PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antibiotic prescribing in neonatal sepsis: an Australian nationwide survey
AUTHORS	McMullan, Brendan; Cooper, Celia; Spotswood, Naomi; James, Rodney; Jones, Cheryl; Konecny, Pamela; Blyth, Christopher; Karen, Thursky

VERSION 1 – REVIEW

REVIEWER	Reviewer name: David Isaacs Institution and Country: Children's Hospital at Westmead Competing interests: Two of the authors (BM, CJ) have been colleagues in the past.
REVIEW RETURNED	23-Jan-2020

GENERAL COMMENTS	Thank you for the opportunity to read your interesting paper. In the Abstract (Setting), I think you mean maternity not maternal hospitals You report in the Abstract and in the Results that 47.5% of antibiotics were given for 2 or more completed days. The usual practice has been, even if cultures are negative, to give antibiotics for 2 or even 3 days. I, therefore, think that the more relevant information is how many received 3 or more days = >2 days (and you might also say how many courses were for >3 days). That means I also suggest you re-think your Conclusions statement "Many prescriptions were given for at least 48 hours despite few confirmed infections." I found Figure 2a and 2b a bit confusing. What do the shaded regions represent? What are the confidence intervals? Why are there dots at 2, 7 and 8mg/kg in Fig 2a? Similar considerations apply to Supplementary Fig 2, although here you have shown a median and explained the other bars are IQR, but still have some floating dots. As far as gentamicin dosing is concerned, you have presented a dose range. Is that a daily dose or a single dose? Surely, part of the problem is that some neonatal units use once daily and some 3 times daily dosing of gentamicin. If that is not what you have done already, are you able to analyse the data in terms of total daily dose of gentamicin?

REVIEWER	Reviewer name: T. Metsvaht Institution and Country: University of Tartu, Estonia Competing interests: none
REVIEW RETURNED	03-Feb-2020

GENERAL COMMENTS	The authors report the results of a nation-wide point prevalence study of antibiotic use in neonates. The data are of interest for the reader and certainly have implications for practice, although there is little novelty in the chosen approach. The manuscript is well focused and written. A few details could be added, though, to improve the readability/ understanding for the readers. Methods. Please add details on the survey methodology, as readers may lack access or time to review the previous publications. The authors themselves question the reliability of the local surveyors' assessment on guideline compliance in the discussion section (see below). Alternately, the indication-dose-interval-age-weight data would allow reviewing the appropriateness/ compliance assessment. these data would be of interest for the reader. Results. How many prescriptions were missed/ excluded because of missing weight data? The statement about the variation of prescription numbers (from 56 to 91) is misleadingly giving the impression of increasing numbers over time, while wide fluctuations are seen in table 1. Please rephrase. Where there any changes in the number and structure of participating hospitals/ units? If yes, please explain. page 8 row 13-15 – „premature neonates accounted for 123 prescriptions (54.4%)." Total prescriptions n=415? total N of neonates n=214? The missing data of gestational age for 45.5% of prescriptions should be referred to here and mentioned in the limitations section of discussion. It would be interesting to know, how many neoates were receiving a combination of two or more antibiotics and how many were on monotherapy. Please, add information on the proven infections type – EOS or LOS. Dosing frequency details should be added – report percentages in text or add to respective figures. Analyzing dosing data for unit dose (not daily dose) may not give the full picture, as it has been demonstrated previously, that with the growing age of the neonate dose interval adjustment recommendations are often not followed. If these data are available, the authors should consider including them in the analysis. Discussion. In the appropriateness/ guideline compliance assessment the authors rely completely on local surveyors decision? However, Page 13 row 3 onward the authors question the assessment of appropriateness of the prescriptions on methodology level (12.8% of prescriptions reported compliant with national Therapeutic Guidelines, while respective guidelines did not include neonates?) – can the high level of appropriateness be claimed in such case? This major methodological issue should be addressed in more detail in the limitations section.

REVIEWER	Reviewer name: Giulia Mandelli Institution and Country: Istituto Di Ricerche Farmacologiche Mario Negri Department of Clinical Epidemiology Italy Competing interests: Epidemiology, mortality, statistics, Intensive care
REVIEW RETURNED	03-Feb-2020

