PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Global epidemiology of septic shock: a protocol for a systematic review and meta-analysis
AUTHORS	Frank Leonel, Tianyi Tianyi; Tochie, Joel Noutakdie; Danwang, Celestin; Mbonda, Aime; Mazou, Temgoua Ngou; Mapoh, Sylvester Yari; Nkemngu, Njinkeng J.; Tallah, Esther; Bigna, Jean Joel

VERSION 1 – REVIEW

REVIEWER	Vincent, Jean-Louis Free University of Brussels
REVIEW RETURNED	04-Jul-2019

GENERAL COMMENTS	The authors propose a review on septic shock around the globe. Although the idea is interesting, the design has problems. Major comments 1-The goal of the study should be better defined. Some goals are simply unachievable. The authors indicate the intention to collect data on 4 items: a) -the global incidence of SS: incidence in which population? Only in ICU patients? That is a restricted view. In hospital? It is very difficult to collect this type of information; moreover patients may develop septic shock as a terminal event, so that it would not be relevant from a public health perspective. b)-the prevalence: again, where? If it is in ICU, several large studies of more than 10,000 patients worldwide have reported this. c) the risk factors: how would the authors determine them from these studies? Data on age, immunosuppression, etc are already known available and more subtle factors are hard to identify. d) the case fatality rate of SS can be determined, but it has also been provided in large studies conducted worldwide. Several studies have already reviewed this for North America and Europe (the most recent paper on this was published by us in Critical Care some weeks ago), and the information in other parts of the world may be limited. Perhaps the authors could add the search on more data on organ dysfunction? 2-The mixture of what is called sepsis-1, sepsis-2 and sepsis-3 can result in major heterogeneity. Also some studies may have slightly different criteria. The authors should rather start from standard criteria and see how the studies fit or differ from those.

	3-Does the study need an analysis of the methodological aspects? This is important for interventional studies, but not here. Moreover, it may be difficult form abstracts, proceedings, etc. Other comments 1. '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...': this needs to be rephrased. The timing of antibiotic therapy is a debated issue, but not antibiotic therapy per se. 2. 'However, there is a huge controversy on risk factors for SS from the available literature': it is very difficult to predict septic shock and I do not think a meta-analysis will help to provide any valuable information on risk factors. 3. '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': the authors fail to mention the worldwide studies (EPIC, ICON...) that provide these data. 4. The reference list is quite incomplete: In addition to the worldwide studies, the recent consensus paper on the challenges in septic shock should be discussed (De Backer et al, ICM 2019), and the recent review on septic shock mortality (Critical Care 2019) should be cited.

REVIEWER	Carolin Fleischmann-Struzek Center for Sepsis Control and Care, Jena, Germany Consultant to WHO on global sepsis epidemiology.
REVIEW RETURNED	03-Sep-2019

GENERAL COMMENTS	The protocol „Global epidemiology of septic shock in critically ill patients: a protocol for a systematic review and meta-analysis" describes background, methodology and dissemination of a systematic review and meta-analysis on the burden of septic shock in critically ill patients. The study follows a systematic approach that will allow for a comprehensive assessment of the epidemiology of septic shock. The draft is well written and guided by the PRIMSA reporting items for systematic reviews and meta-analyses. Major concerns - The condition studied is septic shock in critically ill patients. How is critically ill defined and why was this group chosen as denominator? Is critically ill equivalent to ICU patients? If this is the case, one would restrict the population under observation and thus eligible studies especially in low-and middle income countries, where access to intensive care is very limited. My recommendation is to broaden the population in which the burden of septic shock is assessed. The proportion of ICU patients that suffer from septic shock can still be analyzed as subgroup. - The literature search is based on certain electronic databases which include published studies and conference abstract, but the methods state that also unpublished literature will be assessed. How will authors systematically access this kind of literature? Are any databases for grey literature approached? - Types of outcomes: There are specific definitions for pediatric sepsis that should be included in the inclusion criteria (Goldstein et al. 2005), if children are a target group of the review. I recommend

	stating the definition used for septic shock in the paragraph “types of patients” and explaining relevant outcomes in the paragraph “types of outcomes”, including how incidence and prevalence are defined – this explanation is currently missing, but of crucial importance. How are numerator and denominator defined? What is the population at risk? Will incidence relate to hospital- or ICU treated patients or a (national) population? - Non-English/French/Spanish publications – google translate seems not to be an appropriate tool to translate studies in a proper way. In my option, if there is no language expertise, a language restriction in the search would be more appropriate. - Data synthesis: How do you define clinical homogeneity of studies? Minor points: - The paragraph “Presentation and reporting of results” is doubled.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: jl Vincent
Institution and Country: Free University of Brussels
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below
The authors propose a review on septic shock around the globe. Although the idea is interesting, the design has problems.

Major comments

1-The goal of the study should be better defined. Some goals are simply unachievable. The authors indicate the intention to collect data on 4 items:
a) -the global incidence of SS: incidence in which population? Only in ICU patients? That is a restricted view. In hospital? It is very difficult to collect this type of information; moreover patients may develop septic shock as a terminal event, so that it would not be relevant from a public health perspective.

