PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prospective cohort study of mortality in very low birth weight infants in a single centre in the Eastern Cape Province, South Africa
AUTHORS	Michaelis, Isabel Alexandra Manyisane, Ncomeka Krägeloh-Mann, Ingeborg Mazinu, Mikateko C Jordaan, Esme R

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Lloyd Tooke Institution and Country: University of Cape Town, Neonatology, South Africa Competing interests: None
REVIEW RETURNED	18-Nov-2020

GENERAL COMMENTS	Thank you. This is an important study as there is little information about outcomes from this part of South Africa. There are some minor and significant issues which will need to be addressed to be re-considered for publication. i) the use of the term 'offspring related risk factors'. Rather use infant/neonatal ii) Background: there is a recent paper documenting outcomes in Cape Town private/public sector for <1500g babies which would be useful to include: Van Wyk, Tooke et al in Neonatology 2020 iii) More information about setting is required: Does it occur that there is no space in PICU for ventilation. Which areas do Frere Hospital drain - there are other referral hospitals (maybe a map). How many births in the province. How many births in the referral area? iv) Why infants only admitted within first 24hrs of life? Usually neonatal databases include within first 28 days of life v) Babies were followed up until discharge or death. Is this discharge HOME or discharge including to other hospitals? vi) the paragraph about follow-up appointments needs to be re-written. It is clumsy and difficult to understand vii) Statistics: were variables assessed to see if they were normally distributed? Otherwise Median/IQR should be used. Results: viii) 161 out of 173 babies were included. Most of the ones who had no consent died. This is not prominently mentioned or discussed. This skews the data. The death rate is actually higher. You should not need consent to include these deaths in the totals. ix) Strange there were so many males - any reason for this? x) PCR results need to be presented as +ve, -ve, unknown. xi) What about 6 week PCR results? xii) Why neonatal info before maternal. Usually maternal is first

| | xiii) A figure showing the gestation, weights and deaths would help (there is an example in Levin, HIV Transission to premature VLBW infants, PIDJ 2017
xiv) Don't repeat in the text what we can see in the table
xv) There needs to definitions for many of the risk factors listed in the tables. For example, what defines resuscitation, HMD, weight gain, ICH etc. This should be in methods
xvi) p values can't be 0.000
xvii) No refrigerator in house. ?breast milk storage
xviii) Confidence interval for gestational age?
Discussion
xix) These shouldn't be new information in the discussion (incidence of VLBW etc)
xx) Comparing a hospital's VLBW rates to countries VLBW rates does not make sense. It is appropriate for referral hospitals to have high rates of VLBW deliveries
xxi) Can you talk about the whole E.Cape Province if there are other referal hospitals (Umtata, PE etc)
xxii) Much more needs to be explored in the discussions about unusual or positive findings. Theories need to be explored |

REVIEWER	Reviewer name: Dr. Shalini Ojha Institution and Country: University of Nottingham, School of Medicine, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	04-Nov-2020

| GENERAL COMMENTS | Thank you for asking me to review this manuscript. This is a single centre, prospective, cohort study of association between death and several maternal and neonatal factors in VLBW infants in an LMIC setting.
I have the following points to suggest to the authors:
1. Introduction: Please outline the aim of the study at the end of this section
2. What was the weight cut-off for inclusion <1500g or <1501 g?
3. What is the primary outcome of the study? Please give this as either mortality or survival?
4.Please describe the definitions and/or cut-off for the numerous variables included in the study such as
• what were the definitions for hyaline membrane disease, PDA, sepsis, ICH?
• What was include as "resuscitation at birth"
• What were the criteria for normal vs. abnormal trend of weight gain
• What was the cut-off for PROM?
5. Public and patient involvement: This describes the need for the study and not PPI. Not clear why mothers were not involved in study design. If there was no PPI input in study design, please state this.
6. Line 23: continuous instead of numerical
7. Was there collinearity between birth weight and gestational age? Similar to Apgar scores at 1 and 5 minutes, should only one of GA or BW been included in the model? There is potential for high collinearity between a few other variables included in the model such as HMD, surfactant given, and oxygen support; pre-eclampsia and hypertension; electricity, running water, and refrigerator. Were these considered in the regression analyses? Would the model be simpler if fewer of these highly correlated variables were included? |

8. How was gestational age determined? Was a reliable estimator such as early gestation ultrasound dating available? This is unlikely as 84% did not attend antenatal clinics. If not, this may be relevant to the analysis, and discussion esp. if a significant proportion could have had intrauterine growth restriction. If very few participant's had reliable GA estimation, the model will be improved by not including GA. It also makes me consider if the infants who had better survival associated with maternal pre-eclampsia, were actually more mature but smaller and it was the higher GA that let to better survival rather than the pre-eclampsia itself?

