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A global shortage of neonatal and pediatric antibiotic trials.

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ABSTRACT

Objectives: There have been few clinical trials (CTs) on antibiotics which inform neonatal and pediatric drug labelling. Consequently, the rate of unlicensed and off-label prescribing in pediatrics remains high. This remains a major concern, particularly in neonates. It is unclear whether the current pediatric antibiotic research pipeline is adequate to inform optimal drug dosing. Using ClinicalTrials.gov registry, this review aims to establish the current global status of antibiotic CTs in children up to 18 years of age.

Results: Only 76 registered open CTs of antibiotics in children were identified globally; 23 (30%) were recruiting newborns (only 8 (11%) included preterm neonates), 52 (68%) infants and toddlers, 58 (76%) children, and 54 (71%) adolescents. The majority of registered trials were late phase (10 (15%) Phase 3 and 23 (35%) Phase 4/pharmacovigilance). Two-thirds were sponsored by non-profit organisations, with few sponsored by pharmaceutical companies (50 (66%) vs. 26 (34%) respectively). A greater proportion of non-profit funded trials were efficacy-based strategic trials (n= 34, 68%), in comparison to industry-led trials, which were most often focused on safety or pharmacokinetic data (n=17, 65%). Our search revealed that 2 of the 37 antibiotics listed on the May 2016 Pew Charitable Trusts antibiotic development pipeline, currently being studied in adults, appear to be recruiting in open pediatric CTs.

Conclusions: This review highlights that there are currently very few pediatric antibiotic CTs being conducted globally (especially in neonates). There is striking disparity noted between antibiotic drug development programmes involving adults and children.

Strengths and limitations of this study

- A narrative literature review of registered clinical trials in children.
- Explicit reproducible methodology.
- Search strategy limited to ClinicalTrials.gov and EudraCT. Entirety of clinical research in this field might not have been captured.
- Search strategy also limited to open clinical trials. Active but not yet recruiting trials were not captured.

INTRODUCTION

With the persistence of widespread unlicensed and off-label prescribing in pediatrics – as high as 11.4% and 46.5% respectively – the paucity of clinical research involving children that which is conducted to inform optimal drug dosing, licensing and labelling remains a problem.[1] For certain medicines, drug efficacy can be extrapolated from adult data provided that the pathology and pharmacology (including drug exposure) are the same, or sufficiently similar in children as in adults.[2,3] Advances in modelling and simulation mean smaller focussed studies can now be

performed to help obtain regulatory approval for most medicines, including antimicrobials.[4] Although differences in drug pharmacokinetics (PK) in neonates and children can lead to adverse reactions that are not seen in adult populations, these are very rare and extrapolation of safety data into the pediatric population can further reduce the need for complex study designs.[5]

Since antibiotics are the most commonly prescribed medicines in children, it is important to improve our currently limited understanding of their pharmacokinetic profiles to help determine optimal drug dosing and ultimately to improve patient outcomes.[6] 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] In the last decade several initiatives have been established to encourage pediatric medicines research, thus bridge the gap between adult and pediatric drug development plans. Such initiatives include the Pediatric Regulation (Pediatric Investigation Plans (PIPs), introduced by the European Medicines Agency (EMA),[8] and Pediatric Study Plans (PSPs), by the U.S. Food and Drug Administration (FDA).[9] Despite this, there remain limited advances in the development of antibiotics for this population.[10]

The global status of clinical research on antibiotics in pediatrics is currently unknown. Using registered records of clinical trials (CTs) on *ClinicalTrials.gov*, this review aims (i) to summarise the current global status of registered antibiotic research in children and neonates, and (ii) to stimulate discussion and collaboration among the relevant stakeholders on the neglect of antibiotic research in pediatrics.

METHODS

Data sources

The *ClinicalTrials.gov* registry (last accessed 8th November 2016) is an international platform for the registration of CTs. It is a web-based registry, developed in 2000 by the National Institute of Health (NIH) and the FDA, to which trials from 50 states and 163 countries around the world are registered. All information provided for each trial is updated periodically by the trial's sponsoring organisation. The database has a specific child filter, which uses a key word paradigm to select all registered trials recruiting patients/participants up to 18 years of age.

Study selection

Our records were identified using suitable key word searches, in which the search terms were (antimicrobial* OR antibiotic* OR antiinfective agent*) AND Child AND Open Studies. All identified trials were filtered manually using inclusion and exclusion criteria. Interventional and observational

trials on antimicrobials recruiting children up to 18 years of age were considered eligible for inclusion. No specific temporal filter was applied since only open or ongoing clinical trials were of interest. The following records, which were not investigating one or more antibiotics, were excluded: trials of antifungals, antivirals, antiprotozoal, antimycotics, pro- or pre- biotics, antiseptics, topical or inhalational treatments, prophylactic antibiotics, investigating alternative use for antibiotics (for example as anti-inflammatory agents), and trials involving pregnant women or cystic fibrosis, tuberculosis, HIV, febrile neutropenia, and malaria patients.

All eligible records were identified via manual filtering by GT CB, LF and MS.

Data extraction

The following information was collected from the included records: unique NCT number, recruitment status, study design, trial phase, study sponsor, age group and sex eligibility, clinical indication, geographic region of recruitment, antibiotic being investigated, and endpoint classification. Outcomes were categorised as safety, efficacy or PK. Economic setting (based on geographic region of recruitment) was classified using The World Bank classification.[11]

The specific class of antibiotic studied in each trial was identified and classified using the World Health Organisation (WHO) ATC/DDD index.[12] To investigate whether novel antibiotics are being studied in pediatric and neonatal populations (as well as in adults), the antibiotics currently studied in children were compared with the *Pew Charitable Trusts Antibiotics Currently in Clinical Development* pipeline, which identifies novel antibiotics currently under development for the U.S. market.[13]

RESULTS

Our search identified 1056 records. 603 records were excluded on title because they were studies not involving an antimicrobial. 453 records were investigating one or more antimicrobials and recruiting children below 18 years of age. Among the 195 trials investigating antibiotics, 76 fulfilled our inclusion and exclusion criteria and were included in the final analysis. Reasons for exclusion are summarised in Figure 1.

All 76 CTs identified were open as of 8th November 2016, and 63 (83%) of these were recognised as recruiting participants on this date (Table 1). All trials stated recruitment of both male and female participants.

Table 1. Characteristics of clinical trials.

Characteristic	Category	Number of studies, n (%)
Age group	Preterm neonates	1 (1)[a]
	Neonates (total)	23 (30)
	Infants and toddlers	52 (68)
	Children	58 (76)
	Adolescents	54 (71)
Recruitment status	Recruiting	63 (83)
	Not yet recruiting	13 (17)
Study design	Interventional	66 (87)
	Observational	10 (13)
Trial phase[b]	Phase 1	10 (15)
	Phase 1-2	1 (2)
	Phase 2	9 (14)
	Phase 2-3	3 (5)
	Phase 3	10 (15)
	Phase 4	23 (39)
	Not specified	10 (15)
Sponsor	Industry	26 (34)
	Non-profit	50 (66)
Geographic region	Africa	8 (11)
	Asia	16 (21)
	Europe	22 (29)
	Latin America	6 (8)
	North America	34 (45)
	Oceania	5 (7)
Antibiotic class	J01A Tetracycline	4 (5)
	J01C Beta-lactam, Penicillin	25 (33)
	J01D Other Beta-lactam	22 (29)
	J01E Sulfonamides and trimethoprim	7 (9)
	J01F Macrolide, Lincosamide, Streptogramin	14 (18)
	J01G Aminoglycoside	2 (3)
	J01M Quinolone	8 (11)
	J01X Other[c]	21 (28)
	J01 Not specified	2 (3)

Totals for Age group, Geographic region, and Antibiotic class do not add up to total number of clinical trials (76) as some trials contributed to more than one sub group.
[a] 7 further trials mentioned inclusion of preterm babies in the inclusion criteria.
[b] Trial phase % based on percentage of interventional trials.
[c] J01X includes glycopeptides, polymixins, imidazole derivatives, and nitrofuran.

Age group

On review of the age of participants being recruited, only 23 of the 76 trials (30%) were recruiting newborns (0 to 28 days). 1 of these 23 trials focused solely on recruiting preterm newborns (a further 7 CTs mentioned inclusion of preterm newborns in inclusion criteria). Of the remaining records, 52 (68%) were recruiting infants and toddlers (28 days to 23 months), 58 (76%) children (2

to 11 years), and 54 (71%) adolescents (11 up to 18 years). 29 (38%) trials did not focus solely on the recruitment of children or neonates, with age ranges also spanning across adult populations.

Study type

Interventional trials were most frequently identified (n=66, 87%) with only 10 (13%) observational trials noted. Of the interventional trials, the majority were in the later stages of development; 10 (13%) in Phase 1, 1 (2%) between Phase 1 and 2, 9 (14%) in Phase 2, 3 (5%) between Phase 2 and 3, 10 (15%) in Phase 3 and 23 (35%) in Phase 4. Phase 4 is defined as CTs occurring after an antibiotic has been approved in children. In 10 (15%) of cases, a trial phase had not been specified.

Sponsor and Endpoint Classification

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%). The endpoint classification of the majority of trials (n=43, 57%) was reported as efficacy (Table 2). A greater proportion (n=34, 68%) of non-profit studies measured the efficacy of the drugs as the primary endpoint, with less emphasis on collection of PK or safety data (n=16, 32%). In comparison pharmaceutical-led trials focussed on early PK and safety studies over the drug's efficacy (n=17, 65% vs. n=9, 35% respectively).

Table 2. Clinical trial endpoint classification of identified clinical trials stratified by trial sponsor. Endpoint classification determined by planned primary outcomes.

Endpoint classification	Industry	Non-profit	Total (%)
Efficacy	9	34	43 (57)
Safety	10	2	12 (16)
PK	7	14	21 (28)

Geographic region

Of the 76 antibiotic trials identified, the most frequently recruiting geographic region was North America (n=34, 45%). 22 (29%) trials recruiting in Europe and 16 (21%) in Asia were identified, 6 (8%) in Latin America, 8 (11%) in Africa, and 5 (7%) in Oceania. The great majority of trials were recruiting in High Income Countries (HICs) (n=54, 71%), with fewer trials recruiting in Low Income Countries (LICs) (n=4, 5%), Lower Middle Income Countries (LMICs) (n=4, 5%), Upper Middle Income Countries (UMICs) (n=11, 14%) or a combination of UMICs and HICs (n=3, 4%).

Indication

The most common treatment indications investigated in the 76 antibiotic trials were Lower Respiratory Tract Infection (n=12, 16%) and Sepsis (n=11, 14%), followed by Upper Respiratory Tract Infection (n=8, 11%), Intra-abdominal Infection (IAI) (n=8, 11%), Urinary Tract Infection (UTI) (n=7, 9%), complicated Skin and Soft Tissue Infection (cSSTI) (n=6, 8%), CNS infection (n=3, 4%), and Bone and Joint infection (n=1, 1%) (Table 3). 18 (24%) trials were investigations of unspecified bacterial infections and these were mainly phase 1 PK studies.

Antibiotic class

The majority of antibiotics (n=47, 62%) being investigated were beta-lactams, followed by other antibiotic classes (J01X, including vancomycin, telavancin and dalbavancin) (n=21, 28%). Macrolides or lincosamides (J01F) were the next most commonly studied antibiotic classes (n=14, 18%). Very few of the records reported investigations of tetracyclines (J01A) (n=4, 5%), Sulphonamides and trimethoprim (J01E) (n=7, 9%), aminoglycosides (J01G) (n=2, 3%), or quinolones (J01M) (n=8, 11%). 2 CTs (3%) did not specify the class of antibiotic being investigated. 16 (21%) trials were investigating more than one antibiotic; these trials counted towards more than one J01 category. The breakdown of J01 categories is described in Figure 1.

Antibiotic pipeline

Of the 37 antibiotics listed on the most recent May 2016 edition of the Pew Charitable Trusts Antibiotic Pipeline (last accessed 10th June 2016),[13] as noted by the EMA Opinions and Decisions on Pediatric Investigation Plans, 5 had an agreed PIP: Imipenem/Cilastatin+Relebactam, Cadazolid, Carbavance (Meropenem+Vaborbactam), Eravacycline, and Solithromycin.[8] As of 8th November 2016, our search found that only 2 of the 37 antibiotics listed on the Pew antibiotic pipeline (Carbavance and Solithromycin) was being investigated in 1 and 2 on-going CTs in pediatric patients, respectively (Table 4). A PIP was agreed for Carbavance in 2015 for treatment of Gram-negative infections, and for Solithromycin in 2016 for the treatment of gonococcal infection, and later for treatment of anthrax, tularaemia, and bacterial pneumonia. PIPs were established in 2015 for treatment of urinary tract infection and complicated intra-abdominal infection with Eravacycline, and in 2016 for treatment of Clostridium difficile infection with Cadazolid and of Gram-negative bacterial infection with Imipenem/Cilastin+Relebactam.[14] Despite this, we could not identify any registered trials of these antibiotics in our search.

Table 3. Clinical indication of identified clinical trials stratified by age group being recruited.

Indication	Total (%)	Age group				
		Preterm neonates	Neonates[a]	Infants and toddlers	Children	Adolescents
Unspecified Bacterial Infection	18 (24)	-	11	15	15	14
Lower Respiratory Tract Infection	12 (16)	1	3	12	13	5
Sepsis	11 (14)	-	6	9	9	11
Upper Respiratory Tract	8 (11)	-	1	5	9	7
Intra-abdominal Infection	8 (11)	-	3	5	5	7
Urinary Tract Infection	7 (9)	-	2	6	7	6
Skin and Soft Tissue Infection	6 (8)	-	3	4	4	8
CNS infection	3 (4)	-	1	4	4	4
Bone and Joint Infection	1 (1)	-	-	1	1	1
		1	30	61	67	63

Age group totals do not add up to total number of clinical trials (76) as some trials contributed to more than one age group.
[a] refers to total number of preterm and term neonates.

Table 4. Comparison of antibiotic development pipeline in adults and children. Adapted from Pew Charitable Trusts "Antibiotics currently in clinical development" pipeline (last accessed October 2016).[13]

Antibiotic	Phase	Manufacturer	Indication	Drug development in Adults	Paediatric Investigation Plan for drug development in Children	Number of open clinical trials in children
WCK 4873	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
MGB – BP – 3	Phase 1	MGB Pharma Ltd.	Clostridium *difficile* infection	✓	-	-

OP0595	Phase 1	Meiji Seika Pharma Co. Fedora Pharmaceuticals	Bacterial infection	✓	-	-
BAL30072	Phase 1	Basilea Pharmaceuticals	Multidrug resistant gram negatives	✓	-	-
CRS3123	Phase 1	Crestone Inc.	Clostridium *difficile* infection	✓	-	-
LCB01 – 0371	Phase 1	Legochem Biosciences Inc.	Bacterial infection	✓	-	-
TD – 1607	Phase 1	Theravance Biopharma Inc.	Acute skin infection, HAP, VAP, bacteraemia	✓	-	-
WCK 2349	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
WCK 771	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
Zidebactam+Cefepime	Phase 1	Wockhardt Ltd.	cUTI, HAP, VAP	✓	-	-
TP – 271	Phase 1	Tetraphase Pharmaceuticals Inc.	CAP	✓	-	-
Aztreonam – Avibactam	Phase 2	Astrazeneca PLC Allergan PLC	cIAI	✓	-	-
MRX – 1	Phase 2	MicuRx Pharmaceuticals Inc.	Acute skin infection	✓	-	-
Debio 1450	Phase 2	Debiopharm International SA	Acute skin infection, Staphylococcus *spp*. associated osteomyelitis	✓	-	-

ETX0914	Phase 2	Entasis Therapeutics Inc.	Uncomplicated gonorrhea	✓	-	-
P0L7080	Phase 2	Polyphor Ltd.	Pseudomonas spp. associated VAP, lower respiratory tract infection, bronchiectasis	✓	-	-
Brilacidin	Phase 2	Cellceutix Corporation	Acute skin infection	✓	-	-
Ceftaroline+Avibactam	Phase 2	AstraZeneca PLC Allergan PLC	Bacterial infection	✓	-	-
CG400549	Phase 2	Crystal Genomics Inc.	Acute skin infection, osteomyleitis	✓	-	-
Finafloxacin	Phase 2	MerLion Pharmaceuticals Pte Ltd.	cUTI, cIAI, acute skin infection, pyelonephritis	✓	-	-
Geptidacin	Phase 2	GlaxoSmithKline PLC	cUTI, CAP, uncomplicated urogenital gonorrhea	✓	-	-
Nemonoxacin	Phase 2	TaiGen Biotechnology Co. Ltd.	CAP, acute skin infection, diabetic foot	✓	-	-
Ramoplanin	Phase 2	Nanotherapeutics Inc.	Prevent recurrent Clostridium *difficile* infection	✓	-	-
Ridinilazole	Phase 2	Summet Therapeutics Inc.	Clostridium *difficile*	✓	-	-
Zabofloxacin	Phase 3	Dong Wha Pharmaceuticals Co. Ltd.	CAP	✓	-	-
S – 649266	Phase 3	Shionogi Inc.	HAP, VAP, cUTI, bloodstream infection	✓	-	-

Omadacycline	Phase 3	Paratek Pharmaceuticals Inc.	CAP, cUTI, acute skin infection	✓	-	-
Lefamulin	Phase 3	Nabriva Therapeutics AC	CAP, HAP, VAP, acute skin infection, osteomyelitis, prosthetic joint infections	✓	-	-
Imipenem / Cilastatin+Relebactam	Phase 3	Merck & Co. Inc.	cUTI, cIAI, HAP, VAP, acute pyelonephritis	✓	✓	-
Iclaprim	Phase 3	Motif Bio PLC	HAP, acute skin infection	✓	-	-
Cadazolid	Phase 3	Actelion Pharmaceuticals Ltd.	Clostridium *difficile*	✓	✓	-
Taksta (fusidic acid)	Phase 3	Cempra Inc.	Acute skin infection, prosthetic joint infection	✓	-	-
Carbavance (Meropenem+Vaborbactam)	Phase 3	Rempex Pharmaceuticals Inc.	cUTI, cIAI, HAP, VAP, bacteraemia, pyelonephritis	✓	✓	1
Delafloxacin (Baxdela)	Phase 3	Melinta Therapeutics Inc.	CAP, cUTI, acute skin infections[a]	✓	Waiver granted	-
Eravacycline	Phase 3	Tetraphase Pharma Inc.	cIAI and cUTI	✓	✓	-
Plazomicin	Phase 3	Achaogen Inc.	cUTI, HAP, VAP, cIAI, catheter-associated bloodstream infection[a]	✓	-	-
Solithromycin	Phase 3	Cempra Inc.	CAP, uncomplicated urogenital gonorrhea, urethritis	✓	✓	2

HAP, hospital-acquired pneumonia; VAP, ventilator-acquired pneumonia; cUTI, complicated Urinary Tract Infection; CAP, Community-acquired pneumonia; cIAI, complicated Intra-abdominal Infection.
[a] target carbapenem resistant enterobacteriacae

DISCUSSION

Our search on *ClinicalTrials.gov* identified 76 clinical trials investigating one or more antibiotics recruiting children between 0 and 18 years of age. This is low in comparison to the number of on-going trials in adults, with children representing around a quarter of the global population.[15,16] A review of completed CTs in the U.S. between 2000 and 2010 identified a total of 4078 adult trials compared to just 294 that had recruited children.[17] In our study, the lack of trials recruiting neonates is striking. Just 23 of the 76 trials identified were recruiting neonates, and remarkably just 8 CTs globally were recruiting preterm neonates. There are broadly two types of pediatric trials being conducted globally. Either pharmaceutical-led Phase 1/2 PK and safety trials (n=17) being conducted in the HIC setting, or investigator led, often pragmatic, late phase efficacy trials in the LMIC setting (n=34), with a greater proportion of the on-going trials sponsored by non-profit organisations than industry (66% compared to 34%). As of April 2016, there were 17 agreed antibiotic PIPs agreed by the EMA,[8] covering a range of indications, most commonly cSSTI, complicated IAI (cIAI), and complicated UTI (cUTI).[14] In contrast, treatments for respiratory and systemic infections, the most common indications in pediatrics, do not appear to currently being evaluated.[18] Although the introduction of PIPs on the whole has encouraged the study of medicines in children, the range of infectious indications covered therefore does not match the burden of disease in this age group. Thirty-seven antibiotics are currently being developed in adults, yet to our knowledge just 2 of these are being studied in children. However, some classes of antibiotics that may be of higher risk for children (tetracyclines and fluoroquinolones) may not be pursued as aggressively for pediatric approvals by either industry or regulatory agencies. The substantial lag time is a real concern, particularly for new antibiotics against resistant Gram-negative pathogens, although there is some value in generating substantial safety data in adults prior to exposing children and newborn infants to potentially toxic new agents. However, Gram-negative sepsis is a growing problem in neonates, with a significant increase in the proportion of multi-resistant Gram-negative pathogens.[19]

In 2013, a similar review of European pediatric clinical trials identified 31 trials of antibiotics approved by the EMA in 2000 that were recruiting children in Europe (compared to the 22 trials we found to be now recruiting in this region). They similarly found a very small proportion of neonatal trials (just 2 of 31), as well as a greater proportion of efficacy-based trials.[10] In 2012, a review of interventional trials registered with *ClinicalTrials.gov* between 2007 and 2010 found that only 17% had recruited children below 18 years of age.[20] A similar review of antimicrobial CTs conducted in the U.S. between 2000 and 2012 reported that just 5% had recruited only children compared to the 74% that had recruited only adults, and that, as we have found, the trials were sponsored primarily by non-profit organisations (60% compared to 30% by industry).[17] In our search of global trials, 39% of registered CTs reported collection of PK data in comparison to a similar review in 2009 of

PK research on medicines for children that reported 24% of registered CTs would be collecting PK data.[21] Collection of PK data is particularly important in neonates where developmental differences in physiology lead to significant changes in drug PK, which puts them at increased risk of adverse drug reactions.[3,22] Furthermore, off-label and unlicensed prescribing is at its greatest in neonatal populations (61% and 22% respectively)[14]. A recent review noted a striking lack of harmonisation in study design and outcomes among completed and on-going neonatal and pediatric antibiotic CTs which may make translation of trial data into clinical guidance more difficult.[23]

The search strategy used has some limitations. Since the search was limited to clinical trials registered to *ClinicalTrials.gov*, it is possible that a number of open or on-going trials registered with alternative platforms (for example ICTRP) will have been missed. Together with *ClinicalTrials.gov* these could help to establish the entirety of current clinical research in this field. We did however search EudraCT, and found no further studies to those captured on *ClinicalTrials.gov*. Our search was also limited to open CTs, which means that active but not yet recruiting trials were not captured, as well as those that had closed to recruitment previously. The information recorded for each trial registered with *ClinicalTrials.gov* is updated by the trial investigators, and therefore relies on them to periodically update the registry. On occasion, information such as recruitment status might not be updated in real time.

Concerns around the growing threat of antimicrobial resistance have prompted a number of new initiatives. In 2016, the EMA published the first draft of the Concept Paper to propose the development of an Addendum to the guideline on the evaluation of new anti-bacterial products for treatment of bacterial infections in children.[24] At the same time, the Clinical Trials Transformation Initiative (CTTI) is currently focused on the identification of key barriers in the conduct of pediatric antibacterial CTs, which hamper their successful implementation into clinical practice.[25] Recent evidence states that overall, antibiotic CTs make up less than 1% of all registered pediatric CTs, and that trial completion is slow, with an average time to completion of around two years.[26]

CONCLUSIONS

A number of issues contribute to the difficulties in conducting pediatric antibiotic clinical trials. The lack of regulatory guidance, vulnerability of this population, issues with informed consent and assent, and lack of research-experienced hospital personnel all present challenges in study design, delivery and recruitment. Delays in the initial start-up of CTs in pediatrics due to pediatric-specific protocol issues and complicated ethical approval continue to discourage both academic and pharmaceutical interest. The limited data presented here suggests that the dismal state of ongoing

pediatric antibiotic trials is still continuing. Earlier collaboration between academic research networks and pharmaceutical companies is now vital to accelerate progress.