GENERAL COMMENTS	Antibiotic resistance is a serious public health problem, so it is important to improve the prescriptions of antibiotics in daily practice, in terms of dosage, duration and better choice of the type of antibiotic. The manuscript “Antibiotic prescribing in neonatal sepsis: a nationwide survey” aims to describe the variation and appropriateness in prescribing for neonatal sepsis and variation in gentamicin and benzylpenicillin dosage. The analyzed data come from the NAPS database. Since there are few confirmed infections and potentially excessive durations of prescriptions, the authors recommend standardizing the dosage and duration of antibiotics for suspected neonatal sepsis. I find the manuscript to be well written and easy to follow. From a statistical point of view, few analysis are performed and consequently I have little to comment. 1. It is not clearly explained in the manuscript what “audit date” means (Is it planned? When?). Why are infants with age >7 days at audit date in case of antibiotic start date missing considered LOS? In addition, only 345 neonates are assessed EOS or LOS. Why are 70 neonates missing? 2. The authors use the Chi-squared test for categorical variables. Have they checked the numerosity of groups? In supplementary table 2 we see that there are only 11 suboptimal and 2 inadequate prescriptions. With these numbers is important to check if each group has at least 5 elements. Otherwise a Fisher test is better than the Chi-squared test. 3. The percentage of prescriptions for gentamicin and benzylpenicillin is 77.8%. It is correct in table 2 but not on page 8. 4. On page 9 we read that the benzylpenicillin dose has an IQR of 48-64. However in the figure 2b it does not look the same. I suggest uniforming the two sources.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author
Thank you for the opportunity to read your interesting paper.

In the Abstract (Setting), I think you mean maternity not maternal hospitals

Thank you we have amended this in the Abstract.
You report in the Abstract and in the Results that 47.5% of antibiotics were given for 2 or more completed days. The usual practice has been, even if cultures are negative, to give antibiotics for 2 or even 3 days. I, therefore, think that the more relevant information is how many received 3 or more days = >2 days (and you might also say how many courses were for >3 days). That means I also suggest you re-think your Conclusions statement "Many prescriptions were given for at least 48 hours despite few confirmed infections."
Thank you, we have amended this. We acknowledge there remains lack of consensus in practice of cessation of antibiotics for culture-negative neonatal ‘sepsis’, though there is increasing evidence to support cessation at 48 or even 36 hours with negative cultures (Klingenberg et al, Frontiers in pediatrics. 2018, ref 34). We also note our reporting was potentially misleading (47.5% should have been stated as up to 2 days). We have now reanalysed this and included information for antibiotic durations >48 and >72 hours in the Abstract and Results. We have removed that statement in the abstract conclusions and amended to “A small minority had culture-confirmed infection.”

I found Figure 2a and 2b a bit confusing. What do the shaded regions represent? What are the confidence intervals? Why are there dots at 2, 7 and 8mg/kg in Fig 2a? Similar considerations apply to Supplementary Fig 2, although here you have shown a median and explained the other bars are IQR, but still have some floating dots.

In these box plots the median is given by a thick line in the boxes; the boxes represent the interquartile ranges; the whiskers represent the range of data, excluding outliiers; and the dots represent outlier results. We have clarified this in the figure legends for Figures 2a and 2b and Supplementary Figure 2.

As far as gentamicin dosing is concerned, you have presented a dose range. Is that a daily dose or a single dose? Surely, part of the problem is that some neonatal units use once daily and some 3 times daily dosing of gentamicin. If that is not what you have done already, are you able to analyse the data in terms of total daily dose of gentamicin?

Thank you for this query. In our cohort no neonates were prescribed 3 times daily dosing of gentamicin. According to gestational age/maturity some were prescribed 36-hourly or 48-hourly gentamicin. For this reason we believe reporting the actual dose rather than a converted daily dose is more useful, but we are happy to report on gentamicin frequency prescribed - we have now included this along with benzylpenicillin frequency in Supplementary Table 2.

Reviewer: 2

Comments to the Author

The authors report the results of a nation-wide point prevalence study of antibiotic use in neonates. The data are of interest for the reader and certainly have implications for practice, although there is little novelty in the chosen approach. The manuscript is well focused and written. A few details could be added, though, to improve the readability/ understanding for the readers.

Methods.
Please add details on the survey methodology, as readers may lack access or time to review the previous publications.

Thank you, we have added more extensive details on survey methodology in the Methods section.

The authors themselves question the reliability of the local surveyors' assessment on guideline compliance in the discussion section (see below). Alternately, the indication-dose-interval-age-weight data would allow reviewing the appropriateness/ compliance assessment. these data would be of interest for the reader.

We agree that this information would be of interest, however we do not have access to site-identified data and thus cannot assess prescriptions against individual local guidelines. As we indicate, at the time of survey the national guidelines did not contain prescribing advice for neonates thus these cannot be used as a basis for assessment retrospectively. In contrast, national guidelines now do provide this advice and may form a basis for this assessment in future. We have highlighted these points for the benefits of readers in our the Discussion.

Results.
How many prescriptions were missed/ excluded because of missing weight data?
Thank you for the opportunity to clarify this: all 884 neonatal prescriptions (in the first line of our results) had weight data.