9. There is a discrepancy between total number of participants between the abstract and the results: 173 in abstract (line 28) 161 in Results – page 8 line 46

10. Please present the information in Figure 1 in more detail – does 4207 represent number of live births or all births? Were any <1000g were excluded because they needed invasive ventilatory support and were therefore not admitted to the PICU. Are these counted among the reported deaths? Were there any other delivery room deaths or deaths or exclusions prior to admission for neonatal care?

11. I suggest staring the results section with the number of babies born in the study period, number (%) who were VLBW i.e. the prevalence of VLBW in the hospital followed by a description of the demographic factors. 12. A very long description of demographic factors is given in the text. I suggest retaining some key variable such as GA and birthweight but most others are better described in a table (several are already included in Tables 1 and 2).

13. Lines 36 to 39: I assume this is the result of the primary outcome- it is described as survival "rate" but given as a %. Please correct this and present as stated in the aim and primary outcome of the study.

14. Tables 1 and 2 needs to made more comprehensible – I suggest combining columns headed
- n and % as number (%) of infants
- n died and % died as Deaths n(%)
- RR, 95% CI and last column as Risk ratio (95% CI)
- P value should be presented in the final column.

15. In the discussion Line 39-42: the discussion starts with some results which have not been describe in the Results section and in Line 42 – what does the CI represent in this statement. Prevalence is presented for one year only – I do not understand what the CI is for.

16. Lines 36-40 – this needs more discussion otherwise gives the message that pre-eclampsia is good for the baby.

17. Discussion needs to include more about the limitations of the study particularly that this is single, large hospital based study - is this really representative of the population of the region

18. Minor typographical corrections:
- Page 8 line 5: lie instead of lye
- Suggest present results as mean (SD) in the text rather than as long text sentences.
- Page 9 line 46 – suggest delete related
- Table 1 line 56 – suggest mother instead of Mom
- Table 2 line 27 – stable instead of stale
- Suggestion, please use consistent terminology, such as:
• VLBW cut-off – <1500 or <1501
• HMD or RDS
• HIV or RVD

REVIEWER	Reviewer name: Dr. Eirini Koutoumanou Institution and Country: University College London, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	21-Nov-2020

| GENERAL COMMENTS | Comments specifically for the methods used:
The authors have collected data on a variety of characteristics from mothers and babies. The relationship of each characteristic/variable with survival (main outcome variable) was initially explored separately/independently of other variables via logistic regression. Depending on the results of this univariate exploration, some variables were included in a multivariable model to better understand survival rates. Results have been presented as relative risks (RR) with corresponding p-values and confidence intervals. I would like to invite the authors to make some clarifications regarding the above summary of the methods used:

- The statistically significe results of the univariate analysis should be later enhanced with knowledge driven from clinical expertise, literature, etc in order to produce a meaningful and relevant multiple logistic model. The multivariable model should not be exclusively driven by the univariate results. Did the authors consider this when building the multivariable model?

- Can the authors please clarify if by "log binomial regression", they mean the conventional logistic regression technique with a logit link function? In which case the odds ratios (OR) should be presented, instead of the RR and all subsequent results should refer to the change in the odds and not the risk/chance.

- I don't believe that the following statement (and subsequent related comments) has been justified from this study as the data that was collected did not specifically focus on equipment, facilities, etc. "Equipment, facilities, skills and staffing should be improved in those settings.". Formal statistical significance tests have not been performed to compare survival rates between the Frere hospital and other (better "equipped") hospitals in South Africa.

More generally:

- It was not clear to me what the message from the Patient and Public Involvement (PPI) section was. I was not able to follow the flow of the paragraph nor relate it to PPI.

