Lucia”[tiab] OR “Saint Vincent”[tiab] OR “St.
Vincent”[tiab] OR Sudan* [tiab] OR Surinam*[tiab] OR Swaziland[tiab] OR “Swazi”[tiab] OR
Eswatini[tiab] OR Syria*[tiab] OR Tajikistan*[tiab] OR Tadjikistan*[tiab] OR Tadzhih[tiab]
OR Tanzania*[tiab] OR Tanganyika[tiab] OR Thai*[tiab] OR “Timor-Leste”[tiab] OR “East
Timor” [tiab] OR Togo*[tiab] OR Tonga*[tiab] OR Tunisia*[tiab] OR Tunesia[tiab] OR
Turkey[tiab] OR Turkish[tiab] OR Turkmenistan[tiab] OR Turkmen*[tiab] OR Tuvalu*[tiab]
OR Uganda*[tiab] OR Ukraine[tiab] OR Ukrainian[tiab] OR Ukraina[tiab] OR
Uzbekistan*[tiab] OR Uzbek[tiab] OR Vanuatu*[tiab] OR Venezuela*[tiab] OR Vietnam*[tiab]
OR “Viet Nam” [tiab] OR “West Bank” [tiab] OR “Gaza” [tiab] OR Yemen*[tiab] OR
Zambia*[tiab] OR Zimbabwe*[tiab])

Scopus

= 6,164 results after limiting to English, 1994-present and excluding books, book chapters, editorials, notes, and letters on 6/24/2019

TITLE-ABS-KEY (sepsis OR septic OR pyemia* OR pyohemia* OR pyaemia* OR
septicemia* OR {blood poisoning}) AND TITLE-ABS-KEY (infant OR infants OR baby
OR babies OR newborn OR newborns OR neonate OR neonates OR pediatric OR paediatric
OR child OR children OR toddler OR toddlers OR adolescent OR adolescence OR teen
OR teens OR teenager OR teenagers OR youth OR boy OR boys OR girl OR girls OR
juvenile OR juveniles) AND TITLE-ABS-KEY ({developing country} OR {developing
countries} OR {developing economy} OR {under developed country} OR {under developed
countries} OR {third world} OR {low income country} OR {low income economy} OR {low
income nation} OR {lower income country} OR {lower middle income country} OR {middle
income country} OR {middle income economy} OR {middle income nation} OR {poor

country} OR {poor countries} OR {LAMI country} OR {LAMI countries} OR afghanistan
OR afghani* OR albania* OR algeria* OR {American Samoa} OR samoan* OR angola
OR angolan* OR armenia* OR azerbaijan* OR bangladesh OR bengali* OR belarus* OR
byelorussian OR byelarus OR belorussia OR belize* OR benin* OR bhutan* OR bolivia*
OR bosnia* OR herzegovina OR botswana* OR bechuanaland OR batswana OR motswana
OR brazil* OR bulgaria* OR "Burkina Faso" OR burkinabé OR burundi* OR "Cabo Verde"
OR "Cape Verde" OR "Cape Verdean" OR cambodia* OR khmer OR cameroon* OR
cameroun OR "Central African Republic" OR "Centrafrican Republic" OR "Chad" OR tchad
OR chadian OR china OR chinese OR colombia* OR comoros OR "Comoro Islands" OR
comorian OR "Democratic Republic of the Congo" OR "Democratic Republic Congo" OR
congo* OR "Costa Rica" OR "Costa Rican" OR "Cote d'Ivoire" OR "Ivory Coast" OR ivorian
OR cuba* OR djibouti* OR dominica* OR "Dominican Republic" OR "French Sudan" OR
ecuador* OR egypt* OR "United Arab Republic" OR "El Salvador" OR salvador* OR
eritrea* OR ethiopia* OR "Equatorial Guinea" OR equatoguinean OR fiji* OR gabon* OR
gaboon OR gambia* OR "Republic of Georgia" OR "Georgia SSR" OR ghana* OR grenada
OR grenadian OR guinea* OR "Guinea-Bissau" OR "Portuguese Guinea" OR guatemala*
OR guyana OR guyanese OR haiti* OR hondura* OR india OR "Indian Union" OR
indonesia* OR "Netherlands East Indies" OR "East Indies" OR "West Irian" OR "West New
Guinea" OR timor OR "Java" OR "Irian Jaya" OR bali OR sumatra OR celebes OR
sulawesi OR "Malay Archipelago" OR madura OR iran* OR iraq* OR jamaica* OR jordan*
OR kazakhstan* OR kazakh OR kenya* OR kiribati* OR "Democratic People's Republic of
Korea" OR "North Korea" OR "North Korean" OR kosovo OR kosovar OR kosovan OR
kyrgyzstan* OR kirghizia OR "Kyrgyz Republic" OR "Kirghiz SSR" OR kirgizstan OR
kyrgyzs OR lao OR laos OR laotian* OR lebanon OR lebanese OR lesotho* OR basutoland
OR liberia* OR libya* OR macedonia* OR madagascar OR malagasy OR malawi* OR
nyasaland OR malaysia* OR malaya* OR maldives OR maldivian OR mali OR malian
OR "Marshall Islands" OR mauritania* OR mauretania OR mauritius OR mauritian OR
mexico OR mexican* OR micronesia* OR moldova* OR moldavia* OR mongolia* OR
montenegro OR montenegrin OR morocco OR ifni OR moroccan OR mozambique OR
"Portuguese East Africa" OR mocambique OR mozambican OR myanmar OR burma OR
myanma OR burmese OR namibia* OR nauru* OR nepal* OR nicaragua* OR niger* OR
nigeria* OR pakistan* OR "Papua New Guinea" OR "East New Guinea" OR paraguay* OR
peru* OR philippines OR philippines OR filipino* OR romania* OR rumania* OR
roumania* OR russia* OR rwanda* OR ruanda OR samoa* OR "Sao Tome" OR senegal*
OR serbia* OR "Sierra Leone" OR "Sierra Leonean" OR "Solomon Islands" OR "Solomon
Islander" OR somali* OR "South Africa" OR "South African" OR "South Sudan" OR "South
Sudanese" OR "Sri Lanka" OR "Sri Lankan" OR ceylon OR "Saint Lucia" OR "St. Lucia"
OR "Saint Vincent" OR "St. Vincent" OR sudan* OR surinam* OR swaziland OR "Swazi"
OR eswatini OR syria* OR tajikistan* OR tadjikistan* OR tadjik OR tanzania* OR
tanganyika OR thai* OR "Timor-Leste" OR "East Timor" OR togo* OR tonga* OR tunisia*
OR tunesia OR turkey OR turkish OR turkmenistan OR turkmen* OR tuvalu* OR uganda*
OR ukraine OR ukrainian OR ukraine OR uzbekistan* OR uzbek OR vanuatu* OR
venezuela* OR vietnam* OR "Viet Nam" OR "West Bank" OR "Gaza" OR yemen* OR

zambia* OR zimbabwe*) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000) OR LIMIT-TO (PUBYEAR , 1999) OR LIMIT-TO (PUBYEAR , 1998) OR LIMIT-TO (PUBYEAR , 1997) OR LIMIT-TO (PUBYEAR , 1996) OR LIMIT-TO (PUBYEAR , 1995) OR LIMIT-TO (PUBYEAR , 1994)) AND (EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "bk"))

Cochrane Library

#1: MeSH descriptor: [Sepsis] explode all trees

#2: sepsis OR septic OR pyemia* OR pyohemia* OR pyaemia* OR septicemia* OR “blood poisoning”

#3: #1 OR #2

#4: MeSH descriptor: [Infant, Newborn] explode all trees

#5: MeSH descriptor: [Pediatrics] explode all trees

#6: MeSH descriptor: [Child] explode all trees

#7: MeSH descriptor: [Adolescent] explode all trees

#8: infant OR infants OR baby OR babies OR newborn OR newborns OR neonate OR neonates OR pediatric OR paediatric OR child OR children OR toddler OR toddlers OR adolescent OR adolescence OR teen OR teens OR teenager OR teenagers OR youth OR boy OR boys OR girl OR girls OR juvenile OR juveniles

#9: #4 OR #5 OR #6 OR #7 OR #8

#10: MeSH descriptor: [Developing Countries] explode all trees

#11: (“developing country” OR “developing countries” OR “developing economy” OR “under developed country” OR “under developed countries” OR “third world” OR “low income country” OR “low income economy” OR “low income nation” OR “lower income country” OR “lower middle income country” OR “middle income country” OR “middle income economy” OR “middle income nation” OR “poor country” OR “poor countries” OR “LAMI country” OR “LAMI countries” OR Afghanistan OR Afghani* OR Albania* OR Algeria* OR "American Samoa" OR

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 3 Samoa* OR Angola OR Angolan* OR Armenia* OR Azerbaijan* OR Bangladesh OR Bengali*
 4 OR Belarus* OR Byelorussian OR Byelarus OR Belorussia OR Belize* OR Benin* OR Bhutan*
 5 OR Bolivia* OR Bosnia* OR Herzegovina OR Botswana* OR Bechuanaland OR Batswana OR
 6 Motswana OR Brazil* OR Bulgaria* OR "Burkina Faso" OR Burkinabé OR Burundi* OR "Cabo
 7 Verde" OR "Cape Verde" OR "Cape Verdean" OR Cambodia* OR Khmer OR Cameroon* OR
 8 Cameroun OR "Central African Republic" OR "Centrafrican Republic" OR "Chad" OR Tchad
 9 OR Chadian OR China OR Chinese OR Colombia* OR Comoros OR "Comoro Islands" OR
 10 Comorian OR "Democratic Republic of the Congo" OR "Democratic Republic Congo" OR
 11 Congo* OR "Costa Rica" OR "Costa Rican" OR "Cote d Ivoire" OR "Ivory Coast" OR Ivorian
 12 OR Cuba* OR Djibouti* OR Dominica* OR "Dominican Republic" OR "French Sudan" OR
 13 Ecuador* OR Egypt* OR "United Arab Republic" OR "El Salvador" OR Salvador* OR Eritrea*
 14 OR Ethiopia* OR "Equatorial Guinea" OR Equatoguinean OR Fiji* OR Gabon* OR Gaboon OR
 15 Gambia* OR "Republic of Georgia" OR "Georgia SSR" OR Ghana* OR Grenada OR Grenadian
 16 OR Guinea* OR "Guinea-Bissau" OR "Portuguese Guinea" OR Guatemala* OR Guyana OR
 17 Guyanese OR Haiti* OR Hondura* OR India OR "Indian Union" OR Indonesia* OR "Netherlands
 18 East Indies" OR "East Indies" OR "West Irian" OR "West New Guinea" OR Timor OR "Java"
 19 OR "Irian Jaya" OR Bali OR Sumatra OR Celebes OR Sulawesi OR "Malay Archipelago" OR
 20 Madura OR Iran* OR Iraq* OR Jamaica* OR Jordan* OR Kazakhstan* OR Kazakh OR Kenya*
 21 OR Kiribati* OR "Democratic People's Republic of Korea" OR "North Korea" OR "North
 22 Korean" OR Kosovo OR Kosovar OR Kosovan OR Kyrgyzstan* OR Kirghizia OR "Kyrgyz
 23 Republic" OR "Kirghiz SSR" OR Kirgizstan OR Kyrgyzs OR Lao OR Laos OR Laotian* OR
 24 Lebanon OR Lebanese OR Lesotho* OR Basutoland OR Liberia* OR Libya* OR Macedonia*
 25 OR Madagascar OR Malagasy OR Malawi* OR Nyasaland OR Malaysia* OR Malaya* OR
 26 Maldives OR Maldivian OR Mali OR Malian OR "Marshall Islands" OR Mauritania* OR
 27 Mauretania OR Mauritius OR Mauritian OR Mexico OR Mexican* OR Micronesia* OR
 28 Moldova* OR Moldavia* OR Mongolia* OR Montenegro OR Montenegrin OR Morocco OR Ifni
 29 OR Moroccan OR Mozambique OR "Portuguese East Africa" OR Mocambique OR Mozambican
 30 OR Myanmar OR Burma OR Myanma OR Burmese OR Namibia* OR Nauru* OR Nepal* OR
 31 Nicaragua* OR Niger* OR Nigeria* OR Pakistan* OR "Papua New Guinea" OR "East New
 32 Guinea" OR Paraguay* OR Peru* OR Philippines OR Phillipines OR Filipino* OR Romania*
 33 OR Rumania* OR Roumania* OR Russia* OR Rwanda* OR Ruanda OR Samoa* OR "Sao
 34 Tome" OR Senegal* OR Serbia* OR "Sierra Leone" OR "Sierra Leonean" OR "Solomon
 35 Islands" OR "Solomon Islander" OR Somali* OR "South Africa" OR "South African" OR
 36 "South Sudan" OR "South Sudanese" OR "Sri Lanka" OR "Sri Lankan" OR Ceylon OR "Saint
 37 Lucia" OR "Saint Vincent" OR Sudan* OR Surinam* OR Swaziland OR Swazi OR Eswatini
 38 OR Syria* OR Tajikistan* OR Tadjikistan* OR Tadzihik OR Tanzania* OR Tanganyika OR
 39 Thai* OR "Timor Leste" OR "East Timor" OR Togo* OR Tonga* OR Tunisia* OR Tunesia
 40 OR Turkey OR Turkish OR Turkmenistan OR Turkmen* OR Tuvalu* OR Uganda* OR Ukraine
 41 OR Ukrainian OR Ukraina OR Uzbekistan* OR Uzbek OR Vanuatu* OR Venezuela* OR
 42 Vietnam* OR "Viet Nam" OR "West Bank" OR "Gaza" OR Yemen* OR Zambia* OR
 43 Zimbabwe*)
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For peer review only

Supplementary file 1

PRISMA-P Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1 title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>	<input type="checkbox"/>	Page 2 Methods and analysis
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1 Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5 Manuscript contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No funding
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2 Introduction

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 Methods
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 Methods
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2 Methods
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Supplemental file 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – Types of studies, participants, and interventions
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – Assessment of methodological quality
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable – qualitative systematic review

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable – qualitative systematic review
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable, systematic review only
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page xx – Assessment of Methodologic Quality

BMJ Open

Study protocol for a core outcome set in paediatric sepsis in low and middle-income countries

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034960.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Feb-2020
Complete List of Authors:	Wooldridge, Gavin; BC Children's Hospital, Pediatric Critical Care Murthy, Srinivas; University of British Columbia, Paediatrics Kisson, Niranjana; University of British Columbia, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Global health, Intensive care, Infectious diseases
Keywords:	Paediatric infectious disease & immunisation < PAEDIATRICALS, Community child health < PAEDIATRICALS, Paediatric intensive & critical care < ANAESTHETICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE

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Study protocol for a core outcome set in paediatric sepsis in low and middle-income countries

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ABSTRACT

Introduction

Sepsis is the leading cause of death in children worldwide and has recently been declared a major global health issue. New interventions and a concerted effort to enhance our understanding of sepsis are required to address the huge burden of disease, especially in low and middle-income countries (LMIC) where it is highest. An opportunity therefore exists to ensure that ongoing research in this area is relevant to all stakeholders and is of consistently high quality. One method to address these issues is through the development of a core outcome set (COS).

Methods and analysis

This study protocol outlines the phases in the development of a core outcome set for paediatric sepsis in LMIC. The first step involves performing a systematic review of all outcomes reported in the research of paediatric sepsis in low middle-income countries. A three-stage international Delphi process will then invite a broad range of participants to score each generated outcome for inclusion into the COS. This will include an initial two step online survey and finally, a face to face consensus meeting where each outcome will be reviewed, voted on and ratified for inclusion into the COS.

Ethics and dissemination

No core outcome sets exist for clinical trials in paediatric sepsis. This COS will serve to not only highlight the heavy burden of paediatric sepsis in this setting and aid collaboration and participation between all stakeholders, but to promote ongoing essential high quality and relevant research into the topic. A COS in paediatric sepsis in LMIC will advocate for a common language and facilitate interpretation of findings from a variety of settings. A waiver for ethics approval has been granted by UBC Children's and Women's Research Ethics Board.

Article Summary

Strengths and limitations of this study

- With the continued high burden of disease in low and middle-income countries, a core outcome set (COS) for use in paediatric sepsis research in a resource-limited setting is required to focus efforts and improve research consistency, relevance and quality in this area.
- The protocol uses a well-established process involving a thorough systematic review and an all-encompassing 3 step Delphi survey involving clinicians, researchers, nurses, patients and parents/guardians
- The feasibility of an e-survey is limited in regions with poor internet access, so the use of a local facilitator will ensure patients and the parent/guardian have equal input into the COS development.

Keywords: Paediatric sepsis, core outcome sets, low-middle income countries

INTRODUCTION

Sepsis is the leading cause of death in children, with the highest-burden in those countries least resourced to address it. Now recognised as a major global health issue, in 2017 the WHO adopted a resolution with the aim of reducing the human and economic burden of sepsis (1). Severe paediatric sepsis has a worldwide prevalence of 8% (2) and a mortality of 9 -20% (3). Severe sepsis and septic shock has a mortality of 20 - 40% within developing countries (4)(5). It is thought to be the final common pathway to multi-organ failure and death from a number of infectious diseases (6), including the top four causes of childhood mortality as reported by the WHO.