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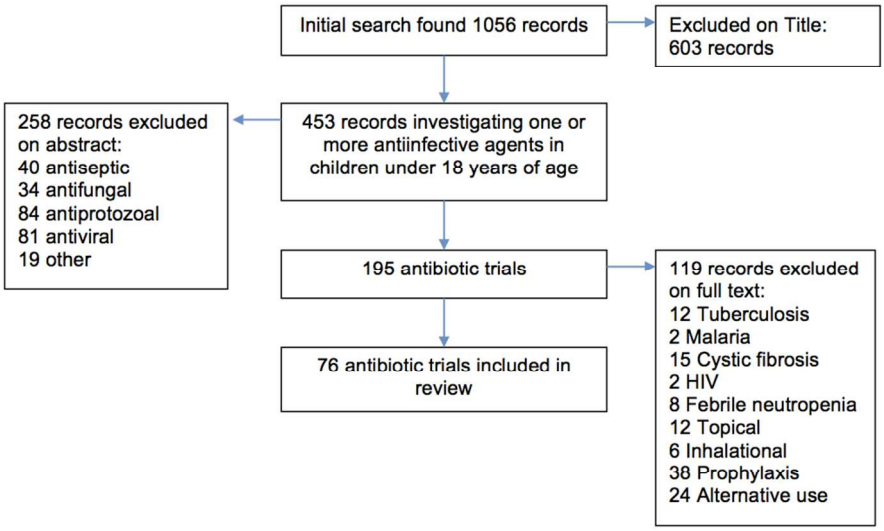

Figure 1. Flow chart. Clinical trial selection process.

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A global shortage of neonatal and pediatric antibiotic trials: a narrative review.

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A global shortage of neonatal and pediatric antibiotic trials: a narrative review.

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ABSTRACT

Objectives: There have been few clinical trials (CTs) on antibiotics which inform neonatal and pediatric drug labelling. Consequently, the rate of unlicensed and off-label prescribing in pediatrics remains high. This remains a major concern, particularly in neonates. It is unclear whether the current pediatric antibiotic research pipeline is adequate to inform optimal drug dosing. Using ClinicalTrials.gov registry, this review aims to establish the current global status of antibiotic CTs in children up to 18 years of age.

Results: Only 76 registered open CTs of antibiotics in children were identified globally; 23 (30%) were recruiting newborns (only 8 (11%) included preterm neonates), 52 (68%) infants and toddlers, 58 (76%) children, and 54 (71%) adolescents. The majority of registered trials were late phase (10 (15%) Phase 3 and 23 (35%) Phase 4/pharmacovigilance). Two-thirds were sponsored by non-profit organisations, with few sponsored by pharmaceutical companies (50 (66%) vs. 26 (34%) respectively). A greater proportion of non-profit funded trials were efficacy-based strategic trials (n= 34, 68%), in comparison to industry-led trials, which were most often focused on safety or pharmacokinetic data (n=17, 65%). Our search revealed that 2 of the 37 antibiotics listed on the May 2016 Pew Charitable Trusts antibiotic development pipeline, currently being studied in adults, appear to be recruiting in open pediatric CTs.

Conclusions: This review highlights that there are currently very few pediatric antibiotic CTs being conducted globally (especially in neonates). There is striking disparity noted between antibiotic drug development programmes involving adults and children.

Strengths and limitations of this study

- A narrative literature review of registered clinical trials in children.
- Explicit reproducible methodology.
- Search strategy limited to ClinicalTrials.gov and EudraCT. Entirety of clinical research in this field might not have been captured.
- Search strategy also limited to open clinical trials. Active but not yet recruiting trials were not captured.

INTRODUCTION

With the persistence of widespread unlicensed and off-label prescribing in pediatrics – as high as 11.4% and 46.5% respectively – the paucity of clinical research involving children that which is conducted to inform optimal drug dosing, licensing and labelling remains a problem.[1] For certain medicines, drug efficacy can be extrapolated from adult data provided that the pathology and drug exposure are the same, or sufficiently similar in children as in adults.[2,3] Advances in modelling and simulation mean smaller focussed studies can now be performed to help obtain regulatory

approval for most medicines, including antimicrobials.[4] Although differences in drug pharmacokinetics (PK) in neonates and children can lead to adverse reactions that are not seen in adult populations, these are very rare and extrapolation of safety data into the pediatric population can further reduce the need for complex study designs.[5] Suboptimal antibiotic dosing, including under- and over-dosing, can lead to toxicity, treatment failure, and may drive antimicrobial resistance by encouraging selection pressures on drug-resistant strains of bacteria.[6]

Since antibiotics are the most commonly prescribed medicines in children, it is important to improve our currently limited understanding of their PK profiles to help determine optimal drug dosing and ultimately to improve patient outcomes.[7] In the last decade several initiatives have been established to encourage pediatric medicines research, thus bridge the gap between adult and pediatric drug development plans. Such initiatives include the Pediatric Regulation (Pediatric Investigation Plans (PIPs), introduced by the European Medicines Agency (EMA),[8] and Pediatric Study Plans (PSPs), by the U.S. Food and Drug Administration (FDA).[9] Despite this, there remain limited advances in the development of antibiotics for this population.[10]

The global status of clinical research on antibiotics in pediatrics is currently unknown. Using registered records of clinical trials (CTs) on *ClinicalTrials.gov*, this review aims (i) to summarise the current global status of registered antibiotic research in children and neonates, and (ii) to stimulate discussion and collaboration among the relevant stakeholders on the neglect of antibiotic research in pediatrics.

METHODS

Data sources

The *ClinicalTrials.gov* registry (last accessed 8th November 2016) is an international platform for the registration of CTs. It is a web-based registry, developed in 2000 by the National Institute of Health (NIH) and the FDA, to which trials from 50 states and 163 countries around the world are registered. All information provided for each trial is updated periodically by the trial's sponsoring organisation. The database has a specific child filter, which uses a key word paradigm to select all registered trials recruiting patients/participants up to 18 years of age.

We were not able to capture all studies being planned in neonates, infants, and children by pharmaceutical companies in compliance with legislation that mandates studies of any drugs under investigation in adults that may have clinical utility in children. Discussions between companies and regulatory agencies are confidential, limiting our ability to fully understand the impact of the PIPs and PSP's noted above on antimicrobial compounds under development.

Study selection

Our records were identified using suitable key word searches, in which the final search terms were (antimicrobial* OR antibiotic* OR antiinfective agent*) AND Child AND Open Studies. All identified trials were filtered manually using inclusion and exclusion criteria. Interventional and observational trials on antimicrobials recruiting children up to 18 years of age were considered eligible for inclusion. No specific temporal filter was applied since only open or ongoing clinical trials were of interest. The following records, which were not investigating one or more antibiotics, were excluded: trials of antiseptics, antifungals, antiprotozoals, antivirals, and pro- or pre- biotics. The following records, which were investigating an antibiotic were excluded: trials involving tuberculosis, malaria, cystic fibrosis, HIV, febrile neutropenic patients, topical or inhalational treatments, prophylactic antibiotics, or records investigating alternative use for antibiotics (for example as an anti-inflammatory agent).

The searches were conducted by GT. All eligible records were identified via manual filtering by GT CB, LF and MS, and any disagreements regarding inclusion and exclusion of records were resolved through discussion.

Data extraction

The following information was collected from the included records: unique NCT number, recruitment status, study design, trial phase, study sponsor, age group and sex eligibility, clinical indication, geographic region of recruitment, antibiotic being investigated, and endpoint classification. Outcomes were categorised as safety, efficacy or PK. Economic setting (based on geographic region of recruitment) was classified using The World Bank classification, where Low Income Countries (LICs) are defined as those with $1,025 or less gross national income per capita, Lower Middle Income Countries (LMICs) $1,026 – 4,035, Upper Middle Income Countries (UMICs) $4,036 – 12,475, and High Income Countries (HICs) $12,476 or more.[11]

The specific class of antibiotic studied in each trial was identified and classified using the World Health Organisation (WHO) ATC/DDD index.[12] To investigate whether novel antibiotics are being studied in pediatric and neonatal populations (as well as in adults), the antibiotics currently studied in children were compared with the *Pew Charitable Trusts Antibiotics Currently in Clinical Development* pipeline, which identifies novel antibiotics currently under development for the U.S. market.[13]

RESULTS

Our search identified 1056 records. 603 records were excluded on title because they were studies not involving an antimicrobial. 453 records were investigating one or more antimicrobials and

recruiting children below 18 years of age. Among the 195 trials investigating antibiotics, 76 fulfilled our inclusion and exclusion criteria and were included in the final analysis. Reasons for exclusion are summarised in Figure 1. Details of included studies can be found in Supplementary file 1.

All 76 CTs identified were open as of 8th November 2016, and 63 (83%) of these were recognised as recruiting participants on this date (Table 1). All trials stated recruitment of both male and female participants.

Table 1. Characteristics of clinical trials.

Characteristic	Category	Number of studies, n (%)
Age group	Preterm neonates	1 (1)[a]
	Neonates (total)	23 (30)
	Infants and toddlers	52 (68)
	Children	58 (76)
	Adolescents	54 (71)
Recruitment status	Recruiting	63 (83)
	Not yet recruiting	13 (17)
Study design	Interventional	66 (87)
	Observational	10 (13)
Trial phase[b]	Phase 1	10 (15)
	Phase 1-2	1 (2)
	Phase 2	9 (14)
	Phase 2-3	3 (5)
	Phase 3	10 (15)
	Phase 4	23 (39)
	Not specified	10 (15)
Sponsor	Industry	26 (34)
	Non-profit	50 (66)
Geographic region	Africa	8 (11)
	Asia	16 (21)
	Europe	22 (29)
	Latin America	6 (8)
	North America	34 (45)
	Oceania	5 (7)
Antibiotic class	J01A Tetracycline	4 (5)
	J01C Beta-lactam, Penicillin	25 (33)
	J01D Other Beta-lactam	22 (29)
	J01E Sulfonamides and trimethoprim	7 (9)
	J01F Macrolide, Lincosamide, Streptogramin	14 (18)
	J01G Aminoglycoside	2 (3)
	J01M Quinolone	8 (11)
	J01X Other antibiotic classes[c]	21 (28)
	J01 Not specified	2 (3)

Totals for Age group, Geographic region, and Antibiotic class do not add up to total number of clinical trials (76) as some trials contributed to more than one sub group.
[a] 7 further trials mentioned inclusion of preterm babies in the inclusion criteria.
[b] Trial phase % based on percentage of interventional trials.
[c] J01X includes glycopeptides, polymixins, imidazole derivatives, and nitrofuran

Age group

Twenty three of the 76 trials (30%) were recruiting newborns (0 to 28 days). One of these 23 trials focused solely on recruiting preterm newborns (a further 7 CTs mentioned inclusion of preterm newborns in inclusion criteria). Of the remaining records, 52 (68%) were recruiting infants and toddlers (28 days to 23 months), 58 (76%) children (2 to 11 years), and 54 (71%) adolescents (11 up to 18 years). 29 (38%) trials did not focus solely on the recruitment of children or neonates, with age ranges also spanning across adult populations.

Study type

Interventional trials were most frequently identified (n=66, 87%) with only 10 (13%) observational trials noted. Of the interventional trials, the majority were in the later stages of development; 10 (13%) in Phase 1, 1 (2%) between Phase 1 and 2, 9 (14%) in Phase 2, 3 (5%) between Phase 2 and 3, 10 (15%) in Phase 3 and 23 (35%) in Phase 4. In 10 (15%) cases, a trial phase had not been specified.

Sponsor and Endpoint Classification

Fifty (66%) trials were sponsored by non-profit organisations (being university, hospital or government funded), and 26 sponsored by industry (34%). The endpoint classification of the majority of trials (n=43, 57%) was reported as efficacy (Table 2). A greater proportion (n=34, 68%) of non-profit studies measured the efficacy of the drugs as the primary endpoint, with less emphasis on collection of PK or safety data (n=16, 32%). In comparison pharmaceutical-led trials focussed on early PK and safety studies over the drug's efficacy (n=17, 65% vs. n=9, 35% respectively).

Table 2. Clinical trial endpoint classification of identified clinical trials stratified by trial sponsor. Endpoint classification determined by planned primary outcomes.

Endpoint classification	Industry	Non-profit	Total (%)
Efficacy	9	34	43 (57)
Safety	10	2	12 (16)
PK	7	14	21 (28)

Geographic region

The most frequently recruiting geographic region was North America (n=34, 45%). 22 (29%) trials recruiting in Europe and 16 (21%) in Asia were identified, 6 (8%) in Latin America, 8 (11%) in Africa, and 5 (7%) in Oceania. Most trials were recruiting in HICs (n=54, 71%), with fewer trials recruiting in

LICs (n=4, 5%), LMICs (n=4, 5%), UMICs (n=11, 14%) or a combination of UMICs and HICs (n=3, 4%).

Indication

The most common treatment indications investigated were Lower Respiratory Tract Infection (n=12, 16%) and Sepsis (n=11, 14%), followed by Upper Respiratory Tract Infection (n=8, 11%), Intra-abdominal Infection (IAI) (n=8, 11%), Urinary Tract Infection (UTI) (n=7, 9%), complicated Skin and Soft Tissue Infection (cSSTI) (n=6, 8%), CNS infection (n=3, 4%), and Bone and Joint infection (n=1, 1%) (Table 3).

Antibiotic class

The majority of antibiotics (n=47, 62%) being investigated were beta-lactams, followed by other antibiotic classes (J01X, including vancomycin, telavancin and dalbavancin) (n=21, 28%). Macrolides or lincosamides (J01F) were the next most commonly studied antibiotic classes (n=14, 18%). Very few of the records reported investigations of tetracyclines (J01A) (n=4, 5%), Sulphonamides and trimethoprim (J01E) (n=7, 9%), aminoglycosides (J01G) (n=2, 3%), or quinolones (J01M) (n=8, 11%). 2 CTs (3%) did not specify the class of antibiotic being investigated. 16 (21%) trials were investigating more than one antibiotic; these trials counted towards more than one J01 category. The breakdown of J01 categories, as per WHO ATC/DDD classification,[12] is described in Table 1.

Antibiotic pipeline

Of the 37 antibiotics listed on the most recent May 2016 edition of the Pew Charitable Trusts Antibiotic Pipeline (last accessed 10th June 2016),[13] as noted by the EMA Opinions and Decisions on Pediatric Investigation Plans, 5 had an agreed PIP: Imipenem/Cilastatin+Relebactam, Cadazolid, Carbavance (Meropenem+Vaborbactam), Eravacycline, and Solithromycin.[8] As of 8th November 2016, our search found that only 2 of the 37 antibiotics listed on the Pew antibiotic pipeline (Carbavance and Solithromycin) was being investigated in 1 and 2 on-going CTs in pediatric patients, respectively (Table 4). A PIP was agreed for Carbavance in 2015 for treatment of Gram-negative infections, and for Solithromycin in 2016 for the treatment of gonococcal infection, and later for treatment of anthrax, tularaemia, and bacterial pneumonia. PIPs were agreed in 2015 for treatment of urinary tract infection and complicated intra-abdominal infection with Eravacycline, and in 2016 for treatment of Clostridium difficile infection with Cadazolid and of Gram-negative bacterial infection with Imipenem/Cilastin+Relebactam.[14] Despite this, we could not identify any registered trials of these antibiotics in our search.

Table 3. Clinical indication of identified clinical trials stratified by age group being recruited.

Indication	Total (%)	Age group				
		Preterm neonates	Neonates[a]	Infants and toddlers	Children	Adolescents
Unspecified Bacterial Infection	18 (24)	-	11	15	15	14
Lower Respiratory Tract Infection	12 (16)	1	3	12	13	5
Sepsis	11 (14)	-	6	9	9	11
Upper Respiratory Tract	8 (11)	-	1	5	9	7
Intra-abdominal Infection	8 (11)	-	3	5	5	7
Urinary Tract Infection	7 (9)	-	2	6	7	6
Skin and Soft Tissue Infection	6 (8)	-	3	4	4	8
CNS infection	3 (4)	-	1	4	4	4
Bone and Joint Infection	1 (1)	-	-	1	1	1
		1	30	61	67	63

Age group totals do not add up to total number of clinical trials (76) as some trials contributed to more than one age group.
[a] refers to total number of preterm and term neonates.

Table 4. Comparison of antibiotic development pipeline in adults and children. Adapted from Pew Charitable Trusts "Antibiotics currently in clinical development" pipeline (last accessed October 2016).[13]

Antibiotic	Phase	Manufacturer	Indication	Drug development in Adults	Paediatric Investigation Plan for drug development in Children	Number of open clinical trials in children
WCK 4873	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
MGB – BP – 3	Phase 1	MGB Pharma Ltd.	Clostridium *difficile* infection	✓	-	-

OP0595	Phase 1	Meiji Seika Pharma Co. Fedora Pharmaceuticals	Bacterial infection	✓	-	-
BAL30072	Phase 1	Basilea Pharmaceuticals	Multidrug resistant gram negatives	✓	-	-
CRS3123	Phase 1	Crestone Inc.	Clostridium *difficile* infection	✓	-	-
LCB01 – 0371	Phase 1	Legochem Biosciences Inc.	Bacterial infection	✓	-	-
TD – 1607	Phase 1	Theravance Biopharma Inc.	Acute skin infection, HAP, VAP, bacteraemia	✓	-	-
WCK 2349	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
WCK 771	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
Zidebactam+Cefepime	Phase 1	Wockhardt Ltd.	cUTI, HAP, VAP	✓	-	-
TP – 271	Phase 1	Tetraphase Pharmaceuticals Inc.	CAP	✓	-	-
Aztreonam – Avibactam	Phase 2	Astrazeneca PLC Allergan PLC	cIAI	✓	-	-
MRX – 1	Phase 2	MicuRx Pharmaceuticals Inc.	Acute skin infection (systemic)	✓	-	-

Debio 1450	Phase 2	Debiopharm International SA	Acute skin infection, Staphylococcus *spp*. associated osteomyelitis	✓	-	-
ETX0914	Phase 2	Entasis Therapeutics Inc.	Uncomplicated gonorrhoea	✓	-	-
P0L7080	Phase 2	Polyphor Ltd.	Pseudomonas spp. associated VAP, lower respiratory tract infection, bronchiectasis	✓	-	-
Brilacidin	Phase 2	Cellceutix Corporation	Acute skin infection (systemic)	✓	-	-
Ceftaroline+Avibactam	Phase 2	AstraZeneca PLC Allergan PLC	Bacterial infection	✓	-	-
CG400549	Phase 2	Crystal Genomics Inc.	Acute skin infection, osteomyelitis	✓	-	-
Finafloxacin	Phase 2	MerLion Pharmaceuticals Pte Ltd.	cUTI, cIAI, acute skin infection, pyelonephritis	✓	-	-
Geptidacin	Phase 2	GlaxoSmithKline PLC	cUTI, CAP, uncomplicated urogenital gonorrhoea	✓	-	-
Nemonoxacin	Phase 2	TaiGen Biotechnology Co. Ltd.	CAP, acute skin infection, diabetic foot	✓	-	-
Ramoplanin	Phase 2	Nanotherapeutics Inc.	Prevent recurrent Clostridium *difficile* infection	✓	-	-
Ridinilazole	Phase 2	Summet Therapeutics Inc.	Clostridium *difficile*	✓	-	-

Zabofloxacin	Phase 3	Dong Wha Pharmaceuticals Co. Ltd.	CAP	✓	-	-
S – 649266	Phase 3	Shionogi Inc.	HAP, VAP, cUTI, bloodstream infection	✓	-	-
Omadacycline	Phase 3	Paratek Pharmaceuticals Inc.	CAP, cUTI, acute skin infection	✓	-	-
Lefamulin	Phase 3	Nabriva Therapeutics AC	CAP, HAP, VAP, acute skin infection, osteomyelitis, prosthetic joint infections	✓	-	-
Imipenem / Cilastatin+Relebactam	Phase 3	Merck & Co. Inc.	cUTI, cIAI, HAP, VAP, acute pyelonephritis	✓	✓	-
Iclaprim	Phase 3	Motif Bio PLC	HAP, acute skin infection	✓	-	-
Cadazolid	Phase 3	Actelion Pharmaceuticals Ltd.	Clostridium *difficile*	✓	✓	-
Taksta (fusidic acid)	Phase 3	Cempra Inc.	Acute skin infection, prosthetic joint infection	✓	-	-
Carbavance (Meropenem+Vaborbactam)	Phase 3	Rempex Pharmaceuticals Inc.	cUTI, cIAI, HAP, VAP, febrile neutropenia, bacteraemia, acute pyelonephritis[a]	✓	✓	1
Delafloxacin (Baxdela)	Phase 3	Melinta Therapeutics Inc.	Acute skin infections, CAP, cUTI	✓	Waiver granted	-
Eravacycline	Phase 3	Tetraphase Pharma Inc.	cIAI and cUTI	✓	✓	-
Plazomicin	Phase 3	Achaogen Inc.	cUTI, HAP, VAP, cIAI, catheter-associated bloodstream infection[a]	✓	-	-

Solithromycin	Phase 3	Cempra Inc.	CAP, uncomplicated urogenital gonorrhea, urethritis	✓	✓	2

HAP, hospital-acquired pneumonia; VAP, ventilator-acquired pneumonia; cUTI, complicated Urinary Tract Infection; CAP, Community-acquired pneumonia; cIAI, complicated Intra-abdominal Infection.
[a] target carbapenem resistant enterobacteriacae

DISCUSSION

Our search on *ClinicalTrials.gov* identified 76 clinical trials investigating one or more antibiotics recruiting children between 0 and 18 years of age. This is low in comparison to the number of on-going trials in adults, with children representing around a quarter of the global population.[15,16] A review of completed CTs in the U.S. between 2000 and 2010 identified a total of 4078 adult trials compared to just 294 that had recruited children.[17] In our study, the lack of trials recruiting neonates is striking. Just 23 of the 76 trials identified were recruiting neonates, and remarkably just 8 CTs globally were recruiting preterm neonates. There are broadly two types of pediatric trials being conducted globally. Either pharmaceutical-led Phase 1/2 PK and safety trials (n=17) being conducted in the HIC setting, or investigator led, often pragmatic, late phase efficacy trials in the LMIC setting (n=34), with a greater proportion of the on-going trials sponsored by non-profit organisations than industry (66% compared to 34%). The rarity of bacterial infections in children, and the ethical and practical barriers to running paediatric trials likely act as deterrents to pharmaceutical interest, resulting in academic investigators focusing on the larger efficacy trials. As of April 2016, there were 17 antibiotic PIPs agreed by the EMA,[8] covering a range of indications, most commonly cSSTI, complicated IAI (cIAI), and complicated UTI (cUTI).[14] In contrast, treatments for respiratory and systemic infections, the most common indications in pediatrics, are not currently being evaluated.[18] Although the introduction of PIPs on the whole has encouraged the study of medicines in children, the range of infectious indications covered therefore does not match the burden of disease in this age group. Thirty-seven antibiotics are currently being developed in adults, yet to our knowledge just 2 of these are being studied in children. However, some classes of antibiotics that may be of higher risk for children (tetracyclines and fluoroquinolones) may not be pursued as aggressively for pediatric approvals by either industry or regulatory agencies due to well-recognized issues of toxicity, particularly relevant in situations for which safer alternative therapy is widely available. The substantial lag time between the submission date (for PIP or waiver) and declared date of completion of PK studies in adults is a real concern, particularly for new antibiotics against resistant Gram-negative pathogens, although there is some value in generating substantial safety data in adults prior to exposing children and newborn infants to potentially toxic new agents. However, Gram-negative sepsis is a growing problem in neonates, with a significant increase in the proportion of multi-resistant Gram-negative pathogens.[19]

In 2013, a similar review of European pediatric clinical trials identified 31 trials of antibiotics approved for adults by the EMA in 2000 that were recruiting children in Europe (compared to the 22 trials we found to be now recruiting in this region). They included both published and ongoing trials, which likely accounts for the higher number of trials reported. They similarly found a very small proportion of neonatal trials (just 2 of 31), as well as a greater proportion of efficacy-based trials.[10] In 2012, a review of interventional trials registered with *ClinicalTrials.gov* between 2007 and 2010

found that only 17% had recruited children below 18 years of age.[20] A similar review of antimicrobial CTs conducted in the U.S. between 2000 and 2012 reported that just 5% had recruited only children compared to the 74% that had recruited only adults, and that, as we have found, the trials were sponsored primarily by non-profit organisations (60% compared to 30% by industry).[17] In our search of global trials, 39% of registered CTs reported collection of PK data in comparison to a similar review in 2009 of PK research on medicines for children that reported 24% of registered CTs would be collecting PK data.[21] Collection of PK data is particularly important in neonates where developmental differences in physiology lead to significant changes in drug PK, which puts them at increased risk of adverse drug reactions.[3,22] Furthermore, off-label and unlicensed prescribing is at its greatest in neonatal populations (61% and 22% respectively)[14]. A recent review noted a striking lack of harmonisation in study design and outcomes among completed and on-going neonatal and pediatric antibiotic CTs which may make translation of trial data into clinical guidance more difficult.[23]

The search strategy used has some limitations. Since the search was limited to clinical trials registered to *ClinicalTrials.gov*, it is possible that a number of open or on-going trials registered with alternative platforms (for example, the WHO International Clinical Trials Registry Platform [ICTRP]) will have been missed. Together with *ClinicalTrials.gov* these could help to establish the entirety of current clinical research in this field. We did however search EudraCT, and found no further studies to those captured on *ClinicalTrials.gov*. Our search was also limited to open CTs, which means that active but not yet recruiting trials were not captured, as well as those that had closed to recruitment previously. The information recorded for each trial registered with *ClinicalTrials.gov* is updated by the trial investigators, and therefore relies on them to periodically update the registry. On occasion, information such as recruitment status might not be updated in real time.

