PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Reducing early infant mortality in India: results of a prospective cohort of pregnant women utilizing emergency medical services
AUTHORS	Bills, Corey; Newberry, Jennifer; Darmstadt, G; Pirrotta, Elizabeth; Rao, G.V. Ramana; Mahadevan, S.; Strehlow, Matthew

VERSION 1 – REVIEW

REVIEWER	Hani Mowafi Yale University (USA)
REVIEW RETURNED	05-Nov-2017

GENERAL COMMENTS	Thank you for the opportunity to review this paper on prehospital transport and neonatal mortality in India. Overall, I think that this is an important study as the findings clearly highlight not only a higher than expected PMR in the studied regions but in addition, represents an important insight into PMR in a patient population frequently overlooked in summary statistics due to lack of medical access / utilization. As such, prehospital data may be THE most complete picture of PMR in rural India as most perinatal mortality occurs prior to reaching medical care. Other than a household census these data may best provide large-scale data that can inform and further detail facility based statistics. For example, the summary PMR for India that is quoted may in fact not be correct. There is no assessment of the background statistic, how it is derived and the level of completeness of the data that formed the background so this may indeed be an underestimate of the actual perinatal mortality in India. As such multi-modal data including household surveys, prehospital records and facility based statistics may be more appropriate in getting to the real number. General: The paper is in need however of some re-organization and reframing to more clearly define the study objectives and place the data in context. In the current format, it is not clear whether the objective is to: a) characterize the PMR as assessed by prehospital data vs. facility based PMR; b) assess the impact of prehospital interventions on reducing PMR (if so, what other interventions are part of the prehospital OB protocols and were they assessed?);

	c) compare PMR between various states in India served by same prehospital service? (in that case, more characteristics of the states included would need to be assessed with the state being the level of analysis such as median distance to facility, median transport time, others by state to assess for differences. Such differences could spotlight areas for intervention in each state's health sector for perinatal services. I would like to see the following in a revision: • a clearer aims statement at the outset (with reference to subanalyses as appropriate). • Additional information on the PMR specific to each state (and the level of confidence associated with those reference statistics at the state and national level, if possible) • A table with side by side comparisons by state as it seems that this was deemed a necessary factor to control for Other various points: • Abstract line 29 (EMT interventions were independent variables not outcome measures). If the outcome was whether or not an intervention was performed that is a measure of EMT recognition or performance not impact of intervention. In that case, would need significant reframing in the paper • Final abstract statement - Emergency medical services have the potential to reduce inequities in accessing healthcare and increase facility-based care, thereby reducing young infant mortality in India o Not well supported by the data presented which is mainly epidemiology of PMR in this convenience sample. • EXCELLENT Follow up rates. Should be more specifically noted in the front end • The sheer size of India makes any attempt at impacting global PMR dependent on significant gains in India, specifically in the rural areas. These areas are most absent in traditional data which makes this type of non-traditional approach desirable • Caste was seemingly used as a surrogate of socioeconomic class but o Not sure that this is a clean surrogate measure (i.e. how much overlap between these groups) o Not sure the utility in this context as unclear if global statistics of PMR are reported by caste in India. If not it is hard to contextualize this information • The first three paragraphs should be combined with a statement about the proportion of PMR outside facilities in India. This will make a clearer more compelling statement about why prehospital data is a novel and important method to assess this phenomenon since most will take place outside the reach of traditional health information systems (other than household surveys). • This is further bolstered by the fact that in India as in Africa, a large percentage of prehospital transport is for pregnancy related conditions. This is STARKLY in contrast to the US and Europe with much lower percentages of obstetric transports. • Is the global PMR reported for India from household surveys, facility based data, summary measure from MoH, is there any info as to how this was derived? • 6 hours per day, 6 days per week is not an insignificant number.

