BMJ Open

Global epidemiology of septic shock in critically ill patients: a protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032289
Article Type:	Protocol
Date Submitted by the Author:	13-Jun-2019
Complete List of Authors:	Frank Leonel, Tianyi Tianyi; Mayo Darle sub-Divisional Hospital, Tochie, Joel Noutakdie; Universite de Yaounde I Faculte de Medecine et des Sciences Biomedicales, Danwang, Celestin; Universite Libre de Bruxelles, School Of Public Health; Mbonda, Aime ; National social Insurance Fond Hospital, Department of Surgery Mazou, Temgoua Ngou ; Faculty of Medecine and Biomedical Sciences, Internal medicine and specialities Mapoh, Sylvester Yari ; University of Louisiana, Department of Family Medicine Nkemngu, Njinkeng J.; University of Toronto, Department of Anesthesia Bigna, Jean Joel; Centre Pasteur of Cameroon, Department of Epidemiology and Public Health
Keywords:	Septic shock, intensive care, case fatality rate, Epidemiology < TROPICAL MEDICINE, critically ill patients

Global epidemiology of septic shock in critically ill patients: a protocol for a systematic review and meta-analysis

Frank-Leonel Tianyi[1], Joel Noutakdie Tochie[2], Celestin Danwang [2,3], Aime Mbonda[4], Mazou N. Temgoua[5], Sylvester Yari Mapoh[6], Njinkeng J. Nkemngu[7], Jean Joel Bigna[8,9]

[1]Department of General Medicine, Ibal sub-Divisional Hospital, Ibal, Cameroon,

[2]Department of Surgery and sub-Specialties, Faculty of Medicine and Biomedical Sciences, Yaoundé, Cameroon.

[3]Department of Public Health, Universite libre de Bruxelles, Bruxelles, Belgium

[4]Department of Surgery, National social Insurance Fond hospital, Yaounde, Cameroon

[5]Department of Internal Medicine and sub-Specialties, Faculty of Medicine and Biomedical Sciences, Yaoundé, Cameroon.

[6]Department of Family Medicine, University of Louissana, Louissana, USA

[7]Department of Anaesthesia, University of Toronto, Canada

[8]Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon.

[9]Faculty of Medicine, University of Paris Sud XI, Le Kremlin Bicêtre, France.

Emails : FLT: tianyifrankleonel@gmail.com; JNT: joeltochie@gmail.com; CD: danram07@yahoo.fr; AM : aimembonda450@gmail.com; MNT: neurotemgoua@yahoo.fr; SYM :mapohyari2007@gmail.com; NJN : njinkeng.nkemngu@mail.utoronto.ca; JJB ; bignarimjj@yahoo.fr

Corresponding author: Joel Noutakdie Tochie, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon. Email: joeltochie@gmail.com.

Telephone: (237) 676 55 88 25

Abstract

Background: Septic shock (SS) is a life-threatening infection common in critically ill patients. There is a dearth of data on a résumé and meta-analysis on the global epidemiology of SS critically ill patients. Therefore, we propose the first systematic review to synthesize existing data on the global incidence, prevalence, risk factors and case fatality rate of SS in critically ill patients.

Methods: We will include cross-sectional, case-control, and cohort studies. Electronic databases including PubMed, EMBASE, WHO Global Health Library, and Web of Science will be searched for relevant records published between 1 January 2000 and 30 May 2019, without language restriction. Independents reviewers will perform study selection and data extraction, as well as assessment of methodological quality of included studies. Appropriate meta-analysis will then be used to pool studies judged to be clinically homogenous. Egger's test and funnel plots will be used to detect publication bias. Findings will be reported and compared by human development level of countries.

Ethics and dissemination: Being a review, ethical approval is not required as it was obtained in the primary study which will make up the review. This review is expected to provide relevant data to help in evaluating the global burden of SS in critically ill patients. The overall findings of this research will be broadcast in a peer-reviewed journal

Prospero registration number: The protocol has been submitted to Prospero for registration.

Keywords : Septic shock, intensive care, case fatality rate, epidemiology, critically ill patients

Strengths and limitations of this study

- With an extensive literature search, this will be the first systematic review summarizing contemporary data on the global occurrence of Septic shock (SS) in critically ill patients, to the best of our knowledge.
- Robust and strong methods, statistical analyses including meta-analysis to help in providing the highest level of evidence to aid in making a better evidence-based decision
- The present review will include primary studies without language restrictions, and thus will allow to enrol the maximum of studies published and unpublished on the subject.
- A limited number of studies on the topic in low-income and middle-income countries could lead to an underestimation of the true burden of SS in critically ill patients in this part of the world
- Any significant heterogeneity in the included studies may precluded the pooling of data to perform a meta-analysis.

