

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A systematic review of global clinical practice guidelines for neonatal hyperbilirubinemia
<b>AUTHORS</b>	Zhang, Meng; Tang, Jun; He, Yang; Li, Wenxing; Chen, Zhong; Xiong, tao; qu, yi; Li, Youping; Mu, Dezhi

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Scott Grosse CDC, United States of America
<b>REVIEW RETURNED</b>	22-Jun-2020

<b>GENERAL COMMENTS</b>	<p>The premise of the study is that a systematic review of clinical guidelines on the diagnosis and management of neonatal jaundice and hyperbilirubinemia can provide useful information to policy makers and practitioners and aid in future guideline development. However, since existing reviews on neonatal jaundice and hyperbilirubinemia already have pointed out the limitations in the evidence base which underlie clinical guidelines it is unclear what is really new.</p> <p>Specific comments</p> <p>P3 L7-9 The sentence appears self-contradictory. If jaundice reflects elevated TSB and 60-70% of infants have elevated TSB, how can only 10% of infants have elevated TSB? It is also incorrect English syntax. Reference 2 makes it clear that these are two different concepts, that the 10% refers to “clinically significant” hyperbilirubinemia and jaundice. It also notes that about 1 in 1000 newborns have severe jaundice, which can be potentially fatal.</p> <p>P3 L9-11: It should be made clear that this sentence refers to deaths from severe neonatal jaundice, which is not common. The authors incompletely characterize the number of neonatal deaths caused by severe jaundice reported in reference 3.</p> <p>P3 L13: Phototherapy, not photography.</p> <p>P3 L16-21: This paragraph is unclear and inadequately sourced. The second sentence has incorrect syntax. The third sentence is unsupported by evidence. The fourth sentence is correct, but the two citations from the previous sentence belong with this sentence. The fifth sentence may be correct but no references were cited.</p> <p>P3 L27-30: Incorrect syntax and logic. A tool does not assess rigour; researchers assess rigorous using a tool. Errors of</p>
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	<p>grammar and syntax in the remainder of the document are not itemized.</p> <p>P7 L16-27: Nine guidelines that reported risk factors for “severe neonatal jaundice” are listed in Table 5. However, the information in the text and table is unclear, imprecise, and incompletely documented. For example, the NICE guideline (reference 16) in Table 5 is said to have listed four risk factors for “severe neonatal jaundice” – prematurity, exclusive breastfeeding, sibling with severe hyperbilirubinemia, and visible jaundice &lt;24 hours. It actually used a cutoff of 38 weeks of gestation, combining early term and preterm births as a risk factor. It also listed siblings with clinically significant jaundice requiring phototherapy, which is not the same as severe hyperbilirubinemia. In addition, Table 5 states that it ruled out male sex and bruises as risk factors, although neither is mentioned in the guideline document or the published summary (reference 16); presumably these factors were addressed in a separate evidence review document. Further, Table 5 asserts that the NICE guideline did not mention Rhesus negativity, sepsis, or G6PD deficiency as risk factors (NA for Not Available). However, the NICE guideline states, “Jaundice has many possible causes, including blood group incompatibility (most commonly rhesus or ABO incompatibility), other causes of haemolysis (breaking down of red blood cells), sepsis (infection), liver disease, bruising and metabolic disorders. Deficiency of a particular enzyme, glucose-6-phosphate-dehydrogenase, can cause severe neonatal jaundice.”</p>
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<b>REVIEWER</b>	<p>Bolajoko Olusanya Centre for Healthy Start Initiative Ikoyi, Lagos Nigeria</p>
<b>REVIEW RETURNED</b>	21-Jul-2020

<b>GENERAL COMMENTS</b>	<p>This systematic review of guidelines for the management of neonatal hyperbilirubinaemia is a potentially valuable addition to the literature.</p> <p>However, the entire manuscript requires considerable language editing for the readership of this journal. For example, the following statement in the introduction would suggest that this finding is no longer valid: “Jaundice affected at least 60% of full-term and 80% of preterm neonates<sup>1</sup>, suggesting that about one-tenth newborn babies were likely to develop hyperbilirubinemia” Whereas, jaundice still affects newborns to this extent.</p> <p>Additionally, it is unclear if only guidelines or recommendations issued by national or regional organisations were eligible for evaluation.</p> <p>A major omission in this review is the identification of guidelines that included or did not include post-discharge neurodevelopmental evaluation of infants with severe hyperbilirubinaemia who were treated with intensive phototherapy and/or exchange transfusion.</p> <p>Additionally, the authors claim that there are no guidelines from Africa and South Asia where the disease burden is greatest is inaccurate. They should carefully study a similar review by Olusanya BO, Ogunlesi TA, Kumar P, et al. Management of late-</p>
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	preterm and term infants with hyperbilirubinaemia in resource-constrained settings. BMC Pediatr. 2015;15:39. Published 2015 Apr 12.
<b>REVIEWER</b>	Taulant Muka ISPM-University of Bern, Bern, Switzerland
<b>REVIEW RETURNED</b>	20-Nov-2020
<b>GENERAL COMMENTS</b>	<p>Zheng et al. have examined systematically the evidence on quality of clinical practice guidelines for neonatal hyperbilirubinemia. Authors find that current guidelines varied in quality. This article provide an important message and has important implications. I have few minor comments that can improve the paper further.</p> <ol style="list-style-type: none"> <li>1. Could authors provide the average quality of existing guidelines based on the continent, for instance Asia vs. USA vs. EU, and how it relates to disease burden?</li> <li>2. Could authors compare their findings with similar analysis on other clinical guidelines? Are the issue they report only applicable to guidelines on neonatal hyperbilirubinemia, or is it a general problem?</li> <li>3. An important finding is the lack of proper methodology in conducting guidelines, such as the lack of systematic search and proper meta-analysis. Could authors discuss more on this topic and provide future recommendations? The 24-Steps to Systematic Review and Meta-analysis article could be recommended/cited (Muka et al. EJEP, 2020)</li> </ol>

