Author's response to reviews

Title: Reducing neonatal infections in south and south central Vietnam: The views of healthcare providers

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Author's response to reviews: see over
The Editor in Chief of BMC Pediatrics

Dear Professor,

Thank you for giving us the opportunity to revise our manuscript entitled “Reducing neonatal infections in south and south central Vietnam: The views of healthcare providers” (MS: 1064302105792962). We would also like to thank the reviewers for their advice.

The paper was revised in response to the Reviewers’ comments, suggestions and questions, and edited for fluency. The revised manuscript is enclosed for your consideration. Below are our responses to the individual issues raised by the Reviewers.

**Reviewer 1 (Fabio Uxa)**

No major issues, but the following suggestions were made.

**Minor Essential Revisions**

1. **“Discussion- Paragraph 7nd : In the last sentence is written that “… maternal contact (i.e. Kangaroo-mother-care) seems to reduce neonatal mortality …”; more that the ‘contact’ is the mother involvement in the process of care, as is in the KMC, that reduce mortality and severe infections mainly in ‘Low Middle Income Countries’ (as in the meta-analysis in the bibliography [19]: Conde-Agudelo A, Belizán JM, Diaz-Rossello J: Kangaroo mother care to reduce morbidity and mortality in low birth weight infants. Cochrane Database Syst Rev 2011).”**

   Page 10; Paragraph 4; Line 5. The sentence “Kangaroo-mother-care is suggested as a method to reduce neonatal mortality and to prevent infection in neonatal intensive care in low resources setting” was replaced with “Maternal involvement in the process of care, through kangaroo-mother-care, is suggested as a method of reducing neonatal mortality and preventing infections in stabilized low birthweight infants in low resources settings.”

**Discretionary Revisions**

2. **Might it be an alternative title : “What Interventions could reduce infections …? : the views of …”**

   We thank the reviewer for the suggestion, but we felt that the original title better describes the intention of the article.

3. **“Background- Paragraph 4th : [6] In this article the 58,6% of the neonatal deaths occurs in the first 24h. It’s an important contribution to distinguish ‘early’ vs. ‘late’ sepsis. Is it so also in the Central and Central-South Regions of Vietnam?”**

   Page 4; Paragraph 2. We amended the sentence for clarity. “We are not aware of any data on the incidence of early- and late-onset neonatal sepsis in Vietnam as a whole, or specifically in the central or south central regions. In a province in northern Vietnam, however, a recent study based on verbal autopsy found that 59% of neonatal deaths occurred in the first 24 hours after birth.”
4. “Background- Paragraph 4th : What is the percentage of births attended by skilled health personnel, vs. home-deliveries, in those areas of Vietnam? [In the WHO World Health Statistics, 2009, the national figure for Vietnam was 88%].”

Page 4; Line 2.
We added the following sentence for clarity: “As an estimated 64% of deliveries are in institutions, and 88% are attended by a skilled attendant [5], a strong network exists for appropriate referral of sick neonates.”

5. “Background- Paragraph 4th : “…infections … responsible for 11% of deaths”. Are these neonatal or U5IM deaths?”

Page 4; Paragraph 2; Line 5. We have specified that these were neonatal deaths in the text.

6. “Methods- Paragraph 3th : Could it be described in more detail what the Authors mean by “family contact.”

Page 5; Paragraph 4; Line 7. The term “family contact” was changed to “family access to the nursery and contact with the infant”.

7. “Results- Paragraph 1st and Table 1 : As described in the contribution [6], is it known the ‘age at death’?”

The “age of death” of patients is unknown. We assume the reviewer was trying to elicit information on the importance of early and late-onset sepsis and have added a sentence to note that we do know of no data on this subject in Vietnam. We also added a clause to state that: “…; disaggregated data by location of birth, and data on age at death were not available.” (Page 7; Line 6)

8. “Results- Paragraph 1st and Table 1 : The dead newborn infants in these data were only in-born, or the out-born infants are included?”