Introduction

According to Sepsis-3, the most recent international consensus on sepsis and septic shock, septic shock (SS) is defined as a sepsis (denoted by a Sequential Organ Failure Assessment ≥ 2 points) plus serum lactate ≥ 2mmol/l and persistent hypotension despite adequate volume resuscitation, necessitating vasopressors to maintain a mean arterial blood pressure ≥ 65mmHg [1]. SS is one of the most common cause of admission, morbidity and mortality in critically ill patients [2]. SS is globally recognized by the World Health Organization (WHO) as a health priority[3]. In patients with SS, the blood perfusion of noble organs is

compromised, leading to encephalopathies, acute respiratory distress syndrome, acute hepatic failure, ischemic heart disease, sepsis-induced coagulopathy, multi-organ dysfunction and ultimately death if not timely and appropriately treated [4,5]. Survivors often have a reduced quality-of-life due to long-term cognitive, psychological, physical sequelae [6,7], and equally have a higher risk for one-year mortality following hospital discharge for SS [8].

SS is a frequent cause of admission to the intensive care unit (ICU) in both the adult and paediatric populations [9,10] and its associated with a significantly high mortality rate [10–14]. There is no doubt that antibiotics play a pivotal point in the management of SS. However, there currently exist several debates on the most efficacious pharmacological management for SS, making immediate treatment with appropriate antibiotics challenging.

Because SS is associated with a high fatality rate, identifying its risk factors is an important step toward determining preventive measures geared at reducing its incidence, prevalence and mortality rate. However, there is a huge controversy on risk factors for SS from the available literature [15–18]

The contemporary epidemiological data on SS in critically ill patients are derived from primary studies in which all major geographical regions are often not represented making it impossible to appraise the burden on a global perspective [2,4,19,20]. Despite this gap in knowledge on the topic, currently, no research has highlighted the global epidemiology of SS in critically ill patients. Accordingly, we propose this systematic review and meta-analysis protocol to critically synthesise contemporary evidence on the occurrence of SS in critically ill patients in the world. The research goal being to provide useful data that may help health authorities in continuous preventive strategies, and help guide resource allocation.

Review Questions

What is the burden of SS in the global population of critically ill patients?

Objective

The aim of this systematic review and meta-analysis is to determine the global incidence, prevalence, risk factors and case fatality rate of SS in critically ill patients.

Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015 Guidelines [21] and applicable to observational studies. This is illustrated in more details in Additional file 1. This review has been submitted to PROSPERO for registration.

Eligibility criteria

Types of studies

We will include cross-sectional, case-control, and cohort studies. Commentaries, editorials, letters and reviews will not be considered. Studies with inaccessible full texts either online or from the corresponding author will be excluded.

Types of patients

We will consider studies including critically ill adults and children.

Types of outcomes

The diagnosis of SS will be based on the Sepsis-1 [22,23], Sepsis-2 [22], and Sepsis-3[1] definitions. We will exclude studies in which relevant data on SS in critically ill patients are impossible to extract even after contacting the corresponding author. A critically ill patient will be defined as any patient admitted to an intensive care unit, neonatal intensive care unit, critical care unit, high dependency unit or specialized unit.

Search strategy for identifying relevant studies

The search strategy will be as follows:

Bibliographic database searches : PubMed, EMBASE, WHO global health library, and Web of Science will be searched for relevant records published between 1 January 2000 and 30 May 2019, without language restriction. The designed search strategy for PubMed using both text words and medical subject heading terms related to SS in critically ill patients is available in the Additional file 3. This search strategy will be adapted to fit with other databases

Searching for other sources

We will scan the references of all relevant articles for additional data sources missed during our search strategy, and their full texts will be sorted. Citations of important reviews will also be scanned. Lastly, the search strategy will extend to include grey literature from conference proceedings, book chapters, theses, government and non-governmental organizations reports.

Selection of studies for inclusion in the review

Two reviewers (TFL and CD) will independently evaluate the records obtained from the searching process, with the aid of an evaluation form to ensure reliably application of the selection criteria. These reviewers will screen the titles and abstracts of records obtained. Next, the full texts of potentially eligible articles will be retrieved by at least one author. The two reviewers will independently review the full text of each potentially eligible article, compare their findings and resolve any discordance by the arbitration of a third author (MNT). For duplicates articles, only the study reporting the largest sample size will be considered. For studies in other languages than French, English, or Spanish; Google Translate will be used.

Assessment of methodological quality and reporting of data

Methodological quality will be assessed for each included studies using the tool of bias assessment for prevalence studies developed by Hoy *et al* [24].