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Scott Grosse

Institution and Country: CDC, United States of America

Please state any competing interests or state 'None declared': None declared

Comments to the Author

The premise of the study is that a systematic review of clinical guidelines on the diagnosis and management of neonatal jaundice and hyperbilirubinemia can provide useful information to policy makers and practitioners and aid in future guideline development. However, since existing reviews on neonatal jaundice and hyperbilirubinemia already have pointed out the limitations in the evidence base which underlie clinical guidelines it is unclear what is really new.

Specific comments

Question 1: P3 L7-9 The sentence appears self-contradictory. If jaundice reflects elevated TSB and 60-70% of infants have elevated TSB, how can only 10% of infants have elevated TSB? It is also incorrect English syntax. Reference 2 makes it clear that these are two different concepts, that the 10% refers to “clinically significant” hyperbilirubinemia and jaundice. It also notes that about 1 in 1000 newborns have severe jaundice, which can be potentially fatal.

Response: Thank you very much. We have corrected the sentence as “Approximately 10% of newborns are likely to develop clinically significant hyperbilirubinemia requiring close monitoring and treatment.” in the revised manuscript.

Question 2: P3 L9-11: It should be made clear that this sentence refers to deaths from severe neonatal jaundice, which is not common. The authors incompletely characterize the number of neonatal deaths caused by severe jaundice reported in reference 3.

Response: Thank you very much. We have corrected the sentence as “In the early period (0-6 days), neonatal hyperbilirubinemia accounted for 1309.3 deaths per 100,000 livebirths and was the seventh most common cause of neonatal deaths.” in the revised manuscript.

Question 3: P3 L13: Phototherapy, not photography.

Response: Thank you very much. This was corrected in the revised manuscript.

Question 4: P3 L16-21: This paragraph is unclear and inadequately sourced. The second sentence has incorrect syntax. The third sentence is unsupported by evidence. The fourth sentence is correct, but the two citations from the previous sentence belong with this sentence. The fifth sentence may be correct but no references were cited.

Response: Thank you very much. We have changed the second and third sentences as “Guidelines have also been developed to bridge the gap between research and clinical practice. Clinical practice guidelines have become increasingly popular in recent years.” In addition, references were adjusted in the revised manuscript.

Question 5: P3 L27-30: Incorrect syntax and logic. A tool does not assess rigor; researchers assess rigorous using a tool. Errors of grammar and syntax in the remainder of the document are not itemized.

Response: Thank you very much. We have corrected the sentence as “The Appraisal of Guidelines for Research & Evaluation (AGREE) instrument was used to assess methodological rigor and transparency of a guideline” in the revised manuscript. The manuscript has been edited by an English professional company (Editage).

Question 6: P7 L16-27: Nine guidelines that reported risk factors for “severe neonatal jaundice” are listed in Table 5. However, the information in the text and table is unclear, imprecise, and incompletely documented. For example, the NICE guideline (reference 16) in Table 5 is said to have listed four risk factors for “severe neonatal jaundice” – prematurity, exclusive breastfeeding, sibling with severe hyperbilirubinemia, and visible jaundice <24 hours. It actually used a cutoff of 38 weeks of gestation, combining early term and preterm births as a risk factor.

Response: Thank you very much. We have replaced “Prematurity” with “under 38 weeks” in Table 5 in the revised manuscript.

Question 7: It also listed siblings with clinically significant jaundice requiring phototherapy, which is not the same as severe hyperbilirubinemia.

Response: Thank you very much. We have included that “siblings with clinically significant jaundice requiring phototherapy” in table 5 in the revised manuscript.

Question 8: In addition, Table 5 states that it ruled out male sex and bruises as risk factors, although neither is mentioned in the guideline document or the published summary (reference 16); presumably these factors were addressed in a separate evidence review document.

Response: Thank you very much. Yes. These factors were addressed in a separate evidence review document in the full guideline. This was cited as reference 25 in the revised manuscript.