- For some numerical variables, the median and IQR should be used for summaries as the presented mean and the SD values indicate that some of the variables were not normally distributed (mean+- 1.96*sd should produce a 95% reference range for a given variable, but in some cases these calculations led to non-feasible results, e.g. birthweight, upper reference rage limit exceeds the max reported value of 1500. Also, it is not clarified by I assume the values in brackets next to mean birthweight is the range, min to max.)

- "All variables with small cell number (n≤6) were excluded from the multiple regression model." Am I right to assume that this |

relates to categorical variables? How many variables were
excluded and what biases might have this introduced?

- Is the "in-hospital survival rate" mentioned on the last paragraph
of the Demographics section, known from another study? The way
this is written, it implies that it was derived from another paper (if
so, a citation is needed), but if not, maybe it should be rephrased
for better clarity.

- Please acknowledge the study's limitations and potential sources
of bias.

Minor:
- Please replace commas with dots for decimal points in the
Tables
- P-values should not be reported as 0.000 but instead as <0.001
- Merge the n and % columns in the Tables. Also, the SE value
can be excluded as not necessary when CIs are presented. The
95% CI columns can be merged into one (2.93 , 5.88) to reduce
the number of separate columns.
- It's also not necessary to include the (0) and (1) codes next to
each category
- Explain acronym ICH in the main text additionally to the footnote
of Table 1
- Please replace the term multivariate at the end of the Results
section and in the 3rd paragraph from the end of the Discussion
section, with multivariable or multiple, as multivariate means
multiple outcomes.

REVIEWER	Reviewer name: Dr. Patrick van Reempts
	Institution and Country: University of Antwerp Faculty of Medicine
	and Health Sciences, Laboratory of Experimental Medicine and
	Pediatrics, Division of Neonatology, University of Antwerp,
	Antwerp, Belgium. Study Centre for Perinatal Epidemiology
	Flanders, Brussels, Belgium
	Competing interests: None
REVIEW RETURNED	14-Nov-2020

GENERAL COMMENTS	BMJ Paediatrics Open
	Manuscript ID bmjpo-2020-000918
	- General comments
	o Overall, this MS is of interest for the general Western Neonatal-
	Pediatric community to realize how low birth weight survival
	remains low and challenging in low- and middle class/low
	resources settings and even low against urban South African
	settings.
	o At the end of the introduction, the aims of the study should be
	specifically mentioned. The authors mainly studied the neonatal
	mortality for VLBW 1500gr.
	o In the subheading "what this study adds" that equipment,
	facilities, skills, staffing should be improved. Although this
	message is well taken, little of these issues are really investigated
	in their study: no data are provided, eg comparisons of these
	issues versus other settings in South Africa or elsewhere, to
	underscore and prove the need for improvement in their own
	setting. Mentioning that the study was carried in a low resource

setting is insufficient and the authors should expand on this to support their findings of a higher neonatal mortality.
- Other comments:
o P7/line 12-13. After "….CPAP" One may assume that a new sentence starts with "ventilation…" and that that the authors mean that ventilation is only provided for those VLBW infants >1000 gr? Furthermore if those <1000gr may receive surfactant,, is performed non-invasively and no ventilation at all is offered except CPAP?
o P8/line 8: mother-newborn pairs were not involved Involved in the study design: why not? And this especially in view of maternal risk factors, eg HIV?
o P8/line 6-13: this sentence is difficult to understand and should be rephrased
o P8/line 46: just a comment: 161 babies were included out of 173 admitted: for 12 babies no consent could be obtained according to the figure. This is good recruitment.
o P10/ table 1: "other",does this include necrotising enterocolitis. Was "other" not included in the multiple regression analysis?
o P11 table2. Title: 'neonatal' should be inserted before mortality, becoming 'neonatal mortality'.
o P12/ line 15-16: isn't there a co-linearity between RDS and surfactant?
o P12/line 24..: maternal hypertension seemed to be protective: could there be a bias? Only VLBWI admitted to the wards were included in the study. How many mothers had an hypertensive disorder during pregnancy and had still births or had babies who died in the delivery room?
o Discussion:
□ Although mortality is sufficiently discussed and the reader understands that the study is carried out in a low resource setting , this deserves more detail, as mentioned above, to convince readers and probably also health officials in South Africa.