Page 7; Line 5. We added the clarification: “Mortality data are shown in Table 1 and refer to both inborn and outborn newborns;…”

9. “Results- Paragraph 1st : in the last sentence of the paragraph “…about 200,000 neonates were born in this hospital” or in these hospitals?”

Page 7; Line 4. Amended: “…in this hospital” was changed with “… in these hospitals.”

10. “Results- Paragraph 3th : What is the usual duration of hospital stay after a normal birth or a caesarean?”

Methods section; Line 8. We added a information on usual length of stay after normal and caesarean delivery

11. “Discussion- Paragraph 2nd : My I propose to the Authors “… ‘Prophylaxis and therapy’ (ante partum antibiotics in case of maternal infection, Premature Rupture of Membranes - PROM, screening for maternal Group B Streptococcus- GBS infection) were …” in place of “… ‘Prophylaxis and therapy’ (screening for maternal Group B Streptococcus- GBS infection, and ante partum antibiotics) were …?”
Page 9; Line 3. We amended the sentence to read: “… and “Prophylaxis and therapy” (ante partum antibiotics in case of maternal infection, Premature Rupture of Membranes [PROM] and screening for maternal Group B Streptococcus [GBS] infection.”

12. “Discussion- Paragraph 3nd : What is the incidence of GBS in the Vietnam population (in North and South)? Is it relevant? The screening cost?”

Page 9, Line 10. The following information was added: “We know of no national data on the prevalence of GBS infection in Vietnam; screening and intervention are not part of the national standard guidelines for antenatal care. In the United States, between 5% and 40% of all pregnant women have recto-vaginal colonization with GBS [14]. In Taiwan, a recent study found that the maternal colonization rate of GBS was around 20% at hospital base and the incidence of neonatal GBS infection was 1 per 1000 live births of infants born at hospitals. The authors concluded that “universal maternal recto-vaginal culture of GBS with intrapartum antibiotic prophylaxis is required to reduce early-onset disease and mortality because of GBS infection in neonates in Taiwan” [15].”

13. “Discussion- Paragraph 4nd : There was any discussion during the course about how are now applied in those hospitals the analyzed interventions?”

During the course, we discussed these interventions with participants. We think, however, that these specific aspects are beyond the scope of this study.

14. “Discussion- Paragraph 5nd : About nurses/patients ratio, are the mothers allowed to assist their healthy or sick babies? Are the Units open to the parents?”

Page 10; Paragraph 4; Line 5. The following clause was added for clarity: “While in Vietnam mothers family members are routinely involved in the care of the newborn, in part as a response to suboptimal nurses patients ratios, …”

15. “Discussion- Paragraph 7nd : In the last sentence is written that “… maternal contact (i.e. Kangaroo-mother-care) seems to reduce neonatal mortality …”; more that the ‘contact’ is the mother involvement in the process of care, as is in the KMC, that reduce mortality and severe infections mainly in ‘Low Middle Income Countries’ (as in the meta-analysis in the bibliography [19]: Conde-Agudelo A, Belizán JM, Diaz-Rossello J: Kangaroo mother care to reduce morbidity and mortality in low birth weight infants. Cochrane Database Syst Rev 2011].”

See Point 1.

16. “Conclusions : May it be appropriate to include in the Background section some data on the breastfeeding rates in Vietnam, if available?”

Page 10; Line 3. The following clarification was added: “National data on breastfeeding in Vietnam, however, indicate that only 58% of neonates are breastfed early, and only 17% of infants are exclusively breastfeeding at 6 months,…”
Reviewer 2 (Lydia Decembreno)
The reviewer is supportive of publication, subject to the following revisions.

Major Compulsory Revisions

1) “The title and purpose concern neonatal infections, the authors should better specified the sample taken into account because in methods section the title of the workshop is “infection prevention and control in the NICU” but in results section the authors report that the majority of participants worked in the pediatric ward n=32 or the neonatal ward n =12. The authors should specify if paediatric wards admit newborns and neonates and describe the organization of pediatric hospitals in Vietnam”.

