Author’s response to reviews

Title: High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination.

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Author’s response to reviews: see over
Thank you for the review and for the comments, which have certainly helped us to further clarify several important issues in the manuscript. Below please find a detailed description of the changes.

Responses to review 1

Reviewer's report

Title: High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination.

Version: 2

Date: 14 January 2015

Reviewer: Stefania Vergnano

Reviewer's report:

Major compulsory revisions

Methods need to be more detailed.

The inclusion criteria (e.g. infants from 0-90 days were included only), which antimicrobials were included (e.g. antivirals/antifungal included?), which routes of administration were considered need to be spelled out here, not in the results, otherwise the reader is not clear about what exactly has been reported.

PNA/PMA/GA bands need to be explained here: this are used frequently and are not explained, the authors should explain the reader what they are and why they are used in the context of antimicrobial dosing. Currently their use is confusing and appears to be random (e.g. line 206)

Response: We agree to this comment and more detailed information on the issues, raised has been added to the manuscript methods section. It now reads as follows (page 5; rows 90):

“For current analysis, all prescriptions for systemic antibiotics in neonates up to 90 days of age, active on the study day morning, chosen by the unit within one of three fixed two-week study periods from January to February; March or May to June, 2012, were retrieved from the ESNEE PPS database. Topical antibiotics, antivirals and antifungals were excluded. Anonymised demographic data including gender, gestational age (GA), birth weight (BW), 1 and 5 minute Apgar score, current body weight (CBW) and postnatal age (PNA) were recorded for each neonate. Postmenstrual age was calculated based on GA and PNA. Due to differences in the pharmacokinetics of antibiotics between term and preterm neonates, but also fast changes occurring over the first weeks of life, dosing recommendations for this age group are based not only on body weight but also GA and/ or PMA. In the dosing analysis further grouping by PMA or PNA was based on the recommendations for the respective antibiotic in the chosen dosing references. Prescription data included active ingredient, route
of administration and individual dosing regimen (unit dose and dosing interval) together with prescription start date.”

Line 110-114. Difficult to understand, the reader needs to know that neonatal doses depend not only on weight but also on the gestational age and post-natal age… this is not explained. Also maybe could be useful to add examples.

Response: As stated in the response to previous question we have added an explanation in the methods section as follows (page 5; row 96). The respective examples are presented in tables 1-2, to which this section also refers now:

“Due to differences in the pharmacokinetics of antibiotics between term and preterm neonates, but also fast changes occurring over the first weeks of life, dosing recommendations are based not only on body weight but also GA and/ or PMA. In the dosing analysis further grouping by PMA or PNA was based on the recommendations for the respective antibiotic in the chosen dosing references (Tables 1-2).”

Introduction
Line 61 “age group” what does it mean? gestational age bands/ post-natal age Groups
Response: Thank you, we have added the following clarification (page 4, row 59):

“The vast majority of antibiotics are used off-label; data on dosing in this patient group are limited or are generally based on expert opinion or small studies not including all gestational age (GA) groups”

Results:
Line 129: please specify what is intended for higher level NICU.
Response: The sentence has been corrected and now reads as follows (page 7; row 136):

“Intermediate- and 3rd level intensive care units predominated in all participating countries”

Line 131: were BW and GA normally distributed? Otherwise a median and IQR would be better measures of spread.

Response: The distribution was normal, there was almost no difference between mean and median values of birth weight (2239 vs 2150 g) and gestational age (34 vs 34 weeks), for the sake of clarity therefore mean and SD were presented.

133-139: Please separate the definitions and include them in the methods

Response: The respective information, including age group and included antibiotic prescriptions (excluding antifungals and antivirals) has now been removed to the methods section, as explained above. The first section of results (page 7; row 138) now reads as follows:

“A total of 2608 prescriptions were reported for 1382 patients, with a mean (SD) BW of 2060 (1032) g and GA of 33 (5) weeks. Among them 342 (25%) patients with mean (SD) BW of 2239 (1075) g and GA of 34 (5) weeks received 586 antibiotic prescriptions (22% of all prescriptions). The proportion of neonates receiving systemic antibiotics by country ranged from 4% to 78% with a median of 26%. The median number of antibiotic prescriptions per patient was 2 (range 1-5). There were 573 (98%) parenteral and 13 (2%) enteral
prescriptions. Three neonates were older than 90 days PNA and were excluded from further analysis.”