	While the convenience method is a limitation there should be some reference to what percentage of weekly obstetric transfers were captured in this window (seems to be 1.7% which is surprisingly low and makes me wonder whether I'm misunderstanding this stat). • The Meghalaya PMR is very high but may be a function of the very small sample size from that state. Were the other states close in PMR? • Surprisingly it appears that 98% had some sort of antenatal care prior to transport. Although it appears only those with more extensive >4 visits were protected. Are there comparative statistics for India as a whole? This would help put the findings in context given that this turned out to be a significant variable. • There were very few higher socioeconomic patients included making comparisons difficult. It could be useful to compare to the facility PMR if this is known or the median PMR for facilities by state to give a sense of the overall PMR in populations with access to care • Pg 12, line 10 – it is reported that most hypotensive or tachycardic patients were placed in LLD position but minority had IVF started. It is hard to interpret this without knowning what the protocols are for these transports. Are the medics following their protocols or deviating? • Pg 12, line 16 – it is reported that 4 women died during this study but no characteristics are given re these maternal deaths • Pg 13, Table 3 – not clear if IVF administration was protective, not reported • Pg 14, Line 41 – not sure what "state to state variability" entails. Variability in incidence? PMR? prehospital transports? other? It seems that in the MVR once this variable (again unclear) was controlled for there was no effect of prehospital interventions on PMR • Pg 15 line 35 – unclear how this study DEMONSTRATES how EMS plays a role in reducing the equity gap. More clarification needed • Pg 17, line 1 - In developing countries, most perinatal deaths occur at home.[24] - this should be brought up sooner in intro paragraphs • Pg 17, para 2 – unclear the significance of this paragraph. Was there a higher incidence of prematurity in this study than in the country as a whole? If so should be clearer •

REVIEWER	Sean Kivlehan Brigham and Women's Hospital, USA
REVIEW RETURNED	09-Dec-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This is an excellent snapshot of the perinatal mortality rate and associated factors in India. Perhaps most striking is the doubling of the mortality rate in these marginalized populations. These data provide strong support for the need to improve access and care for these populations. EMS is an excellent mechanism for this outreach, and I feel that this manuscript provides a foundation for future work to improve EMS training and care. A few questions/comments: Please state what GVK stands for and perhaps elaborate the history of it briefly.

	Please explain why data was only collected Mon-Sat for 6 hours, as this could be seen as a limitation - particularly because more high risk events could be occurring at night or on Sunday when public transport options are more limited. Please explain what training the EMTs have and what their scope of practice is (in regards to OB/GYN/neonatal care. Please clearly explain how EMS care can affect births that occur after hospital arrival (ie not on scene or in transport?). This would be useful to strengthen your argument on the importance of EMS. The inability to differentiate stillbirth vs same day death seems to be a big limitation as this is potentially where EMS can have greatest impact. Please elaborate on this. Typo page 10 line 18 Page 12 line 50 - add neonate after 62 to specify you are talking about the baby and not mother. Table 3 - why are only Gujarat and Meghalaya state evaluated specifically? Page 16 line 18 - unclear meaning of "EMS Overcome" Page 16 discussion - it seems non-disadvantaged people aren't using EMS - is that true? And if so is that affecting interpretation? Thank you again for this work and for the opportunity to review it. I look forward to the revisions.

VERSION 1 – AUTHOR RESPONSE

Regarding the first reviewers comments:

Please state what GVK stands for and perhaps elaborate the history of it briefly.
While the official name of the EMS agency is GVK Emergency Management and Research Institute, we have provided clarification as to what the GVK is in reference to on page 5, line 18, and elaborated on the history briefly. “GVK Emergency Management and Research Institute (GVK EMRI), named after Gunupati Venkata Krishna, is a not-for-profit, public-private partnership that provides free ambulance transport and pre-hospital stabilization care that can be accessed using a three-digit, toll-free phone number.”

Please explain why data was only collected Mon-Sat for 6 hours, as this could be seen as a limitation - particularly because more high risk events could be occurring at night or on Sunday when public transport options are more limited.

Response: We recognize this as a potential limitation and is addressed in the discussion section as a limitation. In order to highlight this limitation we have also included the following statement in the methods section. “Enrollment was limited to this time frame given constraints of research assistant availability, safety and cost.”

Please explain what training the EMTs have and what their scope of practice is (in regards to OB/GYN/neonatal care.

Response: We have included the following text (page 6, lines 8-14) to help clarify this point and have submitted a set of protocols to be published as a supplementary material if needed. “The majority of ambulances are staffed by both a driver and a single emergency medical technician (EMT). EMTs are trained to provide basic emergency obstetric and neonatal care, including resuscitation and administration of life-saving medications, with oversight from real-time physician-guided medical direction available by phone.

EMTs scope of practice around obstetric, gynecologic, and neonatal care are driven by standard protocols (see online supplementary material 1). Patients are transported to the nearest appropriate public or private care facility unless they request an alternate facility."

Comment: Please clearly explain how EMS care can affect births that occur after hospital arrival (i.e. not on scene or in transport?). This would be useful to strengthen your argument on the importance of EMS.

Response: We feel prehospital care can benefit both mom and neonate, even if delivery occurs after hospital arrival and sought to strengthen this point. Starting on page 17, line 7 we provide further support for this idea: "Lastly prehospital interventions whether through patient positioning, fluid resuscitation, or timely diversion of high-risk patients to facilities with trained providers suggestive of a higher level of care all serve to affect births that occur after delivery."