Page 3; paragraph 4. We have added the following description of the organization of pediatric hospitals in Vietnam: “Facility-based neonatal care in Vietnam was very limited at the start of the 21st century, and generally provided by non-specialist paediatricians in the paediatric wards. In under ten years newborn care has been rapidly expanded and today all provincial hospitals have neonatal units, usually in a specially designated area of the obstetric or paediatric wards, with staff drawn from the Pediatric Department. These units are usually referred to as Neonatal Intensive Care Units (NICUs), but relatively few have the capacity to provide long-term mechanical ventilation, so this paper refers to them as nurseries. At a minimum, these nurseries are equipped with CPAP, oxygen, warming devices, phototherapy and essential medicines and supplies to deal with the most common neonatal conditions”.

Page 5; Paragraph 4; Line 5. We specified this point adding the following sentence: “In parts b) and c), no distinction was made between systemic and localized infections”.

3) “Background: In the work is not been made a distinction between NICU and nursery.”

Addressed in response to Point 1.

4) “Background: The authors should stress much more the importance of low cost of hand washing and exclusive breastfeeding in such low resources settings.”

We added the following parts:

Page 10; Line 3. We added additional information on breastfeeding in Vietnam: “National data on breastfeeding in Vietnam, however, indicates that only 58% of neonates are breastfed early, and only 17% of infants are exclusively breastfeeding at 6 months, so community-wide promotion of breastfeeding may be required.

Page 10; Paragraph 3; Line 6. We also added information about hand washing and alcohol-based handrubs: “..., and WHO Guidelines recommend routine use of alcohol-based handrubs as the gold standard in health care worldwide (after initial hand washing)”.

5) “Methods section: Were asked the participants to complete a written questionnaire after they attended the workshop to verify the learning of what was discussed during the workshop?”

Page 5; paragraph 2, Line 5. We added sentence to clarify that “There was no pre- or post-workshop assessment of attendee knowledge or skills”.
Discretionary Revisions

6) “Discussion section: Line 2-3 “the results of the survey could be used to reinforce the importance of antenatal universal screening for GBS in the future hospital strategies”. The authors should support this phrase with some literature paper like this: Consequences of Prophylaxis for Group B Streptococcal Infections of the Neonate. Baltimore R.S. Semin Perinatol 2007. 31:33-38.”

We added the following information: Page 9; Paragraph 2; Line 15. “The results of this survey suggest that advocacy of antenatal universal screening for GBS should be considered as part of future hospital intervention strategies, and at national policy level; such advocacy is dependent on the incidence of GBS infections in neonates which will determine, in large part, the cost-effectiveness of such a strategy,” along with the suggested reference. See also Reviewer 1; Point 12

7) “Discussion section: The phrase: “one third start with a single antibiotic, half start with two antibiotics….These data suggest a need for guidelines…” should be supported by literature like this: Antibiotic Use and Misuse in the Neonatal Intensive Care Unit. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland M. Arch Dis Child Fetal Neonatal 2011;96:F4–F8.”

As suggested, we added the reference.

8) “Discussion section: The authors should investigate the problems related to the diagnosis of infections since in results section is reported: “…clinical evaluation was considered as the most appropriate method to diagnose a neonatal infection by the majority of partecipants....”

The following information was added (Page 12; Line 1): “Seventy-eight percent of attendees considered physical examination to be an appropriate method of detecting infection, while only 63% considered biochemical examination (CRP) to be an appropriate method, and 40% considered culture to be appropriate. The reasons behind these views were not formally investigated as part of this study. Our experience of working in low resource settings suggest a number of possibilities, including lack of 24-hour access to laboratory services and the frequent failure to successfully culture organisms from neonates who have clear signs of infection. In these circumstances, clinicians are forced to make a prompt diagnosis based on clinical signs and treat presumptively.”