Use PNA/PMA and GA more consistently

Response: As antibiotic dosing recommendations are based on both postnatal and postmenstrual age, depending on the drug, this variation cannot be totally eliminated. To clarify this for the reader, a comment has been added to table 2:

“e – please note, that in contrast to gentamicin and vancomycin dosing based on PMA, current amikacin dosing recommendation is based on PNA”

The following clarification made in the text (page 9; row 186):

“For gentamicin and vancomycin different PMA groups with generally similar unit doses for gentamicin and higher doses of vancomycin in the BNFC, were suggested (Table 2). Amikacin dosing recommendations were based on PNA group.”

Discussion:
Can be shortened and the message clarified.
Initially the authors seem to imply that using the same dosing reference in Europe will improve dose prescribing then they affirm that the lack of hard data on PK/PD is lacking for a number of antibiotics in this age group, therefore there is discrepancy in the dose recommended. But finally they note that for some antibiotics there is in fact good evidence base and (e.g single dose gentamicin) but still poor adherence to guidelines. Why do the authors think this happen, how can it be improved? How should results be disseminated.
It would be helpful to add to the discussion whether any other studies on dosing are available e.g. from the US or elsewhere, are the dosing issues similar??

Response: the discussion has been revised significantly and shortened. The reasons for the high variability of dosing of antibiotics are likely multiple and vary between drugs. The three main reasons we have highlighted, based on our results, include lack of appropriate data to rely upon; poor dissemination of existing evidence for some antibiotics (like gentamicin) and existing variations between guidelines (i.e. penicillins; likely also reflecting lack of high-quality evidence).
Previous published studies are mostly single centre and questionnaire based, i.e. have not recorded actual doses prescribed to neonates (as referred in the introduction). To the best of our knowledge, from the ARPEC study, recording actually prescribed doses in children and neonates, only data on antifungal drugs have been published (Lestner, J. M., A. Versporten, et al. (2015). "Systemic Antifungal Prescribing in Neonates and Children: Outcomes from the Antibiotic Resistance and Prescribing in European Children (ARPEC) Study." Antimicrob Agents Chemother 59(2): 782-9). References to this as well as the results of the UK and French questionnaire based study on the dosing of antibiotics have been added to the discussion (Leroux S, Zhao W, Betremieux P, Pladys P, Saliba E, Jacqz-Aigrain E: Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey. Arch Dis Child 2015).

Minor Essential Revisions
For clarity please spell out all abbreviations the first time they are used even if there is an abbreviation list (including in the abstract e.g NICU; CBW etc)
Response: All the abbreviations have been reviewed and spelled out the first time they are used.

There are a few typos errors in the manuscript. 
Response: The manuscript has been revised for typos.

Figure 2 not sure whether this figure adds to the text.
Response: We feel that Figure 2 explains well the timing of the use of different antibiotics in neonates. It has been removed to the electronic supplementary material.

Discretionary revisions
Figure 3 line 513, is the BNFC line representing the lowest recommended dose for pen G? It may be useful to have the lowest and the highest in 2 different colours here.
Response: yes, the zero reference line represents the lowest recommended dose in BNFC; the highest BNFC recommended dose has been added in a light grey line. The two colored dotted lines represent the highest and lowest dosing recommendation in Neofax. We have clarified this further in the figure legend.

may be interesting to have the list of all antibiotics used
Response: the list of all used antibiotics is provided as electronic supplement 1; referred to on page 7, row 141).

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I am a researcher in neonatal infection and se of antimicrobial in this age group.

Review 2
Reviewer’s report
Title: High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination.
Version: 2
Date: 24 January 2015
Reviewer: Gaetano Chirico

Reviewer’s report:
In this interesting study on antibiotic dosing in European NICUs a high variability has been reported, also reflected by the significant differences of recommended dosages observed on the sources used as reference. The methods seem appropriate and well described. The results may serve as a stimulus toward a better standardization of the most frequently used drugs in sick neonates. However, as admitted by the authors, the lack of data regarding the indications for antibiotic use could have significantly limited the interpretation of their findings.
Response: Thank you for your valuable comments. We agree, that the lack of information about the indications, antibiotics were prescribed for, in our study is a major limitation (and has been discussed in the respective part of the discussion). However, we believe, that given the wide use of antibiotics in neonates and rarity of serious infections requiring specific dosing of some antibiotics, variations in indications cannot explain the main finding of extremely high variability of antibiotic dosing in neonates.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare no competing interests in relation to the paper I am reviewing.