Data extraction and management

A data extraction form will be used by two pairs of independent reviewers (JNT and AM) and (SYM and MNT) to collect information on the last name of the first author, year of publication, region, country name, human development index ranking of country economic level, study area(rural vs urban), study setting, study design, mean or median age, sample size, male proportion, specific characteristics of the study population (patients with HIV, cancer, diabetes mellitus, organ transplants, or any other specific condition), prevalence rate, incidence rate, site of infection, SOFA (Sequential Organ Failure Assessment), risk factors for SS, serum late level in mmol/l, bacteria involved in the infection and case fatality rate of SS. For multicentre studies conducted in different countries, the prevalence, incidence or case fatality rate will be reported for the individual countries.

Data synthesis and analysis

After data collection, a meta-analysis will be conducted when there will be clinical homogeneity based on the profile of the population. Unadjusted standard error, case fatality rate, incidence, and prevalence for the study-specific estimates will be resumed based on the crude information of the numerators, and denominators provided by each study. Subgroup analysis will be performed by separate pooling of studies conducted among children and adolescents. To maintain the effect of studies with extremely small or large estimates on the overall estimate to a minimum, the variance of the study-specific incidence/prevalence/case fatality rate will be stabilized with the Freeman-Tukey double arcsine transformation [25]; before pooling the data using a random effects meta-analysis model. Heterogeneity will be assessed using the X^2 test on Cochrane's Q statistic and quantified by calculating I^2 [26]. Values of 25%, 50% and 75% for I^2 will respectively represent low, medium and high heterogeneity. We will assess the presence of publication bias using funnel plots inspection and Egger's test [27]. Where substantial heterogeneity will be detected; meta-regression and

subgroup analyses will be performed to investigate the possible sources of heterogeneity using the aforementioned variables and the study methodological quality. In case of substantial clinical heterogeneity, a narrative summary of our findings will be done. We anticipated that there will be substantial heterogeneity in estimation and reporting of risk factors or predictors associated with SS in critically ill patients. Therefore, we will only use narrative format to synthetized such data. The inter-rater agreement for study inclusion between investigators will be assessed using Cohen's k coefficient [28]. Data analyses will be done using the '*meta*' package of the statistical software R (version 3.5.1, The R Foundation for statistical computing, Vienna, Austria).

Presentation and reporting of results

The study selection process will be summarized in a flow diagram. Quantitative data will be presented in evidence tables of individual studies as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be reported accordingly. This may be tabulated and accompanied by narrative summaries.

Presentation and reporting of results

The study selection process will be summarised in a flow diagram. Quantitative data will be presented in evidence tables of individual studies as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be reported accordingly. This may be tabulated and accompanied by narrative summaries.

Patient and public involvement

In this study, data will be collected directly from published articles available in main databases and unpublished studies. Patient and public are not involved in the development of this protocol.

Potential amendments

Any amendment in the review process will be reported for transparency.

Ethics and disseminations

The current review will use published studies. Therefore, there is no requirement for ethical approval. The review is expected to provide the current global burden of SS in critically ill patients in order to inform health authorities and decision makers to elaborate effective preventive strategies to reduce the burden of SS in this high-risk patient population. The resulting manuscript will be published in a peer-reviewed journal and presented at scientific conferences.

Review status

Preliminary searches.

Contributors : FLT, JNT, CD, NJN and JJB had the idea, designed and conceived the protocol. FLT, JNT, CD, NJN and JJB wrote the first draft. FLT, JNT, CD, AM, MNT, SMY, JNJ, and JJB critically revised the methodology and intellectual content. JNT and JJB are the guarantors of the review. All authors approved the final version of this manuscript.

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

Competing interests: None declared.

Patient consent: Not required.

References

1. Singer M, Deutschman CS, Seymour CV, et al. The third International consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.

2. Quenot JP, Binquet C, Kara F, Martinet O, Ganster F, Navellou JC, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. Crit Care. 2013;17(2):R65.

3. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a Global Health priority – a WHO resolution. N Engl J Med 2017; 377: 414–7.

4. Balcan B, Olgun S, Torlak F, Sağmen SB, Eryüksel E, Karakurt S. Determination of Factors Affecting Mortality of Patients with Sepsis in a Tertiary Intensive Care Unit. Turk Thorac J 2015; 16: 128-32.

5. Cohen J. The immunopathogenesis of sepsis. Nature 2002;420:885-91.

6. Yende S, Austin S, Rhodes A, Finfer S, Opal S, Thompson T et al. Long-term quality of life among survivors of severe sepsis: analyses of two international trials. Crit Care Med 2016; 44: 1461–7.

7. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010; 304: 1787–94.

8. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. BMJ 2016; 353: i2375.

9. Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: current approaches to management. Internal Medicine Journal 2019;40:160–170.

10. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193: 259–72.

11. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC et al. Hospitaldeaths in patients with sepsis from 2 independent cohorts. JAMA 2014; 312: 90–2.

12. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775-87.

13. Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. Open Forum Infectious Diseases 2018. DOI: 10.1093/ofd/ofy313.

14. Annane D, Aegerter P, Jars-Guincestre, Guidet B. Current epidemiology of septic shock: the CUB-Rea ´ network. American Journal of Respiratory and Critical Care Medicine 2003;168:165–172.

15. Yamamoto Y, Fujita K, Nakazawa S, Hayashi T, Tanigawa G, Imamura R, et al. Clinical characteristics and risk factors for septic shock in patients receiving emergency drainage for acute pyelonephritis with upper urinary tract calculi. BMC Urology 2012:12:4.

16. Hsiao C-Y,Yang H-Y, Chang C-H, Lin H-L, Wu C-Y, Hsiao M-C et al. Risk Factors for Development of Septic Shock in Patients with Urinary Tract Infection. BioMed Research International 2015. http://dx.doi.org/10.1155/2015/717094.

17. Kang C-I, Song J-H, Chung DR, Peck KR, Ko KS, Yeom J-S , et al. Risk factors and pathogenic significance of severe sepsis and septic shock in 2286 patients with gram-negative bacteremia. Journal of Infection 2011; 62:26e33.

18. Leibovici L, Drucker M, Konigsberger H, Samra Z, Harrar S, Pitlik SD. Septic Shock in Bacteremic Patients: Risk Factors, Features and Prognosis. Scand J Infect Dis 1997;29: 71-75.

19. Zhang W, Zheng Y, Feng X, Chen M, Kang Y. Systemic inflammatory response syndrome in Sepsis-3: a retrospective study. BMC Infectious Diseases 2019;19:139.

20. Boussekey N, Cantrel J, Debrabant LD, Langlois D, Devos L, Meybeck A, Chiche A, Georges H, Leroy O. Epidemiology, Prognosis, and Evolution of Management of Septic Shock in a French Intensive Care Unit: A Five Years Survey.Critical Care Research and Practice 2010; 436427.

21. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

22. Sartelli M, Kluger Y, Ansaloni L, Hardcastle TC, Rello J, Watkins RR, et al. Raising concerns about the Sepsis-3 definitions. World Journal of Emergency Surgery 2018;13:6.

23. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55.

24. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934–9.

25. Miller JJ. The inverse of the Freeman – Tukey double arcsine transformation. The American Statistician 1978;32:138.

26. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206.

27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

28. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med 2012;22:276–82.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Pages
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Submitted to Prospero
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
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	9
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 to 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5 to 6
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	5 to 6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6 to 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6 to 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7 to 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Not applicable
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7 to 8
	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 (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Table 1 : Definition of septic shock

Disease	Definition
Sepsis-1[22,23]	**Septic shock is defined as :** A systemic inflammatory response syndrome (entailing the presence of one of the following : body temperature > 38.0 or < 36.0 °C, heart rate > 90 beats/min, tachypnea > 20 breaths/min or hyperventilation with PaCO2 < 32 mmHg, white blood cell count > 12,000 cells/mm3 or < 4000 cells/mm3) **Plus** Sepsis defined as a systemic inflammatory response syndrome in the presence of a confirmed or suspected infection **Plus** Severe sepsis defined as a sepsis associated with organ dysfunction, hypoperfusion, or hypotension **Plus** Arterial hypotension despite adequate fluid resuscitation
Sepsis-2[22]	**Septic shock is defined as :** Sepsis : that is the presence of fever (core temperature > 38.3 °C), hypothermia (core temperature < 36 °C), heart rate 90 bpm or > 2 standard deviation above the normal value for age, tachypnea: > 30 bpm, altered mental status, significant oedema or positive fluid balance (> 20 ml/kg over 24 h), hyperglycemia (plasma glucose > 110 mg/dl or 7.7 mM/l) in the absence of diabetes **Plus** The presencen of inflammatory parameters like leucocytosis (white blood cell count > 12,000/µl), or leucopenia (white blood cell count < 4000/µl), normal white blood cell count > 10% immature forms, plasma C reactive protein > 2 standard deviation above the normal value, plasma procalcitonin > 2 standard deviation above the normal value **Plus** Hemodynamic parameters like arterial hypotension (systolic blood pressure < 90 mmHg, mean arterial pressure < 70) Or a systolic blood pressure decrease > 40 mmHg in adults or < 2 standard deviation below normal for age, mixed venous oxygen saturation > 70%, Cardiac index > 3.5 l min- 1 m- 2, organ dysfunction parameters, arterial hypoxemia (PaO2/FIO2 < 300), acute oliguria (urine output > 0.5 ml/kg- 1 h- 1 or 45 mM/l for at least 2 h), creatinine increase ≥ 0.5 mg/dl, coagulation abnormalities (international normalized ratio > 1.5 or activated partial thromboplastin time > 60 s), ileus (absent bowel sounds), thrombocytopenia (platelet count 4 mg/dl or 70 mmol/l) **Plus** Tissue perfusion parameters such as hyperlactatemia (> 3 mmol/l) and decreased capillary refill or mottling
Sepsis-3[1]	**Septic shock** is defined as sepsis denoted by an increase of 2 points or more in the Sequential Organ Failure Assessment (SOFA) score. **Plus** Persistent hypotension (despite adequate volume resuscitation) requiring vasopressors to maintain mean arterial blood bressure greater than or equal to 65 mmHg, **Plus** Serum lactate greater than or equal to 2 mmol/l

