**Evaluating safety reporting in paediatric antibiotic trials 2000-2016: a systematic review and meta-analysis**

**Subheading: Safety reporting in paediatric antibiotic clinical trial 2000-2016**

***Drugs***

**1,2Paola Pansa, MD; 1Yingfen Hsia, PhD; 1,3Julia Bielicki, MD; 4Irja Lutsar, MD; 5A. Sarah Walker, PhD; 1Mike Sharland, MD; 1\*Laura Folgori, MD**

1 Paediatric Infectious Disease Research Group, Institute for Infection and Immunity, St George's University of London, Cranmer Terrace, London SW17 0RE, UK

2 Department of Pediatrics, Sapienza University of Rome, Policlinico Umberto I, Viale Regina Elena 324, 00161 Rome, Italy

3 Paediatric Pharmacology, University Children’s Hospital Basel, Spitalstrasse 33 4056, Basel, Switzerland

4 Institute of Medical Microbiology, University of Tartu, Ravila 19, 50411 Tartu, Estonia

5 Nuffield Department of Clinical Medicine; NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford OX1 3PA, UK

**\*Corresponding author:** Laura Folgori

Mailing address: St George's University of London, Jenner Wing, Level 2, Room 2.215E, Cranmer Terrace, London, SW17 0RE, United Kingdom

E-mail address: lfolgori@sgul.ac.uk

Telephone number: +44 20 87254851

**SEARCH STRATEGY**

**Medline (Ovid MEDLINE(R) without Revisions 1996 to June Week 1 2016). Searched on 02/06/2016**

1. anti?bioti\*.mp.

2. antibiotic.mp. or exp Anti-Bacterial Agents/

3. exp Anti-Bacterial Agents/ or exp Anti-Infective Agents/ or anti infective.mp.

4. antimicrobial.mp.

5. anti microbial.mp.

6. (anti?biot\* or anti?infect\* or anti?bact\* or anti?microb\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7. 1 or 2 or 3 or 4 or 5 or 6

8. randomized controlled trial.pt.

9. controlled clinical trial.pt.

10. randomized.ab.

11. placebo.ab.

12. clinical trials as topic.sh.

13. randomly.ab.

14. trial.ti.

15. 8 or 9 or 10 or 11 or 12 or 13 or 14

16. exp animals/ not humans.sh.

17. 15 not 16

18. exp Safety/ or exp Patient Safety/ or safety.mp.

19. exp "Drug-Related Side Effects and Adverse Reactions"/ or drug reaction.mp. or exp Drug Hypersensitivity/

20. side effect.mp.

21. adverse effect.mp.

22. toxicity.mp.

23. exp Anaphylaxis/ or anaphylaxis.mp.

24. adverse event.mp.

25. Product Surveillance, Postmarketing/ or pharmacovigilance.mp. or exp Adverse Drug Reaction Reporting Systems/ or exp Pharmacovigilance/ or Drug Monitoring/

26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. 7 and 17 and 27

28. limit 27 to (yr="2000 - 2016" and "all child (0 to 18 years)")

29. malaria.mp. or exp Malaria/

30. exp HIV/ or HIV.mp.

31. exp Tuberculosis/

32. 29 or 30 or 31

33. 28 not 32

**CENTRAL (Issue 6 of 12, June 2016). Searched on 02/06/2016**

1. MeSH descriptor: [Anti-Bacterial Agents] explode all trees

2. (anti\* near (infect\* or biotic\* or bacter\* or microb\*))

3. MeSH descriptor: [Safety] explode all trees

4. MeSH descriptor: [Drug Hypersensitivity] explode all trees

5. MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees

6. "toxicity":ti,ab,kw (Word variations have been searched)

7. "anaphylaxis":ti,ab,kw (Word variations have been searched)

8. MeSH descriptor: [Anaphylaxis] explode all trees

9. MeSH descriptor: [Pharmacovigilance] explode all trees

10. "pharmacovigilance":ti,ab,kw (Word variations have been searched)

11. "adverse drug event":ti,ab,kw (Word variations have been searched)