With the high prevalence of disease, new interventions and treatments are essential, as is a concerted effort to better understand the genesis of sepsis. Analysis and comparison of trials involving paediatric sepsis in low and middle-income countries (LMIC) are problematic however due to the significant heterogeneity and inconsistency in reporting outcomes (7, 8). A systematic review into primary outcome measures in paediatric septic shock trials demonstrated that the use of mortality alone had significant limitations and suggested more long term outcomes should be explored (4). A standardised way to evaluate trial outcomes is therefore imperative.

One method that is being increasingly used to address these issues is a minimum core outcome set (COS) (7). These are defined as a minimum set of outcomes that should be consistently measured and reported in clinical trials for a specific clinical area (7). All stakeholders have a role in developing the COS. The use of COS not only aims to improve consistency across trials allowing accurate comparison, including potential meta-analysis, but to limit selective reporting (9, 10) and improve the quality and relevance of clinical research (11).

A number of sepsis COS in sepsis have been developed (<http://www.comet-initiative.org/studies/details/1317?result=true>), including one ongoing in Paediatric Critical Care Medicine research (<http://www.comet-initiative.org/studies/details/1131?result=true>). No core outcome set currently exists for paediatric sepsis however, and very few are region specific. Limited funding and resources, a high sepsis burden of varying infectious aetiologies and a large proportion of children with significant comorbidities determine the differences in outcomes seen in LMICs. These factors are in contrast to HICs and hence necessitate a region-specific COS to better understand these disparities and craft context-specific solutions. As an example total annual expenditure on health in many parts of sub-Saharan Africa is under US \$25 per capita and often less than 3% of the GDP (12) and the number of ICU beds as a percentage of hospital beds is approximately 1.5% in LMIC compared to 2.5 to 9% in HIC (13). Recognising the huge discrepancy in resources between regions is essential as is the potential financial impact. In 2018, 11.7% of the world's population spent over 10% of their annual income on healthcare, leaving an estimated 100 million people impoverished by out of pocket spending. (14) A region-specific COS will ensure relevance and meaning to patients and clinicians alike. By advocating a common language between stakeholders, interpretation of findings from a variety of diverse settings will become simpler and attention can focus on research into the essential outcomes. Potential barriers to development and dissemination of a COS in this setting may be hindered by a lack of access to research capabilities and limited implementation feasibility.

AIMS AND OBJECTIVES

This study aims to develop a COS for use in clinical trials involving paediatric sepsis in LMICs. The specific study objectives are to identify outcomes previously reported in trials of paediatric sepsis in LMIC and to prioritise these outcomes using clinicians, researchers, patients and parents.

The protocol outlines our methods used to establish a COS and aims to raise awareness of paediatric sepsis in LMIC and aid collaboration and participation between all stakeholders. The protocol has been developed using the COS-STAD guidance for developing core outcome sets (15, supplementary file 1) and the COS-

1
2
3 STAP guidance for a protocol for a core outcome set development study (16, supplementary file 2). A
4 stepwise approach to COS development will be undertaken as suggested by The Core Outcome Measures
5 in Effectiveness Trials (COMET) Initiative and the Outcome Measures in Rheumatology (OMERACT)
6 Initiative (17).
7

8 METHODS AND ANALYSIS

9 Our COS development plan has been registered with the COMET initiative ([http://www.comet-](http://www.comet-initiative.org/studies/details/1400?result=true)
10 [initiative.org/studies/details/1400?result=true](http://www.comet-initiative.org/studies/details/1400?result=true)). As per published recommendations (18) and previous core
11 outcome sets (11, 19 – 21), a multi-step process will be utilised to develop an international consensus for
12 paediatric sepsis in low and middle-income countries COS (figure 1):
13

- 14 1. Systematic review of outcomes currently reported in the research of paediatric sepsis in low
15 and middle-income countries.
- 16 2. Three round Delphi process:
 - 17 a. 2 round e-Delphi survey to prioritise outcomes
 - 18 b. Consensus meeting of global experts, clinicians, parent/guardian, patients and nurses and
19 e-survey participants to ratify COS
20
21

22 When complete, the Core Outcome Set Standards for Reporting (COS-STAR) (22) will be applied.
23

24 Scope of core outcome set

25 This COS will be purely focused on clinical outcomes in paediatric sepsis clinical trials in LMIC, and not
26 involve those outcomes that are specific to premature infants or certain conditions, such as meningococcal
27 septicaemia.
28

29 Identification of existing knowledge

30 One prior systematic review in 2017 evaluated all paediatric randomised controlled trials of patients with
31 septic shock. This however included high-income countries and was intensive care specific. Neonates
32 were excluded. Mortality was the most frequent primary outcome whilst long term patient-centred
33 outcomes were rarely used (4).
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35

36 **1. Systematic review**

37 A systematic review will be performed to identify both morbidity and mortality outcomes reported in
38 existing studies involving paediatric sepsis in low and middle-income countries.
39
40

41 Types of studies, participants and interventions

42 All forms of published studies will be included. Subjects will children under the age of 18 with sepsis.
43 Those involving a high proportion (>50%) of premature patients will be excluded. Studies undertaken in a
44 low and middle-income country, as defined by the World Bank (23) , and those describing a clinical
45 outcome that is measured systematically across the population studied will be included. All interventions
46 related to paediatric sepsis in this setting will be applicable. Sepsis, severe sepsis or septic shock will be
47 defined by either the International Consensus Conference on Pediatric Sepsis Definitions, American
48 College of Chest Physicians/ Society of Critical Care Medicine consensus criteria, sepsis-relevant
49 International Classification of Diseases (ICD)-9/ICD-10 codes), Integrated Management of Childhood
50 Illness or clearly self- defined (e.g. positive blood culture with one or more symptoms). Only articles in
51 English from 1st January 1994 to 1st September 2019 will be assessed.
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54 Search methods for identification of studies and study eligibility

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3 The search strategy will be applied to PubMed, Embase, Scopus, Cochrane Central Register of Controlled
4 Trials and the World Health Organisation International Clinical Trials Platform (ICTRP). One review
5 author (GW) will independently screen the abstracts returned from the search strategy and any studies not
6 meeting inclusion criteria will be excluded. Assessment of methodological quality will not be undertaken
7 as we are evaluating outcomes only. The electronic search strategy was developed as per the Preferred
8 Reporting Items for Systematic Reviews and Meta-Analyses guidelines (24). Details are outlined in
9 supplemental files 3 and 4.
10
11

12 Data extraction, analysis and presentation

13 One review author (GW) will perform data extraction using a standardised form. A second reviewer (SM)
14 will provide validation in cases of doubt. The following data will be retrieved: author details, year and
15 journal of publication, sepsis definition, reported outcomes and outcome definition(s). The data will be
16 synthesised and presented in a descriptive table. The outcomes will then be condensed into a list and placed
17 into broader outcome categories, including efficacy, safety, mortality, morbidity, cost effectiveness and
18 quality of life. Each of these categories will be further stratified depending upon the frequency of outcomes.
19 Care will be taken to avoid ambiguity in the language used in the list of outcomes.
20

21 A list of authors will be compiled and invited to participate.
22
23

24 Records will be managed in EndNote X9 reference software (Clarivate Analytics, Boston, MA).
25

26 **2. Delphi process**

27 A two-round international e-Delphi survey involving an electronic-based questionnaire populated by
28 outcomes from the literature review will then be performed to rank the outcomes.
29

30 Selection of panel members

31 A minimum of 50 participants for the Delphi panel will be involved. Nurses, clinicians and researchers will
32 be recruited from around the world, with an aim to have all from low and middle-income countries. This
33 will ensure a direct relevance to the population of children in most need, and give a voice to those rarely
34 heard, a need previously identified in COS development (25). These participants will be identified from
35 prior research papers on paediatric sepsis in LMIC, current involvement in ongoing studies and previous
36 collaborations with members of the research team. The planned start date for the initial online survey is
37 January 5th 2020. The second round will occur 6 weeks after participants after completed round one, and
38 therefore occur in March 2020. The survey and list of outcomes will be translated into French and Spanish.
39
40

41 Delphi Round 1

42 Participants will initially be asked to complete brief questions related to their profession and experience. A
43 list of outcomes generated from the systematic review will then be presented, and the participants required
44 to rank each one on a scale from 1 to 9 (26). A score of 1 -3 indicates an unimportant outcome that should
45 not be included, scores of 4 – 6 demonstrate an important but not critical outcome and scores of 7 - 9 imply
46 an outcome that is essential to inclusion (19, 21, 22). A survey reminder will be sent out after 7 days and
47 then again after 2 weeks. All outcomes will be carried on to the second round. There will be a free-text
48 option for participants to suggest additional outcomes.
49
50

51 Patient and Public Involvement

52 At this point, approximately ten patients and their parents or guardian will be identified by clinicians known
53 to team members and approached after discharge. The questionnaire will be paper-based, and outcome
54 measures simplified into broad domains for the patients to score with the use of a local facilitator, due to
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3 the limited access to internet, possible illiteracy and non-English speaking. The patient survey will generate
4 the relevant domains of key interest, and be incorporated into round 2 of the Delphi. The specific granular
5 outcomes will be defined by the formal Delphi.
6

7 Delphi Round 2

8 In the second phase of the electronic questionnaire, the first round scores for each outcome and number of
9 prior respondents will be fed back to the participants. With this knowledge, each outcome will be rescored
10 as described previously in Delphi round one.
11

12 Once again, a survey reminder will be sent out after 7 days and then again after 2 weeks.
13

14 Analysis of Outcomes

15 Descriptive statistics will be used to analyse the responses from both round one and two, including
16 quantitative (absolute values, percentages) and qualitatively (suggestions given by participants) measures.
17 The denominator will reflect only those outcomes scored. Free text answers will be reviewed by the
18 authorship team to evaluate for uncaptured outcomes in the first-round questionnaire and added if deemed
19 appropriate to the second Delphi round questionnaire.
20

21 Our definition of consensus will follow that of previous COS publications (18). Analysis of the second
22 round outcomes for which $\geq 70\%$ of panellists scored it 7–9 and fewer than 15% of panellists scored it 1–3
23 will have met criteria for inclusion in the consensus meeting discussion. Outcomes for which $\geq 70\%$ of
24 panellists scored it 1–3, and fewer than 15% of panellists scored it 7–9 will be defined to have met consensus
25 for exclusion. (18). Those outcomes not meeting criteria will be defined as lack of consensus.
26
27

28 **3. Consensus Meeting**

29 A face-to-face consensus meeting will be held after completion of the e-Delphi survey to finalise the
30 outcomes for inclusion in the COS. Invites will be sent to those that have completed both rounds of the
31 Delphi survey. All stakeholder groups will be represented, including local patients, parents, nurses and
32 clinicians. The exact final meeting format will depend upon the location and the number of participants
33 able to attend, but most likely occur in June 2020. The outcomes from round two of the e-Delphi survey
34 will be presented and discussed. Participants will then anonymously vote for each outcome for inclusion
35 and exclusion in the finalised COS using a format similar to that of the Delphi survey. Consensus for
36 inclusion will be as before: if $\geq 70\%$ of panellists vote in favour and fewer than 15% of panellists vote
37 against. At this time, we will also enquire of the participants as to the practicality, feasibility and cost-
38 effectiveness of the finalised core outcome set and the ease as to which it could be implemented. A formal
39 feasibility matrix will be incorporated to inform this process so as to ensure that feasibility is assessed in a
40 standardized way. Those outcomes that are deemed feasible by $\geq 70\%$ of panellists, will meet consensus for
41 inclusion into the COS.
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45 **Ethics and dissemination**

46 All participants involved will be asked for their consent before undertaking the Delphi survey, and all
47 procedures will be conducted according to the Declaration of Helsinki. Involvement in the survey will be
48 completely voluntary and the responses anonymised. A waiver for ethics approval has been granted by the
49 UBC Children's and Women's Research Ethics Board.
50

51 Implementation, dissemination and updating the COS

52 Upon completion of the consensus meeting, we will draft a COS guideline including an explanation of our
53 methods using the COS-STAR template (22). It will be submitted to a high impact journal and presented at
54 international meetings. We will seek endorsement and dissemination by major international societies and
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3 journals with an interest in paediatric sepsis and hope that it can be used as a standard in LMICs data sets
4 for paediatric sepsis.

5 The next step will be to determine how best to measure the core outcomes using the COSMIN-Comet (27)
6 guidance. Those attending the consensus meeting and prior Delphi participants will be invited to form a
7 group to develop this further.
8

9 Discussion

10 At present, no core outcome sets exist for clinical trials in paediatric sepsis. Outcomes from HICs cannot
11 be reliably extrapolated to LMICs (28). This region-specific COS aims to reduce heterogeneity that
12 currently exists in this area, limit reporting bias and improve the quality and relevance of outcomes
13 published. It will also hopefully serve to highlight the heavy burden of paediatric sepsis in this setting and
14 aid collaboration and participation between all stakeholders, encouraging ongoing essential high-quality
15 research into the topic and facilitate further understanding of this complex disease.
16
17

18 Author Contributions

19 GW and SM were involved in study conception. GW, SM AND NK were involved in manuscript drafting
20 and editing.
21

22 Patient and Public Involvement

23 Patients will be approached during the second round of the Delphi Survey.
24

25 Funding Statement

26 This research received no specific grant from any funding agency in the public, commercial or not for profit
27 sectors.
28

29 Competing interests

30 All have no conflicts of interest to declare
31

32 Word Count 2930 (excluding references)

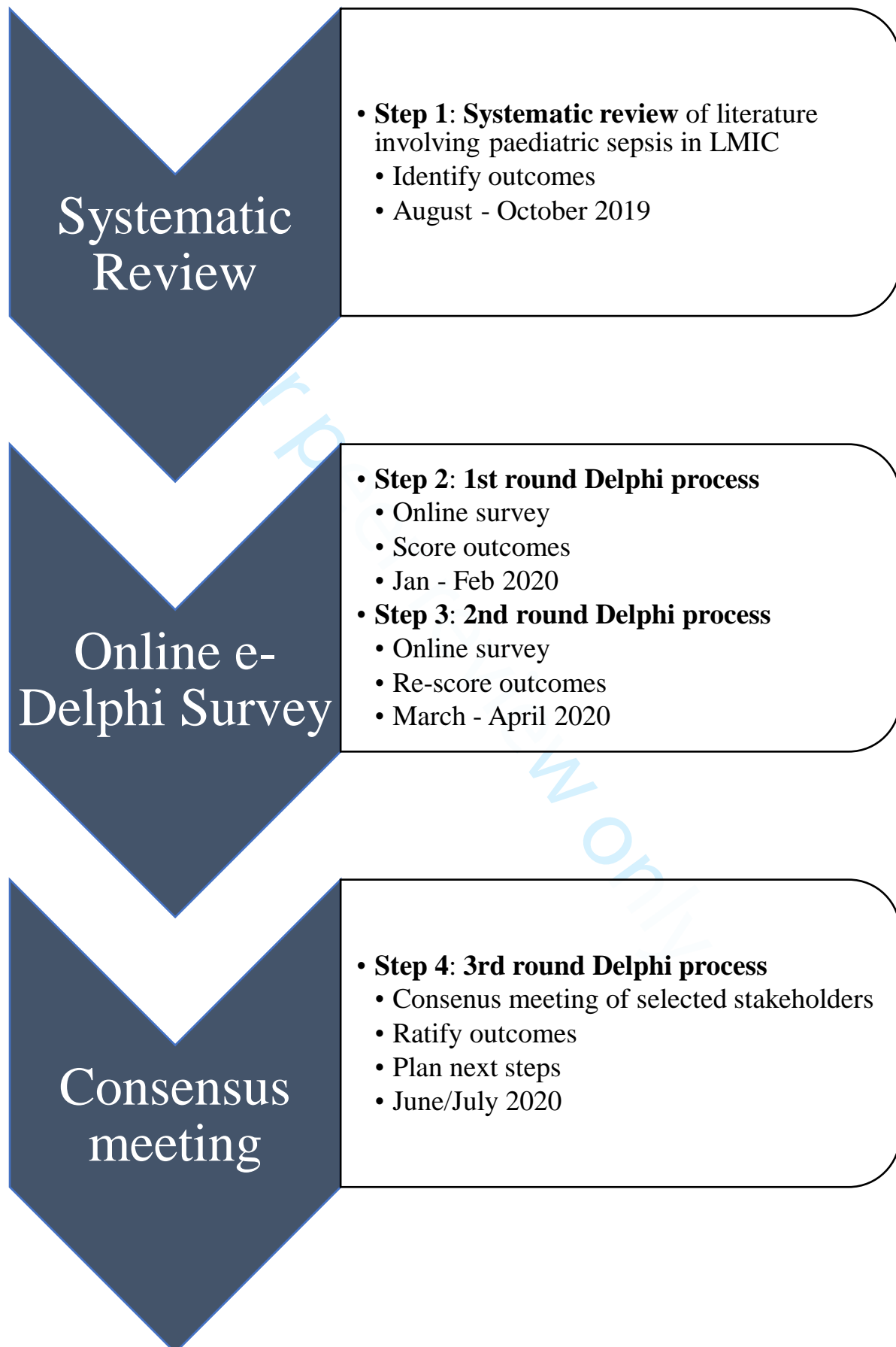
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Figure 1: Timeline of COS Development