Concerns around the growing threat of antimicrobial resistance have prompted a number of new initiatives. In 2016, the EMA published the first draft of the Concept Paper to propose the development of an Addendum to the guideline on the evaluation of new anti-bacterial products for treatment of bacterial infections in children.[24] At the same time, the Clinical Trials Transformation Initiative (CTTI) is currently focused on the identification of key barriers in the conduct of pediatric antibacterial CTs, which hamper their successful implementation into clinical practice.[25] Recent evidence states that overall, antibiotic CTs make up less than 1% of all registered pediatric CTs, and that trial completion is slow, with an average time to completion of around two years.[26] There are a number of specific areas where there is potential for harmonisation and simplification in the design and conduct of paediatric antibiotic CTs. Standardisation of the inclusion and exclusion criteria for specific Clinical Infection Syndromes, and an improved bridging of safety and efficacy

data from other age groups, would allow improved comparison between studies, and potentially more simplified design of CTs, both of which will improve their conduct and efficiency in children.

CONCLUSIONS

A number of issues contribute to the difficulties in conducting pediatric antibiotic clinical trials. The lack of regulatory guidance, vulnerability of this population, issues with informed consent and assent, and lack of research-experienced hospital personnel all present challenges in study design, delivery and recruitment. Delays in the initial start-up of CTs in pediatrics due to pediatric-specific protocol issues and complicated ethical approval continue to discourage both academic and pharmaceutical interest. The limited data presented here suggests that the dismal state of ongoing pediatric antibiotic trials is still continuing. Earlier collaboration between academic research networks and pharmaceutical companies is now vital to accelerate progress.

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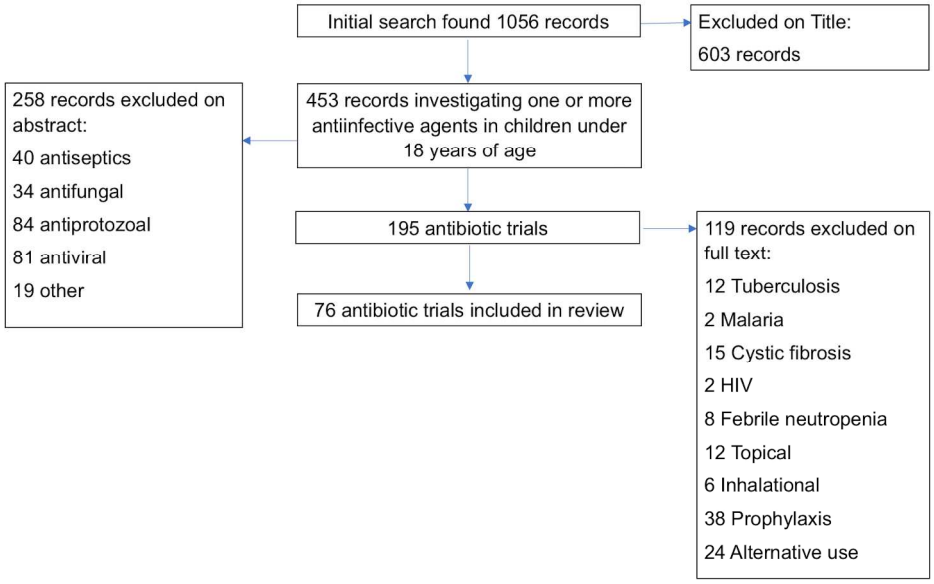

Figure 1. Flow Chart. Clinical trial selection process.

254x190mm (300 x 300 DPI)

DATASET

	A	B	C	D
1	**NCT Number**	**Title**	**Recruitment**	**Study Results**
2	NCT02539407	Population Pharmacokinetics of Anti-infectives in Critically Ill Children	Recruiting	No Results Available
3	NCT02935374	Effect of Antimicrobial Treatment of Acute Otitis Media on the Intestinal Microbiome in Children	Not yet recruiting	No Results Available
4	NCT02899143	Short-course Antimicrobial Therapy in Sepsis	Recruiting	No Results Available
5	NCT01595529	The SCOUT Study: Short Course Therapy for Urinary Tract Infections in Children	Recruiting	No Results Available
6	NCT02380352	Short-course Antimicrobial Therapy for Paediatric Respiratory Infections	Not yet recruiting	No Results Available
7	NCT02891915	Trial to Evaluate Beta-Lactam Antimicrobial Therapy of Community Acquired Pneumonia in Child	Recruiting	No Results Available
8	NCT02746276	Optimising Antibiotic Treatment for Sick Malnourished Children	Recruiting	No Results Available
9	NCT02917551	BALANCE on the Wards: A Pilot RCT	Not yet recruiting	No Results Available
10	NCT01243437	A Clinical Trial to Evaluate the Safety and Efficacy of Ciprofloxacin in the Treatment of Plague in	Recruiting	No Results Available
11	NCT02635191	Tailored Therapy for Helicobacter Pylori in Children	Recruiting	No Results Available
12	NCT01522105	Daptomycin in Pediatric Patients With Bacterial Meningitis	Recruiting	No Results Available
13	NCT02456974	Antibiotic Dosing in Pediatric Intensive Care	Recruiting	No Results Available
14	NCT00579956	A Randomized Double Blinded Comparison of Ceftazidime and Meropenem in Severe Melioidosis	Recruiting	No Results Available
15	NCT00545961	Middle Meatal Bacteriology During Acute Respiratory Infection in Children	Not yet recruiting	No Results Available
16	NCT01431326	Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care	Recruiting	No Results Available
17	NCT02475876	PK of Clindamycin and Trimethoprim-sulfamethoxazole in Infants and Children	Recruiting	No Results Available
18	NCT01420341	Co-trimoxazole as Maintenance Therapy for Meliodosis	Recruiting	No Results Available
19	NCT02266706	Pharmacokinetic and Safety Study of Ceftolozane/Tazobactam in Pediatric Participants Receiving	Recruiting	No Results Available
20	NCT00867789	Antibiotics Versus Placebo in the Treatment of Abscesses in the Emergency Department	Recruiting	No Results Available
21	NCT02879981	A Safety Study of Balsamic Bactrim in Pediatric Participants With Acute Bronchitis	Not yet recruiting	No Results Available
22	NCT01269541	MESS-study MRSA Eradication Study Skl´ne	Recruiting	No Results Available
23	NCT02276482	Study of Tedizolid Phosphate in Adolescents With Complicated Skin and Soft Tissue Infections (cS	Recruiting	No Results Available
24	NCT02663596	Safety and TDM of Continuous Infusion Vancomycin Through Continuous Renal Replacement Th	Not yet recruiting	No Results Available
25	NCT02555059	Special Drug Use Investigation of Ciproxan Injection in Pediatrics	Recruiting	No Results Available
26	NCT02297815	Comparative Effectiveness of Antibiotics for Respiratory Infections	Recruiting	No Results Available
27	NCT02224040	Typhoid Fever: Combined vs. Single Antibiotic Therapy	Recruiting	No Results Available
28	NCT02775968	Population Pharmacokinetics of Cephalosporins and Macrolides in Chinese Children With Comm	Not yet recruiting	No Results Available
29	NCT02687906	Dose-finding, Pharmacokinetics, Safety, and Tolerability of Meropenem-Vaborbactam in Pediatr	Recruiting	No Results Available
30	NCT02783859	Hospitalised Pneumonia With Extended Treatment (HOPE) Study	Recruiting	No Results Available
31	NCT01994993	Antibiotic Safety (SCAMP)	Recruiting	No Results Available

	A	B	C	D
32	NCT02258763	Trial on the Ideal Duration of Oral Antibiotics in Children With Pneumonia	Recruiting	No Results Available
33	NCT02688790	Study Evaluate the PK Profile of Dalbavancin in Hospitalized Infants and Neonates Patients With	Recruiting	No Results Available
34	NCT00323219	Oral Moxifloxacin Versus Cefazolin and Oral Probenecid in the Management of Skin and Soft Tiss	Recruiting	No Results Available
35	NCT02750761	A Study of Oral and Intravenous (IV) Tedizolid Phosphate in Hospitalized Participants, Ages 2 to	Recruiting	No Results Available
36	NCT02466438	Safety and Pharmacokinetics of Piperacillin-tazobactam Extended Infusion in Infants and Childre	Recruiting	No Results Available
37	NCT02260102	Temocillin Pharmacokinetics in Paediatrics	Not yet recruiting	No Results Available
38	NCT02694458	Comparison of Two Dosage Adjustment Strategies of Vancomycin in Children	Recruiting	No Results Available
39	NCT01540838	Slow Initial beta-lactam Infusion With High-dose Paracetamol to Improve the Outcomes of Child	Recruiting	No Results Available
40	NCT00368498	A Trial to Evaluate the Loading Dose Required to Achieve Therapeutic Serum Teicoplanin Concer	Recruiting	No Results Available
41	NCT01785641	Single Versus Combined Antibiotic Therapy for Bacterial Peritonitis in CAPD Patients	Recruiting	No Results Available
42	NCT02554383	Efficacy of Antibiotics in Children With Acute Sinusitis: Which Subgroups Benefit?	Recruiting	No Results Available
43	NCT01265173	Comparison of Efficacy of Cefotaxime, Ceftriaxone, and Ciprofloxacin for the Treatment of Spont	Recruiting	No Results Available
44	NCT02335905	Ceftaroline for Treatment of Hematogenously Acquired Staphylococcus Aureus Osteomyelitis in	Recruiting	No Results Available
45	NCT02922686	Penicillin for the Emergency Department Outpatient Treatment of CELLulitis	Not yet recruiting	No Results Available
46	NCT02848820	Initial Non-operative Treatment Strategy Versus Appendectomy Treatment Strategy for Simple A	Not yet recruiting	No Results Available
47	NCT02475733	Evaluation of Safety,Pharmacokinetics and Efficacy of CAZ-AVI With Metronidazole in Children A	Recruiting	No Results Available
48	NCT02372461	Randomized Trial of Amoxicillin Versus Placebo for (Fast Breathing) Pneumonia	Recruiting	No Results Available
49	NCT01553006	Study of Cefditoren Pivoxil in Treatment of Childhood With Acute Rhinosinusitis	Recruiting	No Results Available
50	NCT02527681	Pharmacokinetics and Safety of Ceftobiprole in Neonates and Infants up to 3 Months Treated W	Recruiting	No Results Available
51	NCT02210169	RCT of Continuous Versus Intermittent Infusion of Vancomycin in Neonates	Recruiting	No Results Available
52	NCT02497781	Evaluation of Safety, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam (CAZ-AVI) Co	Recruiting	No Results Available
53	NCT02814916	Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Children,	Not yet recruiting	No Results Available
54	NCT02210325	Efficacy and Safety Study of Oral Solithromycin Compared to Intramuscular Ceftriaxone Plus Ora	Recruiting	No Results Available
55	NCT02801370	Phase 3 Study of OTO-201 in Acute Otitis Externa	Recruiting	No Results Available
56	NCT02760420	3 Days Amoxicillin Versus Placebo for Fast Breathing Childhood Pneumonia in Malawi	Recruiting	No Results Available
57	NCT02678195	3 Days Versus 5 Days Amoxicillin for Chest-indrawing Childhood Pneumonia in Malawi	Recruiting	No Results Available
58	NCT02605122	Safety and Efficacy of Solithromycin in Adolescents and Children With Community-acquired Bact	Recruiting	No Results Available
59	NCT02570490	Oral Sodium Fusidate (CEM-102) Versus Oral Linezolid for the Treatment of Acute Bacterial Skin	Recruiting	No Results Available
60	NCT02443285	Is Spontaneous Bacterial Peritonitis Still Responding to 3rd Generation Cephalosporins?	Recruiting	No Results Available
61	NCT02334124	Comparing the Intravenous Treatment of Skin Infections in Children, Home Versus Hospital	Recruiting	No Results Available
62	NCT02218372	A Study to Investigate the Safety and Efficacy of Fidaxomicin (Oral Suspension or Tablets) and Va	Recruiting	No Results Available

	A	B	C	D
63	NCT01032499	Open and Comparative Study to Measure Tolerability and Efficacy of Taro Elixir	Not yet recruiting	No Results Available
64	NCT02598362	Pharmacokinetics of Ciprofloxacin in Pediatric Patients	Recruiting	No Results Available
65	NCT02878031	Community Case Management of Chest Indrawing Pneumonia	Recruiting	No Results Available
66	NCT02790996	Neonatal Vancomycin Trial	Not yet recruiting	No Results Available
67	NCT02712307	Study of 5 and 10 Days Treatment With Penicillin Against Sore Throat Caused by Streptococci	Recruiting	No Results Available
68	NCT02424734	Safety, Tolerability and Efficacy of Ceftaroline in Paediatrics With Late-Onset Sepsis	Recruiting	No Results Available
69	NCT02134301	Open-Label, Dose-Finding, Pharmacokinetics, Safety and Tolerability Study of Oritavancin in Ped	Recruiting	No Results Available
70	NCT02013141	An Open-Label Study of the Pharmacokinetics of a Single Dose of Telavancin in Pediatric Subject	Recruiting	No Results Available
71	NCT01427842	Dose Enhancement of Vancomycin IN Everyday Patients	Recruiting	No Results Available
72	NCT01278017	The Role of Short-course Ceftriaxone Therapy in the Treatment of Severe Nontyphoidal Salmone	Recruiting	No Results Available
73	NCT00988026	Safety and Efficacy Comparison of Minocycline Microgranules Versus Lymecycline in the Treatm	Recruiting	No Results Available
74	NCT02288234	Telavancin Observational Use Registry (TOUR)	Recruiting	No Results Available
75	NCT01304459	Vancomycin Serum Concentrations in Pediatric Oncology Patients Under Intensive Care	Recruiting	No Results Available
76	NCT01173575	Assessment of the Efficacy of FOSFOMYCIN in Patients With Bacterial Infection	Recruiting	No Results Available
77	NCT01778634	Trial of Intravenous Azithromycin to Eradicate Ureaplasma Respiratory Tract Infection in Preterm	Recruiting	No Results Available

	E	F
1	**Indication**	**Infection category**
2	Proven or suspected infection (in patients on PICU)	9
3	Acute Otitis Media	3
4	Sepsis	8
5	Urinary Tract Infections (UTI)	7
6	Community-acquired Pneumonia (CAP)	4
7	Pneumonia	4
8	Proven or suspected infection in patients with malnutrition	9
9	Bacteremia	8
10	Plague	8
11	Helicobacter Pylori Infection	7
12	Meningitis	1
13	Proven or suspected bacterial infection (Pharmacokinetics)	9
14	Melioidosis	8
15	Acute Respiratory Infection|Sinusitis	3
16	Various infections (including nosocomial Pneumonia, CAP, Acute Bac	Various
17	Bacterial Infections	9
18	Meliodosis	8
19	Proven or Suspected Gram-negative Bacterial Infection	9
20	Abscess	1
21	Bronchitis	4
22	Throatcarriers of MRSA	3
23	Acute Skin and Soft Tissue infections (aSSTIs)	2
24	Proven or suspected bacterial infection (in CRRT patients)	9
25	Cystitis / Pyelonephritis	7
26	Acute Upper Respiratory Tract Infections (ARTIs)	3
27	Typhoid Fever	8
28	Community Acquired Pneumonia (CAP)	4
29	Bacterial Infections	9
30	Pneumonia	4
31	Complicated Intra Abdominal Infections (cIAIs)	6

	E	F
32	Pneumonia	4
33	Bacterial Infections	9
34	Cellulitis	2
35	Gram-Positive Bacterial Infections	9
36	Infection	9
37	Urinary Tract Infection or suspected Cholangitis	7
38	Methicillin-resistant Staphylococcal Infections	9
39	Bacterial Meningitis	1
40	Staphylococcal Infections	9
41	Peritonitis (in CAPD patients)	6
42	Acute Sinusitis (Respiratory Tract Infections)	3
43	SBP in patients with Liver Cirrhosis	6
44	Hematogenously Acquired Staphylococcus Aureus Osteomyelitis	5
45	Cellulitis or Wound Infection	8
46	Appendicitis	6
47	Complicated Intra-abdominal Infections (cIAIs)	6
48	Pneumonia (fast-breathing)	4
49	Rhinosinusitis	3
50	Bacterial Infections	9
51	Sepsis	8
52	Complicated Urinary Tract Infections (cUTIs)	7
53	Methicillin-Resistant Staphylococcus Aureus Skin Infection	2
54	Uncomplicated Urogenital Gonorrhea	7
55	Acute Otitis Externa	3
56	Pneumonia	4
57	Pneumonia	4
58	Community-acquired Bacterial Pneumonia	4
59	Acute Bacterial Skin and Skin Structure Infections	2
60	Primary Bacterial Peritonitis	6
61	Cellulitis	8
62	Clostridium Difficile-associated Diarrhea (CDAD)	6

	E	F
63	Acne Vulgaris II or III Degree	2
64	Urinary Tract Infection or Pyelonephritis	7
65	Pneumonia	4
66	Late Onset Neonatal Sepsis	8
67	Tonsillitis	3
68	Late-onset Sepsis	8
69	Gram Positive Bacterial Infections	9
70	Gram-Positive Bacterial Infections	9
71	Vancomycin Therapy	9
72	Diarrhea	6
73	Mild to Moderate Acne	2
74	Hospital Acquired Bacterial Pneumonia (HAP), Complicated Skin and	Various
75	Infection	9
76	Bacterial Infection	9
77	Eradicate ureaplasma respiratory tract infection from preterm infant	4

	G	H	I	J
1	**Interventions**	**Antibiotic class (J01 code)**	**Gender**	**Age**
2	Antiinfectives (beta-lactam, aminoglycoside, glycopeptide, fluoroquinolone,	Various	Both	Up to 18 Years
3	Amoxicillin, Amoxicillin-Potassium Clavulanate, Macrolide	Various	Both	6 Months to 7 Years
4	Antibiotic	J01	Both	Up to 18 years
5	Trimethoprim sulfamethoxazole, cefixime, or cephalexin	Various	Both	2 Months to 10 Years
6	Amoxicillin	J01C	Both	6 Months to 10 Years
7	Amoxicillin, Amoxicillin-clavulanate, Cefdinir	Various	Both	6 Months to 71 Months
8	Ceftriaxone, Metronidazole	J01D	Both	2 Months to 59 Months
9	7 days vs 14 days of adequate antibiotic treatment	J01	Both	Up to 18 years
10	Ciprofloxacin, doxyxcycline	Various	Both	8 Years and older
11	Tailored vs standard therapy (Amoxicillin, Clarithromycin, Metronidazole, Ra	Various	Both	4 Years to 18 Years
12	Daptomycin	J01X	Both	3 Months to 16 Years
13	Amoxicillin-clavulanate, Piperacilline-tazobactam, Vancomycin	Various	Both	Up to 16 Years
14	Meropenem, Ceftazidime	J01D	Both	15 Years and older
15	Amoxicillin clavulanate acid	J01C	Both	6 Years to 13 Years
16	Various drugs (Ceftazidime, Ciprofloxacin, Clindamycin, Doxycycline, Levoflo	Various	Both	Up to 18 years
17	Clindamycin, Trimethoprim-sulfamethoxazole	Various	Both	1 Month to 16 Years
18	Co-trimoxazole	J01E	Both	15 Years and older
19	Ceftolozane/Tazobactam	J01D	Both	Up to 17 Years
20	Trimethoprim-sulfamethoxazole	J01E	Both	3 Months to 17 Years
21	Guaifenesin, Sulfamethoxazole trimethoprim	J01E	Both	4 Years to 14 Years
22	Systemic Rifampin and Clindamycine/Trimehoprimsulfa, or Topical mupiroci	Various	Both	5 Years and older
23	Tedizolid Phophate	J01X	Both	12 Years to 18 Years
24	Vancomycin	J01X	Both	Up to 18 years
25	Ciprofloxacin	J01F	Both	Up to 14 Years
26	Antibiotics (Amoxicillin-clavulanate, azithromycin, cefdinir, cefprozil, cefurox	Various	Both	6 Months to 18 Years
27	Ceftriaxone, Ceftriaxone/azithromycin, Azithromycin, Azithromycin/cefixime	Various	Both	2 Years to 80 Years
28	Cephalosporins and Macrolides	Various	Both	1 Year to 18 Years
29	Carbavance	J01D	Both	Up to 17 Years
30	Amoxicillin-clavulanic Acid	J01C	Both	3 Months to 5 Years
31	Ampicillin/metronidazole/gentamicin/clindamycin/Piperacillin-tazobactam c	Various	Both	Up to 120 Days