[1]Singer M, Deutschman CS, Seymour CV, et al. The third International consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.

[22]Sartelli M, Kluger Y, Ansaloni L, Hardcastle TC, Rello J, Watkins RR, et al. Raising concerns about the Sepsis-3 definitions. World Journal of Emergency Surgery 2018;13:6.

[23]Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55.

Table 1	Search strategy for PubMed
Search number	**Search terms**
1	Septic OR shock OR Sepsis-3 OR Sepsis-III
2	Critical OR intensive OR ill OR high dependent unit Or specialised care
3	1 AND 2 Limits: 01/01/2000 to 30/05/2019 on humans with no language restriction

BMJ Open

Global epidemiology of septic shock: a protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032289.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Sep-2019
Complete List of Authors:	Frank Leonel, Tianyi Tianyi; Mayo Darle sub-Divisional Hospital, Tochie, Joel Noutakdie; Universite de Yaounde I Faculte de Medecine et des Sciences Biomedicales, Danwang, Celestin; Universite Libre de Bruxelles, School Of Public Health; Mbonda, Aime ; National social Insurance Fond Hospital, Department of Surgery Mazou, Temgoua Ngou ; Faculty of Medecine and Biomedical Sciences, Internal medicine and specialities Mapoh, Sylvester Yari ; University of Louisiana, Department of Family Medicine Nkemngu, Njinkeng J.; University of Toronto, Department of Anesthesia Tallah, Esther; Cameroon Coalition Against Malaria, Yaounde, Cameroon Bigna, Jean Joel; Centre Pasteur of Cameroon, Department of Epidemiology and Public Health
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Public health, Infectious diseases
Keywords:	Septic shock, case fatality rate, incidence, Epidemiology < INFECTIOUS DISEASES, global

Global epidemiology of septic shock: a protocol for a systematic review and meta-analysis

Frank-Leonel Tianyi[1], Joel Noutakdie Tochie[2], Celestin Danwang [3], Aime Mbonda[4], Mazou N. Temgoua[5], Sylvester Yari Mapoh[6], Njinkeng J. Nkemngu[7], Esther Tallah[8], Jean Joel Bigna[9, 10]

[1]Center for Global Health Sciences and Epidemiology, Nuffield Department of Population Health, University of Oxford, Oxfordshire, UK

[2]Department of Surgery and Anaesthesiology, Faculty of Medicine and Biomedical Sciences, Yaoundé, Cameroon.

[3]Institute of Experimental and Clinical Research, Université Catholique de Louvain, Brussels, Belgium

[4]Department of Surgery, National social Insurance Fond hospital, Yaounde, Cameroon

[5]Department of Internal Medicine and Cardiology, Faculty of Medicine and Biomedical Sciences, Yaoundé, Cameroon.

[6]Department of Family Medicine, University of Louissana, Louissana, USA

[7]Department of Anaesthesia, University of Toronto, Canada

[8]Cameroon Coalition Against Malaria, Yaounde, Cameroon

[9]Department of Epidemiology and Public Health, Centre Pasteur of Cameroon, Yaoundé, Cameroon.

[10]Faculty of Medicine, University of Paris Sud XI, Le Kremlin Bicêtre, France.

Emails : FLT: tianyifrankleonel@gmail.com; JNT: joeltochie@gmail.com; CD: danram07@yahoo.fr; AM : aimembonda450@gmail.com; MNT: neurotemgoua@yahoo.fr; SYM :mapohyari2007@gmail.com; NJN : njinkeng.nkemngu@mail.utoronto.ca; ET : esther.tallah@gmail.com; JJB: bignarimjj@yahoo.fr

Corresponding author: Joel Noutakdie Tochie, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon. Email: joeltochie@gmail.com.