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Core Outcome Set-STAndards for Development: COS-STAD recommendations (15)

DOMAIN	STANDARD NUMBER	METHODOLOGY	PAGE AND SECTION REPORTED
Scope specification	1	The research or practice setting(s) in which the COS is to be applied	Page 3. Scope of COS
	2	The health condition(s) covered by the COS	Page 3. Scope of COS
	3	The population(s) covered by the CO	Page 3. Scope of COS
	4	The intervention(s) covered by the COS	Page 3. Type of studies, participants and interventions
Stakeholders involved	5	Those who will use the COS in research	Page 4. Selection of panel members
	6	Healthcare professionals with experience of patients with the condition	Page 4. Selection of panel members
	7	Patients with the condition or their representatives	Page 4. Selection of panel members
Consensus process	8	The initial list of outcomes considered both healthcare professionals' and patients' views	Page 4. Delphi process
	9	A scoring process and consensus definition were described a priori.	Page 4. Delphi process
	10	Criteria for including/dropping/adding outcomes were described a priori	Page 4. Delphi process
	11	Care was taken to avoid ambiguity of language used in the list of outcomes.	Page 4. Delphi process

Cos – Core outcome set

Core Outcome Set-STANDARDISED Protocol Items: COS-STAP Statement (16)

TITLE/ABSTRACT			PAGE AND SECTION REPORTED
Title	1a.	Identify in the title that the paper describes the protocol for the planned development of a COS	Page 1. Title
Abstract	1b.	Provide a structured abstract	Page 1. Abstract
INTRODUCTION			
Background and objectives	2a.	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation	Page 2. Background
Scope	2b.	Describe the specific objectives with reference to developing a COS	Page 2. Objectives
	3a.	Describe the health condition(s) and population(s) that will be covered by the COS	Page 2. Objectives
	3b.	Describe the intervention(s) that will be covered by the COS	Page 2. Objectives
	3c.	Describe the context of use for which the COS is applied	Page 2. Objectives
METHODS			
Stakeholders	4.	Describe the stakeholder groups to be involved in the COS development process, the nature and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study.	Page 4. Delphi process
Information sources	5a.	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers.	Page 3. Systematic Review
	5b.	Describe how outcomes may be dropped/combined with reasons	Page 4. Delphi process
Consensus process	6.	Describe the plans for how the consensus process will be undertaken	Page 4. Delphi process
Consensus definition	7a.	Describe the consensus definition	Page 4. Delphi process
	7b.	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process.	Page 4. Delphi process
ANALYSIS			
Outcome scoring/feedback	8.	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	Page 4. Delphi process
Missing data	9.	Describe how missing data will be handled during the consensus process	Page 4. Delphi process
ETHICS and DISSEMINATION			
Ethics approval/ informed consent	10.	Describe any plans for obtaining research ethics committee/ institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant).	Page 5. Ethics and dissemination
Dissemination	11.	Describe any plans to communicate the results of study participants and COS users, inclusive of methods and timing of dissemination	Page 5. Implementation, dissemination and updating the COS
ADMINISTRATIVE INFORMATION			
Funders	12.	Describe sources of funding, role of funders	Page 6. Funding Statement
Conflicts of interest	13.	Describe any potential conflicts of interest within the study team and how they will be managed.	Page 6. Competing interests

COS – Core outcome set

Supplemental File 3

Systematic Review Search Strategies

Criteria

- Inclusion:
 - Articles published in English
 - Peer Reviewed articles
 - Focus on paediatric patients with sepsis (those under 18 years of age)
 - Sepsis, severe sepsis or septic shock as defined by international consensus (International Consensus Conference on Pediatric Sepsis Definitions, American College of Chest Physicians/ Society of Critical Care Medicine consensus criteria, sepsis-relevant International Classification of Diseases (ICD)-9/ICD-10 codes), by IMCI and self-defined (e.g. positive blood culture with one or more symptoms)
 - Involve research in low - middle income countries
 - Describe a clinical outcome that is measured systematically across the population studied
 - Years : 1994 to 2019
- Exclusion
 - Adult studies (>18 yrs.)
 - Preterm Sepsis
 - Those performed in high resource countries (as defined by the World Bank)
 - No outcome data
 - Articles which are not peer reviewed
 - Duplicate references
 - Studies missing methods of data collection and eligibility criteria
 - Studies involving sepsis in specific subgroup population
 - Retrospective bacteremia

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('sepsis'/exp OR sepsis:ti,ab,kw OR septic:ti,ab,kw OR pyemia*:ti,ab,kw OR pyohemia*:ti,ab,kw OR pyaemia*:ti,ab,kw OR septicemia*:ti,ab,kw OR 'blood poisoning':ti,ab,kw) AND ('newborn'/exp OR 'pediatrics'/exp OR 'child'/exp OR 'adolescent'/exp OR infant*:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw OR pediatric:ti,ab OR paediatric:ti,ab OR child:ti,ab,kw OR children:ti,ab,kw OR toddler*:ti,ab,kw OR adolescen*:ti,ab,kw OR teen*:ti,ab,kw OR youth*:ti,ab,kw OR boy:ti,ab,kw OR boys:ti,ab,kw OR girl*:ti,ab,kw OR juvenile*:ti,ab,kw) AND ('developing country'/exp OR 'low income country'/exp OR 'middle income country'/exp OR 'afghanistan'/exp OR 'albania'/exp OR 'algeria'/exp OR 'american samoa'/exp OR 'angola'/exp OR 'armenia'/exp OR 'azerbaijan'/exp OR 'bangladesh'/exp OR 'belarus'/exp OR 'belize'/exp OR 'benin'/exp OR 'bhutan'/exp OR 'bolivia'/exp OR 'bosnia and herzegovina'/exp OR 'botswana'/exp OR 'brazil'/exp OR 'bulgaria'/exp OR 'burkina faso'/exp OR 'burundi'/exp OR 'cape verde'/exp OR 'cambodia'/exp OR 'cameroon'/exp OR 'central african republic'/exp OR 'chad'/exp OR 'china'/exp OR 'colombia'/exp OR 'comoros'/exp OR 'democratic republic congo'/exp OR 'congo'/exp OR 'costa rica'/exp OR 'cote d'ivoire'/exp OR 'cuba'/exp OR 'djibouti'/exp OR 'dominica'/exp OR 'dominican republic'/exp OR 'ecuador'/exp OR 'egypt'/exp OR 'el salvador'/exp OR 'eritrea'/exp OR 'ethiopia'/exp OR 'equatorial guinea'/exp OR

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14 OR 'rwanda'/exp OR 'samoa'/exp OR 'sao tome and principe'/exp OR 'senegal'/exp OR 'serbia'/exp
15 OR 'sierra leone'/exp OR 'solomon islands'/exp OR 'somalia'/exp OR 'south africa'/exp OR 'south
16 sudan'/exp OR 'sri lanka'/exp OR 'saint lucia'/exp OR 'saint vincent and the grenadines'/exp OR
17 'sudan'/exp OR 'swaziland'/exp OR 'syrian arab republic'/exp OR 'tajikistan'/exp OR 'tanzania'/exp
18 OR 'thailand'/exp OR 'timor-leste'/exp OR 'togo'/exp OR 'tonga'/exp OR 'tunisia'/exp OR 'turkey
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26 OR 'lower middle income country':ti,ab,kw OR 'middle income country':ti,ab,kw OR 'middle
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28 'poor countries':ti,ab,kw OR 'lami country':ti,ab,kw OR 'lami countries':ti,ab,kw OR
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30 'american samoa':ti,ab,kw OR samoan*:ti,ab,kw OR angola:ti,ab,kw OR angolan*:ti,ab,kw OR
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32 belarus*:ti,ab,kw OR byelorussian:ti,ab,kw OR byelarus:ti,ab,kw OR belorussia:ti,ab,kw OR
33 belize*:ti,ab,kw OR benin*:ti,ab,kw OR bhutan*:ti,ab,kw OR bolivia*:ti,ab,kw OR
34 bosnia*:ti,ab,kw OR herzegovina:ti,ab,kw OR botswana*:ti,ab,kw OR bechuanaland:ti,ab,kw OR
35 batswana:ti,ab,kw OR motswana:ti,ab,kw OR brazil*:ti,ab,kw OR bulgaria*:ti,ab,kw OR 'burkina
36 faso':ti,ab,kw OR burkinese:ti,ab,kw OR burkinabé:ti,ab,kw OR burundi*:ti,ab,kw OR 'cabo
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38 OR cambodia*:ti,ab,kw OR khmer:ti,ab,kw OR cameroon*:ti,ab,kw OR cameroun:ti,ab,kw OR
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43 congo*:ti,ab,kw OR 'costa rica':ti,ab,kw OR 'costa rican':ti,ab,kw OR 'cote d ivoire':ti,ab,kw OR
44 'ivory coast':ti,ab,kw OR ivorian:ti,ab,kw OR cuba*:ti,ab,kw OR djibouti*:ti,ab,kw OR
45 dominica*:ti,ab,kw OR 'dominican republic':ti,ab,kw OR 'french sudan':ti,ab,kw OR

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3 ecuador*:ti,ab,kw OR egypt*:ti,ab,kw OR 'united arab republic':ti,ab,kw OR 'el salvador':ti,ab,kw
4 OR salvador*:ti,ab,kw OR eritrea*:ti,ab,kw OR ethiopia*:ti,ab,kw OR 'equatorial guinea':ti,ab,kw
5 OR equatoguinean:ti,ab,kw OR fiji*:ti,ab,kw OR gabon*:ti,ab,kw OR gaboon:ti,ab,kw OR
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12 irian':ti,ab,kw OR 'west new guinea':ti,ab,kw OR timor:ti,ab,kw OR java:ti,ab,kw OR 'irian
13 jaya':ti,ab,kw OR bali:ti,ab,kw OR sumatra:ti,ab,kw OR celebes:ti,ab,kw OR sulawesi:ti,ab,kw
14 OR 'malay archipelago':ti,ab,kw OR madoera:ti,ab,kw OR madura:ti,ab,kw OR iran*:ti,ab,kw OR
15 iraq*:ti,ab,kw OR jamaica*:ti,ab,kw OR jordan*:ti,ab,kw OR kazakhstan*:ti,ab,kw OR
16 kazakh:ti,ab,kw OR kenya*:ti,ab,kw OR kiribati*:ti,ab,kw OR 'democratic peoples republic of
17 korea':ti,ab,kw OR 'north korea':ti,ab,kw OR 'north korean':ti,ab,kw OR kosovo:ti,ab,kw OR
18 kosovar:ti,ab,kw OR kosovan:ti,ab,kw OR kyrgyzstan*:ti,ab,kw OR kirghizia:ti,ab,kw OR 'kyrgyz
19 republic':ti,ab,kw OR 'kirghiz ssr':ti,ab,kw OR kirgizstan:ti,ab,kw OR kyrgyzs:ti,ab,kw OR
20 lao*:ti,ab,kw OR laotian*:ti,ab,kw OR lebanon:ti,ab,kw OR lebanese:ti,ab,kw OR
21 lesotho*:ti,ab,kw OR basutoland:ti,ab,kw OR liberia*:ti,ab,kw OR libya*:ti,ab,kw OR
22 macedonia*:ti,ab,kw OR madagascar:ti,ab,kw OR malagasy:ti,ab,kw OR malawi*:ti,ab,kw OR
23 nyasaland:ti,ab,kw OR malaysia*:ti,ab,kw OR malaya*:ti,ab,kw OR maldives:ti,ab,kw OR
24 maldivian:ti,ab,kw OR mali:ti,ab,kw OR Malian:ti,ab,kw OR 'marshall islands':ti,ab,kw OR
25 mauritania*:ti,ab,kw OR mauretania:ti,ab,kw OR mauritius:ti,ab,kw OR mauritian:ti,ab,kw OR
26 mexico:ti,ab,kw OR mexican*:ti,ab,kw OR micronesia*:ti,ab,kw OR moldova*:ti,ab,kw OR
27 moldavia*:ti,ab,kw OR mongolia*:ti,ab,kw OR montenegro:ti,ab,kw OR montenegrin:ti,ab,kw
28 OR morocco:ti,ab,kw OR ifni:ti,ab,kw OR moroccan:ti,ab,kw OR mozambique:ti,ab,kw OR
29 'portuguese east africa':ti,ab,kw OR mocambique:ti,ab,kw OR mozambican:ti,ab,kw OR
30 myanmar:ti,ab,kw OR burma:ti,ab,kw OR myanma:ti,ab,kw OR burmese:ti,ab,kw OR
31 namibia*:ti,ab,kw OR nauru*:ti,ab,kw OR nepal*:ti,ab,kw OR nicaragua*:ti,ab,kw OR
32 niger*:ti,ab,kw OR nigeria*:ti,ab,kw OR pakistan*:ti,ab,kw OR 'papua new guinea':ti,ab,kw OR
33 'east new guinea':ti,ab,kw OR paraguay*:ti,ab,kw OR peru*:ti,ab,kw OR philippines:ti,ab,kw OR
34 phillipines:ti,ab,kw OR filipino*:ti,ab,kw OR romania*:ti,ab,kw OR rumania*:ti,ab,kw OR
35 roumania*:ti,ab,kw OR russia*:ti,ab,kw OR rwanda*:ti,ab,kw OR ruanda:ti,ab,kw OR
36 samoa*:ti,ab,kw OR 'navigator islands':ti,ab,kw OR 'sao tome principe':ti,ab,kw OR
37 santomean:ti,ab,kw OR senegal*:ti,ab,kw OR serbia*:ti,ab,kw OR 'sierra leone':ti,ab,kw OR
38 'sierra leonean':ti,ab,kw OR 'solomon islands':ti,ab,kw OR 'solomon islander':ti,ab,kw OR
39 somali*:ti,ab,kw OR 'south africa':ti,ab,kw OR 'south african':ti,ab,kw OR 'south sudan':ti,ab,kw
40 OR 'south sudanese':ti,ab,kw OR 'sri lanka':ti,ab,kw OR 'sri lankan':ti,ab,kw OR ceylon:ti,ab,kw
41 OR 'saint lucia':ti,ab,kw OR 'st. lucia':ti,ab,kw OR 'saint lucian':ti,ab,kw OR 'saint vincent':ti,ab,kw
42 OR 'st. vincent':ti,ab,kw OR grenadines:ti,ab,kw OR sudan*:ti,ab,kw OR surinam*:ti,ab,kw OR
43 swaziland:ti,ab,kw OR 'swazi':ti,ab,kw OR eswatini:ti,ab,kw OR syria*:ti,ab,kw OR
44 tajikistan*:ti,ab,kw OR tadjikistan*:ti,ab,kw OR tadhik:ti,ab,kw OR tanzania*:ti,ab,kw OR
45 tanganyika:ti,ab,kw OR thai*:ti,ab,kw OR 'timor-leste':ti,ab,kw OR 'east timor':ti,ab,kw OR
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togo*:ti,ab,kw OR tonga*:ti,ab,kw OR tunisia*:ti,ab,kw OR tunesia:ti,ab,kw OR turkey:ti,ab,kw
OR turkish:ti,ab,kw OR turkmenistan:ti,ab,kw OR turkmen*:ti,ab,kw OR tuvalu*:ti,ab,kw OR
uganda*:ti,ab,kw OR ukraine:ti,ab,kw OR ukrainian:ti,ab,kw OR ukraina:ti,ab,kw OR
uzbekistan*:ti,ab,kw OR uzbek:ti,ab,kw OR vanuatu*:ti,ab,kw OR venezuela*:ti,ab,kw OR
vietnam*:ti,ab,kw OR 'viet nam':ti,ab,kw OR 'west bank':ti,ab,kw OR 'gaza':ti,ab,kw OR
yemen*:ti,ab,kw OR zambia*:ti,ab,kw OR zimbabwe*:ti,ab,kw)

