PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical prediction models to diagnose neonatal sepsis: a scoping review protocol
AUTHORS	Neal, Samuel; Musorowegomo, David; Gannon, Hannah; Cortina Borja, Mario; Heys, Michelle; Chimhini, Gwen; Fitzgerald, Felicity

VERSION 1 – REVIEW

REVIEWER	Istemi Han Celik Department of Neonatology, University of Health Sciences Turkey, Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital, Ankara, Turkey
REVIEW RETURNED	06-May-2020

GENERAL COMMENTS	This study aimed to find out clinical prediction models to diagnose neonatal sepsis especially in low income countries. Authors concluded that laboratory tests may not be used most parts of world and a clinical prediction models may be used in this parts of world. I think that this kind of models should be used in high income models to avoid unnecessary sepsis work-up in neonates. Authors should add the value of association between clinical prediction models and laboratory findings in methods section. Because the effect of these models can be understood by comparing with laboratory results.

REVIEWER	Shailender Mehta Fiona Stanley Hospital and Curtin University, Perth, WA, Australia
REVIEW RETURNED	01-Jun-2020

GENERAL COMMENTS	Good study protocol, a few minor comments below- 1. would be good to include subgroup analysis on chorioamnionitis as risk factor 2. Include analyses on studies looking at 'culture negative sepsis' as well esp in context of of intrapartum antibiotic usage 3. LMIC countries may also not have access to blood culture if they don't have access to other lab analyses- discuss in context of culture negative sepsis 4. Would be good to include (if possible)- cost analysis of various models e.g. cost of antibiotics as well as cost of missing sepsis and possible consequences esp in LMIC. various models like the sepsis calculator also emphasise on longer and more vigilant observations which may also have cost factor in the form of length of stay- possibly include that in the main study paper

REVIEWER	Zachary Colvin Medical College of Wisconsin, United States
REVIEW RETURNED	07-Jun-2020

GENERAL COMMENTS	Overall, I thought this protocol review was well written. The clinical question is important and study objectives were clearly defined. I thought the protocol review adequately addressed the problem and reviewed difficulties in diagnosing/over diagnosing neonatal sepsis. The comparison of models form HICs and LMICs is an interesting angle. While there is benefit from having a common model, the difference in resource availability, which is addressed here, likely makes it a necessity to have two different models. The subgroup analysis, which groups studies by HIC vs LMIC, EOS vs LOS, and clinical vs laboratory predictors, addresses this. The abstract was complete and concise. The methods were logical and followed Joanna Briggs Institute guidelines. The data extraction form appeared appropriate. I know the limitation of only including English and Spanish studies was addressed. It the Spanish studies are going to be translated, I think including more languages would be beneficial in an effort to have a more inclusive review of existing literature.In conclusion, I think this protocol review should be accepted.

REVIEWER	Aaron Masino University of Pennsylvania, United States Children's Hospital of Philadelphia, United States
REVIEW RETURNED	11-Jun-2020

GENERAL COMMENTS	This is a timely and important review topic. The planning is well done. My only suggestion is to consider adding the following research question to Table 1 which may help model developers navigate the literature: What modeling methods are used? ● Expert rule based ● Stastical ● Machine learning

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Istemi Han Celik

R1.1: “Authors should add the value of association between clinical prediction models and laboratory findings in methods section. Because the effect of these models can be understood by comparing with laboratory results.”

We agree that there is high value in comparing clinical prediction models with laboratory findings, and have used blood culture positivity as a gold standard. We have included laboratory tests as a predictor in Table 1, point 3. However, we accept Reviewer 2’s valid point (R2.2) that the entity of ‘culture-negative sepsis’ is of crucial importance to include, given that many mother-infant pairs are exposed to antibiotics prior to cultures being taken. We will be explicit about the difference between models that use cultures as a gold standard versus those that reply on clinical fetures alone.

Reviewer 2: Shailender Mehta

R2.1: “Would be good to include subgroup analysis on chorioamnionitis as risk factor”

We agree that this would be a useful subgroup to analyse, as the management of asymptomatic

neonates born to mothers with chorioamnionitis is indeed challenging. We have now included this subgroup in our protocol and plan to examine which studies include chorioamnionitis (or surrogates such as intrapartum maternal fever) in their prediction models.