Telephone: (237) 676 55 88 25

Abstract

Background: Septic shock (SS) is a life-threatening infection frequently encountered in hospital. There is a dearth of data on a résumé and meta-analysis on the global epidemiology. Therefore, we propose the first systematic review to synthesize existing data on the global incidence, and case fatality rate of SS worldwide.

Methods: We will include cross-sectional, case-control, and cohort studies. Electronic databases including PubMed, EMBASE, WHO Global Health Library, and Web of Science will be searched for relevant records published between 1 January 2000 and 31 August 2019. Independents reviewers will perform study selection and data extraction, as well as assessment of methodological quality of included studies. Appropriate meta-analysis will then be used to pool studies judged to be clinically homogenous. Egger's test and funnel plots will be used to detect publication bias. Findings will be reported and compared by human development level of countries.

Ethics and dissemination: Being a review, ethical approval is not required as it was obtained in the primary study which will make up the review. This review is expected to provide relevant data to help in evaluating the burden of SS in the general population. The overall findings of this research will be broadcast in a peer-reviewed journal

Prospero registration number: CRD42019129783

Keywords : Septic shock, incidence, case fatality rate, epidemiology, global

Strengths and limitations of this study

- The restriction of septic shock (SS) definitions to the Sepsis-3 consensus and the International pediatric sepsis consensus for adults and children respectively will limit major heterogeneity
- Robust methods and statistical analyses such as meta-analysis will be used to determine the global burden of SS.
- The present review will include primary studies without language restrictions, and thus will allow to enrol the maximum of studies published and unpublished on the subject.
- A limited number of studies on the topic in low-income and middle-income countries could lead to an underestimation of the true global burden of SS.
- Any significant heterogeneity in the included studies may preclude the pooling of data to perform a meta-analysis.

Introduction

According to Sepsis-3, the most recent international consensus on sepsis and septic shock, septic shock (SS) is defined as a sepsis (denoted by a Sequential Organ Failure Assessment ≥ 2 points) plus serum lactate ≥ 2mmol/l and persistent hypotension despite adequate volume resuscitation, necessitating vasopressors to maintain a mean arterial blood pressure ≥ 65mmHg [1]. Globally, SS is one of the most common cause of admission in both the adult and paediatric populations [2,3] and its associated with a significantly high mortality rate [3–7]. SS is globally recognized by the World Health Organization (WHO) as a health

priority[8]. In patients with SS, the blood perfusion of noble organs is compromised, leading to encephalopathies, acute respiratory distress syndrome, acute hepatic failure, ischemic heart disease, sepsis-induced coagulopathy, multi-organ dysfunction and ultimately death if not timely and appropriately treated [9,10]. Survivors often have a reduced quality-of-life due to long-term cognitive, psychological, physical sequelae [11,12], and equally have a higher risk for one-year mortality following hospital discharge for SS [13]. Antibiotics play a key role in pharmacology management of SS, however, the timining of initiation of antiobiotic therapy still remains an important debate in clincal practice. Furthermore, the management of SS currently challenge in identifying the correct hemodynmic control, optimization of fluid resuscitation, choosing the appropriate vassopressors, triage of patients who need ionotropic drugs, beta-blockers and steroids[14].

Some multinatinal studies on the global prevalence of sepsis but not SS, found a prevalence rate varying between 29.5 to 51%[6,15]. A more systematic review found that the frequency and mortality rate of SS stood betwen 8.3 to10.4% and 37.3% respectively in both Europe and North America combined[16]. However, there is a dearth of contemporary data on the global epidemiological of SS, making it impossible to appraise the burden of SS on a global perspective. Despite this gap in knowledge on the topic, currently, no research has highlighted the global epidemiology of SS. Accordingly, we propose this systematic review and meta-analysis protocol to critically synthesise contemporary evidence on the occurrence of SS in order to provide a clear understanding up-to-date burden in the world. The research goal being to provide useful data that may help guide resource allocation by informing health authorities.

Review Questions

What is the burden of SS in the global population?

Objective

The aim of this systematic review and meta-analysis is to determine the global incidence, and case fatality rate of SS on a global basis.

Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015 Guidelines [17] and applicable to observational studies. This is illustrated in more details in Additional file 1. This review has been registratered on PROSPERO under the number CRD42019129783.

Eligibility criteria

Types of studies

We will include cross-sectional, case-control, and cohort studies. Commentaries, editorials, letters and reviews will not be considered. Studies with inaccessible full texts either online or from the corresponding author will be excluded.

Types of patients

We will consider studies including hospitalised adults and children.

Types of outcomes

The diagnosis of SS in adults will be based on the Sepsis-3consensus [1], wheras SS in children wiil be defined in confirmity with the International pediatric sepsis consensus conference [18] (Additional 2). Incidence of SS will be defined number of individuals who developed SS between 1 January 2000 and 31 August 2019. We will exclude studies in which relevant data on SS patients are impossible to extract even after contacting the corresponding author.