VERSION 1 – AUTHOR RESPONSE

Mortality risk factors of Very Low Birth Weight infants at a tertiary hospital in the Eastern Cape, South Africa.

Revisions according to each reviewer and the editor in chief:

Reviewer 1:
Comments to the Author
Thank you for asking me to review this manuscript. This is a single centre, prospective, cohort study of association between death and several maternal and neonatal factors in VLBW infants in an LMIC setting.
I have the following points to suggest to the authors:
1. Introduction: Please outline the aim of the study at the end of this section:

This sentence was added:

The primary aim of this study was to look at the mortality rate in a mixed urban and rural setting in the Eastern Cape Province of South Africa. Secondly the association between death and different maternal and neonatal factors were explored.

2. What was the weight cut-off for inclusion <1500g or <1501 g?

The weight cut – off was 1500 g, and the number was corrected throughout the paper.

3. What is the primary outcome of the study? Please give this as either mortality or survival?

Was changed to mortality rate and this was corrected throughout the paper

4.Please describe the definitions and/or cut-off for the numerous variables included in the study such as
• what were the definitions for hyaline membrane disease, PDA, sepsis, ICH?
• What was include as "resuscitation at birth"
• What were the criteria for normal vs. abnormal trend of weight gain
• What was the cut-off for PROM?

Did change this in method section. PROM was not excluded, as we didn't always have all the data to asses for that

5. Public and patient involvement: This describes the need for the study and not PPI. Not clear why mothers were not involved in study design. If there was no PPI input in study design, please state this.

I changed this section

6. Line 23: continuous instead of numerical

Changed it in the statistical analysis

7. Was there collinearity between birth weight and gestational age? Similar to Apgar scores at 1 and 5 minutes, should only one of GA or BW been included in the model? There is potential for high collinearity between a few other variables included in the model such as HMD, surfactant given, and oxygen support; pre-eclampsia and hypertension; electricity, running water, and refrigerator. Were these considered in the regression analyses? Would the model be simpler if fewer of these highly correlated variables were included?

We agree with this statement. We included all factors in the univariate model, but did not include collinear factors in the multiple model.

The correlation between birth weight and gestation was 0.57 and we therefor only included birth weight in the multiple model

We similarly included hypertension and not pre-eclampsia in the multiple model.

8. How was gestational age determined? Was a reliable estimator such as early gestation ultrasound dating available?

Changed it in the text, that determined by early ultrasound and by Ballard scoring.

This is unlikely as 84% did not attend antenatal clinics.

This is confusing as it is a double no- so actually 84% did go to antenatal clinic

If not, this may be relevant to the analysis, and discussion esp. if a significant proportion could have had intrauterine growth restriction. If very few participant's had reliable GA estimation, the model will be improved by not including GA. It also makes me consider if the infants who had better survival associated with maternal pre-eclampsia, were actually more mature but smaller and it was the higher GA that let to better survival rather than the pre-eclampsia itself?

The part with the growth restriction in hypertensive mothers is very true and we addressed this by adjusting for GA and IUGR

9. There is a discrepancy between total number of participants between the abstract and the results: 173 in abstract (line 28) 161 in Results – page 8 line 46

I changed the first paragraph of the result section, hopefully more clear now.

10. Please present the information in Figure 1 in more detail – does 4207 represent number of live births or all births? Were any <1000g were excluded because they needed invasive ventilatory support and were therefore not admitted to the PICU. Are these counted among the reported deaths? Were there any other delivery room deaths or deaths or exclusions prior to admission for neonatal care?

This is described in the setting section – no baby below 1000g will receive invasive ventilation, but will receive surfactant and CPAP. All babies admitted with a birth weight of 1500g or less were included in the study.

The number of babies dying in the delivery room are not included – this figure is now added in the result section and in the graph.

11. I suggest staring the results section with the number of babies born in the study period, number (%) who were VLBW i.e. the prevalence of VLBW in the hospital followed by a description of the demographic factors.

Done. I left HIV exposure etc in, as I think that is an important factor, but also fine to take it out.

12. A very long description of demographic factors is given in the text. I suggest retaining some key variable such as GA and birthweight but most others are better described in a table (several are already included in Tables 1 and 2).