Page 10, lines 14-16 now read:
Those that specifically consider the management of neonates born to mothers with chorioamnionitis.

R2.2: “Include analyses on studies looking at 'culture negative sepsis' as well esp in context of of intrapartum antibiotic usage”

We will examine this aspect of the prediction models when extracting data relating to the outcome definition for each model. For example, some studies might define their outcome as ‘bacteraemia’ or ‘non-contaminated positive blood culture’, while others will use a broader definition for neonatal sepsis, such as sepsis diagnosed by the treating neonatologist. These outcome definitions will be captured by our data extraction form (as shown in Supplementary Appendix 2) and will be considered during our data synthesis. For clarity, we now explicitly mention this in the “Analysis of the evidence and presentation of the results” section of our protocol.

Page 10, lines 17-18 now read:
Those using different outcome definitions for neonatal sepsis (such as those defining sepsis as a positive blood culture versus those that also include ‘clinical sepsis’).

R2.3: “LMIC countries may also not have access to blood culture if they don't have access to other lab analyses- discuss in context of culture negative sepsis”

We understand this to mean that in low and middle-income countries, a larger proportion of babies may be labelled as having ‘culture-negative sepsis’ due to lack of availability of blood culture facilities. This is a valid point. We will be explicit in our evaluation of prediction models validated in ‘real-world’ observational data (that may be incomplete) versus specific study settings. We will also be clear as to what standard was used to define the outcome of sepsis in each included study.

R2.4: “Would be good to include (if possible)- cost analysis of various models e.g. cost of antibiotics as well as cost of missing sepsis and possible consequences esp in LMIC. various models like the sepsis calculator also emphasise on longer and more vigilant observations which may also have cost factor in the form of length of stay- possibly include that in the main study paper”

While we agree that cost analysis is of crucial importance especially in low-income settings, this is unfortunately beyond the scope and budget of this particular study. We will include this as a limitation and explore the possibility of a health economics analysis for a future project.

Reviewer 3: Zachary Colvin

R3.1: “I know the limitation of only including English and Spanish studies was addressed. It the Spanish studies are going to be translated, I think including more languages would be beneficial in an effort to have a more inclusive review of existing literature. In conclusion, I think this protocol review should be accepted.”

We acknowledge that limiting our review to only include studies published in English and Spanish could introduce bias into our protocol. These two languages were chosen to reflect the languages spoken by the review team and, pragmatically, we do not have the resources nor funding to translate

studies published in other languages. For clarity, we now explain our reasons for selecting these language limits in our protocol.

Page 9, lines 4-6 now read:
No time period or language restrictions will be applied to the search strategy, but studies will be manually limited to the English or Spanish language at the study selection stage to reflect the languages spoken by the review team.

Page 9, lines 40-41 now read:
Studies in Spanish will be translated to English by MCB and then considered for inclusion.

Reviewer 4: Aaron Masino

R4.1: “My only suggestion is to consider adding the following research question to Table 1 which may help model developers navigate the literature:
What modeling methods are used?
Expert rule based
Stastical
Machine learning”

We agree that these are important topics to cover in our review, particularly as new modelling methods are continually being devised. For this review, we are explicitly interested in studies examining clinical prediction models which have been validated (via internal and/or external validation). Thus, we do not consider expert rule based algorithms or decision rules, unless these have been validated in a subsequent study. This point is discussed in Table 2 (page 8, line 24), which reads: “Only internally and/or externally validated models will be included.” We have now amended this line to clarify our protocol.

Page 8, line 25 (within Table 2) now reads:
Management algorithms, decision rules or prediction models based on expert opinion will not be included, unless validated in a subsequent study.

While our initial focus was to examine the clinical utility of existing prediction models within different settings, we agree that incorporating the modelling methods used into our research questions is a natural addition which will benefit an additional group of readers who may be developing prediction models for neonatal sepsis. We had already considered extracting data regarding the type of model used (as shown in our draft data extraction form, Supplementary Appendix 2) and have now included this subject as a specific research question in Table 1, as you have kindly suggested.

Page 7, line 22 (within Table 1) now reads:
2. What modelling methods are used to derive these models?