12. 1 or 2

13. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

14. 12 and 13

15. 14 limited to Publication Year from 2000 to 2016, in Trials

**Clinicaltrials.gov. Searched on 02/06/2016**

**Ongoing trials**

(antibiotic OR antibacterial OR antiinfective OR antimicrobial ) AND (safety OR drug hypersensitivity OR adverse reaction OR side effects OR hypersensitivity OR toxicity OR pharmacovigilance OR anaphylaxis ) AND EXACT ( "Recruiting" OR "Not yet recruiting" OR "Available" ) [OVERALL-STATUS] AND EXACT "Interventional" [STUDY-TYPES] AND EXACT Child [AGE-GROUP] AND ( "01/01/2000" : "06/02/2016" ) [FIRST-RECEIVED-DATE]

**Closed in the last 5 years**

(antibiotic OR antibacterial OR antiinfective OR antimicrobial ) AND (safety OR drug hypersensitivity OR adverse reaction OR side effects OR hypersensitivity OR toxicity OR pharmacovigilance OR anaphylaxis ) AND EXACT NOT ( "Recruiting" OR "Not yet recruiting" OR "Available" ) [OVERALL-STATUS] AND EXACT "Interventional" [STUDY-TYPES] AND EXACT Child [AGE-GROUP] AND ( "01/01/2011" : "06/02/2016" ) [FIRST-RECEIVED-DATE]