Authors' response: we have revised the manuscript to study the global epidemiology of septic shock in all hospital admitted patients and not just does of the ICU. So we will determine a global incidence of septic shock

b)-the prevalence: again, where? If it is in ICU, several large studies of more than 10,000 patients worldwide have reported this.
Authors' response: we will study only the incidence and not the prevalence of septic shock as this seem more difficult to obtain from primary studies

c) the risk factors: how would the authors determine them from these studies? Data on age, immunosuppression, etc are already known available and more subtle factors are hard to identify.
Authors' response: we agree with you. Hence we will no longer seek to determine the risk factors for septic shock

d) the case fatality rate of SS can be determined, but it has also been provided in large studies conducted worldwide. Several studies have already reviewed this for North America and Europe (the most recent paper on this was published by us in Critical Care some weeks ago), and the information in other parts of the world may be limited.
Perhaps the authors could add the search on more data on organ dysfunction?
Authors' response: Page 4, line 12-14: this studies have been cited

2-The mixture of what is called sepsis-1, sepsis-2 and sepsis-3 can result in major heterogeneity. Also some studies may have slightly different criteria. The authors should rather start from standard criteria and see how the studies fit or differ from those.

Authors' response: Page 5, line 16-18: we will restrict the definition of septic shock to the sepsis-3 consensus and the International pediatric sepsis consensus for adults and children respectively to limit heterogeneity

3-Does the study need an analysis of the methodological aspects? This is important for interventional studies, but not here. Moreover, it may be difficult form abstracts, proceedings, etc.

Authors' response: we agree with you ; hence, this has been deleted

Other comments
1. '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...': this needs to be rephrased. The timing of antibiotic therapy is a debated issue, but not antibiotic therapy per se.

Authors' response: Page 4, line 6-11: this has been revised accordingly

2. 'However, there is a huge controversy on risk factors for SS from the available literature': it is very difficult to predict septic shock and I do not think a meta-analysis will help to provide any valuable information on risk factors.
Authors' response: we agree with you. Hence we will no longer seek to determine the risk factors for septic shock

3. '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': the authors fail to mention the worldwide studies (EPIC, ICON...) that provide these data.
Authors' response: Page 4 line 12 to 13 : this has been revised accordingly

4. The reference list is quite incomplete: In addition to the worldwide studies, the recent consensus paper on the challenges in septic shock should be discussed (De Backer et al, ICM 2019), and the recent review on septic shock mortality (Critical Care 2019) should be cited.

Authors' response: Page 4 line 8 to 11 : this has been revised accordingly

Reviewer: 2

Reviewer Name: Carolin Fleischmann-Struzek

Institution and Country: Center for Sepsis Control and Care, Jena, Germany
Please state any competing interests or state 'None declared': Consultant to WHO on global sepsis epidemiology.

Please leave your comments for the authors below
The protocol „Global epidemiology of septic shock in critically ill patients: a protocol for a systematic review and meta-analysis" describes background, methodology and dissemination of a systematic review and meta-analysis on the burden of septic shock in critically ill patients. The study follows a systematic approach that will allow for a comprehensive assessment of the epidemiology of septic shock. The draft is well written and guided by the PRIMSA reporting items for systematic reviews and meta-analyses.
Major concerns
- The condition studied is septic shock in critically ill patients. How is critically ill defined and why was this group chosen as denominator? Is critically ill equivalent to ICU patients? If this is the case, one would restrict the population under observation and thus eligible studies especially in low-and middle income countries, where access to intensive care is very limited. My recommendation is to broaden the population in which the burden of septic shock is assessed. The proportion of ICU patients that suffer from septic shock can still be analyzed as subgroup.

Authors' response: we have revised the manuscript to study to include a worldwide population, hence, we will be studying the global epidemiology of septic shock in all hospital admitted patients and not just does of the ICU. So we will determine a global incidence of septic shock

- The literature search is based on certain electronic databases which include published studies and conference abstract, but the methods state that also unpublished literature will be assessed. How will authors systematically access this kind of literature? Are any databases for grey literature approached?
Authors' response: we have review authors in UK, Canada, France, USA and Africa, hence, we intend to make search the gray literature as exhaustive as possible by searching from conference proceedings, book chapters, theses, government and non-governmental organizations reports by reviewers in these different continents.
- Types of outcomes: There are specific definitions for pediatric sepsis that should be included in the inclusion criteria (Goldstein et al. 2005), if children are a target group of the review. I recommend stating the definition used for septic shock in the paragraph "types of patients" and explaining relevant outcomes in the paragraph "types of outcomes", including how incidence and prevalence are defined – this explanation is currently missing, but of crucial importance. How are numerator and denominator defined? What is the population at risk? Will incidence relate to hospital- or ICU treated patients or a (national) population?

Authors' response: Page 5 line 18 to 11 : this has been revised accordingly

- Non-English/French/Spanish publications – google translate seems not to be an appropriate tool to translate studies in a proper way. In my option, if there is no language expertise, a language restriction in the search would be more appropriate.
Authors' response: Page 6 line 4 : this has been revised accordingly

Minor points:
- The paragraph "Presentation and reporting of results" is doubled.
Authors' response: the duplicate has been deleted

VERSION 2 – REVIEW

REVIEWER	Vincent, Jean-Louis Erasme University Hospital, Department of Intensive Care
REVIEW RETURNED	28-Sep-2019

GENERAL COMMENTS	the protocol has improved