Those included in this study were those who were prescribed drugs for sepsis. We cannot currently state exactly how many neonates without weight data were included in NAPS surveys conducted during our study period, since we accessed a subset of NAPS survey data collected from hospitalised patients in Australia of all ages who simultaneously met criteria of (a) age <28 days and (b) had weight recorded. As we were interested in dosing in mg/kg from the beginning we did not seek data from neonates without weight recorded.

The statement about the variation of prescription numbers (from 56 to 91) is misleadingly giving the impression of increasing numbers over time, while wide fluctuations are seen in table 1. Please rephrase.
We have rephrased this.
Where there any changes in the number and structure of participating hospitals/ units? If yes, please explain.
All hospitals were eligible to participate in NAPS during the entire study period.

page 8 row 13-15 – „premature neonates accounted for 123 prescriptions (54.4%).“ Total prescriptions n=415? total N of neonates n=214? The missing data of gestational age for 45.5% of prescriptions should be referred to here and mentioned in the limitations section of discussion.
We have clarified this sentence in Results and added this to the limitations section of Discussion.

It would be interesting to know, how many neoates were receiving a combination of two or more antibiotics and how many were on monotherapy.
Thank you – we have added this information to Results.

Please, add information on the proven infections type – EOS or LOS.
This has been added as a footnote to Table 4.

Dosing frequency details should be added – report percentages in text or add to respective figures. Analyzing dosing data for unit dose (not daily dose) may not give the full picture, as it has been demonstrated previously, that with the growing age of the neonate dose interval adjustment recommendations are often not followed. If these data are available, the authors should consider including them in the analysis.
We have added data on dosing frequency recorded for the two most common antimicrobials, gentamicin and benzylpenicillin, as Supplementary Table 2.

Discussion.
In the appropriateness/ guideline compliance assessment the authors rely completely on local surveyors decision? However, Page 13 row 3 onward the authors question the assessment of appropriateness of the prescriptions on methodology level (12.8% of prescriptions reported compliant with national Therapeutic Guidelines, while respective guidelines did not include neonates?) – can the high level of appropriateness be claimed in such case? This major methodological issue should be addressed in more detail in the limitations section.
Thank you – we have made further amendments to clarify that appropriateness and compliance figures presented in our paper are as reported by local assessors. We also question the reliability of this assessment in some cases and identify potential challenges to this assessment in our Discussion. We have also added a statement on this in the limitations section of our Discussion.

Reviewer: 3

Comments to the Author

Antibiotic resistance is a serious public health problem, so it is important to improve the prescriptions of antibiotics in daily practice, in terms of dosage, duration and better choice of the type of antibiotic. The manuscript “Antibiotic prescribing in neonatal sepsis: a nationwide survey” aims to describe the variation and appropriateness in prescribing for neonatal sepsis and variation in gentamicin and benzylpenicillin dosage. The analyzed data come from the NAPS database. Since there are few confirmed infections and potentially excessive durations of prescriptions, the authors recommend standardizing the dosage and duration of antibiotics for suspected neonatal sepsis.
I find the manuscript to be well written and easy to follow. From a statistical point of view, few analysis are performed and consequently I have little to comment.

1. It is not clearly explained in the manuscript what “audit date” means (Is it planned? When?).
Thank you for this query. Hospitals can participate in these surveys whenever they choose, though most participate annually - we have clarified this in Methods.
Why are infants with age >7 days at audit date in case of antibiotic start date missing considered LOS? In addition, only 345 neonates are assessed EOS or LOS. Why are 70 neonates missing?
Thank you for the opportunity to clarify: where antibiotic start dates were available, we were able to define EOS or LOS according to age at commencement of antibiotics. Where start date was unavailable, we assumed that a negligible number of neonates would be treated for culture-negative EOS for longer than 7 days, thus those over 7 days of age on antibiotics likely had LOS. For prescriptions in neonates fulfilling neither of these criteria we did not calculate EOS/LOS. We state this in Methods and have now also added a sentence to the limitations section of our Discussion clarifying this and acknowledging consequent uncertainty based on these assumptions.

2. The authors use the Chi-squared test for categorical variables. Have they checked the numerosity of groups? In supplementary table 2 we see that there are only 11 suboptimal and 2 inadequate prescriptions. With these numbers is important to check if each group has at least 5 elements. Otherwise a Fisher test is better than the Chi-squared test.

Thank you for this opportunity to clarify this point. As we state in Methods, we considered “optimal” and “adequate” to be appropriate and “suboptimal” and “inadequate” to be inappropriate. Our analyses were 2x2 according to this and, in each of our comparisons, each group has >5 elements.
3. The percentage of prescriptions for gentamicin and benzylpenicillin is 77.8%. It is correct in table 2 but not on page 8.

We have amended this.

4. On page 9 we read that the benzylpenicillin dose has an IQR of 48-64. However in the figure 2b it does not look the same. I suggest uniforming the two sources.

Thank you we have amended this to IQR of 50-60 as in Figure 2b.