PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A global shortage of neonatal and pediatric antibiotic trials: rapid review.
AUTHORS	Thompson, Georgina; Barker, Charlotte; Folgori, Laura; Bielicki, Julia; Bradley, John; Lutsar, Irja; Sharland, Mike

VERSION 1 – REVIEW

REVIEWER	James A Berkley Centre for Tropical Medicine & Global Health, University of Oxford, UK & KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	This is a timely and sobering report. My only comment is that the text would benefit from editing to be more concise. These are some examples: On page 3, line 14: “Suboptimal antibiotic dosing, including both under- or over-dosing, can lead to toxicity or failure to meet therapeutic targets, which not only contributes to treatment failure, but may also drive antimicrobial resistance through encouragement of selection pressures on drug-resistant strains of bacteria.[7]” could be written more simply as: “Suboptimal antibiotic dosing, including over- and under-dosing, can lead to toxicity, treatment failure, and may drive antimicrobial resistance by selecting bacterial resistance genes.[7]” On page 6, line 54: “On review of the age of participants being recruited, only 23 of the 76 trials (30%) were recruiting newborns (0 to 28 days)” could be: “Twenty three of the 76 trials (30%) were recruiting newborns (0 to 28 days).” On page 6, line 20: “Of the antibiotic clinical trials identified in our search, two-thirds (n=50, 66%) were sponsored by non-profit organisations (being University, Hospital or government funded), with many fewer trials sponsored by Industry (n=26, 34%)” could be: “Fifty (66%) trials were sponsored by non-profit organisations (being

	University, Hospital or government funded), and 26 (34%) were sponsored by industry.”

REVIEWER	Sumanth Gandra Center for Disease Dynamics, Economics & Policy India
REVIEW RETURNED	12-Mar-2017

GENERAL COMMENTS	With rising MDR infections among neonates and children the use/need for off label antibiotics increased dramatically among pediatric patients. This is particularly relevant to regions like South Asia where MDR gram negatives are predominant cause of neonatal sepsis. The article rightly points out the need for better understanding of PK profiles of antibiotics used in pediatric patients as they influence patient outcomes. The article is timely and raises important concerns about dearth of pediatric specific antibiotic clinical trials especially involving preterm and term babies. The following comments suggest mostly minor changes: 1. Page 12 in Discussion section: Line 20-21- “agreed” is repeated twice. 2. The authors could consider adding more discussion on the findings in Table 2. What could be reasons for this discrepancy in sponsorship and endpoint classification? It seems early stage work is mostly sponsored by pharma and large expensive efficacy trials are left to others? 3. Page 11, line 42 -Table 4 footnote – “a”- denotes target CRE. In the table Delafloxacin is denoted as having CRE coverage, which I was not able to verify. Could authors verify this? Should be for other drug like- “Carbavance”?

REVIEWER	Allison H. Bartlett, M.D. University of Chicago Medicine USA
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	The authors performed a thorough review of the current state of antibiotic clinical trials enrolling children and newborns (including preterm neonates). Realizing this deficiency, the European Medicines Agency and the US Food and Drug Administration have launched initiatives to encourage pediatric drug development plans. However, only 5 of 37 antibiotics in the pipeline had a pediatric investigation plan – and only 2 of those were being investigated in pediatric trials. In addition, the types of infections under study does not match the types of infections that occur in this population. The majority of studies were funded by non-profit institutions, and were predominantly efficacy trials. Most safety studies were industry-sponsored. 1. Page 12 line 35: The authors reference a 2013 paper about pediatric clinical trials of antibiotics in Europe which described more trials in 2000 than in the current study – but they make no comment on why. Was there a difference in methodology? Or are there truly fewer trials recruiting children? 2. Page 13 line 41: What is the average time to completion of non-antibiotic trials as a comparison? 3. The authors did not include antiviral agents or antifungal agents in

	their review. Would they expect the same findings to hold true? Would the potential solutions also apply to these agents? In summary, this review provides additional data to support the need for more antibiotic clinical trials focusing on this vulnerable population. No concrete solutions are offered, however.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
- We have revised the manuscript to make the text more concise.

Reviewer 2
- Deleted repeated "agreed".
- Academic investigators focus on larger efficacy studies. We have offered some potential reasons for this in the revised manuscript.
- We revisited the Pew Charitable Trusts Pipeline. Carbavance is targeted for CRE not Delafloxacin - we have revised Table 4 in light of this.

Reviewer 3
- The group responsible for the 2013 paper searched Medline, EMBASE and Cochrane library databases for published papers (Jan 2000 - Dec 2012) on the use of newly licensed antibiotics in children 0-17 years of age, in addition to searching WHO and EU clinical trials registers for ongoing trials. The methodology differs since we only included open clinical trials - we have revised the manuscript to document this difference in methodology.
- We are unable to comment on the average time to completion of non-antibiotic trials as a comparison.
- Antivirals and antifungals were not the focus of this review, so unfortunately we do not have the data available to include them.
- In the revised manuscript we have offered some potential ways in which to improve the conduct of paediatric clinical trials.

VERSION 2 – REVIEW

REVIEWER	Allison H. Bartlett, MD, MS Assistant Professor, Pediatric Infectious Diseases University of Chicago Medicine Comer Children's Hospital USA
REVIEW RETURNED	27-Jun-2017

GENERAL COMMENTS	This version of the manuscript is much more concise than the previous version, but I think there is still room to shorten it. A few minor changes: 1. Page 3 line 18 "bridge" should be "bridging" 2. Page 3 line 21 is missing a) 3. Page 3 line 41 "Institute" should be "Institutes" 4. Page 3 line 52 "in compliance" -- consider changing to "to

	document compliance" 5. Page 7 lines 10-15 - remove capitalization of common treatment indications such as "Lower Respiratory Tract Infection" 6. Page 7 line 36 - "on the most recent (May 2016) edition" or "on the May 2016 edition" 7. Page 13 line 30 remove "therefore" 8. Spelling of pediatric vs paediatric varies throughout the manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer 3.

We have shortened the manuscript as requested.