 **eTable 1** Included studies and quality assessment

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Reference** | **Country** | **Study period** | **Funded by pharmaceutical** | **Safety endpoint** | **Condition** | **Intervention** | **Population N** | **Age** | **Quality assessmenta** |
| Abdel-Hady, 2011 [1] | Egypt | 03/2007-01/2008 | no | Secondary | Neonatal Sepsis | Open label RCT 1:1 to• Amikacin OD• Amikacin BID | 30 | Neonates | 44 |
| Adler, 2000 [2] | Europe, South Africa andAustralia | nr | yes | Secondary | URTI | Open label RCT 1:1:1 to • Cefdinir OD• Cefdinir BID• Amoxicillin | 752 | 6 m - 12 y | 67 |
| Afrinest, 2015 [3] | Democratic Republic ofCongo (DRC), Kenya and Nigeria | 04/2011-03/2013 | no | Primary | Unspecified BI | Open label RCT 1:1 to• Procaine penicillin OD• Gentamicin OD & Amoxicillin BID | 2,196 | 0 - 59 d | 80 |
| Afrinest, 2015 [4] | Democratic Republic ofCongo (DRC), Kenya and Nigeria | 04/2011-2013 | no | Primary | Unspecified BI | Open label RCT 1:1:1:1 to• Gentamicin OD (7 days) + Procaine penicillin OD (7 days)• Gentamicin OD (7 days) + Amoxicillin BID (7 days)• Gentamicin OD (7 days) + Procaine penicillin OD (2 days) + Amoxicillin 5 days• Gentamicin OD (2 days) & Amoxicillin BID (2 days) + Amoxicillin BID (5 days) | 3,564 | 0 - 59 d | 70 |
| Aguilar, 2000 [5] | Worldwide | 07/1998-07/1999 | yes | Secondary | URTI | Double blind RCT 1:1 to• Amoxicillin BID• Amoxicillin TID | 516 | 2 - 12 y | 78 |
| Arguedas, 2005 [6] | Chile, US, CostaRica and Finland | 09/2002-07/2003 | yes | Secondary | URTI | Double blind RCT 1:1 to• Azithromycin OD• Amoxicillin BID (High dose) | 306 | 6 – 30 m | 78 |
| Arguedas, 2009 [7] | Colombia, USA, Slovenia, Chile, Peru, Spain, Romania, South Africa, Malaysia, Brazil, Guatemala, Venezuela, Germany, Singapore | 2002-2003 | yes | Primary and Secondary | UTI, SSTI, LRTI | Double blind RCT 3:1 to• Ertapenem OD or BID• Ceftriaxone OD or BID | 403 | 3 m - 18 y | 80 |
| Arguedas, 2011 [8] | North America, Europe, Latin America | 05/2003-05/2004 | yes | Secondary | URTI | Double blind RCT 1:1 to• Azithromycin ER OD (1 day)• Amoxicillin/clavulanate BID (10 days) | 902 | 3 - 48 m | 56 |
| Arrieta, 2003 [9] | US, Latin American | 03/2001-03/2002 | yes | Secondary | URTI | Double blind RCT 1:1 to• Azithromycin OD (3 days, high-dose)• Amoxicillin/clavulanate BID (10 days) | 300 | 6 m-6 y | 78 |
| Balatsouras, 2005 [10] | Greece | (3 years) | no | Secondary | URTI | Open label RCT 1:1 to• Loracarbef BID (Low dose)• Loracarbef BID (High dose) | 58 | 5 - 12 y | 56 |
| Baqui, 2015 [11] | Bangladesh | 07/ 2009-06/2013 | yes | Primary | Unspecified BI | Open label RCT 1:1:1 to• Procaine benzylpenicillin & gentamicin OD (7 days)• Gentamicin OD & Amoxicillin BID (7 days) | 2,367 | 0 – 59 d | 56 |
| Baysoy, 2012 [12] | Turkey | 10/2008-03/2010 | no | Secondary | GII | Open label RCT 2:3 to • Amoxicillin & Clarithromycin & Lansoprazole (14 days)• Amoxicillin & Lansoprazole (5 days) + Clarithromycin & Ornidazole & Lansoprazole (5 days) | 61 | 4 - 18 y | 44 |
| Begum, 2014 [13] | Bangladesh | 01/2011-12/2011 | no | Secondary | GII | Open label RCT 1:1 to• Azithromycin OD (7 days)• Cefixime BID (14 days) | 60 | children | 33 |
| Block, 2000 [14] | US | 04/1992-08/1993 | yes | Secondary | URTI | Double blind RCT 1:1:1 to• Cefdinir OD• Cefdinir BID | 384 | 6 m - 12 y | 89 |
| Block, 2006 [15] | US | 01/2005-05/2005 | yes | Secondary | URTI | Double blind, phase 4 RCT 1:1 to• Cefdinir BID• Amoxicillin/Clavulanate BID (high dose) | 318 | 6 m - 6 y | 67 |