	G	H	I	J
32	Amoxicillin-Potassium Clavulanate	J01C	Both	3 Months to 59 Months
33	Dalbavancin	J01X	Both	Up to 28 Days
34	Cefazolin/Moxifloxacin	Various	Both	Up to 18 Years
35	Tedizolid Phosphate	J01X	Both	2 Years to 11 Years
36	Piperacillin-tazobactam	J01C	Both	2 Months to 6 Years
37	Temocillin	J01C	Both	6 Months to 3 Years
38	Vancomycin	J01X	Both	1 Month to 16 Years
39	Beta-lactam	J01C	Both	2 Months to 15 Years
40	Teicoplanin	J01X	Both	16 Years and older
41	Ceftazidime/ciprofloxacin, Ceftazidime, Cefazolin/gentamicin, Cefazolin	Various	Both	15 Years and older
42	Amoxicillin-clavulanate	J01C	Both	2 Years to 11 Years
43	Cefotaxime, Ceftriaxone, Ciprofloxacin	Various	Both	16 Years and older
44	Ceftaroline Fosamil	J01D	Both	1 Year to 17 Years
45	Flucloxacillin, Phenoxymethylpenicillin	J01C	Both	16 Years and older
46	Augmentin/Gentamicin, Appendectomy	J01C	Both	7 Years to 17 Years
47	Ceftazidime-avibactam, Meropenem, Metronidazole	Various	Both	3 Months to 18 Years
48	Amoxicillin	J01C	Both	2 Months to 59 Months
49	Cefditoren pivoxil	J01D	Both	1 Year to 15 Years
50	Ceftobiprole	J01D	Both	Up to 3 Months
51	Vancomycin	J01X	Both	Up to 90 Days
52	Ceftazidime-avibactam, Cefepime	J01D	Both	3 Months to 18 Years
53	Dalbavancin single dose	J01X	Both	3 Months to 17 Years
54	Solithromycin, Ceftriaxone, Azithromycin	Various	Both	15 Years and older
55	Ciprofloxacin	J01M	Both	6 Months and older
56	Amoxicillin	J01C	Both	2 Months to 59 Months
57	Amoxicillin	J01C	Both	2 Months to 59 Months
58	Solithromycin	J01F	Both	2 Months to 17 Years
59	Sodium fusidate, Linezolid	J01X	Both	12 Years and older
60	Cefotaxime, Ceftriaxone	J01D	Both	Up to 18 Years
61	Ceftriaxone, Flucloxacillin	Various	Both	6 Months to 18 Years
62	Fidaxomicin, Vancomycin	J01X	Both	Up to 17 Years

	G	H	I	J
63	Taro Elixir	J01A	Both	14 Years and older
64	Ciprofloxacin	J01M	Both	3 Months to 17 Years
65	Amoxicillin	J01C	Both	2 Months to 59 Months
66	Vancomycin	J01X	Both	Up to 90 Days
67	Phenoxymethylpenicillin	J01C	Both	6 Years and older
68	Ceftaroline Fosamil	J01D	Both	Up to 59 Days
69	Oritavancin	J01X	Both	Up to 18 Years
70	Telavancin	J01X	Both	1 Year to 17 Years
71	Vancomycin	J01X	Both	16 Years and older
72	Ceftriaxone	J01D	Both	3 Months to 18 Years
73	Minocycline, Lymecycline	J01A	Both	14 Years to 30 Years
74	Telavancin	J01X	Both	Up to 18 Years
75	Vancomycin	J01X	Both	Up to 18 Years
76	Fosfomycin	J01X	Both	Up to 18 Years
77	Azithromycin	J01F	Both	0 to 72 hours

	K	L	M	N	O
1	**Age group**	**Estimated enrollment**	**Location**	**Income class**	**Geographic region**
2	8	1850	France	High income	Europe
3	9	150	Finland	High income	Europe
4	8	320	Italy	High income	Europe
5	9	746	United States	High income	North America
6	9	270	Canada	High income	North America
7	9	400	United States	High income	North America
8	9	80	Kenya	Lower middle income	Africa
9	8	50	Canada	High income	North America
10	11	200	Uganda	Low income	Africa
11	11	200	China	Upper middle income	Asia
12	10	5	Switzerland	High income	Europe
13	8	200	Belgium	High income	Europe
14	5	750	Thailand	Upper middle income	Asia
15	11	120	Finland	High income	Europe
16	8	3000	Various (United States, Canad	High income	International
17	10	54	United States	High income	North America
18	5	800	Thailand	Upper middle income	Asia
19	8	36	United States	High income	North America
20	10	200	United States	High income	North America
21	11	50	Peru	Upper middle income	Latin America
22	11	69	Sweden	High income	North America
23	5	162	Various (United States, Argent	Upper middle to High income	International
24	8	10	United States	High income	North America
25	8	45	Japan	High income	Asia
26	10	117000	United States	High income	North America
27	11	120	Nepal	Low income	Asia
28	10	750	China	Upper middle income	Asia
29	8	56	United States	High income	North America
30	9	314	Various (Australia, Malaysia)	High income	Oceania
31	6	284	Various (United States, Canad	High income	North America

	K	L	M	N	O
32	9	300	Malaysia	Upper middle income	Asia
33	2	24	United States	High income	North America
34	8	390	Canada	High income	North America
35	4	32	United States	High income	North America
36	9	141	Canada	High income	North America
37	9	45	Belgium	High income	Europe
38	10	100	France	High income	Europe
39	10	400	Angola	Upper middle income	Africa
40	5	20	Taiwan, China	High income	Asia
41	5	300	Thailand	Upper middle income	Asia
42	4	688	United States	High income	North America
43	5	261	Republic of Korea	High income	Asia
44	10	18	United States	High income	North America
45	5	414	Ireland	High income	Europe
46	11	334	Netherlands	High income	Europe
47	10	102	Various (United States, Argent	Upper middle to High income	International
48	9	2500	Pakistan	Lower middle income	Asia
49	10	120	Thailand	Upper middle income	Asia
50	6	45	Various (Belgium, Germany, Li	High income	Europe
51	6	200	Australia	High income	Oceania
52	10	102	Various (United States, Czech	Upper middle to High income	International
53	10	300	United States	High income	North America
54	5	300	Various (United States, Austra	High income	International
55	10	500	Various (United States, Canad	High income	North America
56	9	2000	Malawi	Low income	Africa
57	9	2000	Malawi	Low income	Africa
58	10	400	Various (United States, Bulgar	High income	International
59	5	712	Various (United States, Puerto	High income	International
60	8	100	Egypt	Lower middle income	Africa
61	10	188	Australia	High income	Oceania
62	8	144	Various (United States, Belgiu	High income	International

	K	L	M	N	O
63	5	120	Brazil	Upper middle income	Latin America
64	10	20	Belgium	High income	Europe
65	9	308	Nigeria	Lower middle income	Africa
66	6	300	Various (United Kingdom, Fra	High income	Europe
67	11	432	Sweden	High income	Europe
68	7	24	Various (United States, Hunga	High income	International
69	8	60	United States	High income	North America
70	10	32	United States	High income	North America
71	5	100	Australia	High income	Oceania
72	10	200	Taiwan, China	High income	Asia
73	5	168	Mexico	High income	North America
74	8	1000	United States	High income	North America
75	8	50	Brazil	Upper middle income	Latin America
76	8	200	Various (Austria, Germany)	High income	Europe
77	1	180	United States	High income	North America

	P	Q	R	S	T
1	**Collaborators**	**Sponsor**	**Study Types**	**Phase**	**Endpoint classification**
2	Assistance Publique - Hopitaux de Paris	Hospital	Observational	Not applicable	Pharmacokinetics
3	University of Oulu|Oulu University Hospital	University	Interventional	Phase 4	Efficacy
4	Ospedale Santa Maria delle Croci	Hospital	Interventional	Phase 2	Safety/Efficacy
5	Children's Hospital of Philadelphia|Children's Ho	Hospital	Interventional	Phase 2	Safety/Efficacy
6	Hamilton Health Sciences Corporation|Children's	Hospital	Interventional	Phase 4	Safety/Efficacy
7	National Institute of Allergy and Infectious Diseas	NIH	Interventional	Phase 4	Efficacy
8	University of Oxford|KEMRI Wellcome Trust Rese	University	Interventional	Phase 2	Pharmacokinetics
9	Sunnybrook Health Sciences Centre	Hospital	Interventional	Not specified	Efficacy
10	Centers for Disease Control and Prevention|MRC	CDC	Interventional	Phase 2	Safety/Efficacy
11	Beijing Children's Hospital	Hospital	Interventional	Phase 4	Safety/Efficacy
12	University Hospital Inselspital, Berne	Hospital	Interventional	Phase 1	Pharmacokinetics
13	University Hospital, Ghent|University Hospital, A	Hospital	Observational	Not applicable	Pharmacokinetics
14	University of Oxford|Mahidol University|Wellcor	University	Interventional	Not specified	Efficacy
15	Oulu University Hospital	University	Interventional	Phase 4	Safety/Efficacy
16	Daniel Benjamin|Eunice Kennedy Shriver Nationa	University	Observational	Not applicable	Pharmacokinetics
17	Michael Cohen-Wolkowiez|Eunice Kennedy Shriv	University	Interventional	Phase 1	Pharmacokinetics
18	Khon Kaen University	University	Interventional	Not specified	Efficacy
19	Cubist Pharmaceuticals LLC	Industry	Interventional	Phase 1	Pharmacokinetics
20	Children's Mercy Hospital Kansas City|Blue Cross	Hospital	Interventional	Not specified	Efficacy
21	Hoffmann-La Roche	Industry	Observational	Not applicable	Safety
22	Region Skane	Hospital	Interventional	Not specified	Efficacy
23	Cubist Pharmaceuticals LLC	Industry	Interventional	Phase 3	Safety
24	Drexel University|The Center for Pediatric Pharm	University	Interventional	Phase 1	Safety
25	Bayer	Industry	Observational	Not applicable	Safety/Efficacy
26	Children's Hospital of Philadelphia	Hospital	Observational	Not applicable	Safety/Efficacy
27	Sheba Medical Center	Hospital	Interventional	Phase 4	Efficacy
28	Beijing Children's Hospital	Hospital	Observational	Not applicable	Pharmacokinetics
29	Rempex Pharmaceuticals (a wholly owned subsid	Industry	Interventional	Phase 1	Safety
30	Menzies School of Health Research|Griffith Univ	University	Interventional	Phase 4	Safety/Efficacy
31	Michael Cohen-Wolkowiez|The EMMES Corporat	University	Interventional	Phase 2-3	Safety

	P	Q	R	S	T
32	University of Malaya|Menzies School of Health R	University	Interventional	Phase 4	Efficacy
33	Durata Therapeutics Inc., an affiliate of Allergan p	Industry	Interventional	Phase 1	Pharmacokinetics
34	University of British Columbia	University	Interventional	Phase 3	Efficacy
35	Merck Sharp & Dohme Corp.	Industry	Interventional	Phase 1	Pharmacokinetics
36	St. Justine's Hospital	Hospital	Interventional	Phase 1	Pharmacokinetics
37	Universitì© Catholique de Louvain	University	Interventional	Phase 4	Pharmacokinetics
38	Assistance Publique - Hì«pitaux de Paris	Hospital	Interventional	Not specified	Pharmacokinetics
39	Helsinki University|Foundation for Paediatric Res	University	Interventional	Phase 4	Safety/Efficacy
40	National Taiwan University Hospital	University	Interventional	Phase 4	Pharmacokinetics
41	Chulalongkorn University	University	Interventional	Not specified	Efficacy
42	University of Pittsburgh|National Institute of Alle	University	Interventional	Phase 3	Safety/Efficacy
43	Korea University	University	Interventional	Phase 4	Efficacy
44	Baylor College of Medicine|Forest Laboratories	University	Interventional	Phase 1-2	Safety/Efficacy
45	Royal College of Surgeons, Ireland|Health Resear	University	Interventional	Phase 4	Efficacy
46	Ramon Gorter|ZonMw: The Netherlands Organis	University	Interventional	Phase 4	Efficacy
47	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2	Safety/Efficacy
48	Aga Khan University	University	Interventional	Not specified	Efficacy
49	Thammasat University	University	Interventional	Phase 4	Safety/Efficacy
50	Basilea Pharmaceutica	Industry	Interventional	Phase 1	Pharmacokinetics
51	Murdoch Childrens Research Institute|Royal Chil	University	Interventional	Not specified	Pharmacokinetics
52	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2	Safety/Efficacy
53	Durata Therapeutics Inc., an affiliate of Allergan p	Industry	Interventional	Phase 3	Safety/Efficacy
54	Cempra Inc|National Institute of Allergy and Infe	Industry	Interventional	Phase 3	Efficacy
55	Otonomy, Inc.	Industry	Interventional	Phase 3	Efficacy
56	Save the Children|University of North Carolina|U	Health Organisat	Interventional	Phase 4	Efficacy
57	Save the Children|University of North Carolina|U	Health Organisat	Interventional	Phase 4	Efficacy
58	Cempra Inc	Industry	Interventional	Phase 2-3	Safety/Efficacy
59	Cempra Inc	Industry	Interventional	Phase 3	Safety/Efficacy
60	Tanta University	University	Interventional	Phase 3	Efficacy
61	Murdoch Childrens Research Institute	University	Interventional	Not specified	Efficacy
62	Astellas Pharma Europe B.V.|Merck Sharp & Doh	Industry	Interventional	Phase 3	Safety/Efficacy

	P	Q	R	S	T
63	Laboratorios Goulart S.A.	Industry	Interventional	Phase 3	Safety/Efficacy
64	University Hospital, Ghent|Universitair Ziekenhu	University	Interventional	Phase 4	Pharmacokinetics
65	Malaria Consortium|World Health Organization	Health Organisat	Interventional	Phase 4	Safety
66	PENTA Foundation|St George's, University of Lor	Health Organisat	Interventional	Phase 2	Safety/Efficacy
67	Sigvard Mì¦lstad|Public Health Agency of Swede	University	Interventional	Phase 4	Safety/Efficacy
68	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2-3	Safety/Efficacy
69	The Medicines Company	Industry	Interventional	Phase 1	Pharmacokinetics
70	Theravance Biopharma Antibiotics, Inc.	Industry	Interventional	Phase 4	Pharmacokinetics
71	The Canberra Hospital	Hospital	Interventional	Phase 2	Pharmacokinetics
72	Chang Gung Memorial Hospital	Hospital	Interventional	Phase 4	Efficacy
73	Darier	Industry	Interventional	Phase 4	Safety/Efficacy
74	Theravance Biopharma Antibiotics, Inc.	Industry	Observational	Not applicable	Safety/Efficacy
75	Grupo de Apoio ao Adolescente e a Crianca com	Hospital	Observational	Not applicable	Pharmacokinetics
76	Infectopharm Arzneimittel GmbH|J&P Medical R	Industry	Observational	Not applicable	Efficacy
77	University of Maryland	University	Interventional	Phase 2	Safety/Efficacy

	U	V	W	X	Y	Z	AA	AB
1	**Primary outcome variable**	**PK data collected**	**First Receive**	**Start Date**	**Completion I**	**Last Updated**	**Last Verified**	**Results First Received**
2	PK	PK study design	July 2, 2015	Sep-15	Dec-18	September 1	Sep-16	No Study Results Posted
3	Efficacy	No PK data	September 2	Oct-16	null	October 12, 2	Oct-16	No Study Results Posted
4	Efficacy	No PK data	September 8	Sep-16	null	September 1	Sep-16	No Study Results Posted
5	Efficacy	No PK data	May 8, 2012	May-12	Apr-18	June 27, 201	Jun-16	No Study Results Posted
6	Efficacy	No PK data	March 2, 201	Mar-16	May-18	March 24, 20	Mar-16	No Study Results Posted
7	Efficacy	No PK data	September 1	Oct-16	Mar-19	October 13, 2	Oct-16	No Study Results Posted
8	PK	PK study design	April 4, 2016	Apr-16	Sep-16	April 25, 201	Apr-16	No Study Results Posted
9	Efficacy	No PK data	September 2	Oct-16	Dec-17	September 2	Sep-16	No Study Results Posted
10	Efficacy	No PK data	November 17	Dec-10	null	September 1	Sep-12	No Study Results Posted
11	Efficacy	No PK data	November 25	Mar-14	Jul-16	December 16	Nov-15	No Study Results Posted
12	PK	Primary PK data	January 26, 2	Apr-12	Apr-18	December 10	Dec-15	No Study Results Posted
13	PK	PK study design	May 18, 2015	May-12	null	November 17	Nov-15	No Study Results Posted
14	Efficacy	No PK data	December 18	Dec-07	Sep-10	June 3, 2008	Aug-07	No Study Results Posted
15	Efficacy	No PK data	October 17, 2	Nov-07	Dec-09	October 18, 2	Oct-07	No Study Results Posted
16	PK	PK study design	August 17, 20	Nov-11	Feb-17	February 4, 2	Feb-16	No Study Results Posted
17	PK	PK study design	June 12, 201	Nov-15	Dec-17	August 1, 201	Aug-16	No Study Results Posted
18	Efficacy	No PK data	August 18, 20	Aug-11	Dec-20	August 30, 20	Aug-16	No Study Results Posted
19	PK	PK study design	September 2	Sep-14	Nov-16	October 31, 2	Oct-16	No Study Results Posted
20	Efficacy	No PK data	March 23, 20	Mar-09	Oct-12	June 21, 201	Jun-11	No Study Results Posted
21	Safety	No PK data	August 23, 20	Aug-16	Dec-16	September 1	Sep-16	No Study Results Posted
22	Efficacy	No PK data	January 3, 20	Mar-11	Jun-15	May 25, 201	May-15	No Study Results Posted
23	Safety	Secondary PK data	October 9, 20	Mar-15	Jan-18	October 31, 2	Oct-16	No Study Results Posted
24	Safety	Primary PK data	January 12, 2	Jan-17	Dec-18	September 8	Sep-16	No Study Results Posted
25	Safety	No PK data	September 1	Jul-16	Sep-18	October 19, 2	Oct-16	No Study Results Posted
26	Efficacy	No PK data	November 17	Jan-14	Jul-17	May 6, 2016	May-16	No Study Results Posted
27	Efficacy	No PK data	August 21, 20	Aug-13	Aug-15	August 26, 20	Aug-14	No Study Results Posted
28	PK	PK study design	May 11, 2016	Aug-16	Oct-22	May 17, 2016	May-16	No Study Results Posted
29	Safety	Primary PK data	February 17,	Jul-16	Sep-19	October 6, 20	Oct-16	No Study Results Posted
30	Efficacy	No PK data	May 5, 2016	Jun-16	Dec-20	October 7, 20	Oct-16	No Study Results Posted
31	Safety	No PK data	November 18	Dec-13	Sep-17	August 1, 201	Aug-16	No Study Results Posted

	U	V	W	X	Y	Z	AA	AB
32	Efficacy	No PK data	September 2	Nov-14	Dec-18	December 20	Dec-15	No Study Results Posted
33	PK	PK study design	February 18,	Apr-16	May-17	October 19, 2	Oct-16	No Study Results Posted
34	Efficacy	No PK data	May 8, 2006	Jan-04	Dec-13	February 6, 2	Feb-12	No Study Results Posted
35	PK	PK study design	April 1, 2016	May-16	Feb-18	October 21, 2	Oct-16	No Study Results Posted
36	PK	PK study design	June 2, 2015	Jan-16	Dec-17	April 18, 201	Apr-16	No Study Results Posted
37	PK	PK study design	October 1, 20	Oct-16	Oct-17	October 24, 2	Oct-16	No Study Results Posted
38	PK	PK study design	February 24,	Feb-16	Feb-17	March 8, 201	Mar-16	No Study Results Posted
39	Efficacy	No PK data	February 23,	Feb-12	Jul-17	February 19,	Feb-16	No Study Results Posted
40	PK	PK study design	August 23, 20	Jun-06	Dec-07	August 23, 20	Aug-06	No Study Results Posted
41	Efficacy	No PK data	January 30, 2	Dec-12	Dec-13	February 6, 2	Feb-13	No Study Results Posted
42	Efficacy	No PK data	September 8	Feb-16	Sep-20	October 3, 20	Oct-16	No Study Results Posted
43	Efficacy	No PK data	December 22	Apr-07	Apr-16	April 8, 2014	Apr-14	No Study Results Posted
44	Safety	Secondary PK data	December 31	Jan-15	Jan-20	June 24, 201	Jun-16	No Study Results Posted
45	Efficacy	No PK data	August 9, 201	Dec-16	Dec-19	September 3	Jul-16	No Study Results Posted
46	Efficacy	No PK data	July 24, 2016	Dec-16	Dec-20	July 26, 2016	Jul-16	No Study Results Posted
47	Safety	Secondary PK data	May 25, 2015	Jul-15	Oct-17	October 21, 2	Oct-16	No Study Results Posted
48	Efficacy	No PK data	November 4,	Nov-14	Jul-17	June 3, 2016	Jun-16	No Study Results Posted
49	Efficacy	No PK data	February 17,	Jan-12	Sep-12	March 13, 20	Mar-12	No Study Results Posted
50	PK	PK study design	August 5, 201	Aug-14	Jun-17	October 20, 2	Oct-16	No Study Results Posted
51	PK	PK study design	August 5, 201	Sep-14	Sep-17	March 17, 20	Mar-16	No Study Results Posted
52	Safety	Secondary PK data	June 16, 201	Sep-15	Oct-17	October 21, 2	Oct-16	No Study Results Posted
53	Efficacy	No PK data	June 8, 2016	Jun-16	Jul-18	June 23, 201	Jun-16	No Study Results Posted
54	Efficacy	No PK data	August 1, 201	Aug-14	Apr-17	September 2	Sep-16	No Study Results Posted
55	Efficacy	No PK data	June 13, 201	Jun-16	Nov-16	June 13, 201	Jun-16	No Study Results Posted
56	Efficacy	No PK data	May 1, 2016	Jun-16	Sep-18	June 10, 201	Jun-16	No Study Results Posted
57	Efficacy	No PK data	February 3, 2	Mar-16	null	June 10, 201	Jun-16	No Study Results Posted
58	Safety	No PK data	November 1(	Mar-16	Jan-18	September 1	Sep-16	No Study Results Posted
59	Efficacy	No PK data	October 5, 20	Nov-15	Feb-17	October 5, 20	Oct-16	No Study Results Posted
60	Efficacy	No PK data	May 11, 2015	Jan-15	Dec-16	May 9, 2016	May-16	No Study Results Posted
61	Efficacy	No PK data	January 4, 20	Jan-15	Jan-17	March 16, 20	Mar-16	No Study Results Posted
62	Efficacy	No PK data	August 11, 20	Oct-14	Feb-17	June 17, 201	Jun-16	No Study Results Posted

	U	V	W	X	Y	Z	AA	AB
63	Efficacy	No PK data	December 14	May-10	Oct-10	March 18, 20	Dec-09	No Study Results Posted
64	PK	PK study design	November 4,	Apr-15	Apr-16	November 4,	Nov-15	No Study Results Posted
65	Safety	No PK data	August 17, 2(	Oct-16	Jul-17	October 3, 2(	Oct-16	No Study Results Posted
66	Efficacy	Secondary PK data	April 7, 2016	Jul-16	Mar-18	May 31, 201(	May-16	No Study Results Posted
67	Efficacy	No PK data	March 4, 201	Sep-15	Oct-16	October 4, 2(	Oct-16	No Study Results Posted
68	Safety	Secondary PK data	February 23,	Aug-15	Oct-17	October 14, 2	Oct-16	No Study Results Posted
69	PK	PK study design	May 7, 2014	May-14	Dec-16	November 4,	Nov-15	No Study Results Posted
70	PK	PK study design	December 11	Dec-14	Aug-16	June 24, 201(	Jun-16	No Study Results Posted
71	PK	PK study design	August 31, 2(	Aug-11	Jul-12	September 1	Aug-11	No Study Results Posted
72	Efficacy	No PK data	November 25	Aug-10	Jul-12	January 14, 2	Nov-10	No Study Results Posted
73	Efficacy	No PK data	September 3	Jun-09	Apr-10	September 3	Sep-09	No Study Results Posted
74	Efficacy	No PK data	November 5,	Nov-14	Sep-18	June 29, 201(	Jun-16	No Study Results Posted
75	PK	Primary PK data	February 24,	Jan-11	null	March 21, 20	Mar-12	No Study Results Posted
76	Efficacy	No PK data	July 29, 2010	Aug-10	null	February 5, 2	Feb-16	No Study Results Posted
77	Efficacy	Secondary PK data	January 22, 2	Jul-13	Dec-21	May 28, 201!	May-15	No Study Results Posted