Changed tables and text

13. Lines 36 to 39: I assume this is the result of the primary outcome- it is described as survival "rate" but given as a %. Please correct this and present as stated in the aim and primary outcome of the study.

Corrected

14. Tables 1 and 2 needs to made more comprehensible – I suggest combining columns headed
- n and % as number (%) of infants
- n died and % died as Deaths n(%)
- RR, 95% CI and last column as Risk ratio (95% CI)
- P value should be presented in the final column.

Changed tables

15. In the discussion Line 39-42: the discussion starts with some results which have not been describe in the Results section and in Line 42 – what does the CI represent in this statement. Prevalence is presented for one year only – I do not understand what the CI is for.

Corrected that – didn't make sense at all

16. Lines 36-40 – this needs more discussion otherwise gives the message that pre-eclampsia is good for the baby.

Did explain, that large part of the infants of those mothers are most likely IUGR

17. Discussion needs to include more about the limitations of the study particularly that this is single, large hospital based study - is this really representative of the population of the region

True, limitations section added

18. Minor typographical corrections:
- Page 8 line 5: lie instead of lye
- Suggest present results as mean (SD) in the text rather than as long text sentences.
- Page 9 line 46 – suggest delete related
- Table 1 line 56 – suggest mother instead of Mom
- Table 2 line 27 – stable instead of stale
- Suggestion, please use consistent terminology, such as:
• VLBW cut-off – <1500 or <1501
• HMD or RDS
• HIV or RVD

Done

Reviewer 2:

Overall, this MS is of interest for the general Western Neonatal-Pediatric community to realize how low birth weight survival remains low and challenging in low- and middle class/low resources settings and even low against urban South African settings.
o At the end of the introduction, the aims of the study should be specifically mentioned. The authors mainly studied the neonatal mortality for VLBW 1500gr. – done

o In the subheading "what this study adds" that equipment, facilities, skills, staffing should be improved. Although this message is well taken, little of these issues are really investigated in their study: no data are provided, eg comparisons of these issues versus other settings in South Africa or elsewhere, to underscore and prove the need for improvement in their own setting. Mentioning that the study was carried in a low resource setting is insufficient and the authors should expand on this to support their findings of a higher neonatal mortality.

Added study from CPT, which looked at differences of care and availability of resources in different hospitals and added more of our own resource restrictions in the setting part.

Other comments:
o P7/line 12-13. After "….CPAP" One may assume that a new sentence starts with "ventilation…" and that that the authors mean that ventilation is only provided for those VLBW infants >1000 gr? Furthermore if those <1000gr may receive surfactant,, is performed non-invasively and no ventilation at all is offered except CPAP?

Changed the sentence to make it clearer

o P8/line 8: mother-newborn pairs were not involved Involved in the study design: why not? And this especially in view of maternal risk factors, eg HIV?

As education levels of the mothers in our setting are extremely low, many not having matric and even passing matric is possible with very limited knowledge in life science it is difficult to get input for study design from the mothers.

o P8/line 6-13: this sentence is difficult to understand and should be rephrased

Changed the whole PPI section

o P8/line 46: just a comment: 161 babies were included out of 173 admitted: for 12 babies no consent could be obtained according to the figure. This is good recruitment.
o P10/ table 1: "other",does this include necrotising enterocolitis. Was "other" not included in the multiple regression analysis?

Other means neonatal jaundice, hypoglycaemias, necrotising enterocolitis, added this to the footnote of the table.

o P11 table2. Title: 'neonatal' should be inserted before mortality, becoming 'neonatal mortality'.

done
o P12/ line 15-16: isn't there a co-linearity between RDS and surfactant?

Yes there is – changed the whole section

o P12/line 24..: maternal hypertension seemed to be protective: could there be a bias? Only VLBWI admitted to the wards were included in the study. How many mothers had an hypertensive disorder during pregnancy and had still births or had babies who died in the delivery room?

We adjusted for IUGR and GA. No information available of babies dying in labour ward.

o Discussion:
♣ Although mortality is sufficiently discussed and the reader understands that the study is carried out in a low resource setting , this deserves more detail, as mentioned above, to convince readers and probably also health officials in South Africa.