| Boccazzi, 2000 [16] | Italy | 11/1996-07/1998 | no | Secondary | URTI | Open label RCT 1:1 to• Ceftibuten OD (5 days)• Azithromycin OD (3 days) | 248 | 3 - 16 y | 44 |
| Bradley, 2007 [17] | Argentina, Brazil, Chile, Costa Rica, Mexico, Panama, and US | 08/2002-06/2004 | yes | Secondary | LRTI | Open label RCT 3:1 to• Levofloxacin BID• Comparator:- 6 months-5 years: Amoxicillin/ clavulanate BID orCeftriaxone- 5-16 years: Clarithromycine or Ceftriaxone & erythromycin lactobionate q6h or clarithromycin BID | 533 | 6 m - 16 y | 78 |
| Carapetis, 2001 [18] | Australia | 03/1994-01/1997 | no | Secondary | UTI | Open label RCT 1:1 to• Gentamicin OD• Gentamicin TID | 179 | 1 m - 12 y | 89 |
| Cascio, 2001 [19] | Italy | 06/1998-09/1998 | no | Secondary | Unspecified BI | Open label RCT 1:1 to• Clarithromycin BID (7 days)• Chloramphenicol q6h (7 days) | 51 | 0 - 14 y | 56 |
| Cascio, 2002 [20] | Italy | 06/1999-09/2000 | no | Secondary | Unspecified BI | Open label RCT 1:1 to• Clarithromycin BID (7 days)• Azithromycin OD (3 days) | 87 | 0 - 14 y | 78 |
| Chanta, 2015 [21] | Thailand | 06/2010-05/2013 | no | Secondary | GII | Open label RCT 1:1 to• Azitromycin OD (3 days)• Comparator:- <8 years: IV chloramfenicol q6h;- > 8 years: Doxycycline BID (>5 days) | 29 | 0 - 15 y | 56 |
| Chong, 2003 [22] | Singapore | 01/2000-05/2001 | no | Primary | UTI | Open label RCT 1:1 to• Gentamicin OD• Gentamicin TID | 172 | 1 m - 13 y | 78 |
| Chotigeat, 2001 [23] | Thailand | 08/1999-12/1999 | no | Secondary | Unspecified BI | Open label RCT 1:1 to• Gentamicin BID• Gentamicin OD | 54 | Neonates | 44 |
| Cochereau, 2007 [24] | Guinea, Pakistan | 01/2004-05/2004 | yes | Secondary | Other BI | Double blind RCT 1:1:1 to• Azithromycin topical (2 days)• Azithromycin topical (3 days)• Azithromycin OD (3 days) | 179 | 1 - 10 y | 78 |
| Cohen, 2001 [25] | France | 11/1997-07/1998 | yes | Secondary | URTI | Double blind RCT, 1:1:1 to• Azithromycin OD (3 days)• Azithromycin OD High dose (3 days) | 499 | 2 - 12 y | 67 |
| Damrikarnler, 2000 [26] | Argentina, Brazil, Costa Rica, India, Kenya, Mexico, Morocco, Nigeria, Thailand, Turkey | 08/1996-03/1998 | yes | Secondary | URTI | Single blind RCT 1:1 to• Amoxycillin/clavulanate BID (7 or 10 days)• Amoxycillin/clavulanate TID (7 or 10 days) | 415 | 2 m - 12 y | 78 |
| Demirjian, 2013 [27] | US | 02/2011-01/2012 | no | Secondary | Unspecified BI | Double blind RCT 1:1 to• Vancomycin loading dose + Vancomycin standard dose TID• Vancomicin standard dose TID | 59 | 2 – 18 y | 67 |
| Deville, 2003 [28] | US, Mexico,South America | 02/2001-12/2001 | no | Primary | LRTI | Open label, phase 3 RCT 2:1 to• Linezolid TID• Vancomycin q6h or OD | 62 | 0 - 12 y | 78 |
| English, 2004 [29] | Kenya | 08/2000-02/2001 | no | Secondary | Sepsis | Open label RCT 1:1 to• Gentamicin OD• Gentamicin MD (Multi-dose) | 297 | 0 - 3 m | 67 |
| Eppes, 2002 [30] | US | 1997–1999 | no | Secondary | Other BI | Open label RCT 1:1:1 to• Cefuroxime axetil Low dose & Amoxicillin• Cefuroxime axetil High dose &Amoxicillin | 42 | 6 m - 12 y | 56 |
| Esposito, 2002 [31] | Italy | 11/1998-11/2000 | yes | Secondary | URTI | Single blind RCT 1:1 to• Cefaclor BID (5 days)• Amoxicillin TID (10 days) | 384 | 2 - 14 y | 78 |
| Ferwerda, 2001 [32] | The Netherlands | 06/1995-12/1998 | yes | Secondary | LRTI | Double blind RCT 1:1 to• Azithromycin OD (3 days)• Amoxicillin/clavulanate TID (10 days) | 110 | 3 m - 12 y | 89 |
| Haczyński, 2003 [33] | Poland | nr | no | Secondary | URTI | Double blind RCT 1:1 to• Cefaclor BID (10 days)• Amoxicillin/clavulanate TID (10 days) | 97 | 2 - 12 y | 56 |