	AC	AD	AE	AF	AG
1	**Primary Com**	**URL**			
2	Jul-18	https://ClinicalTrials.gov/show/NCT02539407			
3	Dec-18	https://ClinicalTrials.gov/show/NCT02935374			
4	Sep-18	https://ClinicalTrials.gov/show/NCT02899143			
5	Apr-18	https://ClinicalTrials.gov/show/NCT01595529			
6	Feb-18	https://ClinicalTrials.gov/show/NCT02380352			
7	Jan-19	https://ClinicalTrials.gov/show/NCT02891915			
8	Sep-16	https://ClinicalTrials.gov/show/NCT02746276			
9	Aug-17	https://ClinicalTrials.gov/show/NCT02917551			
10	Jun-13	https://ClinicalTrials.gov/show/NCT01243437			
11	Mar-16	https://ClinicalTrials.gov/show/NCT02635191			
12	Dec-16	https://ClinicalTrials.gov/show/NCT01522105			
13	Dec-17	https://ClinicalTrials.gov/show/NCT02456974			
14	Sep-10	https://ClinicalTrials.gov/show/NCT00579956			
15	null	https://ClinicalTrials.gov/show/NCT00545961			
16	Feb-17	https://ClinicalTrials.gov/show/NCT01431326			
17	Nov-17	https://ClinicalTrials.gov/show/NCT02475876			
18	Dec-20	https://ClinicalTrials.gov/show/NCT01420341			
19	Nov-16	https://ClinicalTrials.gov/show/NCT02266706			
20	Sep-12	https://ClinicalTrials.gov/show/NCT00867789			
21	Dec-16	https://ClinicalTrials.gov/show/NCT02879981			
22	Jun-15	https://ClinicalTrials.gov/show/NCT01269541			
23	Jan-18	https://ClinicalTrials.gov/show/NCT02276482			
24	Dec-18	https://ClinicalTrials.gov/show/NCT02663596			
25	Sep-17	https://ClinicalTrials.gov/show/NCT02555059			
26	Apr-17	https://ClinicalTrials.gov/show/NCT02297815			
27	Dec-14	https://ClinicalTrials.gov/show/NCT02224040			
28	Aug-22	https://ClinicalTrials.gov/show/NCT02775968			
29	Aug-19	https://ClinicalTrials.gov/show/NCT02687906			
30	Dec-19	https://ClinicalTrials.gov/show/NCT02783859			
31	Apr-17	https://ClinicalTrials.gov/show/NCT01994993			

	AC	AD	AE	AF	AG
32	Dec-17	https://ClinicalTrials.gov/show/NCT02258763			
33	May-17	https://ClinicalTrials.gov/show/NCT02688790			
34	Dec-12	https://ClinicalTrials.gov/show/NCT00323219			
35	Feb-18	https://ClinicalTrials.gov/show/NCT02750761			
36	Dec-17	https://ClinicalTrials.gov/show/NCT02466438			
37	Sep-17	https://ClinicalTrials.gov/show/NCT02260102			
38	Jun-16	https://ClinicalTrials.gov/show/NCT02694458			
39	Feb-17	https://ClinicalTrials.gov/show/NCT01540838			
40	null	https://ClinicalTrials.gov/show/NCT00368498			
41	Dec-13	https://ClinicalTrials.gov/show/NCT01785641			
42	Sep-20	https://ClinicalTrials.gov/show/NCT02554383			
43	Mar-16	https://ClinicalTrials.gov/show/NCT01265173			
44	Jan-17	https://ClinicalTrials.gov/show/NCT02335905			
45	Dec-19	https://ClinicalTrials.gov/show/NCT02922686			
46	Dec-20	https://ClinicalTrials.gov/show/NCT02848820			
47	Oct-17	https://ClinicalTrials.gov/show/NCT02475733			
48	May-17	https://ClinicalTrials.gov/show/NCT02372461			
49	Aug-12	https://ClinicalTrials.gov/show/NCT01553006			
50	Mar-17	https://ClinicalTrials.gov/show/NCT02527681			
51	Sep-17	https://ClinicalTrials.gov/show/NCT02210169			
52	Oct-17	https://ClinicalTrials.gov/show/NCT02497781			
53	Apr-18	https://ClinicalTrials.gov/show/NCT02814916			
54	Apr-17	https://ClinicalTrials.gov/show/NCT02210325			
55	Nov-16	https://ClinicalTrials.gov/show/NCT02801370			
56	Aug-18	https://ClinicalTrials.gov/show/NCT02760420			
57	Aug-18	https://ClinicalTrials.gov/show/NCT02678195			
58	Dec-17	https://ClinicalTrials.gov/show/NCT02605122			
59	Feb-17	https://ClinicalTrials.gov/show/NCT02570490			
60	Dec-16	https://ClinicalTrials.gov/show/NCT02443285			
61	Jan-17	https://ClinicalTrials.gov/show/NCT02334124			
62	Feb-17	https://ClinicalTrials.gov/show/NCT02218372			

	AC	AD	AE	AF	AG
63	Jul-10	https://ClinicalTrials.gov/show/NCT01032499			
64	Feb-16	https://ClinicalTrials.gov/show/NCT02598362			
65	Mar-17	https://ClinicalTrials.gov/show/NCT02878031			
66	Dec-17	https://ClinicalTrials.gov/show/NCT02790996			
67	Oct-16	https://ClinicalTrials.gov/show/NCT02712307			
68	Oct-17	https://ClinicalTrials.gov/show/NCT02424734			
69	Dec-16	https://ClinicalTrials.gov/show/NCT02134301			
70	Aug-16	https://ClinicalTrials.gov/show/NCT02013141			
71	Jul-12	https://ClinicalTrials.gov/show/NCT01427842			
72	Jun-11	https://ClinicalTrials.gov/show/NCT01278017			
73	Feb-10	https://ClinicalTrials.gov/show/NCT00988026			
74	Jun-18	https://ClinicalTrials.gov/show/NCT02288234			
75	null	https://ClinicalTrials.gov/show/NCT01304459			
76	Dec-16	https://ClinicalTrials.gov/show/NCT01173575			
77	Dec-19	https://clinicaltrials.gov/ct2/show/NCT01778634			

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A global shortage of neonatal and pediatric antibiotic trials: a narrative review.

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A global shortage of neonatal and pediatric antibiotic trials: rapid review.

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ABSTRACT

Objectives: There have been few clinical trials (CTs) on antibiotics which inform neonatal and pediatric drug labelling. The rate of unlicensed and off-label prescribing in pediatrics remains high. It is unclear whether the current neonatal and pediatric antibiotic research pipeline is adequate to inform optimal drug dosing. Using the ClinicalTrials.gov registry, this review aims to establish the current global status of antibiotic CTs in children up to 18 years of age.

Results: 76 registered open CTs of antibiotics in children were identified globally; 23 (30%) were recruiting newborns (8 of which (11%) included preterm neonates), 52 (68%) infants and toddlers, 58 (76%) children, and 54 (71%) adolescents. The majority of registered trials were late phase (10 (15%) Phase 3 and 23 (35%) Phase 4/pharmacovigilance). Two-thirds were sponsored by non-profit organisations (n=50, 66%), compared to 26 (34%) by pharmaceutical companies. A greater proportion of non-profit funded trials were efficacy-based strategic trials (n= 34, 68%), in comparison to industry-led trials, which were most often focused on safety or pharmacokinetic data (n=17, 65%). Only 2 of the 37 antibiotics listed on the May 2016 Pew Charitable Trusts antibiotic development pipeline, currently being studied in adults, appear to be currently recruiting in open pediatric CTs.

Conclusions: This review highlights that very few pediatric antibiotic CTs are being conducted globally, especially in neonates. There is a striking disparity noted between antibiotic drug development programmes in adults and children.

Strengths and limitations of this study

- A narrative literature review of registered clinical trials in children.
- Explicit reproducible methodology.
- Search strategy limited to ClinicalTrials.gov and EudraCT. Entirety of clinical research in this field might not have been captured.
- Search strategy was limited to open clinical trials. Active but not yet recruiting trials were not captured.

INTRODUCTION

Widespread unlicensed and off-label prescribing in pediatrics persists – as high as 11% and 46%, respectively – yet the paucity of clinical research involving children that is conducted to inform optimal drug dosing, licensing and labelling remains a problem.[1] For certain medicines, drug efficacy can be extrapolated from adult data provided that the pathology and drug exposure are the same, or sufficiently similar in children as in adults.[2,3]. Although differences in drug pharmacokinetics (PK) in neonates and children can lead to adverse reactions that are not seen in adult populations, these are very rare.[4] Suboptimal antibiotic dosing, including under- and over-

dosing, can lead to toxicity, treatment failure, and may drive antimicrobial resistance by encouraging selection pressures on drug-resistant strains of bacteria.[5]

Since antibiotics are the medicines most commonly prescribed for children, it is important to maximize our understanding of their PK profiles to help determine optimal drug dosing and ultimately to improve outcomes.[6] In the last decade several initiatives have been established to encourage pediatric medicines research, bridging the gap between adult and pediatric drug development plans. Such initiatives include the Pediatric Regulation (Pediatric Investigation Plans (PIPs), introduced by the European Medicines Agency (EMA),[7] and Pediatric Study Plans (PSPs), by the U.S. Food and Drug Administration (FDA)).[8] Despite this, there have been few advances in antibiotic development for this population.[9]

The global status of clinical research on antibiotics in pediatrics is unknown. Using registered records of clinical trials (CTs) on *ClinicalTrials.gov*, this review aims (i) to summarise the current global status of registered antibiotic research in children and neonates, and (ii) to stimulate discussion and collaboration among the relevant stakeholders on the neglect of antibiotic research in children.

METHODS

Data sources

The *ClinicalTrials.gov* registry (last accessed 8th November 2016) is an international platform for the registration of CTs. It is a web-based registry, developed in 2000 by the National Institutes of Health (NIH) and the FDA, to which trials from 50 states and 163 countries around the world are registered. Information provided for each trial is updated periodically by the trial's sponsoring organisation. The database has a specific child filter, which uses a key word paradigm to select all registered trials recruiting patients/participants up to 18 years of age.

Study selection

Our records were identified using suitable key word searches, in which the final search terms were (antimicrobial* OR antibiotic* OR anti-infective agent*) AND Child AND Open Studies. All identified trials were filtered manually using inclusion and exclusion criteria. Interventional and observational trials on antimicrobials recruiting children up to 18 years of age were considered eligible for inclusion. No specific temporal filter was applied since only open or ongoing clinical trials were of interest. The following records, which were not investigating one or more antibiotics, were excluded: trials of antiseptics, antifungals, antiprotozoals, antivirals, and pro- or pre- biotics. The following records, which were investigating an antibiotic were excluded: trials involving tuberculosis, malaria,

cystic fibrosis, HIV, febrile neutropenic patients, topical or inhalational treatments, prophylactic antibiotics, or records investigating alternative use for antibiotics (for example as an anti-inflammatory agent).

The searches were conducted by GT. All eligible records were identified via manual filtering by GT CB, LF and MS, and any disagreements regarding inclusion and exclusion of records were resolved through discussion.

Data extraction

The following information was collected from the included records: unique NCT number, recruitment status, study design, trial phase, study sponsor, age group and sex eligibility, clinical indication, geographic region of recruitment, antibiotic being investigated, and endpoint classification. Outcomes were categorised as safety, efficacy or PK. Economic setting (based on geographic region of recruitment) was classified using The World Bank classification to differentiate between Low Income Countries (LICs), Lower Middle Income Countries (LMICs), Upper Middle Income Countries (UMICs), and High Income Countries (HICs).[10]

The specific class of antibiotic studied in each trial was identified and classified using the World Health Organisation (WHO) ATC/DDD index.[11] To investigate whether novel antibiotics are being studied in pediatric populations, the antibiotics currently studied in children were compared with the *Pew Charitable Trusts Antibiotics Currently in Clinical Development* pipeline, which identifies novel antibiotics currently under development for the U.S. market.[12]

RESULTS

Our search identified 1056 records. 603 records were excluded on title because they were studies not involving an antimicrobial. 453 records were investigating one or more antimicrobials and recruiting children below 18 years of age. Among the 195 trials investigating antibiotics, 76 fulfilled our inclusion and exclusion criteria and were included in the final analysis. Reasons for exclusion are summarised in Figure 1. Details of included studies can be found in Supplementary file 1.

All 76 CTs identified were open as of 8th November 2016, and 63 (83%) of these were recognised as recruiting participants on this date (Table 1). All trials were recruiting both male and female participants.

Table 1. Characteristics of clinical trials.

Characteristic	Category	Number of studies, n (%)
Age group	Preterm neonates	1 (1)[a]
	Neonates (total)	23 (30)
	Infants and toddlers	52 (68)
	Children	58 (76)
	Adolescents	54 (71)
Recruitment status	Recruiting	63 (83)
	Not yet recruiting	13 (17)
Study design	Interventional	66 (87)
	Observational	10 (13)
Trial phase[b]	Phase 1	10 (15)
	Phase 1-2	1 (2)
	Phase 2	9 (14)
	Phase 2-3	3 (5)
	Phase 3	10 (15)
	Phase 4	23 (39)
	Not specified	10 (15)
Sponsor	Industry	26 (34)
	Non-profit	50 (66)
Geographic region	Africa	8 (11)
	Asia	16 (21)
	Europe	22 (29)
	Latin America	6 (8)
	North America	34 (45)
	Oceania	5 (7)
Antibiotic class	J01A Tetracycline	4 (5)
	J01C Beta-lactam, Penicillin	25 (33)
	J01D Other Beta-lactam	22 (29)
	J01E Sulfonamides and trimethoprim	7 (9)
	J01F Macrolide, Lincosamide, Streptogramin	14 (18)
	J01G Aminoglycoside	2 (3)
	J01M Quinolone	8 (11)
	J01X Other antibiotic classes[c]	21 (28)
	J01 Not specified	2 (3)

Totals for Age group, Geographic region, and Antibiotic class do not add up to total number of clinical trials (76) as some trials contributed to more than one sub group.
[a] 7 further trials mentioned inclusion of preterm babies in the inclusion criteria.
[b] Trial phase % based on percentage of interventional trials.
[c] J01X includes glycopeptides, polymyxins, imidazole and nitrofuran derivatives.

Age group

Only 23 of the 76 trials (30%) were recruiting newborns (0 to 28 days). One of these 23 trials focused solely on recruiting preterm newborns (a further 7 CTs mentioned inclusion of preterm newborns in inclusion criteria). Of the remaining records, 52 (68%) were recruiting infants and toddlers (28 days to 23 months), 58 (76%) children (2 to 11 years), and 54 (71%) adolescents (11

up to 18 years). 29 (38%) trials did not focus solely on the recruitment of children or neonates, with age ranges also spanning across adult populations.

Study type

Interventional trials were most frequently identified (n=66, 87%) with only 10 (13%) observational trials noted. Of the interventional trials, the majority were in the later stages of development; 10 (13%) in Phase 1, 1 (2%) between Phase 1 and 2, 9 (14%) in Phase 2, 3 (5%) between Phase 2 and 3, 10 (15%) in Phase 3 and 23 (35%) in Phase 4. In 10 (15%) cases, a trial phase was not specified.

Sponsor and Endpoint Classification

Fifty trials (66%) were sponsored by non-profit organisations (being university, hospital or government funded), and 26 sponsored by industry (34%). The endpoint classification of the majority of trials (n=43, 57%) was reported as efficacy (Table 2). A greater proportion (n=34, 68%) of non-profit studies measured the efficacy of the drugs as the primary endpoint, with less emphasis on collection of PK or safety data (n=16, 32%). In comparison pharmaceutical-led trials focussed on early PK and safety studies over drug efficacy (n=17, 65% vs. n=9, 35% respectively).

Table 2. Clinical trial endpoint classification of identified clinical trials stratified by trial sponsor. Endpoint classification determined by planned primary outcomes.

Endpoint classification	Industry	Non-profit	Total (%)
Efficacy	9	34	43 (57)
Safety	10	2	12 (16)
PK	7	14	21 (28)

Geographic region

The most frequently recruiting geographic region was North America (n=34, 45%). 22 (29%) trials recruiting in Europe and 16 (21%) in Asia were identified, 6 (8%) in Latin America, 8 (11%) in Africa, and 5 (7%) in Oceania. Most trials were recruiting in HICs (n=54, 71%), with fewer trials recruiting in LICs (n=4, 5%), LMICs (n=4, 5%), UMICs (n=11, 14%) or a combination of UMICs and HICs (n=3, 4%).

Indication

The most common treatment indications investigated were lower respiratory tract infection (n=12, 16%) and sepsis (n=11, 14%), followed by upper respiratory tract infection (n=8, 11%), intra-

abdominal infection (IAI) (n=8, 11%), urinary tract infection (UTI) (n=7, 9%), complicated skin and soft tissue infection (cSSTI) (n=6, 8%), CNS (central nervous system) infection (n=3, 4%), and bone and joint infection (n=1, 1%) (Table 3).

Antibiotic class

The majority of antibiotics being investigated were beta-lactams (n=47, 62%), followed by other antibiotic classes (J01X, including vancomycin, telavancin and dalbavancin) (n=21, 28%), and macrolides or lincosamides (J01F) (n=14, 18%). Very few trials were investigating tetracyclines (J01A) (n=4, 5%), sulphonamides and trimethoprim (J01E) (n=7, 9%), aminoglycosides (J01G) (n=2, 3%), or quinolones (J01M) (n=8, 11%). 2 CTs (3%) did not specify the class of antibiotic being investigated. 16 (21%) trials were investigating more than one antibiotic; these trials counted towards more than one J01 category. The breakdown of J01 categories, as per WHO ATC/DDD classification,[11] is described in Table 1.

Antibiotic pipeline

Of the 37 antibiotics listed in the May 2016 edition of the Pew Charitable Trusts Antibiotic Pipeline (last accessed 10th June 2016),[12] as noted by the EMA Opinions and Decisions on Pediatric Investigation Plans, 5 had an agreed PIP: Imipenem/Cilastatin+Relebactam, Cadazolid, Carbavance (Meropenem+Vaborbactam), Eravacycline, and Solithromycin.[8] As of 8th November 2016, our search found that only 2 of these 37 antibiotics listed (Carbavance and Solithromycin) were currently being investigated in 1 and 2 on-going CTs in pediatric patients, respectively (Table 4). A PIP was agreed for Carbavance in 2015 for treatment of Gram-negative infections, and for Solithromycin in 2016 for the treatment of gonococcal infection, and later for treatment of anthrax, tularaemia, and bacterial pneumonia. PIPs were agreed in 2015 for treatment of UTI and complicated IAI with Eravacycline, and in 2016 for treatment of Clostridium difficile infection with Cadazolid and Gram-negative bacterial infections with Imipenem/Cilastin+Relebactam.[13] Despite this, we could not identify any registered trials of these antibiotics in our search.

Table 3. Clinical indication of identified clinical trials stratified by age group being recruited.

Indication	Total (%)	Age group				
		Preterm neonates[a]	Neonates[b]	Infants and toddlers	Children	Adolescents
Unspecified Bacterial Infection	18 (24)	-	11	15	15	14
Lower Respiratory Tract Infection	12 (16)	1	3	12	13	5
Sepsis	11 (14)	-	6	9	9	11
Upper Respiratory Tract	8 (11)	-	1	5	9	7
Intra-abdominal Infection	8 (11)	-	3	5	5	7
Urinary Tract Infection	7 (9)	-	2	6	7	6
Skin and Soft Tissue Infection	6 (8)	-	3	4	4	8
CNS (central nervous system) infection	3 (4)	-	1	4	4	4
Bone and Joint Infection	1 (1)	-	-	1	1	1
		1	30	61	67	63

Age group totals do not add up to total number of clinical trials (76) as some trials contributed to more than one age group.
[a] studies conducted using preterm neonates exclusively.
[b] refers to total number of preterm and term neonates.