Comment: The inability to differentiate stillbirth vs same day death seems to be a big limitation as this is potentially where EMS can have greatest impact. Please elaborate on this.

Response: We agree that this is a limitation. However, the inability to differentiate stillbirths vs same day deaths largely impacts 1. those deaths that occur prior to EMS arrival (as no one was on scene to determine death) or 2. after hospital arrival (as our follow-up scheme, via family members, makes it challenging to whether death occurred after delivery) and it is unclear how not being able to make this distinction would make EMS any less important. We have made note of this in the text more explicitly, however: "Additionally we were unable to differentiate stillbirths vs deaths that occurred on day one of life and while this may serve to limit our recommendations we believe emergency response services have the potential to promote equity in access to healthcare services, and improve perinatal survival in India no matter the cause."

Comment: Typo page 10 line 18

Response: This has been changed and is noted on page 10.

Page 12 line 50 - add neonate after 62 to specify you are talking about the baby and not mother.

The sentence now reads: "In sum, 62 neonates died by day 2, 76 neonates died by day 7…"

Table 3 - why are only Gujarat and Meghalaya state evaluated specifically?

Response: We ran univariate analyses for all states, but given that Gujarat and Meghalaya represented the extremes of enrollment we only included these in the table given constraints of space. We have amended the table to include data from all states, as the second reviewer requested this as well. We have provided the text here for clarification: "State was not included in initial multivariate models, though it was controlled for in iterative analysis given the variability in enrollment and proportional variability in early infant death from state to state."

Page 16 line 18 - unclear meaning of "EMS Overcome"

Response: We have clarified this sentence on page 16 line 15: "EMS may serve to overcome many factors that have traditionally been thought to limit healthcare access for poor and marginalized populations…"

Page 16 discussion - it seems non-disadvantaged people aren't using EMS - is that true? And if so is that affecting interpretation?

Response: Proportionally, our cohort includes more disadvantaged people. In general this is the intent of the public EMS system and we are happy to see numbers trend in this way. While this may affect some interpretation, we selected for variables related to socioeconomic strata and none were significantly related to perinatal outcomes. We have further added the wording as expressed in the previous comment on page 16 starting at line 14. “In our study, where the majority of mothers were from disadvantaged backgrounds, this link did not exist. EMS may serve to overcome many factors that have traditionally been thought to limit healthcare access for poor and marginalized populations…”

Regarding the second reviewers comments:

The reviewer had asked for some re-organization and reframing to more clearly define the study objective and to provide further context for the data. We hope the following specific changes as listed below help to clarify the reviewers concerns.

Comment: A clearer aims statement in needed with reference to subanalyses.

Response: We have clarified our aims on page 5, line 1-5. “This study aims to report the perinatal mortality among a cohort of young infants, born to laboring women in five Indian states who were transported by an ambulance service with trained emergency medical technicians (EMTs). Secondarily, we report on the demographic, maternal indicators and clinical management associated with increased rates of perinatal death.”

Comment: The reviewer raised the following points regarding the PMR. We have grouped them here to detail our changes as a whole.

Response: Additional information on the PMR specific to each state and the level of confidence associated with those reference statistics if possible. The first three paragraphs should be combined with a statement about the proportion of PMR outside facilities in India. This will make a clearer more compelling statement about why prehospital data is a novel and important method to assess this phenomenon since most will take place outside the reach of traditional health information systems (other than household surveys). Is the global PMR reported for India from household surveys, facility based data, summary measure from MoH, is there any info as to how this was derived? A table with side-by-side comparisons by state as this was deemed a necessary factor to control for.
We have provided the state specific PMRs in the text and they can be calculated from the absolute numbers now included in what is now Table 4. We have also provided the published reference rates (available for the closest available year (though Meghalaya is not available from the Indian MOH) (2012) in the discussion section. We have also included the following reference supporting the national statistic of neonatal mortality as likely being an underestimate. Sankar MJ, Neogi SB, Sharma J, et al. State of newborn health in India. Journal of Perinatology. 2016;36(Suppl 3):S3-S8. doi:10.1038/jp.2016.183.We have also included a new table (Table 3) with state comparisons of follow-up and 48 7 and 42-day mortality. All subsequent tables have been labeled sequentially. Additionally we have provided known PMR for each of the states and commented on this in the Discussion with the following text: “Yet, even with transport to healthcare facilities, the estimated PMR of 53 deaths per 1000 births is nearly double the reported national average. While PMR varied considerably by state, all, except for Karnataka, had reported PMRs greater than previously reported averages for the year 2013. (7) Comparatively the PMR in our study ranged from 37-167 per 1000 in the five states, while published PMRs for Andhra Pradesh, Assam, Gujarat, and Karnataka ranged from 24-30 per 1000.”