| Jantaush, 2003 [34] | US, Mexico, SouthAmerica | 02/2001-12/2001 | no | Secondary | LRTI, Sepsis | Open label, phase 3 RCT 2:1 to• Linezolid TID• Vancomycin q6h or OD | 151 | 0 - 12 y | 78 |
| Kafetzis, 2000 [35] | Greece | nr | yes | Secondary | UTI | Open label RCT 2:1 to• Isepamicin BID (10–14 days)• Amikacin BID (10–14 days) | 16 | 1 m - 12 y | 67 |
| Kafetzis, 2004 [36] | Greece | 12/1999-04/2002 | no | Secondary | URTI | Open label RCT 1:1:1 to • Penicillin V TID (10 days)• Clarithromycin BID (10 days) | 265 | 3 - 14 y | 67 |
| Kaplan, 2003 [37] | US, Latin America | 02/2001-12/2001 | yes | Secondary | Unspecified BI | Open label RCT 2:1 to• Linezolid TID• Vancomycin q6h or OD | 312 | 0 - 12 y | 100 |
| Khan, 2005 [38] | Bangladesh | nr | no | Secondary | LRTI, GII | Open label RCT 1:1 to• Gentamicin OD & Ceftriaxone OD• Gentamicin TID & Ceftriaxone OD | 310 | 6 m - 5 y | 67 |
| Langley, 2004 [39] | Canada, US | 1995-1998 | yes | Secondary | URTI | Open label RCT 1:1 to• Azithromycin OD (5 days)• Erythromicyn TID (10 days) | 477 | 6 m - 16 y | 78 |
| Lebel, 2001 [40] | Canada | 07/1995-071998 | yes | Secondary | URTI, LRTI | Single blind RCT 1:1 to• Clarithromycin BID (7 days)• Erythromicyn TID (14 days) | 153 | 1 m - 16 y | 89 |
| Lee, 2008 [41] | Taiwan | nr | no | Secondary | LRTI | Open label RCT 1:1 to• Clarithromycin BID (10 days)• Erytromycin q6h (10 days) | 99 | 0 - 15 y | 78 |
| Marild, 2009 [42] | Sweden | 06/1996-02/2001 | yes | Secondary | UTI | Open label RCT 2:1 to• Ceftibuten OD (10 days)• TMP-SMX BID (10 days) | 461 | 1 m - 12 y | 78 |
| McCarty, 2000 [43] | US | 11/1996-03/1997 | no | Secondary | URTI | Double blind, phase 3 RCT 1:1 to• Clarithromycin BID (10 days)• Penicillin V TID | 528 | 6 m - 12 y | 78 |
| Nizic, 2012 [44] | Slovenia | 01/2004-12/2005 | no | Secondary | Other BI | Open label RCT 1:1 to• Clarithromycin BID (14 days)• Amoxicillin TID (14 days) | 130 | 0 - 15 y | 89 |
| Noel, 2008 [45] | Argentina, Brazil, Chile, Costa Rica, Panama, US | 10/2002-05/2005 | yes | Secondary | URTI | Double blind RCT 1:1 to• Levofloxacin BID (10 days)• Amoxicillin/Clavulanate BID (10 days) | 1,607 | 6 m - 2 y | 67 |
| Pareek, 2008 [46] | India | 11/2006-02/2008 | yes | Secondary | LRTI | Open label RCT 1:1 to• Cefotazime-sulbactam TID (7 days)• Amoxicillin/clavulanic TID (7 Days) | 102 | 3 m - 12 y | 89 |
| Perez, 2011 [47] | Costa Rica | 04/2005-02/2006 | no | Primary | GII | Double blind RCT 1:1 to• Amikacin TID & Clindamycin q6h• Amikacin OD & Clindamycin q6h | 100 | 2 - 12 y | 78 |
| Pichichero, 2000 [48] | US, Canada | nr | no | Secondary | URTI | Double blind RCT A- 1:1:1 to• Cefdinir OD (10 days)• Cefdinir BID (10 days)• Penicillin V q6h (10 days)B- 1:1 to • Cefdinir BID (5 days)• Penicillin V q6h (10 days) | 1,273 | 6 m - 12 y | 67 |
| Poachanukoon, 2008 [49] | Thailand | nr | no | Secondary | URTI | Double blind RCT 1:1 to• Cefditoren pivoxil BID (14 days)• Amoxicillin/Clavulanate BID (14 days) | 138 | 1 – 15 y | 89 |
| Portier, 2001 [50] | France | 06/1997-10/1998 | no | Secondary | URTI | Open label RCT 1:1 to• Josamycin BID (5 days)• Penicillin TID (10 days) | 324 | 3 - 12 y | 56 |
| Saez-Llorens, 2002 [51] | US, Latin America,Egypt, South Africa and Hungary | 04/1998-07/1999 | no | Secondary | CNS infection | Open label RCT 1:1 to• Alatrofloxacin BID• Ceftriaxone OD +/- Vancomycin q6h | 162 | 3 m - 12 y | 78 |
| Sakata, 2008 [52] | Japan | 06/2006-02/2007 | no | Secondary | URTI | Open label RCT 1:1:1 to• Cefcapene–pivoxil TID (5 or 10 days)• Amoxicillin TID (10 days) | 236 | 6 m - 13 y | 44 |