Table 4. Comparison of antibiotic development pipeline in adults and children. Adapted from Pew Charitable Trusts "Antibiotics currently in clinical development" pipeline (last accessed October 2016).[12]

Antibiotic	Phase	Manufacturer	Indication	Drug development in Adults	Pediatric Investigation Plan for drug development in Children	Number of open clinical trials in children
WCK 4873	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-

MGB – BP – 3	Phase 1	MGB Pharma Ltd.	*Clostridium difficile* infection	✓	-	-
OP0595	Phase 1	Meiji Seika Pharma Co. Fedora Pharmaceuticals	Bacterial infection	✓	-	-
BAL30072	Phase 1	Basilea Pharmaceuticals	Multidrug resistant Gram negative infections	✓	-	-
CRS3123	Phase 1	Crestone Inc.	*Clostridium difficile* infection	✓	-	-
LCB01 – 0371	Phase 1	Legochem Biosciences Inc.	Bacterial infection	✓	-	-
TD – 1607	Phase 1	Theravance Biopharma Inc.	Acute skin infection, HAP, VAP, bacteraemia	✓	-	-
WCK 2349	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
WCK 771	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
Zidebactam+Cefepime	Phase 1	Wockhardt Ltd.	cUTI, HAP, VAP	✓	-	-
TP – 271	Phase 1	Tetraphase Pharmaceuticals Inc.	CAP	✓	-	-
Aztreonam – Avibactam	Phase 2	Astrazeneca PLC Allergan PLC	cIAI	✓	-	-

MRX – 1	Phase 2	MicuRx Pharmaceuticals Inc.	Acute skin infection (systemic)	✓	-	-
Debio 1450	Phase 2	Debiopharm International SA	Acute skin infection, Staphylococcus *spp*. associated osteomyelitis	✓	-	-
ETX0914	Phase 2	Entasis Therapeutics Inc.	Uncomplicated gonorrhoea	✓	-	-
P0L7080	Phase 2	Polyphor Ltd.	Pseudomonas spp. associated VAP, lower respiratory tract infection, bronchiectasis	✓	-	-
Brilacidin	Phase 2	Cellceutix Corporation	Acute skin infection (systemic)	✓	-	-
Ceftaroline+Avibactam	Phase 2	AstraZeneca PLC Allergan PLC	Bacterial infection	✓	-	-
CG400549	Phase 2	Crystal Genomics Inc.	Acute skin infection, osteomyelitis	✓	-	-
Finafloxacin	Phase 2	MerLion Pharmaceuticals Pte Ltd.	cUTI, cIAI, acute skin infection, pyelonephritis	✓	-	-
Geptidacin	Phase 2	GlaxoSmithKline PLC	cUTI, CAP, uncomplicated urogenital gonorrhoea	✓	-	-
Nemonoxacin	Phase 2	TaiGen Biotechnology Co. Ltd.	CAP, acute skin infection, diabetic foot	✓	-	-
Ramoplanin	Phase 2	Nanotherapeutics Inc.	Prevent recurrent *Clostridium difficile* infection	✓	-	-

Ridinilazole	Phase 2	Summet Therapeutics Inc.	*Clostridium difficile*	✓	-	-
Zabofloxacin	Phase 3	Dong Wha Pharmaceuticals Co. Ltd.	CAP	✓	-	-
S – 649266	Phase 3	Shionogi Inc.	HAP, VAP, cUTI, bloodstream infection	✓	-	-
Omadacycline	Phase 3	Paratek Pharmaceuticals Inc.	CAP, cUTI, acute skin infection	✓	-	-
Lefamulin	Phase 3	Nabriva Therapeutics AC	CAP, HAP, VAP, acute skin infection, osteomyelitis, prosthetic joint infections	✓	-	-
Imipenem / Cilastatin+Relebactam	Phase 3	Merck & Co. Inc.	cUTI, cIAI, HAP, VAP, acute pyelonephritis	✓	✓	-
Iclaprim	Phase 3	Motif Bio PLC	HAP, acute skin infection	✓	-	-
Cadazolid	Phase 3	Actelion Pharmaceuticals Ltd.	*Clostridium difficile*	✓	✓	-
Taksta (fusidic acid)	Phase 3	Cempra Inc.	Acute skin infection, prosthetic joint infection	✓	-	-
Carbavance (Meropenem+Vaborbactam)	Phase 3	Rempex Pharmaceuticals Inc.	cUTI, cIAI, HAP, VAP, febrile neutropenia, bacteraemia, acute pyelonephritis[a]	✓	✓	1
Delafloxacin (Baxdela)	Phase 3	Melinta Therapeutics Inc.	Acute skin infections, CAP, cUTI	✓	Waiver granted	-
Eravacycline	Phase 3	Tetraphase Pharma Inc.	cIAI and cUTI	✓	✓	-

Plazomicin	Phase 3	Achaogen Inc.	cUTI, HAP, VAP, cIAI, catheter-associated bloodstream infection[a]	✓	-	-
Solithromycin	Phase 3	Cempra Inc.	CAP, uncomplicated urogenital gonorrhoea, urethritis	✓	✓	2

CAP, Community-acquired pneumonia; cIAI, complicated Intra-abdominal Infection; UTI, complicated Urinary Tract Infection; HAP, hospital-acquired pneumonia; VAP, ventilator-acquired pneumonia.
[a] target carbapenem resistant Enterobacteriaceae

DISCUSSION

Our search identified 76 clinical trials investigating one or more antibiotics recruiting children between birth and 18 years of age. This is low in comparison to the number of on-going trials in adults, despite children representing nearly a quarter of the global population.[14,15] A review of completed CTs in the U.S. between 2000 and 2010 identified a total of 4078 adult trials compared to just 294 that had recruited children.[16] In our study, the lack of trials recruiting neonates is striking. Just 23 of the 76 trials identified were recruiting neonates and just 8 CTs globally were recruiting preterm neonates. There are broadly two types of pediatric trials conducted globally: pharmaceutical-led Phase 1/2 PK and safety trials (n=17) in the HIC setting, or investigator-led, often pragmatic, late phase efficacy trials in the LMIC setting (n=34), with a greater proportion of on-going trials being sponsored by non-profit organisations over industry (66% compared to 34%). As of April 2016, there were 17 antibiotic PIPs agreed by the EMA,[8] covering a range of indications, most commonly cSSTI, complicated IAI (cIAI), and complicated UTI (cUTI).[13] In contrast, treatments for respiratory and systemic infections, the most common clinical indications for antibiotics in pediatrics, are not currently being evaluated.[14] Thirty-seven antibiotics are being developed in adults, yet to our knowledge just 2 of these are being studied in children. Some classes of antibiotics that may be of higher risk for children (tetracyclines and fluoroquinolones) may not be pursued as aggressively for pediatric approvals due to well-recognized issues of toxicity, particularly when safer alternatives are widely available. Given that Gram-negative sepsis is a growing problem in neonates, with a significant increase in the proportion of multi-resistant Gram-negative pathogens,[15] the substantial lag time between the submission date (for PIP or waiver) and declared completion date of PK studies in adults is a real concern; however, there is value in generating substantial safety data in adults prior to exposing children and newborns to potentially toxic new agents.

In 2013, a similar review of European pediatric clinical trials identified 31 trials of antibiotics approved for adults by the EMA in 2000 that were recruiting children in Europe (compared to the 22 that we identified). They included both published and ongoing trials, which likely accounts for the higher number of trials reported. They also found a very small proportion of neonatal trials (2 of 31), as well as a greater proportion of efficacy-based trials.[9] A review of interventional trials registered with *ClinicalTrials.gov* between 2007 and 2010 found that only 17% had recruited children below 18 years of age.[17] A similar review of antimicrobial CTs conducted in the U.S. between 2000 and 2012 reported that just 5% had recruited only children compared to 74% that recruited only adults, and that, as we have found, the trials were sponsored primarily by non-profit organisations (60% versus 30% by industry).[16] In our search of global trials, 39% of registered CTs reported collection of PK data in comparison to the 24% identified in a 2009 paediatric PK research review.[18]

The search strategy used has clear limitations. Since the search was limited to clinical trials registered with *ClinicalTrials.gov*, it is possible that other open or on-going trials registered with alternative platforms (for example, the WHO International Clinical Trials Registry Platform [ICTRP]) will have been missed. Together with *ClinicalTrials.gov* these could help to establish the entirety of current clinical research in this field. We did however search EudraCT, and found no further studies beyond those captured on *ClinicalTrials.gov*. Our search was also limited to open CTs, thereby missing active but not yet recruiting trials, and those that had already closed to recruitment. The information recorded for each trial registered with *ClinicalTrials.gov* is updated by the trial investigators, and therefore relies on them to periodically update the registry. Occasionally, information such as recruitment status might not be updated in real time.

Concerns around the growing threat of antimicrobial resistance have prompted several new initiatives. In 2016, the EMA published a draft Concept Paper to propose the development of an Addendum to the guideline on the evaluation of new anti-bacterial products for treatment of bacterial infections in children.[19] At the same time, the Clinical Trials Transformation Initiative (CTTI) is currently focused on the identification of key barriers in the conduct of pediatric antibacterial CTs, which hamper their successful implementation into clinical practice.[20] Recent evidence states that overall, antibiotic CTs make up less than 1% of all registered pediatric CTs, and that trial completion is slow, with an average time to completion of around two years.[21] There are specific areas where the design and conduct of pediatric antibiotic CTs can be harmonized and simplified, such as the standardisation of the inclusion and exclusion criteria for specific Clinical Infection Syndromes, and improved bridging of safety and efficacy data from other age groups; these advances could improve trial conduct and efficiency in children.[22]

CONCLUSIONS

This review highlights that very few pediatric antibiotic CTs are being conducted globally, particularly in neonates. There is a marked disparity between antibiotic drug development programmes in adults and children. Many issues contribute to the difficulties in conducting pediatric antibiotic clinical trials. The lack of regulatory guidance, vulnerability of this population, issues with informed consent and assent, and lack of research-experienced hospital personnel all present challenges in study design, delivery and recruitment. Delays in the initial start-up of CTs in children due to pediatric-specific protocol issues and complicated ethical approval continue to discourage both academic and pharmaceutical interest. The limited data presented here suggest that the dismal state of pediatric antibiotic research continues. Earlier collaboration between global academic research networks and pharmaceutical companies is now vital to accelerate progress.

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LIST OF FIGURES

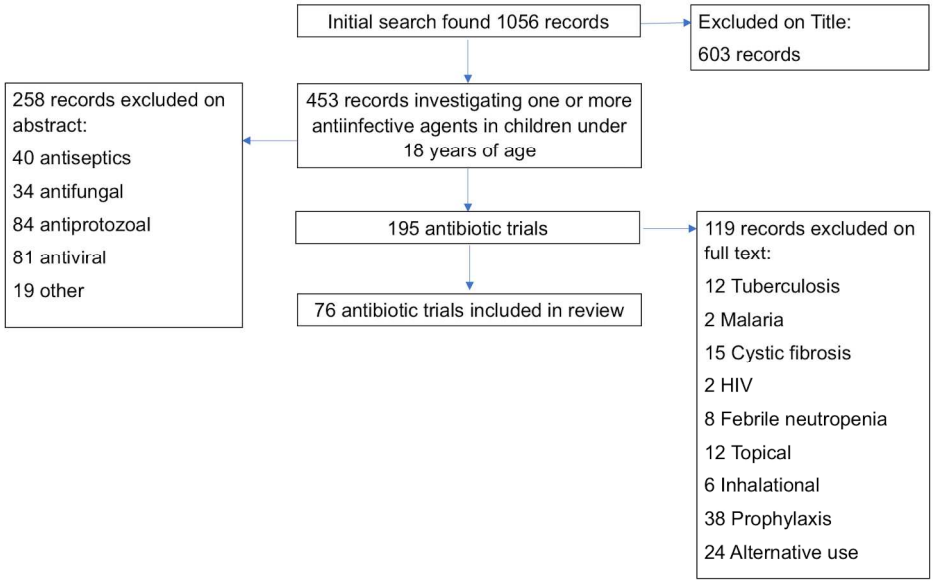

Figure 1. Flow Chart. Clinical trial selection process.

254x190mm (300 x 300 DPI)

DATASET

	A	B	C	D
1	**NCT Number**	**Title**	**Recruitment**	**Study Results**
2	NCT02539407	Population Pharmacokinetics of Anti-infectives in Critically Ill Children	Recruiting	No Results Available
3	NCT02935374	Effect of Antimicrobial Treatment of Acute Otitis Media on the Intestinal Microbiome in Children	Not yet recruiting	No Results Available
4	NCT02899143	Short-course Antimicrobial Therapy in Sepsis	Recruiting	No Results Available
5	NCT01595529	The SCOUT Study: Short Course Therapy for Urinary Tract Infections in Children	Recruiting	No Results Available
6	NCT02380352	Short-course Antimicrobial Therapy for Paediatric Respiratory Infections	Not yet recruiting	No Results Available
7	NCT02891915	Trial to Evaluate Beta-Lactam Antimicrobial Therapy of Community Acquired Pneumonia in Child	Recruiting	No Results Available
8	NCT02746276	Optimising Antibiotic Treatment for Sick Malnourished Children	Recruiting	No Results Available
9	NCT02917551	BALANCE on the Wards: A Pilot RCT	Not yet recruiting	No Results Available
10	NCT01243437	A Clinical Trial to Evaluate the Safety and Efficacy of Ciprofloxacin in the Treatment of Plague in	Recruiting	No Results Available
11	NCT02635191	Tailored Therapy for Helicobacter Pylori in Children	Recruiting	No Results Available
12	NCT01522105	Daptomycin in Pediatric Patients With Bacterial Meningitis	Recruiting	No Results Available
13	NCT02456974	Antibiotic Dosing in Pediatric Intensive Care	Recruiting	No Results Available
14	NCT00579956	A Randomized Double Blinded Comparison of Ceftazidime and Meropenem in Severe Melioidosis	Recruiting	No Results Available
15	NCT00545961	Middle Meatal Bacteriology During Acute Respiratory Infection in Children	Not yet recruiting	No Results Available
16	NCT01431326	Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care	Recruiting	No Results Available
17	NCT02475876	PK of Clindamycin and Trimethoprim-sulfamethoxazole in Infants and Children	Recruiting	No Results Available
18	NCT01420341	Co-trimoxazole as Maintenance Therapy for Meliodosis	Recruiting	No Results Available
19	NCT02266706	Pharmacokinetic and Safety Study of Ceftolozane/Tazobactam in Pediatric Participants Receiving	Recruiting	No Results Available
20	NCT00867789	Antibiotics Versus Placebo in the Treatment of Abscesses in the Emergency Department	Recruiting	No Results Available
21	NCT02879981	A Safety Study of Balsamic Bactrim in Pediatric Participants With Acute Bronchitis	Not yet recruiting	No Results Available
22	NCT01269541	MESS-study MRSA Eradication Study Skl´ne	Recruiting	No Results Available
23	NCT02276482	Study of Tedizolid Phosphate in Adolescents With Complicated Skin and Soft Tissue Infections (cS	Recruiting	No Results Available
24	NCT02663596	Safety and TDM of Continuous Infusion Vancomycin Through Continuous Renal Replacement Th	Not yet recruiting	No Results Available
25	NCT02555059	Special Drug Use Investigation of Ciproxan Injection in Pediatrics	Recruiting	No Results Available
26	NCT02297815	Comparative Effectiveness of Antibiotics for Respiratory Infections	Recruiting	No Results Available
27	NCT02224040	Typhoid Fever: Combined vs. Single Antibiotic Therapy	Recruiting	No Results Available
28	NCT02775968	Population Pharmacokinetics of Cephalosporins and Macrolides in Chinese Children With Comm	Not yet recruiting	No Results Available
29	NCT02687906	Dose-finding, Pharmacokinetics, Safety, and Tolerability of Meropenem-Vaborbactam in Pediatr	Recruiting	No Results Available
30	NCT02783859	Hospitalised Pneumonia With Extended Treatment (HOPE) Study	Recruiting	No Results Available
31	NCT01994993	Antibiotic Safety (SCAMP)	Recruiting	No Results Available

	A	B	C	D
32	NCT02258763	Trial on the Ideal Duration of Oral Antibiotics in Children With Pneumonia	Recruiting	No Results Available
33	NCT02688790	Study Evaluate the PK Profile of Dalbavancin in Hospitalized Infants and Neonates Patients With	Recruiting	No Results Available
34	NCT00323219	Oral Moxifloxacin Versus Cefazolin and Oral Probenecid in the Management of Skin and Soft Tiss	Recruiting	No Results Available
35	NCT02750761	A Study of Oral and Intravenous (IV) Tedizolid Phosphate in Hospitalized Participants, Ages 2 to	Recruiting	No Results Available
36	NCT02466438	Safety and Pharmacokinetics of Piperacillin-tazobactam Extended Infusion in Infants and Childre	Recruiting	No Results Available
37	NCT02260102	Temocillin Pharmacokinetics in Paediatrics	Not yet recruiting	No Results Available
38	NCT02694458	Comparison of Two Dosage Adjustment Strategies of Vancomycin in Children	Recruiting	No Results Available
39	NCT01540838	Slow Initial beta-lactam Infusion With High-dose Paracetamol to Improve the Outcomes of Child	Recruiting	No Results Available
40	NCT00368498	A Trial to Evaluate the Loading Dose Required to Achieve Therapeutic Serum Teicoplanin Concer	Recruiting	No Results Available
41	NCT01785641	Single Versus Combined Antibiotic Therapy for Bacterial Peritonitis in CAPD Patients	Recruiting	No Results Available
42	NCT02554383	Efficacy of Antibiotics in Children With Acute Sinusitis: Which Subgroups Benefit?	Recruiting	No Results Available
43	NCT01265173	Comparison of Efficacy of Cefotaxime, Ceftriaxone, and Ciprofloxacin for the Treatment of Spont	Recruiting	No Results Available
44	NCT02335905	Ceftaroline for Treatment of Hematogenously Acquired Staphylococcus Aureus Osteomyelitis in	Recruiting	No Results Available
45	NCT02922686	Penicillin for the Emergency Department Outpatient Treatment of CELLulitis	Not yet recruiting	No Results Available
46	NCT02848820	Initial Non-operative Treatment Strategy Versus Appendectomy Treatment Strategy for Simple A	Not yet recruiting	No Results Available
47	NCT02475733	Evaluation of Safety,Pharmacokinetics and Efficacy of CAZ-AVI With Metronidazole in Children A	Recruiting	No Results Available
48	NCT02372461	Randomized Trial of Amoxicillin Versus Placebo for (Fast Breathing) Pneumonia	Recruiting	No Results Available
49	NCT01553006	Study of Cefditoren Pivoxil in Treatment of Childhood With Acute Rhinosinusitis	Recruiting	No Results Available
50	NCT02527681	Pharmacokinetics and Safety of Ceftobiprole in Neonates and Infants up to 3 Months Treated W	Recruiting	No Results Available
51	NCT02210169	RCT of Continuous Versus Intermittent Infusion of Vancomycin in Neonates	Recruiting	No Results Available
52	NCT02497781	Evaluation of Safety, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam (CAZ-AVI) Co	Recruiting	No Results Available
53	NCT02814916	Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Children,	Not yet recruiting	No Results Available
54	NCT02210325	Efficacy and Safety Study of Oral Solithromycin Compared to Intramuscular Ceftriaxone Plus Ora	Recruiting	No Results Available
55	NCT02801370	Phase 3 Study of OTO-201 in Acute Otitis Externa	Recruiting	No Results Available
56	NCT02760420	3 Days Amoxicillin Versus Placebo for Fast Breathing Childhood Pneumonia in Malawi	Recruiting	No Results Available
57	NCT02678195	3 Days Versus 5 Days Amoxicillin for Chest-indrawing Childhood Pneumonia in Malawi	Recruiting	No Results Available
58	NCT02605122	Safety and Efficacy of Solithromycin in Adolescents and Children With Community-acquired Bact	Recruiting	No Results Available
59	NCT02570490	Oral Sodium Fusidate (CEM-102) Versus Oral Linezolid for the Treatment of Acute Bacterial Skin	Recruiting	No Results Available
60	NCT02443285	Is Spontaneous Bacterial Peritonitis Still Responding to 3rd Generation Cephalosporins?	Recruiting	No Results Available
61	NCT02334124	Comparing the Intravenous Treatment of Skin Infections in Children, Home Versus Hospital	Recruiting	No Results Available
62	NCT02218372	A Study to Investigate the Safety and Efficacy of Fidaxomicin (Oral Suspension or Tablets) and Va	Recruiting	No Results Available

	A	B	C	D
63	NCT01032499	Open and Comparative Study to Measure Tolerability and Efficacy of Taro Elixir	Not yet recruiting	No Results Available
64	NCT02598362	Pharmacokinetics of Ciprofloxacin in Pediatric Patients	Recruiting	No Results Available
65	NCT02878031	Community Case Management of Chest Indrawing Pneumonia	Recruiting	No Results Available
66	NCT02790996	Neonatal Vancomycin Trial	Not yet recruiting	No Results Available
67	NCT02712307	Study of 5 and 10 Days Treatment With Penicillin Against Sore Throat Caused by Streptococci	Recruiting	No Results Available
68	NCT02424734	Safety, Tolerability and Efficacy of Ceftaroline in Paediatrics With Late-Onset Sepsis	Recruiting	No Results Available
69	NCT02134301	Open-Label, Dose-Finding, Pharmacokinetics, Safety and Tolerability Study of Oritavancin in Ped	Recruiting	No Results Available
70	NCT02013141	An Open-Label Study of the Pharmacokinetics of a Single Dose of Telavancin in Pediatric Subject	Recruiting	No Results Available
71	NCT01427842	Dose Enhancement of Vancomycin IN Everyday Patients	Recruiting	No Results Available
72	NCT01278017	The Role of Short-course Ceftriaxone Therapy in the Treatment of Severe Nontyphoidal Salmone	Recruiting	No Results Available
73	NCT00988026	Safety and Efficacy Comparison of Minocycline Microgranules Versus Lymecycline in the Treatm	Recruiting	No Results Available
74	NCT02288234	Telavancin Observational Use Registry (TOUR)	Recruiting	No Results Available
75	NCT01304459	Vancomycin Serum Concentrations in Pediatric Oncology Patients Under Intensive Care	Recruiting	No Results Available
76	NCT01173575	Assessment of the Efficacy of FOSFOMYCIN in Patients With Bacterial Infection	Recruiting	No Results Available
77	NCT01778634	Trial of Intravenous Azithromycin to Eradicate Ureaplasma Respiratory Tract Infection in Preterm	Recruiting	No Results Available

	E	F
1	**Indication**	**Infection category**
2	Proven or suspected infection (in patients on PICU)	9
3	Acute Otitis Media	3
4	Sepsis	8
5	Urinary Tract Infections (UTI)	7
6	Community-acquired Pneumonia (CAP)	4
7	Pneumonia	4
8	Proven or suspected infection in patients with malnutrition	9
9	Bacteremia	8
10	Plague	8
11	Helicobacter Pylori Infection	7
12	Meningitis	1
13	Proven or suspected bacterial infection (Pharmacokinetics)	9
14	Melioidosis	8
15	Acute Respiratory Infection|Sinusitis	3
16	Various infections (including nosocomial Pneumonia, CAP, Acute Bac	Various
17	Bacterial Infections	9
18	Meliodosis	8
19	Proven or Suspected Gram-negative Bacterial Infection	9
20	Abscess	1
21	Bronchitis	4
22	Throatcarriers of MRSA	3
23	Acute Skin and Soft Tissue infections (aSSTIs)	2
24	Proven or suspected bacterial infection (in CRRT patients)	9
25	Cystitis / Pyelonephritis	7
26	Acute Upper Respiratory Tract Infections (ARTIs)	3
27	Typhoid Fever	8
28	Community Acquired Pneumonia (CAP)	4
29	Bacterial Infections	9
30	Pneumonia	4
31	Complicated Intra Abdominal Infections (cIAIs)	6

	E	F
32	Pneumonia	4
33	Bacterial Infections	9
34	Cellulitis	2
35	Gram-Positive Bacterial Infections	9
36	Infection	9
37	Urinary Tract Infection or suspected Cholangitis	7
38	Methicillin-resistant Staphylococcal Infections	9
39	Bacterial Meningitis	1
40	Staphylococcal Infections	9
41	Peritonitis (in CAPD patients)	6
42	Acute Sinusitis (Respiratory Tract Infections)	3
43	SBP in patients with Liver Cirrhosis	6
44	Hematogenously Acquired Staphylococcus Aureus Osteomyelitis	5
45	Cellulitis or Wound Infection	8
46	Appendicitis	6
47	Complicated Intra-abdominal Infections (cIAIs)	6
48	Pneumonia (fast-breathing)	4
49	Rhinosinusitis	3
50	Bacterial Infections	9
51	Sepsis	8
52	Complicated Urinary Tract Infections (cUTIs)	7
53	Methicillin-Resistant Staphylococcus Aureus Skin Infection	2
54	Uncomplicated Urogenital Gonorrhea	7
55	Acute Otitis Externa	3
56	Pneumonia	4
57	Pneumonia	4
58	Community-acquired Bacterial Pneumonia	4
59	Acute Bacterial Skin and Skin Structure Infections	2
60	Primary Bacterial Peritonitis	6
61	Cellulitis	8
62	Clostridium Difficile-associated Diarrhea (CDAD)	6

	E	F
63	Acne Vulgaris II or III Degree	2
64	Urinary Tract Infection or Pyelonephritis	7
65	Pneumonia	4
66	Late Onset Neonatal Sepsis	8
67	Tonsillitis	3
68	Late-onset Sepsis	8
69	Gram Positive Bacterial Infections	9
70	Gram-Positive Bacterial Infections	9
71	Vancomycin Therapy	9
72	Diarrhea	6
73	Mild to Moderate Acne	2
74	Hospital Acquired Bacterial Pneumonia (HAP), Complicated Skin and	Various
75	Infection	9
76	Bacterial Infection	9
77	Eradicate ureaplasma respiratory tract infection from preterm infant	4