9) “Discussion section: The costs problems did not adequately discussed in the work, although in discussion section the authors underline the need for continued research on cost effectiveness of key interventions in setting with limited resources.”

In the Discussion section, we gave additional information about hand washing, breastfeeding, alcohol-based handrubs, and incidence of GBS infections, and noted that the cost-effectiveness of GBS screening would need to be assessed in light of the incidence on neonatal GBS infection. (Page 9; Paragraph 2; Line 8)

Minor Essential Revisions

10) “Background: The aim of this study was to explore the views should be replaced by the aim of our study was....”

Page 4; Paragraph 3; Line 1. “The aim of this study…” was changed to “The aim of our study...”
**Reviewer 3 (Giovanni Vento)**

The reviewer is supportive of publication, subject to the following revisions.

**Major Compulsory Revisions**

1. “In comparison to developed countries, where group B streptococcus (GBS) is often the most important pathogen, in developing countries the causal organisms of sepsis, acute respiratory infection, meningitis etc. are frequently gram-negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli*, that likely originate in the maternal genital tract. Do the Authors have some data about the etiology of episodes of infections occurring in the hospitals where participants were working at the time of the survey? Do the Authors have knowledge of the role of perinatal infections in the same hospitals, to eventually focus their attention in the prevention of this type of infection, by using intrapartum and peri-partum therapeutic aids?”

Unfortunately, we have no data about the etiology of episodes of infections occurring in the hospitals where participants were working at the time of the survey. Neither do we have specific knowledge of the role of perinatal infections in these hospitals. We reported this limitation of our study adding a paragraph to the Discussion section which states: Page 12; Paragraph 3: “While information from this survey identifies issues which may need to be addressed during any hospital-based intervention, the final content of an intervention must be guided by the actual circumstances in the target hospitals. The descriptive data provided by each hospital as part of this study is too limited to provide a detailed prescription. A first step in any hospital where intervention is planned is likely to include early introduction of universal protocols for low-cost interventions such as initial hand washing and subsequent use of alcohol-based handrubs, and advocacy of early skin to skin contact and initiation of breastfeeding, while at the same time establishing data collection systems that can provide local epidemiological information about neonatal infectious disease.”

2. “Considering that the aim of this study was “….how to improve neonatal infection prevention and control”, do the Authors evaluate in their survey the significant role of potential low-cost interventions in significantly reducing the mortality and severe morbidity associated with infection in perinatal care? In these settings of promising high-impact preventative and curative interventions, studies of chlorhexidine in developing countries have focused on three primary uses: a) intrapartum vaginal and neonatal wiping, b) neonatal wiping alone, and c) umbilical cord cleansing. This point should be discussed.”

We appreciate this suggestion. We added the following paragraph (Page 11; Paragraph 3): “The report of a conference on potential use of chlorhexidine in low-resource settings [25] notes that, studies of chlorhexidine have focused on three primary uses: a) intrapartum vaginal and neonatal wiping, b) neonatal wiping alone, and c) umbilical cord cleansing. Studies of chlorhexidine vaginal and infant wipes have not shown reductions in perinatal mortality and morbidity [26, 27]. Data from three cluster-randomized trials, however, demonstrate that a single application of 4% chlorhexidine to the umbilical cord stump following delivery reduces the incidence of omphalitis and neonatal mortality, especially in preterm newborns [28]. This intervention, which is safe and inexpensive and requires minimal training and skill, should be considered for home births. The WHO currently recommends dry cord care for newborns [11], and this practice is the standard of care in Vietnamese hospitals. It remains to be demonstrated if the application of 4% chlorhexidine to the umbilical cord stump following hospital deliveries could be effective in improving neonatal outcomes.” Three relevant references were added.
Quality of written English:
“Not suitable for publication unless extensively edited.”
The manuscript was revised to ensure fluency.

Best regards,
Daniele Trevisanuto