| Shahid, 2008 [53] | Malaysia | 04/2004-08/2005 | no | Secondary | LRTI | Open label RCT 1:1 to• Cefepime BID• Ceftazidime TID | 30 | 0 – 12 m | 33 |
| Sher, 2005 [54] | Costa Rica, US | 03/2001-06/2002 | no | Secondary | URTI | Double blind RCT 1:1 to• Gatifloxacin OD (10 days)• Amoxicillin/Clavulanate BID (10 days) | 349 | 6 m - 7 y | 44 |
| Tiwari, 2009 [55] | India | 05/2005-03/2006 | no | Secondary | Unspecified BI | Open label RCT 1:1 to• Gentamicin OD• Gentamicin BID or TID | 400 | 0 - 12 y | 56 |
| Uijtendaal, 2001 [56] | The Netherlands | nr | no | Primary | Unspecified BI | Open label RCT 1:1 to• Gentamicin OD• Gentamicin multiple daily | 40 | 1 m - 16 y | 78 |
| Vasquez-Mendoza, 2007 [57] | Mexico | 10/2001-08/2003 | no | Primary | Neonatal Sepsis | Double blind RCT 1:1 to• Amikacin OD & Ampicillin• Amikacin BID & Ampicillin | 120 | 0 - 28 d | 100 |
| Wang, 2003 [58] | Taiwan | 02/2000-04/2002 | no | Secondary | URTI | Open label RCT 1:1 to• Amikacin OD• Amikacin BID | 109 | 3 m- 6 y | 67 |
| Wible, 2003 [59] | US, Canada, Mexico, Argentina, Brazil, Chile and Peru. | 06/2000-02/2001 | yes | Secondary | SSTI | Double blind RCT 1:1 to• Linezolid BID• Cefadroxil BID | 494 | 5 - 17 y | 78 |
| Yellin, 2007 [60] | US, Mexico, Brazil | 03/2002-01/2004 | no | Primary | GII, other BI | Open label RCT 3:1 to• Ertapenem BID • Ticarcillin/clavulanate q6h or q4h | 105 | 2 - 17 y | 78 |
| Yogev, 2003 [61] | US, Mexico, South America | 02/2001-12/2001 | no | Secondary | SSTI | Open label RCT 2:1 to• Linezolid BID• Vancomycin q6h or OD | 119 | 0 - 12 y | 78 |
| Zimbasa Dysentery Study Group, 2002 [62] | Zimbabwe, South Africa, Bangladesh | 05/1996-06/2000 | yes | Secondary | GII | Double blind RCT 1:1 to• Ciprofloxacin BID (3 days) + placebo• Ciprofloxacin BID (5 days) | 252 | 12 m - 11 y | 67 |
| NCT01400867 [63] | US, Argentina, Chile, Georgia, Latvia, Lithuania, Poland, Romania, South Africa, Spain | 12/2011-07/2014 | yes | Primary | Other BI | Single blind, phase 2, phase 3 RCT• Ceftaroline fosamil• Vancomycin +/- Aztreonam or Cefazolin +/- Aztreonam• Cephalexin or Clindamycin or Linezolid | 163 | 2 m - 17 y | na |
| NCT01530763 [64] | US, Argentina, Bulgaria, Georgia, Greece, Hungary, Poland, Spain, Ukraine | 09/2012-07/2014 | yes | Primary | Other BI, LRTI | Single blind, phase 2, phase 3 RCT • Ceftaroline fosamil• Amoxicillin/clavulanate | 161 | 2 m - 18 y | na |
| NCT01551394 [65] | Italy, Spain, Greece, Lithuania, Estonia | 09/2012-12/2014 | yes | Secondary | Sepsis | Open label RCT to• Meropenem (11±3 days)• Ampicillin/Gentamicin or Cefotaxime/Gentamicin | 272 | 0 - 90 d | na |
| NCT01669980 [66] | US, Argentina, Georgia, Ukraine | 10/2012-08/2014 | yes | Primary | Other BI, LRTI | Single blind, phase 4 RCT • Ceftaroline fosamil• Ceftriaxone & Vancomycin | 40 | 2 m - 18 y | na |
| NCT01707485 [67] | Canada | 11/2012-05/2014 | no | Secondary | LRTI | Double blind, phase 4 RCT • Amoxicillin TID (5 days)• Amoxicillin TID (10 days) | 60 | 1 - 10 y | na |
| NCT01728376 [68] | Argentina, Australia, Brazil, Chile, Colombia, Greece, Guatemala, Hungary, Israel, Italy, Malaysia, Panama, Romania, Spain, Taiwan, Thailand, Ukraine, US | 11/2012-01/2016 | yes | Primary | Sepsis | Open label, phase 4 RCT • Daptomycin OD• SOC: Vancomycin, Semi-synthetic penicillin, First-generation cephalosporins, Clindamycin | 82 | 1 - 17 y | na |