Question 9: Further, Table 5 asserts that the NICE guideline did not mention Rhesus negativity, sepsis, or G6PD deficiency as risk factors (NA for Not Available). However, the NICE guideline states, “Jaundice has many possible causes, including blood group incompatibility (most commonly rhesus or ABO incompatibility), other causes of hemolysis (breaking down of red blood cells), sepsis (infection), liver disease, bruising and metabolic disorders. Deficiency of a particular enzyme, glucose-6-phosphate-dehydrogenase, can cause severe neonatal jaundice.”

Response: Thank you very much. We have corrected these labels in table 5 in the revised manuscript.

Reviewer: 2

Reviewer Name: Bolajoko Olusanya

Institution and Country: Centre for Healthy Start Initiative

Ikoyi, Lagos

Nigeria

Please state any competing interests or state 'None declared': None declared

Comments to the Author

This systematic review of guidelines for the management of neonatal hyperbilirubinaemia is a potentially valuable addition to the literature.

Question 1: However, the entire manuscript requires considerable language editing for the readership of this journal. For example, the following statement in the introduction would suggest that this finding is no longer valid: "Jaundice affected at least 60% of full-term and 80% of preterm neonates<sup>1</sup>, suggesting that about one-tenth newborn babies were likely to develop hyperbilirubinemia" Whereas, jaundice still affects newborns to this extent.

Response: Thank you very much. Actually, reviewer 1 raised the same question. We have corrected this in the revised manuscript.

Question 2: Additionally, it is unclear if only guidelines or recommendations issued by national or regional organisations were eligible for evaluation.

Response: According to the "AGREE II" introduction, guidelines produced by local, regional, national or international groups or affiliated governmental organizations were all eligible for evaluation. We have added this in page 3 in the revised manuscript.

Question 3: A major omission in this review is the identification of guidelines that included or did not include post-discharge neurodevelopmental evaluation of infants with severe hyperbilirubinemia who were treated with intensive phototherapy and/or exchange transfusion.

Response: Thank you very much for your suggestion. We have added a paragraph to describe the follow-up of infants with severe hyperbilirubinemia in Page 7 in the revised manuscript.

Question 4: Additionally, the authors claim that there are no guidelines from Africa and South Asia where the disease burden is greatest is inaccurate. They should carefully study a similar review by Olusanya BO, Ogunlesi TA, Kumar P, et al. Management of late-preterm and term infants with hyperbilirubinaemia in resource-constrained settings. BMC Pediatr. 2015;15:39. Published 2015 Apr 12.

Response: Thank you very much for your indicating. We carefully read the review by Dr. Olusanya and added a paragraph to discuss how to manage late-preterm and term infants ( $\geq 35$  weeks of gestation) with clinically significant hyperbilirubinemia in low- and middle-income countries lacking local practice guidelines in page 8. We have removed the sentence "there are no guidelines from Africa and South Asia where the disease burden" in the revised manuscript.

Reviewer: 3

Reviewer Name: Taulant Muka

Institution and Country: ISPM-University of Bern, Bern, Switzerland

Please state any competing interests or state 'None declared': No conflicts of interest

Comments to the Author

Zheng et al. have examined systematically the evidence on quality of clinical practice guidelines for neonatal hyperbilirubinemia. Authors find that current guidelines varied in quality. This article provide an important message and has important implications.

I have few minor comments that can improve the paper further.

Question 1: Could authors provide the average quality of existing guidelines based on the continent, for instance Asia vs. USA vs. EU, and how it relates to disease burden?

Response: Thank you very much for your suggestions. We added a paragraph to discuss the average quality of existing guidelines based on the continent and the disease burden in page 9 in the revised manuscript.

Question 2: Could authors compare their findings with similar analysis on other clinical guidelines? Are the issue they report only applicable to guidelines on neonatal hyperbilirubinemia, or is it a general problem?

Response: Thank you very much. In this review, we found that the scores in domain 1 (scope and purpose) and domain 2 (clarity of presentation) are greater than 80 %. The scores in the other four domains were lower 50%. These findings were similar to the findings by Dr. Alonso-Coello et al. 2010. Therefore, we think it is a general problem. We have discussed these in page 7 in the revised manuscript.

Question 3: An important finding is the lack of proper methodology in conducting guidelines, such as the lack of systematic search and proper meta-analysis. Could authors discuss more on this topic and provide future recommendations? The 24-Steps to Systematic Review and Meta-analysis article could be recommended/cited (Muka et al. EJEP, 2020)

Response: Thank you very much for your suggestions. We have discussed more in detail about how to perform a systematic review and proper meta-analysis in page 8. Muka et al. 2020 was also cited in the revised manuscript.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Bolajoko Olusanya Centre for Healthy Start Initiative, Ikoyi, Lagos, Nigeria
<b>REVIEW RETURNED</b>	18-Dec-2020

<b>GENERAL COMMENTS</b>	No further comments.
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<b>REVIEWER</b>	Taulant Muka ISPM, University of Bern
<b>REVIEW RETURNED</b>	14-Dec-2020

<b>GENERAL COMMENTS</b>	The authors have addressed all my comments
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