Comment: Abstract line 29 (EMT interventions were independent variables not outcome measures). If the outcome was whether or not an intervention was performed that is a measure of EMT recognition or performance not impact of intervention. In that case, would need significant reframing in the paper.

Response: We agree with this point and recognize the confusion and have removed the following text from the main outcome measure: “Emergency medical technicians (EMT) interventions.” The primary outcome now reads as: “Death at 2, 7 and 42 days after delivery.”

Final abstract statement - Emergency medical services have the potential to reduce inequities in accessing healthcare and increase facility-based care, thereby reducing young infant mortality in India. Not well supported by the data presented which is mainly epidemiology of PMR in this convenience sample.

Response: We have revised this statement to more clearly reflect the manuscripts findings on page 3, line 1. “Emergency medical services data has the potential to provide more robust estimates of PMR and work toward reducing inequities in timely access to healthcare and increase facility-based care through service of marginalized populations.”

Comment: EXCELLENT Follow up rates. Should be more specifically noted in the front end.

Response: We had previously noted this in the bulleted Strengths and Limitations Section, but have amended the text slightly on page 3, line 7: “Follow-up rates were excellent, with over 99% of patients followed at 7 days.” Additionally, we have included this point in the results section of the abstract on page 2, line 16: “Follow-up rates at 2, 7 and 42 days were 99.8%, 99.3% and 94.1%, respectively.”

Comment: The sheer size of India makes any attempt at impacting global PMR dependent on significant gains in India, specifically in the rural areas. These areas are most absent in traditional data which makes this type of non-traditional approach desirable.

Response: We couldn’t agree more, and think this should be emphasized. Given the 1. concerns about the final abstract statement raised above, and 2. the importance of this approach, we have modified the final conclusion to better reflect this this point. The wording of this change is noted above.

Comment: Caste was seemingly used as a surrogate of socioeconomic class but not sure that this is a clean surrogate measure (i.e. how much overlap between these groups). Not sure the utility in this context as unclear if global statistics of PMR are reported by caste in India. If not it is hard to contextualize this information

Response: We agree that caste alone is a limited marker of socioeconomic status. However, caste is a recognized descriptor of social class by the government of India. We also included the presence of a ration card as an indicator of economic class. These two in combination with other determinants of socioeconomic status, including geography and education, provide some semblance of socioeconomic status. Generalizing caste specific PMRs to global statistics on other marginalized communities may prove challenging as the reviewer suggests and recognize this as a constraint of the external validity of our study. That being said there is strong data to support the relationship between lower caste and increased risk of early childhood death in India. Contextualized within prior research may help to understand the importance.

Within India, this relationship has enormous consequences and may help to determine for whom interventions to reduce infant death should be targeted.

This is further bolstered by the fact that in India as in Africa, a large percentage of prehospital transport is for pregnancy related conditions. This is STARKLY in contrast to the US and Europe with much lower percentages of obstetric transports.
Given the importance of this point we have strengthened the contrast between India (and similarly in Africa) as compared to the US and Europe and have added the following sentence. “This is in comparison to the US and European countries where maternal and pregnancy calls are often <1% of total.” We have provided the following reference, as well. NEMSIS. V2 911 Call Complaint vs. EMS Provider Findings Dashboard. 2016. https://nemsis.org/view-reports/public-reports/version-2-public-dashboards/v2-911-call-complaint-vs-ems-provider-findings-dashboard/. Accessed December 20, 2017

Comment: 6 hours per day, 6 days per week is not an insignificant number. While the convenience method is a limitation there should be some reference to what percentage of weekly obstetric transfers were captured in this window (seems to be 1.7% which is surprisingly low and makes me wonder whether I’m misunderstanding this stat).

Response: The previous reviewer asked that we clarify the limitations of this study design (see above). The 1.7% is correct and is there to give a magnitude of the EMS system we are reporting on. We were not able to collect all calls during the collection periods.

Comment: The Meghalaya PMR is very high but may be a function of the very small sample size from that state. Were the other states close in PMR?

Response: The PMR by state is now included (see above and Table 3).

Comment: Surprisingly it appears that 98% had some sort of antenatal care prior to transport. Although it appears only those with more extensive >4 visits were protected. Are there comparative statistics for India as a whole? This would help put the findings in context given that this turned out to be a significant variable.