PubMed

("Sepsis" [Mesh] OR sepsis[tiab] OR septic[tiab] OR pyemia*[tiab] OR pyohemia*[tiab] OR
pyaemia*[tiab] OR septicemia*[tiab] OR "blood poisoning"[tiab]) AND ("Infant,
Newborn"[Mesh] OR "Pediatrics"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR
infant[tiab] OR infants[tiab] OR baby[tiab] OR babies[tiab] OR newborn[tiab] OR newborns[tiab]
OR neonate[tiab] OR neonates[tiab] OR pediatric [tiab] OR paediatric[tiab] OR child[tiab] OR
children[tiab] OR toddler[tiab] OR toddlers[tiab] OR adolescent[tiab] OR adolescence[tiab] OR
teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR youth[tiab] OR boy[tiab] OR
boys[tiab] OR girl[tiab] OR girls[tiab] OR juvenile[tiab] OR juveniles[tiab]) AND ("Developing
Countries"[Mesh] OR "Afghanistan"[Mesh] OR "Albania"[Mesh] OR "Algeria"[Mesh] OR
"American Samoa"[Mesh] OR "Angola"[Mesh] OR "Armenia"[Mesh] OR "Azerbaijan"[Mesh]
OR "Bangladesh"[Mesh] OR "Republic of Belarus"[Mesh] OR "Belize"[Mesh] OR
"Benin"[Mesh] OR "Bhutan"[Mesh] OR "Bolivia"[Mesh] OR "Bosnia and Herzegovina"[Mesh]
OR "Botswana"[Mesh] OR "Brazil"[Mesh] OR "Bulgaria"[Mesh] OR "Burkina Faso"[Mesh] OR
"Burundi"[Mesh] OR "Cabo Verde"[Mesh] OR "Cambodia"[Mesh] OR "Cameroon"[Mesh] OR
"Central African Republic"[Mesh] OR "Chad"[Mesh] OR "China"[Mesh:NoExp] OR
"Colombia"[Mesh] OR "Comoros"[Mesh] OR "Democratic Republic of the Congo"[Mesh] OR
"Congo"[Mesh] OR "Costa Rica"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Cuba"[Mesh] OR
"Djibouti"[Mesh] OR "Dominica"[Mesh] OR "Dominican Republic"[Mesh] OR "Ecuador"[Mesh]
OR "Egypt"[Mesh] OR "El Salvador"[Mesh] OR "Eritrea"[Mesh] OR "Ethiopia"[Mesh] OR
"Equatorial Guinea"[Mesh] OR "Fiji"[Mesh] OR "Gabon"[Mesh] OR "Gambia"[Mesh] OR
"Georgia (Republic)"[Mesh] OR "Ghana"[Mesh] OR "Grenada"[Mesh] OR "Guinea"[Mesh] OR
"Guinea-Bissau"[Mesh] OR "Guatemala"[Mesh] OR "Guyana"[Mesh] OR "Haiti"[Mesh] OR
"Honduras"[Mesh] OR "India"[Mesh] OR "Indonesia"[Mesh] OR "Iran"[Mesh] OR "Iraq"[Mesh]
OR "Jamaica"[Mesh] OR "Jordan"[Mesh] OR "Kazakhstan"[Mesh] OR "Kenya"[Mesh] OR
"Democratic People's Republic of Korea"[Mesh] OR "Kosovo"[Mesh] OR "Kyrgyzstan"[Mesh]
OR "Laos"[Mesh] OR "Lebanon"[Mesh] OR "Lesotho"[Mesh] OR "Liberia"[Mesh] OR
"Libya"[Mesh] OR "Macedonia (Republic)"[Mesh] OR "Madagascar"[Mesh] OR
"Malawi"[Mesh] OR "Malaysia"[Mesh] OR "Mali"[Mesh] OR "Mauritania"[Mesh] OR
"Mauritius"[Mesh] OR "Mexico"[Mesh] OR "Micronesia"[Mesh] OR "Moldova"[Mesh] OR
"Mongolia"[Mesh] OR "Montenegro"[Mesh] OR "Morocco"[Mesh] OR "Mozambique"[Mesh]
OR "Myanmar"[Mesh] OR "Namibia"[Mesh] OR "Nepal"[Mesh] OR "Nicaragua"[Mesh] OR
"Niger"[Mesh] OR "Nigeria"[Mesh] OR "Pakistan"[Mesh] OR "Papua New Guinea"[Mesh] OR
"Paraguay"[Mesh] OR "Peru"[Mesh] OR "Philippines"[Mesh] OR "Romania"[Mesh] OR

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3 "Russia"[Mesh] OR "Rwanda"[Mesh] OR "Samoa"[Mesh] OR "Sao Tome and Principe"[Mesh]
4 OR "Senegal"[Mesh] OR "Serbia"[Mesh] OR "Sierra Leone"[Mesh] OR "Somalia"[Mesh] OR
5 "South Africa"[Mesh] OR "South Sudan"[Mesh] OR "Sri Lanka"[Mesh] OR "Saint Lucia"[Mesh]
6 OR "Saint Vincent and the Grenadines"[Mesh] OR "Sudan"[Mesh] OR "Suriname"[Mesh] OR
7 "Swaziland"[Mesh] OR "Syria"[Mesh] OR "Tajikistan"[Mesh] OR "Tanzania"[Mesh] OR
8 "Thailand"[Mesh] OR "Timor-Leste"[Mesh] OR "Togo"[Mesh] OR "Tonga"[Mesh] OR
9 "Tunisia"[Mesh] OR "Turkey"[Mesh] OR "Turkmenistan"[Mesh] OR "Uganda"[Mesh] OR
10 "Ukraine"[Mesh] OR "Uzbekistan"[Mesh] OR "Vanuatu"[Mesh] OR "Venezuela"[Mesh] OR
11 "Vietnam"[Mesh] OR "Yemen"[Mesh] OR "Zambia"[Mesh] OR "Zimbabwe"[Mesh] OR
12 "developing country" OR "developing countries" OR "developing economy" OR "under
13 developed country" OR "under developed countries" OR "third world" OR "low income country"
14 OR "low income economy" OR "low income nation" OR "lower income country" OR "lower
15 middle income country" OR "middle income country" OR "middle income economy" OR "middle
16 income nation" OR "poor country" OR "poor countries" OR "LAMI country" OR "LAMI
17 countries" OR Afghanistan[tiab] OR Afghani*[tiab] OR Albania*[tiab] OR Algeria*[tiab] OR
18 "American Samoa"[tiab] OR Samoan*[tiab] OR Angola[tiab] OR Angolan*[tiab] OR
19 Armenia*[tiab] OR Azerbaijan*[tiab] OR Bangladesh[tiab] OR Bengali*[tiab] OR Belarus*[tiab]
20 OR Byelorussian[tiab] OR Byelarus[tiab] OR Belorussia[tiab] OR Belize*[tiab] OR Benin*[tiab]
21 OR Bhutan*[tiab] OR Bolivia*[tiab] OR Bosnia*[tiab] OR Herzegovina[tiab] OR
22 Botswana*[tiab] OR Bechuanaland[tiab] OR Batswana[tiab] OR Motswana[tiab] OR Brazil*[tiab]
23 OR Bulgaria*[tiab] OR "Burkina Faso"[tiab] OR Burkinabé[tiab] OR Burundi*[tiab] OR "Cabo
24 Verde"[tiab] OR "Cape Verde"[tiab] OR "Cape Verdean"[tiab] OR Cambodia*[tiab] OR
25 Khmer[tiab] OR Cameroon*[tiab] OR Cameroun[tiab] OR "Central African Republic"[tiab] OR
26 "Centrafrican Republic"[tiab] OR "Chad"[tiab] OR Tchad [tiab] OR Chadian[tiab] OR China[tiab]
27 OR Chinese[tiab] OR Colombia*[tiab] OR Comoros[tiab] OR "Comoro Islands"[tiab] OR
28 Comorian[tiab] OR "Democratic Republic of the Congo"[tiab] OR "Democratic Republic
29 Congo"[tiab] OR Congo*[tiab] OR "Costa Rica"[tiab] OR "Costa Rican"[tiab] OR "Cote
30 d'Ivoire"[tiab] OR "Ivory Coast"[tiab] OR Ivorian[tiab] OR Cuba*[tiab] OR Djibouti*[tiab] OR
31 Dominica*[tiab] OR "Dominican Republic"[tiab] OR "French Sudan"[tiab] OR Ecuador*[tiab]
32 OR Egypt*[tiab] OR "United Arab Republic"[tiab] OR "El Salvador"[tiab] OR Salvador*[tiab]
33 OR Eritrea*[tiab] OR Ethiopia*[tiab] OR "Equatorial Guinea"[tiab] OR Equatoguinean[tiab] OR
34 Fiji*[tiab] OR Gabon*[tiab] OR Gaboon[tiab] OR Gambia*[tiab] OR "Republic of Georgia"[tiab]
35 OR "Georgia SSR"[tiab] OR Ghana*[tiab] OR Grenada[tiab] OR Grenadian[tiab] OR
36 Guinea*[tiab] OR "Guinea-Bissau"[tiab] OR "Portuguese Guinea"[tiab] OR Guatemala*[tiab] OR
37 Guyana[tiab] OR Guyanese[tiab] OR Haiti*[tiab] OR Hondura*[tiab] OR India[tiab] OR "Indian
38 Union"[tiab] OR Indonesia*[tiab] OR "Netherlands East Indies"[tiab] OR "East Indies"[tiab] OR
39 "West Irian"[tiab] OR "West New Guinea"[tiab] OR Timor[tiab] OR "Java"[tiab] OR "Irian
40 Jaya"[tiab] OR Bali[tiab] OR Sumatra[tiab] OR Celebes[tiab] OR Sulawesi[tiab] OR "Malay
41 Archipelago"[tiab] OR Madura[tiab] OR Iran*[tiab] OR Iraq*[tiab] OR Jamaica*[tiab] OR
42 Jordan*[tiab] OR Kazakhstan*[tiab] OR Kazakh[tiab] OR Kenya*[tiab] OR Kiribati*[tiab] OR
43 "Democratic People's Republic of Korea"[tiab] OR "North Korea"[tiab] OR "North Korean"[tiab]
44 OR Kosovo[tiab] OR Kosovar[tiab] OR Kosovan[tiab] OR Kyrgyzstan*[tiab] OR Kirghizia[tiab]
45 OR "Kyrgyz Republic"[tiab] OR "Kirghiz SSR"[tiab] OR Kirgizstan[tiab] OR Kyrgyzs[tiab] OR
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3 Lao[tiab] OR Laos[tiab] OR Laotian*[tiab] OR Lebanon[tiab] OR Lebanese[tiab] OR
4 Lesotho*[tiab] OR Basutoland[tiab] OR Liberia*[tiab] OR Libya*[tiab] OR Macedonia*[tiab] OR
5 Madagascar[tiab] OR Malagasy[tiab] OR Malawi*[tiab] OR Nyasaland[tiab] OR Malaysia*[tiab]
6 OR Malaya*[tiab] OR Maldives[tiab] OR Maldivian[tiab] OR Mali[tiab] OR Malian[tiab] OR
7 “Marshall Islands”[tiab] OR Mauritania*[tiab] OR Mauretania[tiab] OR Mauritius[tiab] OR
8 Mauritian[tiab] OR Mexico[tiab] OR Mexican*[tiab] OR Micronesia*[tiab] OR Moldova*[tiab]
9 OR Moldavia*[tiab] OR Mongolia*[tiab] OR Montenegro[tiab] OR Montenegrin[tiab] OR
10 Morocco[tiab] OR Ifni[tiab] OR Moroccan[tiab] OR Mozambique[tiab] OR “Portuguese East
11 Africa”[tiab] OR Mocambique[tiab] OR Mozambican[tiab] OR Myanmar[tiab] OR Burma[tiab]
12 OR Myanma[tiab] OR Burmese[tiab] OR Namibia*[tiab] OR Nauru*[tiab] OR Nepal*[tiab] OR
13 Nicaragua*[tiab] OR Niger*[tiab] OR Nigeria*[tiab] OR Pakistan*[tiab] OR “Papua New
14 Guinea”[tiab] OR “East New Guinea” [tiab] OR Paraguay*[tiab] OR Peru*[tiab] OR
15 Philippines[tiab] OR Phillipines[tiab] OR Filipino*[tiab] OR Romania*[tiab] OR
16 Rumania*[tiab] OR Roumania*[tiab] OR Russia*[tiab] OR Rwanda*[tiab] OR Ruanda[tiab]
17 OR Samoa*[tiab] OR “Sao Tome”[tiab] OR Senegal*[tiab] OR Serbia*[tiab] OR “Sierra
18 Leone”[tiab] OR “Sierra Leonean” [tiab] OR “Solomon Islands” [tiab] OR “Solomon Islander”
19 [tiab] OR Somali*[tiab] OR “South Africa”[tiab] OR “South African” [tiab] OR “South
20 Sudan”[tiab] OR “South Sudanese” [tiab] OR “Sri Lanka”[tiab] OR “Sri Lankan” [tiab] OR
21 Ceylon[tiab] OR “Saint Lucia”[tiab] OR “St. Lucia”[tiab] OR “Saint Vincent”[tiab] OR “St.
22 Vincent”[tiab] OR Sudan* [tiab] OR Surinam*[tiab] OR Swaziland[tiab] OR “Swazi”[tiab] OR
23 Eswatini[tiab] OR Syria*[tiab] OR Tajikistan*[tiab] OR Tadjikistan*[tiab] OR Tadzihik[tiab]
24 OR Tanzania*[tiab] OR Tanganyika[tiab] OR Thai*[tiab] OR “Timor-Leste”[tiab] OR “East
25 Timor” [tiab] OR Togo*[tiab] OR Tonga*[tiab] OR Tunisia*[tiab] OR Tunesia[tiab] OR
26 Turkey[tiab] OR Turkish[tiab] OR Turkmenistan[tiab] OR Turkmen*[tiab] OR Tuvalu*[tiab]
27 OR Uganda*[tiab] OR Ukraine[tiab] OR Ukrainian[tiab] OR Ukraina[tiab] OR
28 Uzbekistan*[tiab] OR Uzbek[tiab] OR Vanuatu*[tiab] OR Venezuela*[tiab] OR Vietnam*[tiab]
29 OR “Viet Nam” [tiab] OR “West Bank” [tiab] OR “Gaza” [tiab] OR Yemen*[tiab] OR
30 Zambia*[tiab] OR Zimbabwe*[tiab]

Scopus

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41 = 6,164 results after limiting to English, 1994-present and excluding books, book chapters,
42 editorials, notes, and letters on 6/24/2019