| NCT01922011 [69] | Argentina, Australia, Brazil, Bulgaria, Chile, Colombia, Estonia, France, Georgia, Germany, Greece, Guatemala, Hungary, Israel, Italy, Korea, Republic of, Latvia, Malaysia, Moldova, Republic of, New Zealand, Panama, Peru, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, Ukraine, UK, US | 09/2013-ongoing | yes | Secondary | Other BI | Double blind RCT to• Daptomycin OD• Vancomycin q6h, or nafcillin q6h | 144 | 1 - 17 y | na |
| NCT01994993 [70] | US, Canada | 12/2013-ongoing | no | Secondary | GII | Double blind RCT to• Ampicillin & Metronidazole & Gentamicin• Ampicillin & Gentamicin & Clindamycin• Gentamicin and Piperacillin- tazobactam • Standard of care antibiotics and Metronidazole• Metronidazole & clindamycin or peracillin-tazobactam | 284 | 0 - 120 d | na |
| NCT02258763 [71] | Malaysia | 09/2014-ongoing | no | Secondary | LRTI | Double blind, phase 4 RCT • Amoxicillin/Clavulanate BID (10 days)• Amoxicillin/Clavulanate BID (3 days) | 300 | 3 - 59 m | na |
| NCT02276482 [72] | US, Argentina, Bulgaria, Chile, Czech Republic, Georgia, Germany, Latvia, Lithuania, Panama, Poland, Slovenia, South Africa, Spain | 03/2015-ongoing | yes | Primary | SSTI | Single blind, RCT to• Tedizolid Phophate (6 days)• Antibiotic comparator | 162 | 12 - 17 y | na |
| NCT02334124 [73] | Australia | 01/2015-ongoing | no | Primary and Secondary | SSTI | Single blind, RCT to• Ceftriaxone• Flucloxacillin | 188 | 6 m - 18 y | na |
| NCT02380352 [74] | Canada | 03/2016-ongoing | no | Secondary | LRTI | Double blind RCT • Amoxicillin TID (5 days)• Amoxicillin TID (10 days) | 270 | 6 m - 10 y | na |
| NCT02475733 [75] | Argentina, Chile, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Spain, Taiwan, Turkey, US | 05/2015-ongoing | yes | Primary | GII | Single blind, phase 2 RCT 3:1 to• Ceftazidime -avibactam TID & metronidazole TID• Meropenem TID | 102 | 3 m - 18 y | na |
| NCT02497781 [76] | Czech Republic, Greece, Hungary, Poland, Romania, Russia, South Korea, Taiwan, Turkey, US | 06/2015-ongoing | yes | Primary | UTI | Single blind, phase 2 RCT 3:1 to• Ceftazidime-avibactam TID• Cefepime | 102 | 3 m - 18 y | na |
| NCT02503761 [77] | Egypt | 06/2015-ongoing | no | Secondary | Neonatal Sepsis | Open label, phase 3 RCT • Meropenem TID (infused over 4 hours)• Meropenem TID (infused over 30 minutes) | 100 | 0 - 28 d | na |
| NCT02554383 [78] | US | 02/2016-ongoing | no | Secondary | URTI | Double blind, placebo controlled RCT to• Amoxicillin-clavulanate (10 days)• Placebo | 688 | 2 - 11 y | na |
| NCT02605122 [79] | US, Hungary | 11/2015-ongoing | yes | Primary | LRTI | Open label, phase 2, phase 3 RCT • Solithromycin• SOC (intravenous ceftriaxone, ampicillin, and amoxicillin and oral amoxicillin and amoxicillin-clavulanic acid) | 400 | 2 m - 17 y | na |
| NCT02635191 [80] | China | 03/2014-ongoing | no | Secondary | GII | Open label RCT to• Proton Pump Inhibitor & two antibiotics (Amoxicillin BID, Clarithromycin BID, Metronidazole BID)• Omeprazole BID & Amoxicillin BID & Clarithromycin BID | 200 | 4 - 18 y | na |
| NCT02783859 [81] | Australia, Malaysia | 06/2016-ongoing | no | Secondary | LRTI | Double blind, placebo controlled RCT to• Amoxicillin-clavulanic Acid BID (8 days)• Placebo | 314 | 3 m - 5 y | na |
| NCT02790996 [82] | UK, Estonia, Italy, Spain, Greece | 05/2016-ongoing (Not yet recruiting) | no | Secondary | Sepsis | Open label RCT to• Vancomycin (Optimised Regimen)• Vancomycin (Standard Regimen) | 300 | 0 - 90 d | na |
| NCT02795793 [83] | Australia | 05/2016-ongoing (Not yet recruiting) | no | Secondary | GII | Open label, RCT to• Piperacillin tazobactam TID• Appendectomy | 226 | 5 - 16 y | na |