I tried to make it more clear in the setting section and the discussion

Reviewer: 3

Comments to the Author
Thank you. This is an important study as there is little information about outcomes from this part of South Africa.

There are some minor and significant issues which will need to be addressed to be re-considered for publication.

i) the use of the term 'offspring related risk factors'. Rather use infant/neonatal

Did change it

ii) Background: there is a recent paper documenting outcomes in Cape Town private/public sector for <1500g babies which would be useful to include: Van Wyk, Tooke et al in Neonatology 2020

inserted in introduction, great paper

iii) More information about setting is required: Does it occur that there is no space in PICU for ventilation.

 Yes, rephrased

Which areas do Frere Hospital drain - there are other referral hospitals (maybe a map).

Added information in the setting part, couldn't find map which shows referral pathways clearly

 How many births in the province. How many births in the referral area?

I don't have that information

iv) Why infants only admitted within first 24hrs of life? Usually neonatal databases include within first 28 days of life – mentioned, as not enough information of them when coming later from referral (insufficient information in referral letters, in the first 24 hours, not much more than birth and referral have happened usually)

v) Babies were followed up until discharge or death. Is this discharge HOME or discharge including to other hospitals? – both, mentioned now in the text

vi) the paragraph about follow-up appointments needs to be re-written. It is clumsy and difficult to understand – it is the PPI part, I changed the whole part

vii) Statistics: were variables assessed to see if they were normally distributed? Otherwise Median/IQR should be used. –

Agreed, we included median, Q1 and Q3 in the description

Results:

viii) 161 out of 173 babies were included. Most of the ones who had no consent died. This is not prominently mentioned or discussed. This skews the data. The death rate is actually higher. You should not need consent to include these deaths in the totals.

Mentioned it clearer in the first sentence of the result section

ix) Strange there were so many males - any reason for this?

Do you mean lesser males than females – not sure why – do they die in the labour ward already?

x) PCR results need to be presented as +ve, -ve, unknown.

done

xi) What about 6 week PCR results?

Were all –ve, but not included as some children were already d/c

xii) Why neonatal info before maternal. Usually maternal is first

We changed that

xiii) A figure showing the gestation, weights and deaths would help (there is an example in Levin, HIV Transission to premature VLBW infants, PIDJ 2017

Difficult to do a table with 45 infants showing all the factors

xiv) Don't repeat in the text what we can see in the table

changed that

xv) There needs to definitions for many of the risk factors listed in the tables. For example, what defines resuscitation, HMD, weight gain, ICH etc. This should be in methods

done

xvi) p values can't be 0.000

done

xvii) No refrigerator in house. ?breast milk storage

is only about mortality in hospital
Discussion

xix) These shouldn't be new information in the discussion (incidence of VLBW etc)

did change it

xx) Comparing a hospital's VLBW rates to countries VLBW rates does not make sense. It is appropriate for referral hospitals to have high rates of VLBW deliveries

changed it

xxi) Can you talk about the whole E.Cape Province if there are other referal hospitals (Umtata, PE etc)

We are only talking about Frere Hospital mainly, but Eastern Cape is known to be deprived (especially for skills and knowledge)

xxii) Much more needs to be explored in the discussions about unusual or positive findings. Theories need to be explored

We addressed this

Reviewer: 4

Comments to the Author

Comments specifically for the methods used:
The authors have collected data on a variety of characteristics from mothers and babies. The relationship of each characteristic/variable with survival (main outcome variable) was initially explored separately/independently of other variables via logistic regression. Depending on the results of this univariate exploration, some variables were included in a multivariable model to better understand survival rates. Results have been presented as relative risks (RR) with corresponding p-values and confidence intervals. I would like to invite the authors to make some clarifications regarding the above summary of the methods used:

- The statistically significance results of the univariate analysis should be later enhanced with knowledge driven from clinical expertise, literature, etc in order to produce a meaningful and relevant multiple logistic model. The multivariable model should not be exclusively driven by the univariate results. Did the authors consider this when building the multivariable model?

As discussed in the text, the inclusion of the factors for the analysis were driven by the literature

- Can the authors please clarify if by "log binomial regression", they mean the conventional logistic regression technique with a logit link function? In which case the odds ratios (OR) should be presented, instead of the RR and all subsequent results should refer to the change in the odds and not the risk/chance.