43
44 TITLE-ABS-KEY (sepsis OR septic OR pyemia* OR pyohemia* OR pyaemia* OR
45 septicemia* OR {blood poisoning}) AND TITLE-ABS-KEY (infant OR infants OR baby
46 OR babies OR newborn OR newborns OR neonate OR neonates OR pediatric OR paediatric
47 OR child OR children OR toddler OR toddlers OR adolescent OR adolescence OR teen
48 OR teens OR teenager OR teenagers OR youth OR boy OR boys OR girl OR girls OR
49 juvenile OR juveniles) AND TITLE-ABS-KEY ({developing country} OR {developing
50 countries} OR {developing economy} OR {under developed country} OR {under developed
51 countries} OR {third world} OR {low income country} OR {low income economy} OR {low
52 income nation} OR {lower income country} OR {lower middle income country} OR {middle
53 income country} OR {middle income economy} OR {middle income nation} OR {poor
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3 country} OR {poor countries} OR {LAMI country} OR {LAMI countries} OR afghanistan
4 OR afghani* OR albania* OR algeria* OR {American Samoa} OR samoan* OR angola
5 OR angolan* OR armenia* OR azerbaijan* OR bangladesh OR bengali* OR belarus* OR
6 byelorussian OR byelarus OR belorussia OR belize* OR benin* OR bhutan* OR bolivia*
7 OR bosnia* OR herzegovina OR botswana* OR bechuanaland OR batswana OR motswana
8 OR brazil* OR bulgaria* OR "Burkina Faso" OR burkinabé OR burundi* OR "Cabo Verde"
9 OR "Cape Verde" OR "Cape Verdean" OR cambodia* OR khmer OR cameroon* OR
10 cameroun OR "Central African Republic" OR "Centrafrican Republic" OR "Chad" OR tchad
11 OR chadian OR china OR chinese OR colombia* OR comoros OR "Comoro Islands" OR
12 comorian OR "Democratic Republic of the Congo" OR "Democratic Republic Congo" OR
13 congo* OR "Costa Rica" OR "Costa Rican" OR "Cote d'Ivoire" OR "Ivory Coast" OR ivorian
14 OR cuba* OR djibouti* OR dominica* OR "Dominican Republic" OR "French Sudan" OR
15 ecuador* OR egypt* OR "United Arab Republic" OR "El Salvador" OR salvador* OR
16 eritrea* OR ethiopia* OR "Equatorial Guinea" OR equatoguinean OR fiji* OR gabon* OR
17 gaboon OR gambia* OR "Republic of Georgia" OR "Georgia SSR" OR ghana* OR grenada
18 OR grenadian OR guinea* OR "Guinea-Bissau" OR "Portuguese Guinea" OR guatemala*
19 OR guyana OR guyanese OR haiti* OR hondura* OR india OR "Indian Union" OR
20 indonesia* OR "Netherlands East Indies" OR "East Indies" OR "West Irian" OR "West New
21 Guinea" OR timor OR "Java" OR "Irian Jaya" OR bali OR sumatra OR celebes OR
22 sulawesi OR "Malay Archipelago" OR madura OR iran* OR iraq* OR jamaica* OR jordan*
23 OR kazakhstan* OR kazakh OR kenya* OR kiribati* OR "Democratic People's Republic of
24 Korea" OR "North Korea" OR "North Korean" OR kosovo OR kosovar OR kosovan OR
25 kyrgyzstan* OR kirghizia OR "Kyrgyz Republic" OR "Kirghiz SSR" OR kirgizstan OR
26 kyrgyzs OR lao OR laos OR laotian* OR lebanon OR lebanese OR lesotho* OR basutoland
27 OR liberia* OR libya* OR macedonia* OR madagascar OR malagasy OR malawi* OR
28 nyasaland OR malaysia* OR malaya* OR maldives OR maldivian OR mali OR malian
29 OR "Marshall Islands" OR mauritania* OR mauretania OR mauritius OR mauritian OR
30 mexico OR mexican* OR micronesia* OR moldova* OR moldavia* OR mongolia* OR
31 montenegro OR montenegrin OR morocco OR ifni OR moroccan OR mozambique OR
32 "Portuguese East Africa" OR mocambique OR mozambican OR myanmar OR burma OR
33 myanma OR burmese OR namibia* OR nauru* OR nepal* OR nicaragua* OR niger* OR
34 nigeria* OR pakistan* OR "Papua New Guinea" OR "East New Guinea" OR paraguay* OR
35 peru* OR philippines OR philipines OR filipino* OR romania* OR rumania* OR
36 roumania* OR russia* OR rwanda* OR ruanda OR samoa* OR "Sao Tome" OR senegal*
37 OR serbia* OR "Sierra Leone" OR "Sierra Leonean" OR "Solomon Islands" OR "Solomon
38 Islander" OR somali* OR "South Africa" OR "South African" OR "South Sudan" OR "South
39 Sudanese" OR "Sri Lanka" OR "Sri Lankan" OR ceylon OR "Saint Lucia" OR "St. Lucia"
40 OR "Saint Vincent" OR "St. Vincent" OR sudan* OR surinam* OR swaziland OR "Swazi"
41 OR eswatini OR syria* OR tajikistan* OR tadjikistan* OR tadjhik OR tanzania* OR
42 tanganyika OR thai* OR "Timor-Leste" OR "East Timor" OR togo* OR tonga* OR tunisia*
43 OR tunesia OR turkey OR turkish OR turkmenistan OR turkmen* OR tuvalu* OR uganda*
44 OR ukraine OR ukrainian OR ukraine OR uzbekistan* OR uzbek OR vanuatu* OR
45 venezuela* OR vietnam* OR "Viet Nam" OR "West Bank" OR "Gaza" OR yemen* OR
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3 zambia* OR zimbabwe*) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-
4 TO(PUBYEAR, 2019) OR LIMIT-TO(PUBYEAR, 2018) OR LIMIT-TO(PUBYEAR,
5 2017) OR LIMIT-TO(PUBYEAR, 2016) OR LIMIT-TO(PUBYEAR, 2015) OR LIMIT-
6 TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR,
7 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-
8 TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR,
9 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-
10 TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR,
11 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-
12 TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR,
13 1997) OR LIMIT-TO(PUBYEAR, 1996) OR LIMIT-TO(PUBYEAR, 1995) OR LIMIT-
14 TO(PUBYEAR, 1994)) AND (EXCLUDE(DOCTYPE, "no") OR EXCLUDE(
15 DOCTYPE, "ed") OR EXCLUDE(DOCTYPE, "ch") OR EXCLUDE(DOCTYPE, "sh"
16) OR EXCLUDE(DOCTYPE, "bk"))

21 22 23 Cochrane Library

24 #1: MeSH descriptor: [Sepsis] explode all trees

25
26 #2: sepsis OR septic OR pyemia* OR pyohemia* OR pyaemia* OR septicemia* OR "blood
27 poisoning"

28
29 #3: #1 OR #2

30
31 #4: MeSH descriptor: [Infant, Newborn] explode all trees

32
33 #5: MeSH descriptor: [Pediatrics] explode all trees

34
35 #6: MeSH descriptor: [Child] explode all trees

36
37 #7: MeSH descriptor: [Adolescent] explode all trees

38
39 #8: infant OR infants OR baby OR babies OR newborn OR newborns OR neonate OR neonates
40 OR pediatric OR paediatric OR child OR children OR toddler OR toddlers OR adolescent OR
41 adolescence OR teen OR teens OR teenager OR teenagers OR youth OR boy OR boys OR girl OR
42 girls OR juvenile OR juveniles

43
44 #9: #4 OR #5 OR #6 OR #7 OR #8

45
46 #10: MeSH descriptor: [Developing Countries] explode all trees

47
48 #11: ("developing country" OR "developing countries" OR "developing economy" OR "under
49 developed country" OR "under developed countries" OR "third world" OR "low income country"
50 OR "low income economy" OR "low income nation" OR "lower income country" OR "lower
51 middle income country" OR "middle income country" OR "middle income economy" OR "middle
52 income nation" OR "poor country" OR "poor countries" OR "LAMI country" OR "LAMI
53 countries" OR Afghanistan OR Afghani* OR Albania* OR Algeria* OR "American Samoa" OR
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3 Samoa* OR Angola OR Angolan* OR Armenia* OR Azerbaijan* OR Bangladesh OR Bengali*
4 OR Belarus* OR Byelorussian OR Byelarus OR Belorussia OR Belize* OR Benin* OR Bhutan*
5 OR Bolivia* OR Bosnia* OR Herzegovina OR Botswana* OR Bechuanaland OR Batswana OR
6 Motswana OR Brazil* OR Bulgaria* OR "Burkina Faso" OR Burkinabé OR Burundi* OR "Cabo
7 Verde" OR "Cape Verde" OR "Cape Verdean" OR Cambodia* OR Khmer OR Cameroon* OR
8 Cameroun OR "Central African Republic" OR "Centrafican Republic" OR "Chad" OR Tchad
9 OR Chadian OR China OR Chinese OR Colombia* OR Comoros OR "Comoro Islands" OR
10 Comorian OR "Democratic Republic of the Congo" OR "Democratic Republic Congo" OR
11 Congo* OR "Costa Rica" OR "Costa Rican" OR "Cote d Ivoire" OR "Ivory Coast" OR Ivorian
12 OR Cuba* OR Djibouti* OR Dominica* OR "Dominican Republic" OR "French Sudan" OR
13 Ecuador* OR Egypt* OR "United Arab Republic" OR "El Salvador" OR Salvador* OR Eritrea*
14 OR Ethiopia* OR "Equatorial Guinea" OR Equatoguinean OR Fiji* OR Gabon* OR Gaboon OR
15 Gambia* OR "Republic of Georgia" OR "Georgia SSR" OR Ghana* OR Grenada OR Grenadian
16 OR Guinea* OR "Guinea-Bissau" OR "Portuguese Guinea" OR Guatemala* OR Guyana OR
17 Guyanese OR Haiti* OR Hondura* OR India OR "Indian Union" OR Indonesia* OR "Netherlands
18 East Indies" OR "East Indies" OR "West Irian" OR "West New Guinea" OR Timor OR "Java"
19 OR "Irian Jaya" OR Bali OR Sumatra OR Celebes OR Sulawesi OR "Malay Archipelago" OR
20 Madura OR Iran* OR Iraq* OR Jamaica* OR Jordan* OR Kazakhstan* OR Kazakh OR Kenya*
21 OR Kiribati* OR "Democratic People's Republic of Korea" OR "North Korea" OR "North
22 Korean" OR Kosovo OR Kosovar OR Kosovan OR Kyrgyzstan* OR Kirghizia OR "Kyrgyz
23 Republic" OR "Kirghiz SSR" OR Kirgizstan OR Kyrgyzs OR Lao OR Laos OR Laotian* OR
24 Lebanon OR Lebanese OR Lesotho* OR Basutoland OR Liberia* OR Libya* OR Macedonia*
25 OR Madagascar OR Malagasy OR Malawi* OR Nyasaland OR Malaysia* OR Malaya* OR
26 Maldives OR Maldivian OR Mali OR Malian OR "Marshall Islands" OR Mauritania* OR
27 Mauretania OR Mauritius OR Mauritian OR Mexico OR Mexican* OR Micronesia* OR
28 Moldova* OR Moldavia* OR Mongolia* OR Montenegro OR Montenegrin OR Morocco OR Ifni
29 OR Moroccan OR Mozambique OR "Portuguese East Africa" OR Mocambique OR Mozambican
30 OR Myanmar OR Burma OR Myanma OR Burmese OR Namibia* OR Nauru* OR Nepal* OR
31 Nicaragua* OR Niger* OR Nigeria* OR Pakistan* OR "Papua New Guinea" OR "East New
32 Guinea" OR Paraguay* OR Peru* OR Philippines OR Phillipines OR Filipino* OR Romania*
33 OR Rumania* OR Roumania* OR Russia* OR Rwanda* OR Ruanda OR Samoa* OR "Sao
34 Tome" OR Senegal* OR Serbia* OR "Sierra Leone" OR "Sierra Leonean" OR "Solomon
35 Islands" OR "Solomon Islander" OR Somali* OR "South Africa" OR "South African" OR
36 "South Sudan" OR "South Sudanese" OR "Sri Lanka" OR "Sri Lankan" OR Ceylon OR "Saint
37 Lucia" OR "Saint Vincent" OR Sudan* OR Surinam* OR Swaziland OR Swazi OR Eswatini
38 OR Syria* OR Tajikistan* OR Tadjikistan* OR Tadzhik OR Tanzania* OR Tanganyika OR
39 Thai* OR "Timor Leste" OR "East Timor" OR Togo* OR Tonga* OR Tunisia* OR Tunesia
40 OR Turkey OR Turkish OR Turkmenistan OR Turkmen* OR Tuvalu* OR Uganda* OR Ukraine
41 OR Ukrainian OR Ukraina OR Uzbekistan* OR Uzbek OR Vanuatu* OR Venezuela* OR
42 Vietnam* OR "Viet Nam" OR "West Bank" OR "Gaza" OR Yemen* OR Zambia* OR
43 Zimbabwe*)

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55 #12: #10 OR #11
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For peer review only

Supplementary file 4

PRISMA-P Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1 title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>	<input type="checkbox"/>	Page 2 Methods and analysis
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1 Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5 Manuscript contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No funding
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2 Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 Methods
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 Methods
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2 Methods
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Supplemental file 3
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – Types of studies, participants, and interventions
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – Assessment of

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					methodological quality
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable – qualitative systematic review
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable – qualitative systematic review
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable, systematic review only
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not applicable

BMJ Open

Study protocol for a core outcome set in paediatric sepsis in low and middle-income countries

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034960.R2
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-2020
Complete List of Authors:	Wooldridge, Gavin; BC Children's Hospital, Pediatric Critical Care Murthy, Srinivas; University of British Columbia, Paediatrics Kisson, Niranjana; University of British Columbia, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Global health, Intensive care, Infectious diseases
Keywords:	Paediatric infectious disease & immunisation < PAEDIATRICALS, Community child health < PAEDIATRICALS, Paediatric intensive & critical care < ANAESTHETICS, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE

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Study protocol for a core outcome set in paediatric sepsis in low and middle-income countries

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ABSTRACT

Introduction

Sepsis is the leading cause of death in children worldwide and has recently been declared a major global health issue. New interventions and a concerted effort to enhance our understanding of sepsis are required to address the huge burden of disease, especially in low and middle-income countries (LMIC) where it is highest. An opportunity therefore exists to ensure that ongoing research in this area is relevant to all stakeholders and is of consistently high quality. One method to address these issues is through the development of a core outcome set (COS).

Methods and analysis

This study protocol outlines the phases in the development of a core outcome set for paediatric sepsis in LMIC. The first step involves performing a systematic review of all outcomes reported in the research of paediatric sepsis in low middle-income countries. A three-stage international Delphi process will then invite a broad range of participants to score each generated outcome for inclusion into the COS. This will include an initial two step online survey and finally, a face to face consensus meeting where each outcome will be reviewed, voted on and ratified for inclusion into the COS.

Ethics and dissemination

No core outcome sets exist for clinical trials in paediatric sepsis. This COS will serve to not only highlight the heavy burden of paediatric sepsis in this setting and aid collaboration and participation between all stakeholders, but to promote ongoing essential high quality and relevant research into the topic. A COS in paediatric sepsis in LMIC will advocate for a common language and facilitate interpretation of findings from a variety of settings. A waiver for ethics approval has been granted by UBC Children's and Women's Research Ethics Board.

Article Summary

Strengths and limitations of this study

- With the continued high burden of disease in low and middle-income countries, a core outcome set (COS) for use in paediatric sepsis research in a resource-limited settings required to focus efforts and improve research consistency, relevance and quality in this area.
- The protocol uses a well-established process involving a thorough systematic review and an all-encompassing 3 step Delphi survey involving clinicians, researchers, nurses, patients and parents/guardians
- The feasibility of an e-survey is limited in regions with poor internet access, so the use of a local facilitator will ensure patients and the parent/guardian have equal input into the COS development.

Keywords: Paediatric sepsis, core outcome sets, low-middle income countries

INTRODUCTION

Sepsis is the leading cause of death in children, with the highest-burden in those countries least resourced to address it. Now recognised as a major global health issue, in 2017 the WHO adopted a resolution with the aim of reducing the human and economic burden of sepsis (1). Severe paediatric sepsis has a worldwide prevalence of 8% (2) and a mortality of 9 -20% (3). Severe sepsis and septic shock has a mortality of 20 - 40% within developing countries (4)(5). It is thought to be the final common pathway to multi-organ failure and death from a number of infectious diseases (6), including the top four causes of childhood mortality as reported by the WHO.

With the high prevalence of disease, new interventions and treatments are essential, as is a concerted effort to better understand the genesis of sepsis. Analysis and comparison of trials involving paediatric sepsis in low and middle-income countries (LMIC) are problematic however due to the significant heterogeneity and inconsistency in reporting outcomes (7,8). A systematic review into primary outcome measures in paediatric septic shock trials demonstrated that the use of mortality alone had significant limitations and suggested more long term outcomes should be explored (4). A standardised way to evaluate trial outcomes is therefore imperative.

One method that is being increasingly used to address these issues is a minimum core outcome set (COS) (7). These are defined as a minimum set of outcomes that should be consistently measured and reported in clinical trials for a specific clinical area (7). All stakeholders have a role in developing the COS. The use of COS not only aims to improve consistency across trials allowing accurate comparison, including potential meta-analysis, but to limit selective reporting (9,10) and improve the quality and relevance of clinical research (11).

A number of sepsis COS in sepsis have been developed (<http://www.comet-initiative.org/studies/details/1317?result=true>), including one ongoing in Paediatric Critical Care Medicine research (<http://www.comet-initiative.org/studies/details/1131?result=true>). No core outcome set currently exists for paediatric sepsis however, and very few are region specific. Limited funding and resources, a high sepsis burden of varying infectious aetiologies and a large proportion of children with significant comorbidities determine the differences in outcomes seen in LMIC. These factors are in contrast to high income countries (HIC) and hence necessitate a region-specific COS to better understand these disparities and craft context-specific solutions. As an example total annual expenditure on health in many parts of sub-Saharan Africa is under US \$25 per capita and often less than 3% of the GDP (12) and the number of ICU beds as a percentage of hospital beds is approximately 1.5% in LMIC compared to 2.5 to 9% in HIC (13). Recognising the huge discrepancy in resources between regions is essential as is the potential financial impact. In 2018, 11.7% of the world's population spent over 10% of their annual income on healthcare, leaving an estimated 100 million people impoverished by out of pocket spending. (14) A region-specific COS will ensure relevance and meaning to patients and clinicians alike. By advocating a common language between stakeholders, interpretation of findings from a variety of diverse settings will become simpler and attention can focus on research into the essential outcomes. Potential barriers to development and dissemination of a COS in this setting may be hindered by a lack of access to research capabilities and limited implementation feasibility.

AIMS AND OBJECTIVES

This study aims to develop a COS for use in clinical trials involving paediatric sepsis in LMIC. The specific study objectives are to identify outcomes previously reported in trials of paediatric sepsis in LMIC and to prioritise these outcomes using clinicians, researchers, patients and parents.

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3 The protocol outlines our methods used to establish a COS and aims to raise awareness of paediatric
4 sepsis in LMIC and aid collaboration and participation between all stakeholders. The protocol has been
5 developed using the COS-STAD guidance for developing core outcome sets (15, supplementary file
6 1) and the COS-STAP guidance for a protocol for a core outcome set development study (16,
7 supplementary file 2). A stepwise approach to COS development will be undertaken as suggested by The
8 Core Outcome Measures in Effectiveness Trials (COMET) Initiative and the Outcome Measures in
9 Rheumatology (OMERACT) Initiative (17).