	G	H	I	J
1	**Interventions**	**Antibiotic class (J01 code)**	**Gender**	**Age**
2	Antiinfectives (beta-lactam, aminoglycoside, glycopeptide, fluoroquinolone,	Various	Both	Up to 18 Years
3	Amoxicillin, Amoxicillin-Potassium Clavulanate, Macrolide	Various	Both	6 Months to 7 Years
4	Antibiotic	J01	Both	Up to 18 years
5	Trimethoprim sulfamethoxazole, cefixime, or cephalexin	Various	Both	2 Months to 10 Years
6	Amoxicillin	J01C	Both	6 Months to 10 Years
7	Amoxicillin, Amoxicillin-clavulanate, Cefdinir	Various	Both	6 Months to 71 Months
8	Ceftriaxone, Metronidazole	J01D	Both	2 Months to 59 Months
9	7 days vs 14 days of adequate antibiotic treatment	J01	Both	Up to 18 years
10	Ciprofloxacin, doxyxcycline	Various	Both	8 Years and older
11	Tailored vs standard therapy (Amoxicillin, Clarithromycin, Metronidazole, Ra	Various	Both	4 Years to 18 Years
12	Daptomycin	J01X	Both	3 Months to 16 Years
13	Amoxicillin-clavulanate, Piperacilline-tazobactam, Vancomycin	Various	Both	Up to 16 Years
14	Meropenem, Ceftazidime	J01D	Both	15 Years and older
15	Amoxicillin clavulanate acid	J01C	Both	6 Years to 13 Years
16	Various drugs (Ceftazidime, Ciprofloxacin, Clindamycin, Doxycycline, Levoflo	Various	Both	Up to 18 years
17	Clindamycin, Trimethoprim-sulfamethoxazole	Various	Both	1 Month to 16 Years
18	Co-trimoxazole	J01E	Both	15 Years and older
19	Ceftolozane/Tazobactam	J01D	Both	Up to 17 Years
20	Trimethoprim-sulfamethoxazole	J01E	Both	3 Months to 17 Years
21	Guaifenesin, Sulfamethoxazole trimethoprim	J01E	Both	4 Years to 14 Years
22	Systemic Rifampin and Clindamycine/Trimehoprimsulfa, or Topical mupiroci	Various	Both	5 Years and older
23	Tedizolid Phophate	J01X	Both	12 Years to 18 Years
24	Vancomycin	J01X	Both	Up to 18 years
25	Ciprofloxacin	J01F	Both	Up to 14 Years
26	Antibiotics (Amoxicillin-clavulanate, azithromycin, cefdinir, cefprozil, cefurox	Various	Both	6 Months to 18 Years
27	Ceftriaxone, Ceftriaxone/azithromycin, Azithromycin, Azithromycin/cefixime	Various	Both	2 Years to 80 Years
28	Cephalosporins and Macrolides	Various	Both	1 Year to 18 Years
29	Carbavance	J01D	Both	Up to 17 Years
30	Amoxicillin-clavulanic Acid	J01C	Both	3 Months to 5 Years
31	Ampicillin/metronidazole/gentamicin/clindamycin/Piperacillin-tazobactam c	Various	Both	Up to 120 Days

	G	H	I	J
32	Amoxicillin-Potassium Clavulanate	J01C	Both	3 Months to 59 Months
33	Dalbavancin	J01X	Both	Up to 28 Days
34	Cefazolin/Moxifloxacin	Various	Both	Up to 18 Years
35	Tedizolid Phosphate	J01X	Both	2 Years to 11 Years
36	Piperacillin-tazobactam	J01C	Both	2 Months to 6 Years
37	Temocillin	J01C	Both	6 Months to 3 Years
38	Vancomycin	J01X	Both	1 Month to 16 Years
39	Beta-lactam	J01C	Both	2 Months to 15 Years
40	Teicoplanin	J01X	Both	16 Years and older
41	Ceftazidime/ciprofloxacin, Ceftazidime, Cefazolin/gentamicin, Cefazolin	Various	Both	15 Years and older
42	Amoxicillin-clavulanate	J01C	Both	2 Years to 11 Years
43	Cefotaxime, Ceftriaxone, Ciprofloxacin	Various	Both	16 Years and older
44	Ceftaroline Fosamil	J01D	Both	1 Year to 17 Years
45	Flucloxacillin, Phenoxymethylpenicillin	J01C	Both	16 Years and older
46	Augmentin/Gentamicin, Appendectomy	J01C	Both	7 Years to 17 Years
47	Ceftazidime-avibactam, Meropenem, Metronidazole	Various	Both	3 Months to 18 Years
48	Amoxicillin	J01C	Both	2 Months to 59 Months
49	Cefditoren pivoxil	J01D	Both	1 Year to 15 Years
50	Ceftobiprole	J01D	Both	Up to 3 Months
51	Vancomycin	J01X	Both	Up to 90 Days
52	Ceftazidime-avibactam, Cefepime	J01D	Both	3 Months to 18 Years
53	Dalbavancin single dose	J01X	Both	3 Months to 17 Years
54	Solithromycin, Ceftriaxone, Azithromycin	Various	Both	15 Years and older
55	Ciprofloxacin	J01M	Both	6 Months and older
56	Amoxicillin	J01C	Both	2 Months to 59 Months
57	Amoxicillin	J01C	Both	2 Months to 59 Months
58	Solithromycin	J01F	Both	2 Months to 17 Years
59	Sodium fusidate, Linezolid	J01X	Both	12 Years and older
60	Cefotaxime, Ceftriaxone	J01D	Both	Up to 18 Years
61	Ceftriaxone, Flucloxacillin	Various	Both	6 Months to 18 Years
62	Fidaxomicin, Vancomycin	J01X	Both	Up to 17 Years

	G	H	I	J
63	Taro Elixir	J01A	Both	14 Years and older
64	Ciprofloxacin	J01M	Both	3 Months to 17 Years
65	Amoxicillin	J01C	Both	2 Months to 59 Months
66	Vancomycin	J01X	Both	Up to 90 Days
67	Phenoxymethylpenicillin	J01C	Both	6 Years and older
68	Ceftaroline Fosamil	J01D	Both	Up to 59 Days
69	Oritavancin	J01X	Both	Up to 18 Years
70	Telavancin	J01X	Both	1 Year to 17 Years
71	Vancomycin	J01X	Both	16 Years and older
72	Ceftriaxone	J01D	Both	3 Months to 18 Years
73	Minocycline, Lymecycline	J01A	Both	14 Years to 30 Years
74	Telavancin	J01X	Both	Up to 18 Years
75	Vancomycin	J01X	Both	Up to 18 Years
76	Fosfomycin	J01X	Both	Up to 18 Years
77	Azithromycin	J01F	Both	0 to 72 hours

	K	L	M	N	O
1	**Age group**	**Estimated enrollment**	**Location**	**Income class**	**Geographic region**
2	8	1850	France	High income	Europe
3	9	150	Finland	High income	Europe
4	8	320	Italy	High income	Europe
5	9	746	United States	High income	North America
6	9	270	Canada	High income	North America
7	9	400	United States	High income	North America
8	9	80	Kenya	Lower middle income	Africa
9	8	50	Canada	High income	North America
10	11	200	Uganda	Low income	Africa
11	11	200	China	Upper middle income	Asia
12	10	5	Switzerland	High income	Europe
13	8	200	Belgium	High income	Europe
14	5	750	Thailand	Upper middle income	Asia
15	11	120	Finland	High income	Europe
16	8	3000	Various (United States, Canad	High income	International
17	10	54	United States	High income	North America
18	5	800	Thailand	Upper middle income	Asia
19	8	36	United States	High income	North America
20	10	200	United States	High income	North America
21	11	50	Peru	Upper middle income	Latin America
22	11	69	Sweden	High income	North America
23	5	162	Various (United States, Argent	Upper middle to High income	International
24	8	10	United States	High income	North America
25	8	45	Japan	High income	Asia
26	10	117000	United States	High income	North America
27	11	120	Nepal	Low income	Asia
28	10	750	China	Upper middle income	Asia
29	8	56	United States	High income	North America
30	9	314	Various (Australia, Malaysia)	High income	Oceania
31	6	284	Various (United States, Canad	High income	North America

	K	L	M	N	O
32	9	300	Malaysia	Upper middle income	Asia
33	2	24	United States	High income	North America
34	8	390	Canada	High income	North America
35	4	32	United States	High income	North America
36	9	141	Canada	High income	North America
37	9	45	Belgium	High income	Europe
38	10	100	France	High income	Europe
39	10	400	Angola	Upper middle income	Africa
40	5	20	Taiwan, China	High income	Asia
41	5	300	Thailand	Upper middle income	Asia
42	4	688	United States	High income	North America
43	5	261	Republic of Korea	High income	Asia
44	10	18	United States	High income	North America
45	5	414	Ireland	High income	Europe
46	11	334	Netherlands	High income	Europe
47	10	102	Various (United States, Argent	Upper middle to High income	International
48	9	2500	Pakistan	Lower middle income	Asia
49	10	120	Thailand	Upper middle income	Asia
50	6	45	Various (Belgium, Germany, Li	High income	Europe
51	6	200	Australia	High income	Oceania
52	10	102	Various (United States, Czech	Upper middle to High income	International
53	10	300	United States	High income	North America
54	5	300	Various (United States, Austra	High income	International
55	10	500	Various (United States, Canad	High income	North America
56	9	2000	Malawi	Low income	Africa
57	9	2000	Malawi	Low income	Africa
58	10	400	Various (United States, Bulgar	High income	International
59	5	712	Various (United States, Puerto	High income	International
60	8	100	Egypt	Lower middle income	Africa
61	10	188	Australia	High income	Oceania
62	8	144	Various (United States, Belgiu	High income	International

	K	L	M	N	O
63	5	120	Brazil	Upper middle income	Latin America
64	10	20	Belgium	High income	Europe
65	9	308	Nigeria	Lower middle income	Africa
66	6	300	Various (United Kingdom, Fra	High income	Europe
67	11	432	Sweden	High income	Europe
68	7	24	Various (United States, Hunga	High income	International
69	8	60	United States	High income	North America
70	10	32	United States	High income	North America
71	5	100	Australia	High income	Oceania
72	10	200	Taiwan, China	High income	Asia
73	5	168	Mexico	High income	North America
74	8	1000	United States	High income	North America
75	8	50	Brazil	Upper middle income	Latin America
76	8	200	Various (Austria, Germany)	High income	Europe
77	1	180	United States	High income	North America

	P	Q	R	S	T
1	**Collaborators**	**Sponsor**	**Study Types**	**Phase**	**Endpoint classification**
2	Assistance Publique - Hopitaux de Paris	Hospital	Observational	Not applicable	Pharmacokinetics
3	University of Oulu|Oulu University Hospital	University	Interventional	Phase 4	Efficacy
4	Ospedale Santa Maria delle Croci	Hospital	Interventional	Phase 2	Safety/Efficacy
5	Children's Hospital of Philadelphia|Children's Ho	Hospital	Interventional	Phase 2	Safety/Efficacy
6	Hamilton Health Sciences Corporation|Children's	Hospital	Interventional	Phase 4	Safety/Efficacy
7	National Institute of Allergy and Infectious Diseas	NIH	Interventional	Phase 4	Efficacy
8	University of Oxford|KEMRI Wellcome Trust Rese	University	Interventional	Phase 2	Pharmacokinetics
9	Sunnybrook Health Sciences Centre	Hospital	Interventional	Not specified	Efficacy
10	Centers for Disease Control and Prevention|MRC	CDC	Interventional	Phase 2	Safety/Efficacy
11	Beijing Children's Hospital	Hospital	Interventional	Phase 4	Safety/Efficacy
12	University Hospital Inselspital, Berne	Hospital	Interventional	Phase 1	Pharmacokinetics
13	University Hospital, Ghent|University Hospital, A	Hospital	Observational	Not applicable	Pharmacokinetics
14	University of Oxford|Mahidol University|Wellcor	University	Interventional	Not specified	Efficacy
15	Oulu University Hospital	University	Interventional	Phase 4	Safety/Efficacy
16	Daniel Benjamin|Eunice Kennedy Shriver Nationa	University	Observational	Not applicable	Pharmacokinetics
17	Michael Cohen-Wolkowiez|Eunice Kennedy Shriv	University	Interventional	Phase 1	Pharmacokinetics
18	Khon Kaen University	University	Interventional	Not specified	Efficacy
19	Cubist Pharmaceuticals LLC	Industry	Interventional	Phase 1	Pharmacokinetics
20	Children's Mercy Hospital Kansas City|Blue Cross	Hospital	Interventional	Not specified	Efficacy
21	Hoffmann-La Roche	Industry	Observational	Not applicable	Safety
22	Region Skane	Hospital	Interventional	Not specified	Efficacy
23	Cubist Pharmaceuticals LLC	Industry	Interventional	Phase 3	Safety
24	Drexel University|The Center for Pediatric Pharm	University	Interventional	Phase 1	Safety
25	Bayer	Industry	Observational	Not applicable	Safety/Efficacy
26	Children's Hospital of Philadelphia	Hospital	Observational	Not applicable	Safety/Efficacy
27	Sheba Medical Center	Hospital	Interventional	Phase 4	Efficacy
28	Beijing Children's Hospital	Hospital	Observational	Not applicable	Pharmacokinetics
29	Rempex Pharmaceuticals (a wholly owned subsid	Industry	Interventional	Phase 1	Safety
30	Menzies School of Health Research|Griffith Univ	University	Interventional	Phase 4	Safety/Efficacy
31	Michael Cohen-Wolkowiez|The EMMES Corporat	University	Interventional	Phase 2-3	Safety

	P	Q	R	S	T
32	University of Malaya|Menzies School of Health R	University	Interventional	Phase 4	Efficacy
33	Durata Therapeutics Inc., an affiliate of Allergan p	Industry	Interventional	Phase 1	Pharmacokinetics
34	University of British Columbia	University	Interventional	Phase 3	Efficacy
35	Merck Sharp & Dohme Corp.	Industry	Interventional	Phase 1	Pharmacokinetics
36	St. Justine's Hospital	Hospital	Interventional	Phase 1	Pharmacokinetics
37	Universitì© Catholique de Louvain	University	Interventional	Phase 4	Pharmacokinetics
38	Assistance Publique - Hì«pitaux de Paris	Hospital	Interventional	Not specified	Pharmacokinetics
39	Helsinki University|Foundation for Paediatric Res	University	Interventional	Phase 4	Safety/Efficacy
40	National Taiwan University Hospital	University	Interventional	Phase 4	Pharmacokinetics
41	Chulalongkorn University	University	Interventional	Not specified	Efficacy
42	University of Pittsburgh|National Institute of Alle	University	Interventional	Phase 3	Safety/Efficacy
43	Korea University	University	Interventional	Phase 4	Efficacy
44	Baylor College of Medicine|Forest Laboratories	University	Interventional	Phase 1-2	Safety/Efficacy
45	Royal College of Surgeons, Ireland|Health Resear	University	Interventional	Phase 4	Efficacy
46	Ramon Gorter|ZonMw: The Netherlands Organis	University	Interventional	Phase 4	Efficacy
47	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2	Safety/Efficacy
48	Aga Khan University	University	Interventional	Not specified	Efficacy
49	Thammasat University	University	Interventional	Phase 4	Safety/Efficacy
50	Basilea Pharmaceutica	Industry	Interventional	Phase 1	Pharmacokinetics
51	Murdoch Childrens Research Institute|Royal Chil	University	Interventional	Not specified	Pharmacokinetics
52	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2	Safety/Efficacy
53	Durata Therapeutics Inc., an affiliate of Allergan p	Industry	Interventional	Phase 3	Safety/Efficacy
54	Cempra Inc|National Institute of Allergy and Infe	Industry	Interventional	Phase 3	Efficacy
55	Otonomy, Inc.	Industry	Interventional	Phase 3	Efficacy
56	Save the Children|University of North Carolina|U	Health Organisat	Interventional	Phase 4	Efficacy
57	Save the Children|University of North Carolina|U	Health Organisat	Interventional	Phase 4	Efficacy
58	Cempra Inc	Industry	Interventional	Phase 2-3	Safety/Efficacy
59	Cempra Inc	Industry	Interventional	Phase 3	Safety/Efficacy
60	Tanta University	University	Interventional	Phase 3	Efficacy
61	Murdoch Childrens Research Institute	University	Interventional	Not specified	Efficacy
62	Astellas Pharma Europe B.V.|Merck Sharp & Doh	Industry	Interventional	Phase 3	Safety/Efficacy

	P	Q	R	S	T
63	Laboratorios Goulart S.A.	Industry	Interventional	Phase 3	Safety/Efficacy
64	University Hospital, Ghent|Universitair Ziekenhu	University	Interventional	Phase 4	Pharmacokinetics
65	Malaria Consortium|World Health Organization	Health Organisat	Interventional	Phase 4	Safety
66	PENTA Foundation|St George's, University of Lor	Health Organisat	Interventional	Phase 2	Safety/Efficacy
67	Sigvard Mì¦lstad|Public Health Agency of Swede	University	Interventional	Phase 4	Safety/Efficacy
68	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2-3	Safety/Efficacy
69	The Medicines Company	Industry	Interventional	Phase 1	Pharmacokinetics
70	Theravance Biopharma Antibiotics, Inc.	Industry	Interventional	Phase 4	Pharmacokinetics
71	The Canberra Hospital	Hospital	Interventional	Phase 2	Pharmacokinetics
72	Chang Gung Memorial Hospital	Hospital	Interventional	Phase 4	Efficacy
73	Darier	Industry	Interventional	Phase 4	Safety/Efficacy
74	Theravance Biopharma Antibiotics, Inc.	Industry	Observational	Not applicable	Safety/Efficacy
75	Grupo de Apoio ao Adolescente e a Crianca com	Hospital	Observational	Not applicable	Pharmacokinetics
76	Infectopharm Arzneimittel GmbH|J&P Medical R	Industry	Observational	Not applicable	Efficacy
77	University of Maryland	University	Interventional	Phase 2	Safety/Efficacy

	U	V	W	X	Y	Z	AA	AB
1	**Primary outcome variable**	**PK data collected**	**First Receive**	**Start Date**	**Completion I**	**Last Updated**	**Last Verified**	**Results First Received**
2	PK	PK study design	July 2, 2015	Sep-15	Dec-18	September 1	Sep-16	No Study Results Posted
3	Efficacy	No PK data	September 2	Oct-16	null	October 12, 2	Oct-16	No Study Results Posted
4	Efficacy	No PK data	September 8	Sep-16	null	September 1	Sep-16	No Study Results Posted
5	Efficacy	No PK data	May 8, 2012	May-12	Apr-18	June 27, 201	Jun-16	No Study Results Posted
6	Efficacy	No PK data	March 2, 201	Mar-16	May-18	March 24, 20	Mar-16	No Study Results Posted
7	Efficacy	No PK data	September 1	Oct-16	Mar-19	October 13, 2	Oct-16	No Study Results Posted
8	PK	PK study design	April 4, 2016	Apr-16	Sep-16	April 25, 201	Apr-16	No Study Results Posted
9	Efficacy	No PK data	September 2	Oct-16	Dec-17	September 2	Sep-16	No Study Results Posted
10	Efficacy	No PK data	November 17	Dec-10	null	September 1	Sep-12	No Study Results Posted
11	Efficacy	No PK data	November 25	Mar-14	Jul-16	December 16	Nov-15	No Study Results Posted
12	PK	Primary PK data	January 26, 2	Apr-12	Apr-18	December 10	Dec-15	No Study Results Posted
13	PK	PK study design	May 18, 2015	May-12	null	November 17	Nov-15	No Study Results Posted
14	Efficacy	No PK data	December 18	Dec-07	Sep-10	June 3, 2008	Aug-07	No Study Results Posted
15	Efficacy	No PK data	October 17, 2	Nov-07	Dec-09	October 18, 2	Oct-07	No Study Results Posted
16	PK	PK study design	August 17, 20	Nov-11	Feb-17	February 4, 2	Feb-16	No Study Results Posted
17	PK	PK study design	June 12, 201	Nov-15	Dec-17	August 1, 201	Aug-16	No Study Results Posted
18	Efficacy	No PK data	August 18, 20	Aug-11	Dec-20	August 30, 20	Aug-16	No Study Results Posted
19	PK	PK study design	September 2	Sep-14	Nov-16	October 31, 2	Oct-16	No Study Results Posted
20	Efficacy	No PK data	March 23, 20	Mar-09	Oct-12	June 21, 201	Jun-11	No Study Results Posted
21	Safety	No PK data	August 23, 20	Aug-16	Dec-16	September 1	Sep-16	No Study Results Posted
22	Efficacy	No PK data	January 3, 20	Mar-11	Jun-15	May 25, 201	May-15	No Study Results Posted
23	Safety	Secondary PK data	October 9, 20	Mar-15	Jan-18	October 31, 2	Oct-16	No Study Results Posted
24	Safety	Primary PK data	January 12, 2	Jan-17	Dec-18	September 8	Sep-16	No Study Results Posted
25	Safety	No PK data	September 1	Jul-16	Sep-18	October 19, 2	Oct-16	No Study Results Posted
26	Efficacy	No PK data	November 17	Jan-14	Jul-17	May 6, 2016	May-16	No Study Results Posted
27	Efficacy	No PK data	August 21, 20	Aug-13	Aug-15	August 26, 20	Aug-14	No Study Results Posted
28	PK	PK study design	May 11, 2016	Aug-16	Oct-22	May 17, 2016	May-16	No Study Results Posted
29	Safety	Primary PK data	February 17,	Jul-16	Sep-19	October 6, 20	Oct-16	No Study Results Posted
30	Efficacy	No PK data	May 5, 2016	Jun-16	Dec-20	October 7, 20	Oct-16	No Study Results Posted
31	Safety	No PK data	November 18	Dec-13	Sep-17	August 1, 201	Aug-16	No Study Results Posted

	U	V	W	X	Y	Z	AA	AB
32	Efficacy	No PK data	September 2	Nov-14	Dec-18	December 20	Dec-15	No Study Results Posted
33	PK	PK study design	February 18,	Apr-16	May-17	October 19, 2	Oct-16	No Study Results Posted
34	Efficacy	No PK data	May 8, 2006	Jan-04	Dec-13	February 6, 2	Feb-12	No Study Results Posted
35	PK	PK study design	April 1, 2016	May-16	Feb-18	October 21, 2	Oct-16	No Study Results Posted
36	PK	PK study design	June 2, 2015	Jan-16	Dec-17	April 18, 201	Apr-16	No Study Results Posted
37	PK	PK study design	October 1, 20	Oct-16	Oct-17	October 24, 2	Oct-16	No Study Results Posted
38	PK	PK study design	February 24,	Feb-16	Feb-17	March 8, 201	Mar-16	No Study Results Posted
39	Efficacy	No PK data	February 23,	Feb-12	Jul-17	February 19,	Feb-16	No Study Results Posted
40	PK	PK study design	August 23, 20	Jun-06	Dec-07	August 23, 20	Aug-06	No Study Results Posted
41	Efficacy	No PK data	January 30, 2	Dec-12	Dec-13	February 6, 2	Feb-13	No Study Results Posted
42	Efficacy	No PK data	September 8	Feb-16	Sep-20	October 3, 20	Oct-16	No Study Results Posted
43	Efficacy	No PK data	December 22	Apr-07	Apr-16	April 8, 2014	Apr-14	No Study Results Posted
44	Safety	Secondary PK data	December 31	Jan-15	Jan-20	June 24, 201	Jun-16	No Study Results Posted
45	Efficacy	No PK data	August 9, 201	Dec-16	Dec-19	September 3	Jul-16	No Study Results Posted
46	Efficacy	No PK data	July 24, 2016	Dec-16	Dec-20	July 26, 2016	Jul-16	No Study Results Posted
47	Safety	Secondary PK data	May 25, 2015	Jul-15	Oct-17	October 21, 2	Oct-16	No Study Results Posted
48	Efficacy	No PK data	November 4,	Nov-14	Jul-17	June 3, 2016	Jun-16	No Study Results Posted
49	Efficacy	No PK data	February 17,	Jan-12	Sep-12	March 13, 20	Mar-12	No Study Results Posted
50	PK	PK study design	August 5, 201	Aug-14	Jun-17	October 20, 2	Oct-16	No Study Results Posted
51	PK	PK study design	August 5, 201	Sep-14	Sep-17	March 17, 20	Mar-16	No Study Results Posted
52	Safety	Secondary PK data	June 16, 201	Sep-15	Oct-17	October 21, 2	Oct-16	No Study Results Posted
53	Efficacy	No PK data	June 8, 2016	Jun-16	Jul-18	June 23, 201	Jun-16	No Study Results Posted
54	Efficacy	No PK data	August 1, 201	Aug-14	Apr-17	September 2	Sep-16	No Study Results Posted
55	Efficacy	No PK data	June 13, 201	Jun-16	Nov-16	June 13, 201	Jun-16	No Study Results Posted
56	Efficacy	No PK data	May 1, 2016	Jun-16	Sep-18	June 10, 201	Jun-16	No Study Results Posted
57	Efficacy	No PK data	February 3, 2	Mar-16	null	June 10, 201	Jun-16	No Study Results Posted
58	Safety	No PK data	November 1(	Mar-16	Jan-18	September 1	Sep-16	No Study Results Posted
59	Efficacy	No PK data	October 5, 20	Nov-15	Feb-17	October 5, 20	Oct-16	No Study Results Posted
60	Efficacy	No PK data	May 11, 2015	Jan-15	Dec-16	May 9, 2016	May-16	No Study Results Posted
61	Efficacy	No PK data	January 4, 20	Jan-15	Jan-17	March 16, 20	Mar-16	No Study Results Posted
62	Efficacy	No PK data	August 11, 20	Oct-14	Feb-17	June 17, 201	Jun-16	No Study Results Posted