Search strategy for identifying relevant studies

The search strategy will be as follows:

Bibliographic database searches : PubMed, EMBASE, WHO global health library, and Web of Science will be searched for relevant records published in English or French between 1 January 2000 and 30 May 2019. The designed search strategy for PubMed using both text words and medical subject heading terms related to sepsis, septicaemia, bacteraemia, infection, and shock as seen in Additional file 3. This search strategy will be adapted to fit with other databases

Searching for other sources

We will scan the references of all relevant articles for additional data sources missed during our search strategy, and their full texts will be sorted. Citations of important reviews will also be scanned. Lastly, the search strategy will extend to include grey literature from conference proceedings, book chapters, theses, government and non-governmental organizations reports.

Selection of studies for inclusion in the review

Two reviewers (TFL and CD) will independently evaluate the records obtained from the searching process, with the aid of an evaluation form to ensure reliably application of the selection criteria. These reviewers will screen the titles and abstracts of records obtained. Next, the full texts of potentially eligible articles will be retrieved by at least one author. The two reviewers will independently review the full text of each potentially eligible article, compare their findings and resolve any discordance by the arbitration of a third author (MNT). For duplicates articles, only the study reporting the largest sample size will be considered.

Data extraction and management

A data extraction form will be used by two pairs of independent reviewers (JNT and AM) and (SYM and MNT) to collect information on the last name of the first author, year of

publication, region, country name, human development index ranking of country economic level, study area(rural vs urban), study setting, study design, mean or median age, sample size, male proportion, specific characteristics of the study population (patients with HIV, cancer, diabetes mellitus, organ transplants, or any other specific condition), incidence rate, site of infection, SOFA (Sequential Organ Failure Assessment), serum late level in mmol/l, bacteria involved in the infection and case fatality rate of SS. For multicentre studies conducted in different countries, the incidence or case fatality rate will be reported for the individual countries.

Data synthesis and analysis

After data collection, a meta-analysis will be conducted when there will be clinical homogeneity based on the profile of the population. Unadjusted standard error, case fatality rate, and incidence for the study-specific estimates will be resumed based on the crude information of the numerators, and denominators provided by each study. Subgroup analysis will be performed by separate pooling of studies conducted among children and adolescents. To maintain the effect of studies with extremely small or large estimates on the overall estimate to a minimum, the variance of the study-specific incidence/case fatality rate will be stabilized with the Freeman-Tukey double arcsine transformation [19]; before pooling the data using a random effects meta-analysis model. Heterogeneity will be assessed using the X^2 test on Cochrane's Q statistic and quantified by calculating I^2 [20]. Values of 25%, 50% and 75% for I^2 will respectively represent low, medium and high heterogeneity. We will assess the presence of publication bias using funnel plots inspection and Egger's test [21]. Where substantial heterogeneity will be detected; meta-regression and subgroup analyses will be performed to investigate the possible sources of heterogeneity using the aforementioned variables and the study methodological quality. In case of substantial clinical heterogeneity, a narrative summary of our findings will be done. The inter-rater agreement for study inclusion

between investigators will be assessed using Cohen's k coefficient [22]. Data analyses will be done using the '*meta*' package of the statistical software R (version 3.5.1, The R Foundation for statistical computing, Vienna, Austria).

Presentation and reporting of results

The study selection process will be summarised in a flow diagram. Quantitative data will be presented in evidence tables of individual studies as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be reported accordingly. This may be tabulated and accompanied by narrative summaries.

Patient and public involvement

In this study, data will be collected directly from published articles available in main databases and unpublished studies. Patient and public are not involved in the development of this protocol.

Potential amendments

Amendments made include broadening the scope of the study to a global epidemiology of SS; no synthesizing the risk factors and prevalence of SS anymore and harmorning the definition of SS to sepsis-3 consensus and the International pediatric sepsis consensus for adults and children respectively. This amendmets will be updated in the review submited to PROSPERO for better transparency.

Ethics and disseminations

The current review will use published studies. Therefore, there is no requirement for ethical approval. The review is expected to provide the current global burden of SS in the global population of in- patients in order to inform health authorities and decision makers to elaborate effective preventive strategies to reduce the burden of SS in this high-risk patient

population. The resulting manuscript will be published in a peer-reviewed journal and presented at scientific conferences.

Review status

Preliminary searches.

Contributors : FLT and JNT had the idea, designed and conceived the protocol. JNT wrote the first draft. FLT, JNT, CD, AM, MNT, SMY, NJN, ET and JJB critically revised the methodology and intellectual content. JNT is the guarantor of the review. All authors approved the final version of this manuscript.