11 METHODS AND ANALYSIS

12 Our COS development plan has been registered with the COMET initiative ([http://www.comet-](http://www.comet-initiative.org/studies/details/1400?result=true)
13 [initiative.org/studies/details/1400?result=true](http://www.comet-initiative.org/studies/details/1400?result=true)). As per published recommendations (18) and previous core
14 outcome sets (11, 19 – 21), a multi-step process will be utilised to develop an international consensus for
15 paediatric sepsis in low and middle-income countries COS (figure 1):

- 16 1. Systematic review of outcomes currently reported in the research of paediatric sepsis in low
17 and middle-income countries.
- 18 2. Three round Delphi process:
 - 19 a. 2 round Delphi survey to prioritise outcomes
 - 20 b. Consensus meeting of global experts, clinicians, parent/guardians, patients and nurses and
21 e-survey participants to ratify COS

22 When complete, the Core Outcome Set Standards for Reporting (COS-STAR) (22) will be applied.

23 Scope of core outcome set

24 This COS will be purely focused on clinical outcomes in paediatric sepsis clinical trials in LMIC, and not
25 involve those outcomes that are specific to premature infants or certain conditions, such as meningococcal
26 septicaemia. The population will include those from newborn up to under eighteen years of age.

27 Identification of existing knowledge

28 One prior systematic review in 2017 evaluated all paediatric randomised controlled trials of patients with
29 septic shock. This however included high-income countries and was intensive care specific. Neonates
30 were also excluded. Mortality was the most frequent primary outcome whilst long term patient-centred
31 outcomes were rarely used (4).

32 **1. Systematic review**

33 A systematic review will be performed to identify both morbidity and mortality outcomes reported in
34 existing studies involving paediatric sepsis in low and middle-income countries.

35 Types of studies, participants and interventions

36 All forms of published studies will be included. Subjects will children under the age of 18 with sepsis.
37 Those involving a high proportion (>50%) of premature patients will be excluded. Studies undertaken in a
38 low and middle-income country, as defined by the World Bank (23), and those describing a clinical
39 outcome that is measured systematically across the population studied will be included. Outcome will be
40 defined to be a measurement or observation used to capture and assess the effect of treatment such as
41 assessment of side effects (risk) or effectiveness (benefits) (24). All interventions related to paediatric
42 sepsis in this setting will be applicable. Sepsis, severe sepsis or septic shock will be defined by either the
43 International Consensus Conference on Pediatric Sepsis Definitions, American College of Chest
44 Physicians/ Society of Critical Care Medicine consensus criteria, sepsis-relevant International
45 Classification of Diseases (ICD)-9/ICD-10 codes), Integrated Management of Childhood Illness or clearly

self- defined (e.g. positive blood culture with one or more symptoms). Only articles in English from 1st January 1994 to 1st September 2019 will be assessed.

Search methods for identification of studies and study eligibility

The search strategy will be applied to PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials and the World Health Organisation International Clinical Trials Platform (ICTRP). One review author (GW) will independently screen the abstracts returned from the search strategy and any studies not meeting inclusion criteria will be excluded. Assessment of methodological quality will not be undertaken as we are evaluating outcomes only. The electronic search strategy was developed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (25). Details are outlined in supplemental files 3 and 4.

Data extraction, analysis and presentation

One review author (GW) will perform data extraction using a standardised form. A second reviewer (SM) will provide validation in cases of doubt. The following data will be retrieved: author details, year and journal of publication, sepsis definition, reported outcomes and outcome definition(s). The data will be synthesised and presented in a descriptive table. The outcomes will then be condensed into a list and placed into one of the 38 domains in the outcome taxonomy (26). Care will be taken to avoid ambiguity in the language used in the list of outcomes, with the final list of outcomes being reviewed by multiple healthcare professionals from around the world prior to commencement of the Delphi.

A list of authors will be compiled and invited to participate.

Records will be managed in EndNote X9 reference software (Clarivate Analytics, Boston, MA).

2. Delphi process

A two-round international e-Delphi survey involving an electronic-based questionnaire populated by outcomes from the literature review will then be performed to rank the outcomes.

Selection of panel members

A minimum of 50 participants for the Delphi panel will be involved. Nurses, clinicians and researchers will be recruited from around the world, with an aim to have all from low and middle-income countries. This will ensure a direct relevance to the population of children in most need, and give a voice to those rarely heard, a need previously identified in COS development (27). These participants will be identified from prior research papers on paediatric sepsis in LMIC, current involvement in ongoing studies and previous collaborations with members of the research team. The planned start date for the initial online survey is January 5th 2020. The second round will occur 6 weeks after participants after completed round one, and therefore occur in March 2020. The survey and list of outcomes will be translated into French and Spanish.

Delphi Round 1

Participants will initially be asked to complete brief questions related to their profession and experience. A list of outcomes generated from the systematic review will then be presented, and the participants required to rank each one on a scale from 1 to 9 (28). A score of 1 -3 indicates an unimportant outcome that should not be included, scores of 4 – 6 demonstrate an important but not critical outcome and scores of 7 - 9 imply an outcome that is essential to inclusion (19, 20, 21). A survey reminder will be sent out after 7 days and then again after 2 weeks. All outcomes will be carried on to the second round. There will be a free-text option for participants to suggest additional outcomes.

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3 At this point, approximately ten patients and their parents or guardian will be identified by clinicians
4 known to team members and approached after discharge. The questionnaire will be paper-based, and
5 outcome measures simplified into broad domains for the patients to score with the use of a local
6 facilitator, due to the limited access to internet, possible illiteracy and non-English speaking. The patient
7 survey will generate the relevant domains of key interest, and be incorporated into the outcomes for round
8 2 of the Delphi. The patient and parent/guardian generated outcomes and associated scores will be
9 displayed to the remaining stakeholders in round two. The specific granular outcomes will be defined by
10 the formal Delphi
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13 Delphi Round 2

14 In the second phase of the electronic questionnaire, the first round scores for each outcome and number of
15 prior respondents will be fed back to the participants. With this knowledge, including the patient scored
16 outcomes, each outcome will be rescored as described previously in Delphi round one.

17 Once again, a survey reminder will be sent out after 7 days and then again after 2 weeks.
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20 Analysis of Outcomes

21 Descriptive statistics will be used to analyse the responses from both round one and two, including
22 quantitative (absolute values, percentages) and qualitatively (suggestions given by
23 participants) measures. The denominator will reflect only those outcomes scored. Free text answers will be
24 reviewed by the authorship team to evaluate for uncaptured outcomes in the first-round questionnaire and
25 added if deemed appropriate to the second Delphi round questionnaire.
26

27 Our definition of consensus will follow that of previous COS publications (18). Analysis of the second
28 round outcomes for which $\geq 70\%$ of panellists scored it 7–9 and fewer than 15% of panellists scored it 1–3
29 will have met criteria for inclusion in the consensus meeting discussion. Outcomes for which $\geq 70\%$ of
30 panellists scored it 1–3, and fewer than 15% of panellists scored it 7–9 will be defined to have met
31 consensus for exclusion (18). Those outcomes not meeting criteria will be defined as lack of consensus.
32
33

34 **3. Consensus Meeting**

35 A face-to-face consensus meeting will be held after completion of the e-Delphi survey to finalise the
36 outcomes for inclusion in the COS. Invites will be sent to those that have completed both rounds of the
37 Delphi survey. All stakeholder groups will be represented, including local patients, parents, nurses and
38 clinicians. The exact final meeting format will depend upon the location and the number of participants
39 able to attend, but most likely occur in June 2020. All outcomes from round two of the e-Delphi survey
40 will be presented, including the results of the patient survey. Both the aggregate score for each outcome
41 and the individual score for each stakeholder group will be displayed in order to ensure any important
42 differences are highlighted and discussed. Participants will then anonymously vote for each outcome for
43 inclusion and exclusion in the finalised COS using a format similar to that of the Delphi survey.
44 Consensus for inclusion will be as before: if $\geq 70\%$ of panellists vote in favour and fewer than 15% of
45 panellists vote against. At this time, we will also enquire of the participants as to the practicality,
46 feasibility and cost-effectiveness of the finalised core outcome set and the ease as to which it could be
47 implemented. A formal feasibility matrix will be incorporated to inform this process so as to ensure that
48 feasibility is assessed in a standardized way. Those outcomes that are deemed feasible by $\geq 70\%$ of
49 panellists, will meet consensus for inclusion into the COS.
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53 **Ethics and dissemination**

54 All participants involved will be asked for their consent before undertaking the Delphi survey, and all
55 procedures will be conducted according to the Declaration of Helsinki. Involvement in the survey will be
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3 completely voluntary and the responses anonymised. A waiver for ethics approval has been granted by the
4 UBC Children's and Women's Research Ethics Board.
5

6 Implementation, dissemination and updating the COS

7 Upon completion of the consensus meeting, we will draft a COS guideline including an explanation of
8 our methods using the COS-STAR template (22). It will be submitted to a high impact journal and
9 presented at international meetings. We will seek endorsement and dissemination by major international
10 societies and journals with an interest in paediatric sepsis and hope that it can be used as a standard in
11 LMIC data sets for paediatric sepsis.

12 The next step will be to determine how best to measure the core outcomes using the COSMIN-Comet
13 (29) guidance. Those attending the consensus meeting and prior Delphi participants will be invited to
14 form a group to develop this further.
15

16 Discussion

17 At present, no core outcome sets exist for clinical trials in paediatric sepsis in LMIC. Outcomes from HIC
18 cannot be reliably extrapolated to this setting (30). This region-specific COS aims to reduce heterogeneity
19 that currently exists in this area, limit reporting bias and improve the quality and relevance of outcomes
20 published. It will also hopefully serve to highlight the heavy burden of paediatric sepsis in this setting
21 and aid collaboration and participation between all stakeholders, encouraging ongoing essential high-
22 quality research into the topic and facilitate further understanding of this complex disease.
23
24

25 Author Contributions

26 GW and SM were involved in study conception. GW, SM AND NK were involved in manuscript drafting
27 and editing.
28

29 Patient and Public Involvement

30 Patients will be approached during the second round of the Delphi Survey.
31

32 Funding Statement

33 This research received no specific grant from any funding agency in the public, commercial or not for
34 profit sectors.
35

36 Competing interests

37 All have no conflicts of interest to declare
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39

40 Figure 1. Timeline of COS development
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42 Word Count 3047 (including abstract and excluding references)
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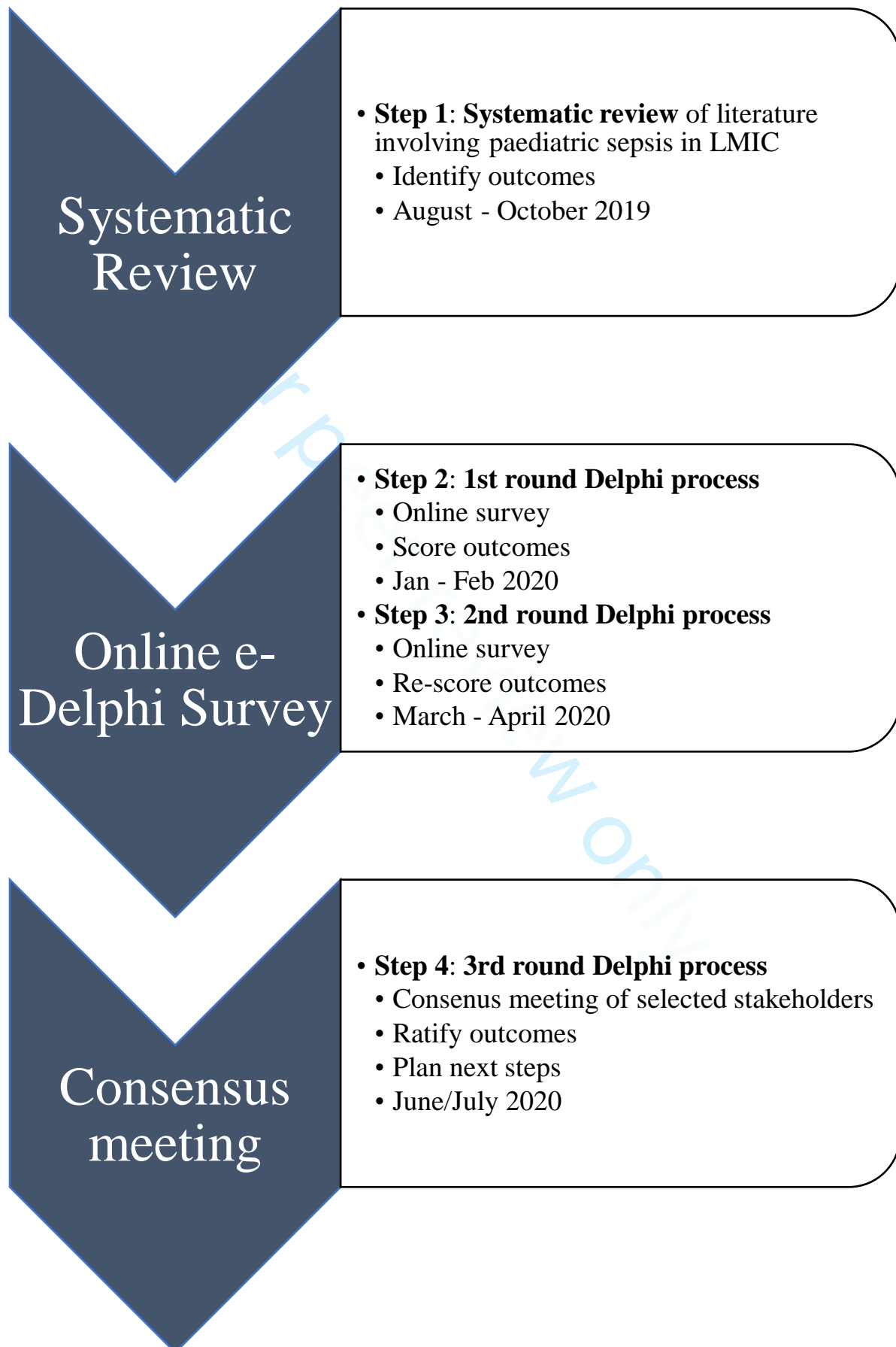
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Figure 1: Timeline of COS Development



Core Outcome Set-STAndards for Development: COS-STAD recommendations (15)

DOMAIN	STANDARD NUMBER	METHODOLOGY	HOW STANDARD WAS OR WAS NOT MET	PAGE AND SECTION REPORTED
Scope specification	1	The research or practice setting(s) in which the COS is to be applied	Paediatric research in low- and middle-income countries	Page 3. Scope of COS
	2	The health condition(s) covered by the COS	Sepsis – multiple definitions as mentioned in text	Page 3. Scope of COS
	3	The population(s) covered by the COS	Paediatric - The population will include those from newborn up to under eighteen years of age.	Page 3. Scope of COS
	4	The intervention(s) covered by the COS	All interventions related to paediatric sepsis in this setting will be applicable.	Page 3. Type of studies, participants and interventions
Stakeholders involved	5	Those who will use the COS in research	Researchers working in LMIC in paediatric sepsis	Page 4. Selection of panel members
	6	Healthcare professionals with experience of patients with the condition	Paediatricians and paediatric nurses working in LMIC	Page 4. Selection of panel members
	7	Patients with the condition or their representatives	Parents and guardians included of patients with previous sepsis in LMIC	Page 4. Selection of panel members
Consensus process	8	The initial list of outcomes considered both healthcare professionals' and patients' views A scoring process and consensus definition were described a priori.	Round two of the Delphi includes both health care professionals' and patient/parents' views	Page 4. Delphi process
	9		A list of outcomes generated from the systematic review will then be presented, and the participants required to rank each one on a scale from 1 to 9. A score of 1 -3 indicates an unimportant outcome that should not be included, scores of 4 – 6 demonstrate an important but not critical outcome and scores of 7 - 9 imply an outcome that is essential to inclusion. Analysis of the second-round outcomes for which ≥70% of panellists scored it 7-9 and fewer than 15% of panellists scored it 1-3 will have met criteria for inclusion in the consensus meeting discussion. Outcomes for which ≥70% of panellists scored it 1-3, and fewer than 15% of panellists scored it 7-9 will be defined to have met consensus for exclusion. Those outcomes not meeting criteria will be defined as lack of consensus	Page 4. Delphi process
	10	Criteria for including/dropping/adding outcomes were described a priori	All patient and participant suggested outcomes will be added to the second round Delphi. All outcomes from the first round will be carried over.	Page 4. Delphi process
	11	Care was taken to avoid ambiguity of language used in the list of outcomes.	The final list of outcomes will be reviewed by multiple healthcare professionals from around the world prior to commencement of the Delphi	Page 4. Delphi process

COS – Core outcome set

Core Outcome Set-STANDARDISED Protocol Items: COS-STAP Statement (16)

TITLE/ABSTRACT			PAGE AND SECTION REPORTED
Title	1a.	Identify in the title that the paper describes the protocol for the planned development of a COS	Page 1. Title
Abstract	1b.	Provide a structured abstract	Page 1. Abstract
INTRODUCTION			
Background and objectives	2a.	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation	Page 2. Background
	2b.		Page 2. Objectives
Scope	3a.	Describe the health condition(s) and population(s) that will be covered by the COS	Page 2. Objectives
	3b.		Page 2. Objectives
	3c.		Page 2. Objectives
		Describe the context of use for which the COS is applied	Page 2. Objectives
METHODS			
Stakeholders	4.	Describe the stakeholder groups to be involved in the COS development process, the nature and rationale for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study.	Page 4. Delphi process
Information sources	5a.		Page 3. Systematic Review
Consensus process	5b.	Describe how outcomes may be dropped/combined with reasons	Page 4. Delphi process
	6.		Page 4. Delphi process
Consensus definition	7a.	Describe the plans for how the consensus process will be undertaken	Page 4. Delphi process
	7b.		Page 4. Delphi process
		Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process.	Page 4. Delphi process
ANALYSIS			
Outcome scoring/feedback	8.	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	Page 4. Delphi process
Missing data	9.		Page 4. Delphi process
		Describe how missing data will be handled during the consensus process	Page 4. Delphi process
ETHICS and DISSEMINATION			
Ethics approval/informed consent	10.	Describe any plans for obtaining research ethics committee/ institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant).	Page 5. Ethics and dissemination
Dissemination	11.		Page 5. Implementation, dissemination and updating the COS
		Describe any plans to communicate the results of study participants and COS users, inclusive of methods and timing of dissemination	
ADMINISTRATIVE INFORMATION			
Funders	12.	Describe sources of funding, role of funders	Page 6. Funding Statement
Conflicts of interest	13.		Page 6. Competing interests
		Describe any potential conflicts of interest within the study team and how they will be managed.	