Response: Given the interest in ANC we have provided the following for context on page 18, line 17-20.
“Population based data for India shows similar ANC visitation rates at around 51%. (new reference, UNICEF) The risk associated with a lack of ANC visits supports consensus based recommendations emphasizing the importance of family planning and antenatal care, as women in this study may have had complications that went unrecognized in the perinatal period and that presented as emergencies necessitating the use of EMS.”

Comment: There were very few higher socioeconomic patients included making comparisons difficult. It could be useful to compare to the facility PMR if this is known or the median PMR for facilities by state to give a sense of the overall PMR in populations with access to care.

Response: We have strengthened our reporting on known PMR data as reported above. Unfortunately, this amount of granularity around PMR does not seem to be reported in the literature or by the government of India at this time. See above for further discussion of PMR.

Pg 12, line 10 – it is reported that most hypotensive or tachycardic patients were placed in LLD position but minority had IVF started. It is hard to interpret this without knowing what the protocols are for these transports.

Response: The previous Reviewer had a similar question. We are now including the published protocols as a supplement to this paper, page 6 line 13.

Pg 12, line 16 – it is reported that 4 women died during this study but no characteristics are given re these maternal deaths

Response: Given the constraints of this paper and the results of maternal outcomes having been previously published we elected to limit details. A reference to where one can read about more about this population has now been added in the text on page 12, line 7: In sum, four women died during this study, and all within 48 hours after hospital arrival (for a further discussion of this high risk group see reference 11).

Pg 13, Table 3 – not clear if IVF administration was protective, not reported
IVF administration was not protective and is added to what is now Table 4. Text of this is now provided on page 14, line 4. “Univariate analysis among all mothers identified the following maternal risk factors for elevated neonatal mortality at 7 days: less than four antenatal care (ANC) visits (p=0.019), abnormal vital signs (p=0.049), maternal IV placement (p=0.007) and IV fluids given (p=0.018), and mother not placed in left lateral position during transport (p=0.047).”

Pg 14, Line 41 – not sure what “state to state variability” entails. Variability in incidence? PMR? prehospital transports? other? It seems that in the MVR once this variable (again unclear) was controlled for there was no effect of prehospital interventions on PMR

Response: We primarily mean the variability in number of transports and overall state PMR. We have made changes to emphasize this point as noted previously and are including the table of state comparisons, as described above, in Table 3.

Pg 15 line 35 – unclear how this study DEMONSTRATES how EMS plays a role in reducing the equity gap. More clarification needed

Response: We have clarified this sentence to be more specific. “This prospective study suggests EMS plays an important, but under-appreciated role in reaching women from a lower socioeconomic strata and adds to prior data supporting the role of centralized EMS services in maternal and neonatal health policy.”

Pg 17, line 1 - In developing countries, most perinatal deaths occur at home.[24] - this should be brought up sooner in intro paragraphs

Response: This has been added to the introduction as suggested on page 4. “Most agree that this likely underestimates the overall perinatal mortality given the difficulty in capturing stillbirths and deaths that occur at home.” We have included the reference Sankar et al. to support this claim.

Pg 17, para 2 – unclear the significance of this paragraph. Was there a higher incidence of prematurity in this study than in the country as a whole? If so should be clearer

Response: We have clarified the wording and provided some comparison to rates of prematurity in India.
“The high PMR is likely multifactorial. Prematurity (based on maternal report of gestational age) was found to be one of the strongest predictors of death. This relationship is consistent with global data identifying this as the number one cause of neonatal death.

[28] While the proportion of prematurity in this study was similar to reported rates of India as a whole, the proportion of infants born premature who died within the first 7 days of life was higher than previous hospital-based studies. (Rather GN, Jan M, Rafiq W, Gattoo I, Hussain SQ, Latief M. Morbidity and Mortality Pattern in Late Preterm Infants at a Tertiary Care Hospital in Jammu & Kashmir, Northern India.
J Clin Diagn Res. 2015; 9(12): SC01–SC04.

Thank you again for giving us the opportunity to revise this manuscript and look forward to hearing back soon.

Sincerely,

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VERSION 2 – REVIEW

REVIEWER	Hani Mowafi Yale University USA
REVIEW RETURNED	12-Jan-2018

GENERAL COMMENTS	Thanks for the revision

REVIEWER	Sean Kivlehan Instructor of Emergency Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, USA
REVIEW RETURNED	13-Jan-2018

GENERAL COMMENTS	Thank you for taking the time to address all of the comments.