**aproportion of items of the CONSORT 2004 on safety quality reporting [Ref] checklist that were adequately reported. UTI: Urinary tract infections, LRTI: Low Respiratory Tract Infection, URTI: Upper Respiratory Tract Infection, SSTI: Skin and Soft Tissue Infection, GI: Gastrointestinal Infection, BI: Bacterial Infection, na: not applicable**

**eTable 2** Patients distribution per drug class in included trials

|  |  |  |
| --- | --- | --- |
| **Drug class** | **Number of patients (%)****[N = 27,693]** | **Number of trials (%)****[N = 83]** |
| **Penicillins** | 11,408 (41.2) | 23 (27.7) |
| **Aminoglycosides** | 9,852 (35.6) | 15 (18.1) |
| **Cephalosporins** | 4,014 (14.5) | 25 (30.1) |
| **Penicillins and β-lactamase inhibitor** | 3,617 (13.1) | 18 (21.7) |
| **Macrolides** | 3,292 (11.9) | 21 (25.3) |
| **Fluoroquinolones** | 1,920 (6.9) | 5 (6.0) |
| **Lincosamides** | 1,429 (5.2) | 3 (3.6) |
| **Oxazolidinone** | 764 (2.8) | 6 (7.2) |
| **Carbapenems** | 646 (2.3) | 5 (6.0) |
| **Glycopeptides** | 585 (2.1) | 7 (8.4) |
| **Sulfonamides and trimethoprim** | 152 (0.5) | 1 (1.2) |
| **Imidazole derivates** | 133 (0.5) | 2 (2.4) |
| **Lipopeptides** | 113 (0.4) | 2 (2.4) |
| **Cephalosporins and β-lactamase inhibitor** | 50 (0.2) | 1 (1.2) |
| **Amphenicols** | 25 (0.1) | 1 (1.2) |

**eTable 3** Overall and specific reported Adverse Events (AEs) per drug class

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug class** | **N patients** | **Overall****AEs** | **Sum of specific AEs** | **Discontinuation due to AEs (11,566)\*** | **Systemica** | **Nephro****toxicity****(2,223)\*** | **Oto****toxicity****(1,576)\*** | **Gastro****Intestinal** | **Neurological** | **Respiratory** | **Dermatologic** | **Muscolo-skeletal** | **Infusional** | **Laboratory****(5,064)\*** |
| **Penicillins** | 3,019 | 333 | 205 | 49 | 7 | 3 | 0 | 145 | 6 | 0 | 22 | 0 | 6 | 16 |
| **Aminoglycosides** | 1,308 | 129 | 90 | nr | 0 | 75 | 6 | 0 | 9 | 0 | 0 | 0 | 0 | 0 |
| **Cephalosporins** | 2,462 | 507 | 470 | 53 | 10 | 0 | 0 | 316 | 11 | 56 | 52 | 0 | 6 | 19 |
| **Macrolides** | 2,931 | 802 | 640 | 34 | 34 | 0 | 0 | 511 | 0 | 3 | 79 | 0 | 0 | 13 |
| **Penicillins +** **β-lactamase inhib** | 2,566 | 1,394 | 1325 | 50 | 84 | 0 | 4 | 758 | 0 | 175 | 281 | 22 | 1 | 0 |
| **Fluoroquinolones** | 1,920 | 1,304 | 916 | 44 | 89 | 0 | 0 | 388 | 0 | 202 | 119 | 56 | 0 | 62 |
| **Carbapenems** | 385 | 122 | 111 | 6 | 0 | 0 | 0 | 27 | 0 | 0 | 0 | 0 | 42 | 42 |
| **Linezolid** | 683 | 398 | 357 | 10 | 9 | 0 | 0 | 81 | 20 | 25 | 9 | 0 | 2 | 215 |
| **Glycopeptides** | 265 | 192 | 181 | 8 | 48 | 5 | 0 | 23 | 1 | 0 | 21 | 0 | 0 | 84 |
| **Sulfonamides + trimethoprim** | 152 | 7 | 7 | 4 | 2 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Amphenicols** | 25 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **15,716** | **5,189** | **4,308** | **258** | **283** | **83** | **10** | **2,254** | **47** | **461** | **584** | **78** | **57** | **451** |

**\*Population in which this parameter was evaluated; aincluding fever, anaphylaxis and Red Man Syndrome. Patients on combination of Aminoglycosides/Penicillin were included in Aminoglycosides only when class specific AEs (Nephrotoxicity and Ototoxicity) were reported.**

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