COS – Core outcome set

Supplemental File 3

Systematic Review Search Strategies

Criteria

- Inclusion:
 - Articles published in English
 - Peer Reviewed articles
 - Focus on paediatric patients with sepsis (those under 18 years of age)
 - Sepsis, severe sepsis or septic shock as defined by international consensus (International Consensus Conference on Pediatric Sepsis Definitions, American College of Chest Physicians/ Society of Critical Care Medicine consensus criteria, sepsis-relevant International Classification of Diseases (ICD)-9/ICD-10 codes), by IMCI and self-defined (e.g. positive blood culture with one or more symptoms)
 - Involve research in low - middle income countries
 - Describe a clinical outcome that is measured systematically across the population studied
 - Years : 1994 to 2019

- Exclusion
 - Adult studies (>18 yrs.)
 - Preterm Sepsis
 - Those performed in high resource countries (as defined by the World Bank)
 - No outcome data
 - Articles which are not peer reviewed
 - Duplicate references
 - Studies missing methods of data collection and eligibility criteria
 - Studies involving sepsis in specific subgroup population
 - Retrospective bacteremia

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('sepsis'/exp OR sepsis:ti,ab,kw OR septic:ti,ab,kw OR pyemia*:ti,ab,kw OR pyohemia*:ti,ab,kw OR pyaemia*:ti,ab,kw OR septicemia*:ti,ab,kw OR 'blood poisoning':ti,ab,kw) AND ('newborn'/exp OR 'pediatrics'/exp OR 'child'/exp OR 'adolescent'/exp OR infant*:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw OR pediatric:ti,ab OR paediatric:ti,ab OR child:ti,ab,kw OR children:ti,ab,kw OR toddler*:ti,ab,kw OR adolescen*:ti,ab,kw OR teen*:ti,ab,kw OR youth*:ti,ab,kw OR boy:ti,ab,kw OR boys:ti,ab,kw OR girl*:ti,ab,kw OR juvenile*:ti,ab,kw) AND ('developing country'/exp OR 'low income country'/exp OR 'middle income country'/exp OR 'afghanistan'/exp OR 'albania'/exp OR 'algeria'/exp OR 'american samoa'/exp OR 'angola'/exp OR 'armenia'/exp OR 'azerbaijan'/exp OR 'bangladesh'/exp OR 'belarus'/exp OR 'belize'/exp OR 'benin'/exp OR 'bhutan'/exp OR 'bolivia'/exp OR 'bosnia and herzegovina'/exp OR 'botswana'/exp OR 'brazil'/exp OR 'bulgaria'/exp OR 'burkina faso'/exp OR 'burundi'/exp OR 'cape verde'/exp OR 'cambodia'/exp OR 'cameroon'/exp OR 'central african republic'/exp OR 'chad'/exp OR 'china'/exp OR 'colombia'/exp OR 'comoros'/exp OR 'democratic republic congo'/exp OR 'congo'/exp OR 'costa rica'/exp OR 'cote d'ivoire'/exp OR 'cuba'/exp OR 'djibouti'/exp OR 'dominica'/exp OR 'dominican republic'/exp OR 'ecuador'/exp OR 'egypt'/exp OR 'el salvador'/exp OR 'eritrea'/exp OR 'ethiopia'/exp OR 'equatorial guinea'/exp OR

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4 'guinea-bissau'/exp OR 'guatemala'/exp OR 'guyana'/exp OR 'haiti'/exp OR 'honduras'/exp OR
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11 'mozambique'/exp OR 'myanmar'/exp OR 'namibia'/exp OR 'nauru'/exp OR 'nepal'/exp OR
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16 sudan'/exp OR 'sri lanka'/exp OR 'saint lucia'/exp OR 'saint vincent and the grenadines'/exp OR
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uzbekistan*:ti,ab,kw OR uzbek:ti,ab,kw OR vanuatu*:ti,ab,kw OR venezuela*:ti,ab,kw OR
vietnam*:ti,ab,kw OR 'viet nam':ti,ab,kw OR 'west bank':ti,ab,kw OR 'gaza':ti,ab,kw OR
yemen*:ti,ab,kw OR zambia*:ti,ab,kw OR zimbabwe*:ti,ab,kw)

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("Sepsis" [Mesh] OR sepsis[tiab] OR septic[tiab] OR pyemia*[tiab] OR pyohemia*[tiab] OR
pyaemia*[tiab] OR septicemia*[tiab] OR "blood poisoning"[tiab]) AND ("Infant,
Newborn"[Mesh] OR "Pediatrics"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR
infant[tiab] OR infants[tiab] OR baby[tiab] OR babies[tiab] OR newborn[tiab] OR newborns[tiab]
OR neonate[tiab] OR neonates[tiab] OR pediatric [tiab] OR paediatric[tiab] OR child[tiab] OR
children[tiab] OR toddler[tiab] OR toddlers[tiab] OR adolescent[tiab] OR adolescence[tiab] OR
teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR youth[tiab] OR boy[tiab] OR
boys[tiab] OR girl[tiab] OR girls[tiab] OR juvenile[tiab] OR juveniles[tiab]) AND ("Developing
Countries"[Mesh] OR "Afghanistan"[Mesh] OR "Albania"[Mesh] OR "Algeria"[Mesh] OR
"American Samoa"[Mesh] OR "Angola"[Mesh] OR "Armenia"[Mesh] OR "Azerbaijan"[Mesh]
OR "Bangladesh"[Mesh] OR "Republic of Belarus"[Mesh] OR "Belize"[Mesh] OR
"Benin"[Mesh] OR "Bhutan"[Mesh] OR "Bolivia"[Mesh] OR "Bosnia and Herzegovina"[Mesh]
OR "Botswana"[Mesh] OR "Brazil"[Mesh] OR "Bulgaria"[Mesh] OR "Burkina Faso"[Mesh] OR
"Burundi"[Mesh] OR "Cabo Verde"[Mesh] OR "Cambodia"[Mesh] OR "Cameroon"[Mesh] OR
"Central African Republic"[Mesh] OR "Chad"[Mesh] OR "China"[Mesh:NoExp] OR
"Colombia"[Mesh] OR "Comoros"[Mesh] OR "Democratic Republic of the Congo"[Mesh] OR
"Congo"[Mesh] OR "Costa Rica"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Cuba"[Mesh] OR
"Djibouti"[Mesh] OR "Dominica"[Mesh] OR "Dominican Republic"[Mesh] OR "Ecuador"[Mesh]
OR "Egypt"[Mesh] OR "El Salvador"[Mesh] OR "Eritrea"[Mesh] OR "Ethiopia"[Mesh] OR
"Equatorial Guinea"[Mesh] OR "Fiji"[Mesh] OR "Gabon"[Mesh] OR "Gambia"[Mesh] OR
"Georgia (Republic)"[Mesh] OR "Ghana"[Mesh] OR "Grenada"[Mesh] OR "Guinea"[Mesh] OR
"Guinea-Bissau"[Mesh] OR "Guatemala"[Mesh] OR "Guyana"[Mesh] OR "Haiti"[Mesh] OR
"Honduras"[Mesh] OR "India"[Mesh] OR "Indonesia"[Mesh] OR "Iran"[Mesh] OR "Iraq"[Mesh]
OR "Jamaica"[Mesh] OR "Jordan"[Mesh] OR "Kazakhstan"[Mesh] OR "Kenya"[Mesh] OR
"Democratic People's Republic of Korea"[Mesh] OR "Kosovo"[Mesh] OR "Kyrgyzstan"[Mesh]
OR "Laos"[Mesh] OR "Lebanon"[Mesh] OR "Lesotho"[Mesh] OR "Liberia"[Mesh] OR
"Libya"[Mesh] OR "Macedonia (Republic)"[Mesh] OR "Madagascar"[Mesh] OR
"Malawi"[Mesh] OR "Malaysia"[Mesh] OR "Mali"[Mesh] OR "Mauritania"[Mesh] OR
"Mauritius"[Mesh] OR "Mexico"[Mesh] OR "Micronesia"[Mesh] OR "Moldova"[Mesh] OR
"Mongolia"[Mesh] OR "Montenegro"[Mesh] OR "Morocco"[Mesh] OR "Mozambique"[Mesh]
OR "Myanmar"[Mesh] OR "Namibia"[Mesh] OR "Nepal"[Mesh] OR "Nicaragua"[Mesh] OR
"Niger"[Mesh] OR "Nigeria"[Mesh] OR "Pakistan"[Mesh] OR "Papua New Guinea"[Mesh] OR
"Paraguay"[Mesh] OR "Peru"[Mesh] OR "Philippines"[Mesh] OR "Romania"[Mesh] OR

1
2
3 "Russia"[Mesh] OR "Rwanda"[Mesh] OR "Samoa"[Mesh] OR "Sao Tome and Principe"[Mesh]
4 OR "Senegal"[Mesh] OR "Serbia"[Mesh] OR "Sierra Leone"[Mesh] OR "Somalia"[Mesh] OR
5 "South Africa"[Mesh] OR "South Sudan"[Mesh] OR "Sri Lanka"[Mesh] OR "Saint Lucia"[Mesh]
6 OR "Saint Vincent and the Grenadines"[Mesh] OR "Sudan"[Mesh] OR "Suriname"[Mesh] OR
7 "Swaziland"[Mesh] OR "Syria"[Mesh] OR "Tajikistan"[Mesh] OR "Tanzania"[Mesh] OR
8 "Thailand"[Mesh] OR "Timor-Leste"[Mesh] OR "Togo"[Mesh] OR "Tonga"[Mesh] OR
9 "Tunisia"[Mesh] OR "Turkey"[Mesh] OR "Turkmenistan"[Mesh] OR "Uganda"[Mesh] OR
10 "Ukraine"[Mesh] OR "Uzbekistan"[Mesh] OR "Vanuatu"[Mesh] OR "Venezuela"[Mesh] OR
11 "Vietnam"[Mesh] OR "Yemen"[Mesh] OR "Zambia"[Mesh] OR "Zimbabwe"[Mesh] OR
12 "developing country" OR "developing countries" OR "developing economy" OR "under
13 developed country" OR "under developed countries" OR "third world" OR "low income country"
14 OR "low income economy" OR "low income nation" OR "lower income country" OR "lower
15 middle income country" OR "middle income country" OR "middle income economy" OR "middle
16 income nation" OR "poor country" OR "poor countries" OR "LAMI country" OR "LAMI
17 countries" OR Afghanistan[tiab] OR Afghani*[tiab] OR Albania*[tiab] OR Algeria*[tiab] OR
18 "American Samoa"[tiab] OR Samoan*[tiab] OR Angola[tiab] OR Angolan*[tiab] OR
19 Armenia*[tiab] OR Azerbaijan*[tiab] OR Bangladesh[tiab] OR Bengali*[tiab] OR Belarus*[tiab]
20 OR Byelorussian[tiab] OR Byelarus[tiab] OR Belorussia[tiab] OR Belize*[tiab] OR Benin*[tiab]
21 OR Bhutan*[tiab] OR Bolivia*[tiab] OR Bosnia*[tiab] OR Herzegovina[tiab] OR
22 Botswana*[tiab] OR Bechuanaland[tiab] OR Batswana[tiab] OR Motswana[tiab] OR Brazil*[tiab]
23 OR Bulgaria*[tiab] OR "Burkina Faso"[tiab] OR Burkinabé[tiab] OR Burundi*[tiab] OR "Cabo
24 Verde"[tiab] OR "Cape Verde"[tiab] OR "Cape Verdean"[tiab] OR Cambodia*[tiab] OR
25 Khmer[tiab] OR Cameroon*[tiab] OR Cameroun[tiab] OR "Central African Republic"[tiab] OR
26 "Centrafrican Republic"[tiab] OR "Chad"[tiab] OR Tchad [tiab] OR Chadian[tiab] OR China[tiab]
27 OR Chinese[tiab] OR Colombia*[tiab] OR Comoros[tiab] OR "Comoro Islands"[tiab] OR
28 Comorian[tiab] OR "Democratic Republic of the Congo"[tiab] OR "Democratic Republic
29 Congo"[tiab] OR Congo*[tiab] OR "Costa Rica"[tiab] OR "Costa Rican"[tiab] OR "Cote
30 d'Ivoire"[tiab] OR "Ivory Coast"[tiab] OR Ivorian[tiab] OR Cuba*[tiab] OR Djibouti*[tiab] OR
31 Dominica*[tiab] OR "Dominican Republic"[tiab] OR "French Sudan"[tiab] OR Ecuador*[tiab]
32 OR Egypt*[tiab] OR "United Arab Republic"[tiab] OR "El Salvador"[tiab] OR Salvador*[tiab]
33 OR Eritrea*[tiab] OR Ethiopia*[tiab] OR "Equatorial Guinea"[tiab] OR Equatoguinean[tiab] OR
34 Fiji*[tiab] OR Gabon*[tiab] OR Gaboon[tiab] OR Gambia*[tiab] OR "Republic of Georgia"[tiab]
35 OR "Georgia SSR"[tiab] OR Ghana*[tiab] OR Grenada[tiab] OR Grenadian[tiab] OR
36 Guinea*[tiab] OR "Guinea-Bissau"[tiab] OR "Portuguese Guinea"[tiab] OR Guatemala*[tiab] OR
37 Guyana[tiab] OR Guyanese[tiab] OR Haiti*[tiab] OR Hondura*[tiab] OR India[tiab] OR "Indian
38 Union"[tiab] OR Indonesia*[tiab] OR "Netherlands East Indies"[tiab] OR "East Indies"[tiab] OR
39 "West Irian"[tiab] OR "West New Guinea"[tiab] OR Timor[tiab] OR "Java"[tiab] OR "Irian
40 Jaya"[tiab] OR Bali[tiab] OR Sumatra[tiab] OR Celebes[tiab] OR Sulawesi[tiab] OR "Malay
41 Archipelago"[tiab] OR Madura[tiab] OR Iran*[tiab] OR Iraq*[tiab] OR Jamaica*[tiab] OR
42 Jordan*[tiab] OR Kazakhstan*[tiab] OR Kazakh[tiab] OR Kenya*[tiab] OR Kiribati*[tiab] OR
43 "Democratic People's Republic of Korea"[tiab] OR "North Korea"[tiab] OR "North Korean"[tiab]
44 OR Kosovo[tiab] OR Kosovar[tiab] OR Kosovan[tiab] OR Kyrgyzstan*[tiab] OR Kirghizia[tiab]
45 OR "Kyrgyz Republic"[tiab] OR "Kirghiz SSR"[tiab] OR Kirgizstan[tiab] OR Kyrgyzs[tiab] OR
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3 Lao[tiab] OR Laos[tiab] OR Laotian*[tiab] OR Lebanon[tiab] OR Lebanese[tiab] OR
4 Lesotho*[tiab] OR Basutoland[tiab] OR Liberia*[tiab] OR Libya*[tiab] OR Macedonia*[tiab] OR
5 Madagascar[tiab] OR Malagasy[tiab] OR Malawi*[tiab] OR Nyasaland[tiab] OR Malaysia*[tiab]
6 OR Malaya*[tiab] OR Maldives[tiab] OR Maldivian[tiab] OR Mali[tiab] OR Malian[tiab] OR
7 “Marshall Islands”[tiab] OR Mauritania*[tiab] OR Mauretania[tiab] OR Mauritius[tiab] OR
8 Mauritian[tiab] OR Mexico[tiab] OR Mexican*[tiab] OR Micronesia*[tiab] OR Moldova*[tiab]
9 OR Moldavia*[tiab] OR Mongolia*[tiab] OR Montenegro[tiab] OR Montenegrin[tiab] OR
10 Morocco[tiab] OR Ifni[tiab] OR Moroccan[tiab] OR Mozambique[tiab] OR “Portuguese East
11 Africa”[tiab] OR Mocambique[tiab] OR Mozambican[tiab] OR Myanmar[tiab] OR Burma[tiab]
12 OR Myanma[tiab] OR Burmese[tiab] OR Namibia*[tiab] OR Nauru*[tiab] OR Nepal*[tiab] OR
13 Nicaragua*[tiab] OR Niger*[tiab] OR Nigeria*[tiab] OR Pakistan*[tiab] OR “Papua New
14 Guinea”[tiab] OR “East New Guinea” [tiab] OR Paraguay*[tiab] OR Peru*[tiab] OR
15 Philippines[tiab] OR Phillipines[tiab] OR Filipino*[tiab] OR Romania*[tiab] OR
16 Rumania*[tiab] OR Roumania*[tiab] OR Russia*[tiab] OR Rwanda*[tiab] OR Ruanda[tiab]
17 OR Samoa*[tiab] OR “Sao Tome”[tiab] OR Senegal*[tiab] OR Serbia*[tiab] OR “Sierra
18 Leone”[tiab] OR “Sierra Leonean” [tiab] OR “Solomon Islands” [tiab] OR “Solomon Islander”
19 [tiab] OR Somali*[tiab] OR “South Africa”[tiab] OR “South African” [tiab] OR “South
20 Sudan”[tiab] OR “South Sudanese” [tiab] OR “Sri Lanka”[tiab] OR “Sri Lankan” [tiab] OR
21 Ceylon[tiab] OR “Saint Lucia”[tiab] OR “St. Lucia”[tiab] OR “Saint Vincent”[tiab] OR “St.
22 Vincent”[tiab] OR Sudan* [tiab] OR Surinam*[tiab] OR Swaziland[tiab] OR “Swazi”[tiab] OR
23 Eswatini[tiab] OR Syria*[tiab] OR Tajikistan*[tiab] OR Tadjikistan*[tiab] OR Tadzihik[tiab]
24 OR Tanzania*[tiab] OR Tanganyika[tiab] OR Thai*[tiab] OR “Timor-Leste”[tiab] OR “East
25 Timor” [tiab] OR Togo*[tiab] OR Tonga*[tiab] OR Tunisia*[tiab] OR Tunesia[tiab] OR
26 Turkey[tiab] OR Turkish[tiab] OR Turkmenistan[tiab] OR Turkmen*[tiab] OR Tuvalu*[tiab]
27 OR Uganda*[tiab] OR Ukraine[tiab] OR Ukrainian[tiab] OR Ukraina[tiab] OR
28 Uzbekistan*[tiab] OR Uzbek[tiab] OR Vanuatu*[tiab] OR Venezuela*[tiab] OR Vietnam*[tiab]
29 OR “Viet Nam” [tiab] OR “West Bank” [tiab] OR “Gaza” [tiab] OR Yemen*[tiab] OR
30 Zambia*[tiab] OR Zimbabwe*[tiab]