Since this is a cohort study, it is more desirable to estimate relative risk or risk ratios (RR) instead of odds ratio, especially since the death is quite common (>10%) and to estimate the RRs the log-Binomial model is appropriate

- I don't believe that the following statement (and subsequent related comments) has been justified from this study as the data that was collected did not specifically focus on equipment, facilities, etc. "Equipment, facilities, skills and staffing should be improved in those settings.".

Formal statistical significance tests have not been performed to compare survival rates between the Frere hospital and other (better "equipped") hospitals in South Africa.

True, I rephrased it

More generally:

- It was not clear to me what the message from the Patient and Public Involvement (PPI) section was. I was not able to follow the flow of the paragraph nor relate it to PPI.

Changed

- For some numerical variables, the median and IQR should be used for summaries as the presented mean and the SD values indicate that some of the variables were not normally distributed (mean+- 1.96*sd should produce a 95% reference range for a given variable, but in some cases these calculations led to non-feasible results, e.g. birthweight, upper reference rage limit exceeds the max reported value of 1500. Also, it is not clarified by I assume the values in brackets next to mean birthweight is the range, min to max.)

Agreed, we included median, Q1 and Q3 in the description

- "All variables with small cell number (n≤6) were excluded from the multiple regression model." Am I right to assume that this relates to categorical variables? How many variables were excluded and what biases might have this introduced?

Medication was the only maternal variable that was not included in the multiple model since only 4 babies died whose mothers were on medication

Only two babies with no Oxygon support died and therefor this variable could not be entered into the multiple model

- Is the "in-hospital survival rate" mentioned on the last paragraph of the Demographics section, known from another study? The way this is written, it implies that it was derived from another paper (if so, a citation is needed), but if not, maybe it should be rephrased for better clarity.

Rephrased it

- Please acknowledge the study's limitations and potential sources of bias.

done

Minor:
- Please replace commas with dots for decimal points in the Tables

done
- P-values should not be reported as 0.000 but instead as <0.001

done
- Merge the n and % columns in the Tables. Also, the SE value can be excluded as not necessary when CIs are presented. The 95% CI columns can be merged into one (2.93 , 5.88) to reduce the number of separate columns.

Done

\- It's also not necessary to include the (0) and (1) codes next to each category

done

\- Explain acronym ICH in the main text additionally to the footnote of Table 1

done

\- Please replace the term multivariate at the end of the Results section

couldn't find that one

 and in the 3rd paragraph from the end of the Discussion section, with multivariable or multiple, as multivariate means multiple outcomes.

done

Editor in Chief
Comments to the Author:
The strength of your study is that it was prospective. You need to focus on describing the outcomes in your cohort. Determining risk factors from a small single centre cohort is NOT recommended. Far better to describe the factors associated with mortality in your small cohort and state how they are in keeping with known risk factors from larger studies.

We addressed this in introduction and discussion

 All 4 reviewers have raised concerns re your paper. If you want to get your paper published, you need to make the following changes as well as respond to the reviewers fully:
Title amend to "Prospective cohort study of mortality in very low birth weight infants in a single centre in the Eastern Cape Province, South Africa."

done

Describe the outcomes in your cohort clearly. Revise Table 1 presenting demographic data only,ie upto %died only. Use only one decimal point only for %. When presenting results for each factor give the positive responses first,ie HIV exposed yes then no.

done

Similarly revise Table 2.

done

Statistical analysis can then be presented separately in additional shortened tables.
The subheading "Risk factors for in hospital mortality" should be replaced with "Factors associated with in hospital mortality"

done

Avoid using the term "risk" throughout your paper, where possible, eg table heading would become "Univariate analysis of factors associated with mortality in our cohort of VLBW infants"
Abstract Conclusion delete the first sentence. Avoid stating this is the first study (see instructions to authors)

done

What is already known replace with "The neonatal mortality rate in South Africa is ???. Preterm and VLBW infants account for a large number of neonatal deaths. Survival of VLBW infants in studies from South Africa are about 75%"

What this study adds replace with "Survival of VLBW infants was 68% in our cohort. This is lower than in larger centres in larger cities in South Africa"

done

Expand the last paragraph in the Setting section.
Discussion avoid use of the term "developed/developing" for countries. Use "high/middle/low income"

done

Discussion page 13. Use the language used in the 1st sentence in para 2 throughout rather than that used in para 3,ie "confirm". Your study is too small to confirm risk factors
Discussion needs rewriting focussing on inequalities in child health in South Africa, which you suggest is the reason for the lower survival rate in your hospital.