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

Competing interests: None declared.

Patient consent: Not required.

References

1. Singer M, Deutschman CS, Seymour CV, et al. The third International consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
2. Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: current approaches to management. Internal Medicine Journal 2019;40:160–170.
3. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016; 193: 259–72.
4. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC et al. Hospitaldeaths in patients with sepsis from 2 independent cohorts. JAMA 2014; 312: 90–2.
5. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):775-87.

6. Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. Open Forum Infectious Diseases 2018. DOI: 10.1093/ofd/ofy313.

7. Annane D, Aegerter P, Jars-Guincestre, Guidet B. Current epidemiology of septic shock: the CUB-Rea ´ network. American Journal of Respiratory and Critical Care Medicine 2003;168:165–172.

8. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a Global Health priority – a WHO resolution. N Engl J Med 2017; 377: 414–7.

9. Balcan B, Olgun S, Torlak F, Sağmen SB, Eryüksel E, Karakurt S. Determination of Factors Affecting Mortality of Patients with Sepsis in a Tertiary Intensive Care Unit. Turk Thorac J 2015; 16: 128-32.

10. Cohen J. The immunopathogenesis of sepsis. Nature 2002;420:885-91.

11. Yende S, Austin S, Rhodes A, Finfer S, Opal S, Thompson T et al. Long-term quality of life among survivors of severe sepsis: analyses of two international trials. Crit Care Med 2016; 44: 1461–7.

12. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010; 304: 1787–94.

13. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. BMJ 2016; 353: i2375.

14. De Backer D, Cecconi M, Lipman J, Machado F, Myatra SN, Ostermann M et al. Challenges in the management of septic shock: a narrative review. ;Intensive Care Medicine 2019;45:420-433.

15. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323-9.

16. Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Critical Care 2019;23:196.

17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

18. Goldstein B, Giroir B, Randolph A, and the Members of the International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.

19. Miller JJ. The inverse of the Freeman – Tukey double arcsine transformation. The American Statistician 1978;32:138.

20. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206.

21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.

22. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med 2012;22:276–82.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Pages
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	CRD42019129783
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
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	9
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 to 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5 to 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
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	6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7 to 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Not applicable
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	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7 to 8
	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 (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Table: Definition of septic shock

Disease	Definition
Sepsis-3 definition for adult septic shock[1]	**Septic shock** is defined as sepsis denoted by an increase of 2 points or more in the Sequential Organ Failure Assessment (SOFA) score. **Plus** Persistent hypotension (despite adequate volume resuscitation) requiring vasopressors to maintain mean arterial blood bressure greater than or equal to 65 mmHg, **Plus** Serum lactate greater than or equal to 2 mmol/l[2]
International pediatric sepsis consensus conference for pediatric septic shock [18]	**Septic shock** is defined as the presence of systemic inflammatory response syndrome (SIRS), and infection and cardiovascular dysfunction as follows; **SIRS** The presence of at least two of the following four criteria, one of which must be abnormal temperature or leucocyte count -Core temperature above 38.5◦C or less than 36◦C -Tachycardia defined as a mean heart rate > 2SD above normal for age in the absence of external stimulus, chronic drugs or painful stimuli; orotherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children<1 year old: bradycardia, defined as a as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blockers drugs, or congenital heart disease; or otherwise unexplained persistent depression pber 0.5-hr time period. -Mean respiratory rate > 2SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia -Leucocytes count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or >10% immature neutophils **Infection** A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection causedby any pathogenOR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory test (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or pupuric rash, or purpura fulminans) **Cardiovascular organ dysfunction** Despite administration of isotonic intravenous fluid bolus ≥ 40ml/kg in 1 hr Decrease blood pressure< 5th percentile for age or systolic blood pressure < 2SD below normalfor age OR Need for vasoactive drug to maintain blood pressure in normal range (dopamine>5ug/kg/min or dobutamine, epinephrine, or noradrenaline at any dose) OR two of the follwing -Unexplained metabolic acidosis: base deficit > 5.0mEq/L -Increased arterial lactate > 2 times upper limit of normal -Oliguria: urine output < 0.5 ml/kg/hr -Prolonged capillary refill:> 5 seconds -Core to peripheral temperature gap > 3◦C

[1]Singer M, Deutschman CS, Seymour CV, et al. The third International consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.

[18]Goldstein B, Giroir B, Randolph A, and the Members of the International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.

Table: Search strategy for PubMed

Search number	Search terms
1	Sepsis OR Septicaemia OR Bacteremia OR infection OR Septic OR Shock
2	1 AND 2 Limits: 01/01/2000 to 30/05/2019 on humans with no language restriction