Scopus

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41 = 6,164 results after limiting to English, 1994-present and excluding books, book chapters,
42 editorials, notes, and letters on 6/24/2019

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44 TITLE-ABS-KEY (sepsis OR septic OR pyemia* OR pyohemia* OR pyaemia* OR
45 septicemia* OR {blood poisoning}) AND TITLE-ABS-KEY (infant OR infants OR baby
46 OR babies OR newborn OR newborns OR neonate OR neonates OR pediatric OR paediatric
47 OR child OR children OR toddler OR toddlers OR adolescent OR adolescence OR teen
48 OR teens OR teenager OR teenagers OR youth OR boy OR boys OR girl OR girls OR
49 juvenile OR juveniles) AND TITLE-ABS-KEY ({developing country} OR {developing
50 countries} OR {developing economy} OR {under developed country} OR {under developed
51 countries} OR {third world} OR {low income country} OR {low income economy} OR {low
52 income nation} OR {lower income country} OR {lower middle income country} OR {middle
53 income country} OR {middle income economy} OR {middle income nation} OR {poor
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country} OR {poor countries} OR {LAMI country} OR {LAMI countries} OR afghanistan
OR afghani* OR albania* OR algeria* OR {American Samoa} OR samoan* OR angola
OR angolan* OR armenia* OR azerbaijan* OR bangladesh OR bengali* OR belarus* OR
byelorussian OR byelarus OR belorussia OR belize* OR benin* OR bhutan* OR bolivia*
OR bosnia* OR herzegovina OR botswana* OR bechuanaland OR batswana OR motswana
OR brazil* OR bulgaria* OR "Burkina Faso" OR burkinabé OR burundi* OR "Cabo Verde"
OR "Cape Verde" OR "Cape Verdean" OR cambodia* OR khmer OR cameroon* OR
cameroun OR "Central African Republic" OR "Centrafrican Republic" OR "Chad" OR tchad
OR chadian OR china OR chinese OR colombia* OR comoros OR "Comoro Islands" OR
comorian OR "Democratic Republic of the Congo" OR "Democratic Republic Congo" OR
congo* OR "Costa Rica" OR "Costa Rican" OR "Cote d'Ivoire" OR "Ivory Coast" OR ivorian
OR cuba* OR djibouti* OR dominica* OR "Dominican Republic" OR "French Sudan" OR
ecuador* OR egypt* OR "United Arab Republic" OR "El Salvador" OR salvador* OR
eritrea* OR ethiopia* OR "Equatorial Guinea" OR equatoguinean OR fiji* OR gabon* OR
gaboon OR gambia* OR "Republic of Georgia" OR "Georgia SSR" OR ghana* OR grenada
OR grenadian OR guinea* OR "Guinea-Bissau" OR "Portuguese Guinea" OR guatemala*
OR guyana OR guyanese OR haiti* OR hondura* OR india OR "Indian Union" OR
indonesia* OR "Netherlands East Indies" OR "East Indies" OR "West Irian" OR "West New
Guinea" OR timor OR "Java" OR "Irian Jaya" OR bali OR sumatra OR celebes OR
sulawesi OR "Malay Archipelago" OR madura OR iran* OR iraq* OR jamaica* OR jordan*
OR kazakhstan* OR kazakh OR kenya* OR kiribati* OR "Democratic People's Republic of
Korea" OR "North Korea" OR "North Korean" OR kosovo OR kosovar OR kosovan OR
kyrgyzstan* OR kirghizia OR "Kyrgyz Republic" OR "Kirghiz SSR" OR kirgizstan OR
kyrgyzs OR lao OR laos OR laotian* OR lebanon OR lebanese OR lesotho* OR basutoland
OR liberia* OR libya* OR macedonia* OR madagascar OR malagasy OR malawi* OR
nyasaland OR malaysia* OR malaya* OR maldives OR maldivian OR mali OR malian
OR "Marshall Islands" OR mauritania* OR mauretania OR mauritius OR mauritian OR
mexico OR mexican* OR micronesia* OR moldova* OR moldavia* OR mongolia* OR
montenegro OR montenegrin OR morocco OR ifni OR moroccan OR mozambique OR
"Portuguese East Africa" OR mocambique OR mozambican OR myanmar OR burma OR
myanma OR burmese OR namibia* OR nauru* OR nepal* OR nicaragua* OR niger* OR
nigeria* OR pakistan* OR "Papua New Guinea" OR "East New Guinea" OR paraguay* OR
peru* OR philippines OR philipines OR filipino* OR romania* OR rumania* OR
roumania* OR russia* OR rwanda* OR ruanda OR samoa* OR "Sao Tome" OR senegal*
OR serbia* OR "Sierra Leone" OR "Sierra Leonean" OR "Solomon Islands" OR "Solomon
Islander" OR somali* OR "South Africa" OR "South African" OR "South Sudan" OR "South
Sudanese" OR "Sri Lanka" OR "Sri Lankan" OR ceylon OR "Saint Lucia" OR "St. Lucia"
OR "Saint Vincent" OR "St. Vincent" OR sudan* OR surinam* OR swaziland OR "Swazi"
OR eswatini OR syria* OR tajikistan* OR tadjikistan* OR tadjhik OR tanzania* OR
tanganyika OR thai* OR "Timor-Leste" OR "East Timor" OR togo* OR tonga* OR tunisia*
OR tunesia OR turkey OR turkish OR turkmenistan OR turkmen* OR tuvalu* OR uganda*
OR ukraine OR ukrainian OR ukraine OR uzbekistan* OR uzbek OR vanuatu* OR
venezuela* OR vietnam* OR "Viet Nam" OR "West Bank" OR "Gaza" OR yemen* OR

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3 zambia* OR zimbabwe*) AND (LIMIT-TO(LANGUAGE, "English")) AND (LIMIT-
4 TO(PUBYEAR, 2019) OR LIMIT-TO(PUBYEAR, 2018) OR LIMIT-TO(PUBYEAR,
5 2017) OR LIMIT-TO(PUBYEAR, 2016) OR LIMIT-TO(PUBYEAR, 2015) OR LIMIT-
6 TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR,
7 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-
8 TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR,
9 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-
10 TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR,
11 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000) OR LIMIT-
12 TO(PUBYEAR, 1999) OR LIMIT-TO(PUBYEAR, 1998) OR LIMIT-TO(PUBYEAR,
13 1997) OR LIMIT-TO(PUBYEAR, 1996) OR LIMIT-TO(PUBYEAR, 1995) OR LIMIT-
14 TO(PUBYEAR, 1994)) AND (EXCLUDE(DOCTYPE, "no") OR EXCLUDE(
15 DOCTYPE, "ed") OR EXCLUDE(DOCTYPE, "ch") OR EXCLUDE(DOCTYPE, "sh"
16) OR EXCLUDE(DOCTYPE, "bk"))

21 22 23 Cochrane Library

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25 #1: MeSH descriptor: [Sepsis] explode all trees

26
27 #2: sepsis OR septic OR pyemia* OR pyohemia* OR pyaemia* OR septicemia* OR "blood
28 poisoning"

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30 #3: #1 OR #2

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32 #4: MeSH descriptor: [Infant, Newborn] explode all trees

33
34 #5: MeSH descriptor: [Pediatrics] explode all trees

35
36 #6: MeSH descriptor: [Child] explode all trees

37
38 #7: MeSH descriptor: [Adolescent] explode all trees

39
40 #8: infant OR infants OR baby OR babies OR newborn OR newborns OR neonate OR neonates
41 OR pediatric OR paediatric OR child OR children OR toddler OR toddlers OR adolescent OR
42 adolescence OR teen OR teens OR teenager OR teenagers OR youth OR boy OR boys OR girl OR
43 girls OR juvenile OR juveniles

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45 #9: #4 OR #5 OR #6 OR #7 OR #8

46
47 #10: MeSH descriptor: [Developing Countries] explode all trees

48
49 #11: ("developing country" OR "developing countries" OR "developing economy" OR "under
50 developed country" OR "under developed countries" OR "third world" OR "low income country"
51 OR "low income economy" OR "low income nation" OR "lower income country" OR "lower
52 middle income country" OR "middle income country" OR "middle income economy" OR "middle
53 income nation" OR "poor country" OR "poor countries" OR "LAMI country" OR "LAMI
54 countries" OR Afghanistan OR Afghani* OR Albania* OR Algeria* OR "American Samoa" OR

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3 Samoa* OR Angola OR Angolan* OR Armenia* OR Azerbaijan* OR Bangladesh OR Bengali*
4 OR Belarus* OR Byelorussian OR Byelarus OR Belorussia OR Belize* OR Benin* OR Bhutan*
5 OR Bolivia* OR Bosnia* OR Herzegovina OR Botswana* OR Bechuanaland OR Batswana OR
6 Motswana OR Brazil* OR Bulgaria* OR "Burkina Faso" OR Burkinabé OR Burundi* OR "Cabo
7 Verde" OR "Cape Verde" OR "Cape Verdean" OR Cambodia* OR Khmer OR Cameroon* OR
8 Cameroun OR "Central African Republic" OR "Centrafican Republic" OR "Chad" OR Tchad
9 OR Chadian OR China OR Chinese OR Colombia* OR Comoros OR "Comoro Islands" OR
10 Comorian OR "Democratic Republic of the Congo" OR "Democratic Republic Congo" OR
11 Congo* OR "Costa Rica" OR "Costa Rican" OR "Cote d Ivoire" OR "Ivory Coast" OR Ivorian
12 OR Cuba* OR Djibouti* OR Dominica* OR "Dominican Republic" OR "French Sudan" OR
13 Ecuador* OR Egypt* OR "United Arab Republic" OR "El Salvador" OR Salvador* OR Eritrea*
14 OR Ethiopia* OR "Equatorial Guinea" OR Equatoguinean OR Fiji* OR Gabon* OR Gaboon OR
15 Gambia* OR "Republic of Georgia" OR "Georgia SSR" OR Ghana* OR Grenada OR Grenadian
16 OR Guinea* OR "Guinea-Bissau" OR "Portuguese Guinea" OR Guatemala* OR Guyana OR
17 Guyanese OR Haiti* OR Hondura* OR India OR "Indian Union" OR Indonesia* OR "Netherlands
18 East Indies" OR "East Indies" OR "West Irian" OR "West New Guinea" OR Timor OR "Java"
19 OR "Irian Jaya" OR Bali OR Sumatra OR Celebes OR Sulawesi OR "Malay Archipelago" OR
20 Madura OR Iran* OR Iraq* OR Jamaica* OR Jordan* OR Kazakhstan* OR Kazakh OR Kenya*
21 OR Kiribati* OR "Democratic People's Republic of Korea" OR "North Korea" OR "North
22 Korean" OR Kosovo OR Kosovar OR Kosovan OR Kyrgyzstan* OR Kirghizia OR "Kyrgyz
23 Republic" OR "Kirghiz SSR" OR Kirgizstan OR Kyrgyzs OR Lao OR Laos OR Laotian* OR
24 Lebanon OR Lebanese OR Lesotho* OR Basutoland OR Liberia* OR Libya* OR Macedonia*
25 OR Madagascar OR Malagasy OR Malawi* OR Nyasaland OR Malaysia* OR Malaya* OR
26 Maldives OR Maldivian OR Mali OR Malian OR "Marshall Islands" OR Mauritania* OR
27 Mauretania OR Mauritius OR Mauritian OR Mexico OR Mexican* OR Micronesia* OR
28 Moldova* OR Moldavia* OR Mongolia* OR Montenegro OR Montenegrin OR Morocco OR Ifni
29 OR Moroccan OR Mozambique OR "Portuguese East Africa" OR Mocambique OR Mozambican
30 OR Myanmar OR Burma OR Myanma OR Burmese OR Namibia* OR Nauru* OR Nepal* OR
31 Nicaragua* OR Niger* OR Nigeria* OR Pakistan* OR "Papua New Guinea" OR "East New
32 Guinea" OR Paraguay* OR Peru* OR Philippines OR Phillipines OR Filipino* OR Romania*
33 OR Rumania* OR Roumania* OR Russia* OR Rwanda* OR Ruanda OR Samoa* OR "Sao
34 Tome" OR Senegal* OR Serbia* OR "Sierra Leone" OR "Sierra Leonean" OR "Solomon
35 Islands" OR "Solomon Islander" OR Somali* OR "South Africa" OR "South African" OR
36 "South Sudan" OR "South Sudanese" OR "Sri Lanka" OR "Sri Lankan" OR Ceylon OR "Saint
37 Lucia" OR "Saint Vincent" OR Sudan* OR Surinam* OR Swaziland OR Swazi OR Eswatini
38 OR Syria* OR Tajikistan* OR Tadjikistan* OR Tadzhik OR Tanzania* OR Tanganyika OR
39 Thai* OR "Timor Leste" OR "East Timor" OR Togo* OR Tonga* OR Tunisia* OR Tunesia
40 OR Turkey OR Turkish OR Turkmenistan OR Turkmen* OR Tuvalu* OR Uganda* OR Ukraine
41 OR Ukrainian OR Ukraina OR Uzbekistan* OR Uzbek OR Vanuatu* OR Venezuela* OR
42 Vietnam* OR "Viet Nam" OR "West Bank" OR "Gaza" OR Yemen* OR Zambia* OR
43 Zimbabwe*)

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55 #12: #10 OR #11
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3 #13: #3 AND #9 AND #12
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For peer review only

Supplementary file 4

PRISMA-P Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1 title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>	<input type="checkbox"/>	Page 2 Methods and analysis
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1 Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5 Manuscript contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No funding
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2 Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 Methods
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 Methods
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2 Methods
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Supplemental file 3
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – Types of studies, participants, and interventions
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – data extraction
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3 – Assessment of

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					methodological quality
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable – qualitative systematic review
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable – qualitative systematic review
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not applicable, systematic review only
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not applicable