Tried to address this

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Lloyd Tooke Institution and Country: University of Cape Town, Neonatology, South Africa Competing interests: None
REVIEW RETURNED	07-Jan-2021

GENERAL COMMENTS	An important message and a much improved manuscript which has addressed most of the shortcomings of the initial submission. There is now much clearer information about the setting of the hospital. There are a few minor comments: The abstract (page 4) mentions <1500g in the objectives but <= 1500g in the methods. This should be consistent in the whole paper. Gestational age assessment: Please give approximate % of early ultrasound vs Ballard Page 7: There were 231 VLBW infants born but only 173 admitted to the neonatal high care/PICU. In most hospitals all VLBW infants are admitted to high care so what happened to the other 58? This is a high percentage of unaccounted for infants which may influence the mortality rates even further.

REVIEWER	Reviewer name: Dr. Shalini Ojha Institution and Country: University of Nottingham, School of Medicine, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	11-Jan-2021

GENERAL COMMENTS	Thank you for revising our manuscript. I have a few, remaining, minor suggestions: 1. Section "What does this stud add?" - please specify this survival of 68% was among VLBW infants admitted for care as you have not included the 58 babies who died before admission.

	2. The PPI section could be shorten to just mention that there was no PPI involvement in planning this study and that the results will be shared verbally. The details mentioned are not relevant to PPI.

REVIEWER	Reviewer name: Dr. Patrick van Reempts
	Institution and Country: University of Antwerp Faculty of Medicine and Health Sciences, Laboratory of Experimental Medicine and Pediatrics, Division of Neonatology, University of Antwerp, Antwerp, Belgium. Study Centre for Perinatal Epidemiology Flanders, Brussels, Belgium
	Competing interests: None
REVIEW RETURNED	12-Jan-2021

GENERAL COMMENTS	Thank you for letting me review this R1 MS .
	This R1 version looks much better now. The authors sufficiently responded to my comments and also, in my view, to the other reviewers comments .
	One minor comment on the presentation of the p values throughout text and tables: limit to 2 digits or use p<0.01

VERSION 2 – AUTHOR RESPONSE

Dear Dr. Allegaert, dear Prof. Choonara ,

Thank you for your letter.
Please find attached the paper with the minor revision requested by the reviewer and the Editor in Chief. The following changes were made:
Reviewer 1:
1. Section "What does this stud add?" - please specify this survival of 68% was among VLBW infants admitted for care as you have not included the 58 babies who died before admission. - I was unable to find the where about of all of those 58 babies, 8 were not included into the study as they had dysmorphism or malformations (actually they all, except 1, died during neonatal admission), it seems that the other 50 died in the labour ward. I changed the sentence now to 173 met inclusion criteria and I changed the recruitment graph.
2. The PPI section could be shorten to just mention that there was no PPI involvement in planning this study and that the results will be shared verbally. The details mentioned are not relevant to PPI. – Shortened that section accordingly

Reveiwer 2:
The abstract (page 4) mentions <1500g in the objectives but <= 1500g in the methods. This should be consistent in the whole paper. – corrected throughout the paper

Gestational age assessment: Please give approximate % of early ultrasound vs Ballard. Added a sentence appropriately 70% receive early U/S – assumption by the head of department.

Page 7: There were 231 VLBW infants born but only 173 admitted to the neonatal high care/PICU. In most hospitals all VLBW infants are admitted to high care so what happened to the other 58? This is a high percentage of unaccounted for infants which may influence the mortality rates even further- as reviewer 1 comment.

Reviewer 3:
One minor comment on the presentation of the p values throughout text and tables: limit to 2 digits or use p<0.01. We changed all the p values to to digits and used p<0.01 where applicable.

Editor in Chief:
I changed and revised all sentences as suggested.

I hope you find this all in order.
Thank you for your assistance and help in this publication.

Kind regards

Isabel Michaelis