	U	V	W	X	Y	Z	AA	AB
63	Efficacy	No PK data	December 14	May-10	Oct-10	March 18, 20	Dec-09	No Study Results Posted
64	PK	PK study design	November 4,	Apr-15	Apr-16	November 4,	Nov-15	No Study Results Posted
65	Safety	No PK data	August 17, 2(	Oct-16	Jul-17	October 3, 2(	Oct-16	No Study Results Posted
66	Efficacy	Secondary PK data	April 7, 2016	Jul-16	Mar-18	May 31, 201(	May-16	No Study Results Posted
67	Efficacy	No PK data	March 4, 201	Sep-15	Oct-16	October 4, 2(	Oct-16	No Study Results Posted
68	Safety	Secondary PK data	February 23,	Aug-15	Oct-17	October 14, 2	Oct-16	No Study Results Posted
69	PK	PK study design	May 7, 2014	May-14	Dec-16	November 4,	Nov-15	No Study Results Posted
70	PK	PK study design	December 11	Dec-14	Aug-16	June 24, 201(	Jun-16	No Study Results Posted
71	PK	PK study design	August 31, 2(	Aug-11	Jul-12	September 1	Aug-11	No Study Results Posted
72	Efficacy	No PK data	November 25	Aug-10	Jul-12	January 14, 2	Nov-10	No Study Results Posted
73	Efficacy	No PK data	September 3	Jun-09	Apr-10	September 3	Sep-09	No Study Results Posted
74	Efficacy	No PK data	November 5,	Nov-14	Sep-18	June 29, 201(	Jun-16	No Study Results Posted
75	PK	Primary PK data	February 24,	Jan-11	null	March 21, 20	Mar-12	No Study Results Posted
76	Efficacy	No PK data	July 29, 2010	Aug-10	null	February 5, 2	Feb-16	No Study Results Posted
77	Efficacy	Secondary PK data	January 22, 2	Jul-13	Dec-21	May 28, 201!	May-15	No Study Results Posted

	AC	AD	AE	AF	AG
1	**Primary Com**	**URL**			
2	Jul-18	https://ClinicalTrials.gov/show/NCT02539407			
3	Dec-18	https://ClinicalTrials.gov/show/NCT02935374			
4	Sep-18	https://ClinicalTrials.gov/show/NCT02899143			
5	Apr-18	https://ClinicalTrials.gov/show/NCT01595529			
6	Feb-18	https://ClinicalTrials.gov/show/NCT02380352			
7	Jan-19	https://ClinicalTrials.gov/show/NCT02891915			
8	Sep-16	https://ClinicalTrials.gov/show/NCT02746276			
9	Aug-17	https://ClinicalTrials.gov/show/NCT02917551			
10	Jun-13	https://ClinicalTrials.gov/show/NCT01243437			
11	Mar-16	https://ClinicalTrials.gov/show/NCT02635191			
12	Dec-16	https://ClinicalTrials.gov/show/NCT01522105			
13	Dec-17	https://ClinicalTrials.gov/show/NCT02456974			
14	Sep-10	https://ClinicalTrials.gov/show/NCT00579956			
15	null	https://ClinicalTrials.gov/show/NCT00545961			
16	Feb-17	https://ClinicalTrials.gov/show/NCT01431326			
17	Nov-17	https://ClinicalTrials.gov/show/NCT02475876			
18	Dec-20	https://ClinicalTrials.gov/show/NCT01420341			
19	Nov-16	https://ClinicalTrials.gov/show/NCT02266706			
20	Sep-12	https://ClinicalTrials.gov/show/NCT00867789			
21	Dec-16	https://ClinicalTrials.gov/show/NCT02879981			
22	Jun-15	https://ClinicalTrials.gov/show/NCT01269541			
23	Jan-18	https://ClinicalTrials.gov/show/NCT02276482			
24	Dec-18	https://ClinicalTrials.gov/show/NCT02663596			
25	Sep-17	https://ClinicalTrials.gov/show/NCT02555059			
26	Apr-17	https://ClinicalTrials.gov/show/NCT02297815			
27	Dec-14	https://ClinicalTrials.gov/show/NCT02224040			
28	Aug-22	https://ClinicalTrials.gov/show/NCT02775968			
29	Aug-19	https://ClinicalTrials.gov/show/NCT02687906			
30	Dec-19	https://ClinicalTrials.gov/show/NCT02783859			
31	Apr-17	https://ClinicalTrials.gov/show/NCT01994993			

	AC	AD	AE	AF	AG
32	Dec-17	https://ClinicalTrials.gov/show/NCT02258763			
33	May-17	https://ClinicalTrials.gov/show/NCT02688790			
34	Dec-12	https://ClinicalTrials.gov/show/NCT00323219			
35	Feb-18	https://ClinicalTrials.gov/show/NCT02750761			
36	Dec-17	https://ClinicalTrials.gov/show/NCT02466438			
37	Sep-17	https://ClinicalTrials.gov/show/NCT02260102			
38	Jun-16	https://ClinicalTrials.gov/show/NCT02694458			
39	Feb-17	https://ClinicalTrials.gov/show/NCT01540838			
40	null	https://ClinicalTrials.gov/show/NCT00368498			
41	Dec-13	https://ClinicalTrials.gov/show/NCT01785641			
42	Sep-20	https://ClinicalTrials.gov/show/NCT02554383			
43	Mar-16	https://ClinicalTrials.gov/show/NCT01265173			
44	Jan-17	https://ClinicalTrials.gov/show/NCT02335905			
45	Dec-19	https://ClinicalTrials.gov/show/NCT02922686			
46	Dec-20	https://ClinicalTrials.gov/show/NCT02848820			
47	Oct-17	https://ClinicalTrials.gov/show/NCT02475733			
48	May-17	https://ClinicalTrials.gov/show/NCT02372461			
49	Aug-12	https://ClinicalTrials.gov/show/NCT01553006			
50	Mar-17	https://ClinicalTrials.gov/show/NCT02527681			
51	Sep-17	https://ClinicalTrials.gov/show/NCT02210169			
52	Oct-17	https://ClinicalTrials.gov/show/NCT02497781			
53	Apr-18	https://ClinicalTrials.gov/show/NCT02814916			
54	Apr-17	https://ClinicalTrials.gov/show/NCT02210325			
55	Nov-16	https://ClinicalTrials.gov/show/NCT02801370			
56	Aug-18	https://ClinicalTrials.gov/show/NCT02760420			
57	Aug-18	https://ClinicalTrials.gov/show/NCT02678195			
58	Dec-17	https://ClinicalTrials.gov/show/NCT02605122			
59	Feb-17	https://ClinicalTrials.gov/show/NCT02570490			
60	Dec-16	https://ClinicalTrials.gov/show/NCT02443285			
61	Jan-17	https://ClinicalTrials.gov/show/NCT02334124			
62	Feb-17	https://ClinicalTrials.gov/show/NCT02218372			

	AC	AD	AE	AF	AG
63	Jul-10	https://ClinicalTrials.gov/show/NCT01032499			
64	Feb-16	https://ClinicalTrials.gov/show/NCT02598362			
65	Mar-17	https://ClinicalTrials.gov/show/NCT02878031			
66	Dec-17	https://ClinicalTrials.gov/show/NCT02790996			
67	Oct-16	https://ClinicalTrials.gov/show/NCT02712307			
68	Oct-17	https://ClinicalTrials.gov/show/NCT02424734			
69	Dec-16	https://ClinicalTrials.gov/show/NCT02134301			
70	Aug-16	https://ClinicalTrials.gov/show/NCT02013141			
71	Jul-12	https://ClinicalTrials.gov/show/NCT01427842			
72	Jun-11	https://ClinicalTrials.gov/show/NCT01278017			
73	Feb-10	https://ClinicalTrials.gov/show/NCT00988026			
74	Jun-18	https://ClinicalTrials.gov/show/NCT02288234			
75	null	https://ClinicalTrials.gov/show/NCT01304459			
76	Dec-16	https://ClinicalTrials.gov/show/NCT01173575			
77	Dec-19	https://clinicaltrials.gov/ct2/show/NCT01778634			

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A global shortage of neonatal and pediatric antibiotic trials: rapid review.

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A global shortage of neonatal and pediatric antibiotic trials: rapid review.

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ABSTRACT

Objectives: There have been few clinical trials (CTs) on antibiotics which inform neonatal and pediatric drug labelling. The rate of unlicensed and off-label prescribing in pediatrics remains high. It is unclear whether the current neonatal and pediatric antibiotic research pipeline is adequate to inform optimal drug dosing. Using the ClinicalTrials.gov registry, this review aims to establish the current global status of antibiotic CTs in children up to 18 years of age.

Methods: Studies were identified using key word searches of the ClinicalTrials.gov registry, and were manually filtered using pre-specified inclusion/exclusion criteria.

Results: 76 registered open CTs of antibiotics in children were identified globally; 23 (30%) were recruiting newborns (only 8 (11%) included preterm neonates), 52 (68%) infants and toddlers, 58 (76%) children, and 54 (71%) adolescents. The majority of registered trials were late phase (10 (15%) Phase 3 and 23 (35%) Phase 4/pharmacovigilance). Two-thirds were sponsored by non-profit organisations, compared to pharmaceutical companies (50 (66%) vs. 26 (34%) respectively). A greater proportion of non-profit funded trials were efficacy-based strategic trials (n= 34, 68%), in comparison to industry-led trials, which were most often focused on safety or pharmacokinetic data (n=17, 65%). Only 2 of the 37 antibiotics listed on the May 2016 Pew Charitable Trusts antibiotic development pipeline, currently being studied in adults, appear to be currently recruiting in open pediatric CTs.

Conclusions: This review highlights that very few pediatric antibiotic CTs are being conducted globally, especially in neonates. There is a striking disparity noted between antibiotic drug development programmes in adults and children.

Strengths and limitations of this study

- A narrative literature review of registered clinical trials in children.
- Explicit reproducible methodology.
- Search strategy limited to ClinicalTrials.gov and EudraCT. Entirety of clinical research in this field might not have been captured.
- Search strategy was limited to open clinical trials. Active but not yet recruiting trials were not captured.

INTRODUCTION

Widespread unlicensed and off-label prescribing in pediatrics persists – as high as 11.4% and 46.5%, respectively – yet the paucity of clinical research involving children that is conducted to inform optimal drug dosing, licensing and labelling remains a problem.[1] For certain medicines, drug efficacy can be extrapolated from adult data provided that the pathology and drug exposure are the same, or sufficiently similar in children as in adults.[2,3]. Although differences in drug

pharmacokinetics (PK) in neonates and children can lead to adverse reactions that are not seen in adult populations, these are very rare.[4] Suboptimal antibiotic dosing, including under- and over-dosing, can lead to toxicity, treatment failure, and may drive antimicrobial resistance by encouraging selection pressures on drug-resistant strains of bacteria.[5]

Since antibiotics are the most commonly prescribed medicines in children, it is important to maximize our understanding of their PK profiles to help determine optimal drug dosing and ultimately to improve outcomes.[6] In the last decade several initiatives have been established to encourage pediatric medicines research, bridging the gap between adult and pediatric drug development plans. Such initiatives include the Pediatric Regulation (Pediatric Investigation Plans (PIPs), introduced by the European Medicines Agency (EMA),[7] and Pediatric Study Plans (PSPs), by the U.S. Food and Drug Administration (FDA)).[8] Despite this, there have been few advances in antibiotic development for this population.[9]

The global status of clinical research on antibiotics in pediatrics is unknown. Using registered records of clinical trials (CTs) on *ClinicalTrials.gov*, this review aims (i) to summarise the current global status of registered antibiotic research in children and neonates, and (ii) to stimulate discussion and collaboration among the relevant stakeholders on the neglect of antibiotic research in children.

METHODS

Data sources

The *ClinicalTrials.gov* registry (last accessed 8th November 2016) is an international platform for the registration of CTs. It is a web-based registry, developed in 2000 by the National Institutes of Health (NIH) and the FDA, to which trials from 50 states and 163 countries around the world are registered. Information provided for each trial is updated periodically by the trial's sponsoring organisation. The database has a specific child filter, which uses a key word paradigm to select all registered trials recruiting patients/participants up to 18 years of age.

Study selection

Our records were identified using suitable key word searches, in which the final search terms were (antimicrobial* OR antibiotic* OR anti-infective agent*) AND Child AND Open Studies. All identified trials were filtered manually using inclusion and exclusion criteria. Interventional and observational trials on antimicrobials recruiting children up to 18 years of age were considered eligible for inclusion. No specific temporal filter was applied since only open or ongoing clinical trials were of interest. The following records, which were not investigating one or more antibiotics, were excluded:

trials of antiseptics, antifungals, antiprotozoals, antivirals, and pro- or pre- biotics. The following records, which were investigating an antibiotic were excluded: trials involving tuberculosis, malaria, cystic fibrosis, HIV, febrile neutropenic patients, topical or inhalational treatments, prophylactic antibiotics, or records investigating alternative use for antibiotics (for example as an anti-inflammatory agent).

The searches were conducted by GT. All eligible records were identified via manual filtering by GT CIB, LF and MS, and any disagreements regarding inclusion and exclusion of records were resolved through discussion.

Data extraction

The following information was collected from the included records: unique NCT number, recruitment status, study design, trial phase, study sponsor, age group and sex eligibility, clinical indication, geographic region of recruitment, antibiotic being investigated, and endpoint classification. Outcomes were categorised as safety, efficacy or PK. Economic setting (based on geographic region of recruitment) was classified using The World Bank classification to differentiate between Low Income Countries (LICs), Lower Middle Income Countries (LMICs), Upper Middle Income Countries (UMICs), and High Income Countries (HICs).[10]

The specific class of antibiotic studied in each trial was identified and classified using the World Health Organisation (WHO) ATC/DDD index.[11] To investigate whether novel antibiotics are being studied in pediatric populations, the antibiotics currently studied in children were compared with the *Pew Charitable Trusts Antibiotics Currently in Clinical Development* pipeline, which identifies novel antibiotics currently under development for the U.S. market.[12]

RESULTS

Our search identified 1056 records. 603 records were excluded on title because they were studies not involving an antimicrobial. 453 records were investigating one or more antimicrobials and recruiting children below 18 years of age. Among the 195 trials investigating antibiotics, 76 fulfilled our inclusion and exclusion criteria and were included in the final analysis. Reasons for exclusion are summarised in Figure 1. Details of included studies can be found in Supplementary file 1.

All 76 CTs identified were open as of 8th November 2016, and 63 (83%) of these were recognised as recruiting participants on this date (Table 1). All trials stated recruitment of both male and female participants.

Table 1. Characteristics of clinical trials.

Characteristic	Category	Number of studies, n (%)
Age group	Preterm neonates	1 (1)[a]
	Neonates (total)	23 (30)
	Infants and toddlers	52 (68)
	Children	58 (76)
	Adolescents	54 (71)
Recruitment status	Recruiting	63 (83)
	Not yet recruiting	13 (17)
Study design	Interventional	66 (87)
	Observational	10 (13)
Trial phase[b]	Phase 1	10 (15)
	Phase 1-2	1 (2)
	Phase 2	9 (14)
	Phase 2-3	3 (5)
	Phase 3	10 (15)
	Phase 4	23 (39)
	Not specified	10 (15)
Sponsor	Industry	26 (34)
	Non-profit	50 (66)
Geographic region	Africa	8 (11)
	Asia	16 (21)
	Europe	22 (29)
	Latin America	6 (8)
	North America	34 (45)
	Oceania	5 (7)
Antibiotic class	J01A Tetracycline	4 (5)
	J01C Beta-lactam, Penicillin	25 (33)
	J01D Other Beta-lactam	22 (29)
	J01E Sulfonamides and trimethoprim	7 (9)
	J01F Macrolide, Lincosamide, Streptogramin	14 (18)
	J01G Aminoglycoside	2 (3)
	J01M Quinolone	8 (11)
	J01X Other antibiotic classes[c]	21 (28)
	J01 Not specified	2 (3)

Totals for Age group, Geographic region, and Antibiotic class do not add up to total number of clinical trials (76) as some trials contributed to more than one sub group.
[a] 7 further trials mentioned inclusion of preterm babies in the inclusion criteria.
[b] Trial phase % based on percentage of interventional trials.
[c] J01X includes glycopeptides, polymyxins, imidazole and nitrofuran derivatives.

Age group

Twenty three of the 76 trials (30%) were recruiting newborns (0 to 28 days). One of these 23 trials focused solely on recruiting preterm newborns (a further 7 CTs mentioned inclusion of preterm newborns in inclusion criteria). Of the remaining records, 52 (68%) were recruiting infants and toddlers (28 days to 23 months), 58 (76%) children (2 to 11 years), and 54 (71%) adolescents (11 up to 18 years). 29 (38%) trials did not focus solely on the recruitment of children or neonates, with age ranges also spanning across adult populations.

Study type

Interventional trials were most frequently identified (n=66, 87%) with only 10 (13%) observational trials noted. Of the interventional trials, the majority were in the later stages of development; 10 (13%) in Phase 1, 1 (2%) between Phase 1 and 2, 9 (14%) in Phase 2, 3 (5%) between Phase 2 and 3, 10 (15%) in Phase 3 and 23 (35%) in Phase 4. In 10 (15%) cases, a trial phase was not specified.

Sponsor and Endpoint Classification

Fifty trials (66%) were sponsored by non-profit organisations (being university, hospital or government funded), and 26 sponsored by industry (34%). The endpoint classification of the majority of trials (n=43, 57%) was reported as efficacy (Table 2). A greater proportion (n=34, 68%) of non-profit studies measured the efficacy of the drugs as the primary endpoint, with less emphasis on collection of PK or safety data (n=16, 32%). In comparison pharmaceutical-led trials focussed on early PK and safety studies over the drug's efficacy (n=17, 65% vs. n=9, 35% respectively).

Table 2. Clinical trial endpoint classification of identified clinical trials stratified by trial sponsor. Endpoint classification determined by planned primary outcomes.

Endpoint classification	Industry	Non-profit	Total (%)
Efficacy	9	34	43 (57)
Safety	10	2	12 (16)
PK	7	14	21 (28)

Geographic region

The most frequently recruiting geographic region was North America (n=34, 45%). 22 (29%) trials recruiting in Europe and 16 (21%) in Asia were identified, 6 (8%) in Latin America, 8 (11%) in Africa, and 5 (7%) in Oceania. Most trials were recruiting in HICs (n=54, 71%), with fewer trials recruiting in LICs (n=4, 5%), LMICs (n=4, 5%), UMICs (n=11, 14%) or a combination of UMICs and HICs (n=3, 4%).

Indication

The most common treatment indications investigated were lower respiratory tract infection (n=12, 16%) and sepsis (n=11, 14%), followed by upper respiratory tract infection (n=8, 11%), intra-abdominal infection (IAI) (n=8, 11%), urinary tract infection (UTI) (n=7, 9%), complicated skin and soft tissue infection (cSSTI) (n=6, 8%), CNS infection (n=3, 4%), and bone and joint infection (n=1, 1%) (Table 3).

Table 3. Clinical indication of identified clinical trials stratified by age group being recruited.

Indication	Total (%)	Age group				
		Preterm neonates	Neonates[a]	Infants and toddlers	Children	Adolescents
Unspecified Bacterial Infection	18 (24)	-	11	15	15	14
Lower Respiratory Tract Infection	12 (16)	1	3	12	13	5
Sepsis	11 (14)	-	6	9	9	11
Upper Respiratory Tract	8 (11)	-	1	5	9	7
Intra-abdominal Infection	8 (11)	-	3	5	5	7
Urinary Tract Infection	7 (9)	-	2	6	7	6
Skin and Soft Tissue Infection	6 (8)	-	3	4	4	8
CNS infection	3 (4)	-	1	4	4	4
Bone and Joint Infection	1 (1)	-	-	1	1	1
		1	30	61	67	63

Age group totals do not add up to total number of clinical trials (76) as some trials contributed to more than one age group.
[a] refers to total number of preterm and term neonates.

Antibiotic class

The majority of antibiotics being investigated were beta-lactams (n=47, 62%), followed by other antibiotic classes (J01X, including vancomycin, telavancin and dalbavancin) (n=21, 28%). Macrolides or lincosamides (J01F) were the next most commonly studied antibiotic classes (n=14, 18%). Very few trials were investigating of tetracyclines (J01A) (n=4, 5%), Sulphonamides and trimethoprim (J01E) (n=7, 9%), aminoglycosides (J01G) (n=2, 3%), or quinolones (J01M) (n=8, 11%). 2 CTs (3%) did not specify the class of antibiotic being investigated. 16 (21%) trials were investigating more than one antibiotic; these trials counted towards more than one J01 category. The breakdown of J01 categories, as per WHO ATC/DDD classification,[11] is described in Table 1.

Antibiotic pipeline

Of the 37 antibiotics listed in the May 2016 edition of the Pew Charitable Trusts Antibiotic Pipeline (last accessed 10th June 2016),[12] as noted by the EMA Opinions and Decisions on Pediatric Investigation Plans, 5 had an agreed PIP: Imipenem/Cilastatin+Relebactam, Cadazolid, Carbavance (Meropenem+Vaborbactam), Eravacycline, and Solithromycin.[8] As of 8th November 2016, our search found that only 2 of these 37 antibiotics listed (Carbavance and Solithromycin) were being investigated in 1 and 2 on-going CTs in pediatric patients, respectively (Table 4). A PIP was agreed for Carbavance in 2015 for treatment of Gram-negative infections, and for Solithromycin in 2016 for the treatment of gonococcal infection, and later for treatment of anthrax, tularaemia, and bacterial pneumonia. PIPs were agreed in 2015 for treatment of UTI and complicated IAI with Eravacycline, and in 2016 for treatment of Clostridium difficile infection with Cadazolid and of Gram-negative bacterial infection with Imipenem/Cilastin+Relebactam.[13] Despite this, we could not identify any registered trials of these antibiotics in our search.

Table 4. Comparison of antibiotic development pipeline in adults and children. Adapted from Pew Charitable Trusts "Antibiotics currently in clinical development" pipeline (last accessed October 2016).[12]

Antibiotic	Phase	Manufacturer	Indication	Drug development in Adults	Pediatric Investigation Plan for drug development in Children	Number of open clinical trials in children
WCK 4873	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
MGB – BP – 3	Phase 1	MGB Pharma Ltd.	Clostridium *difficile* infection	✓	-	-
OP0595	Phase 1	Meiji Seika Pharma Co. Fedora Pharmaceuticals	Bacterial infection	✓	-	-
BAL30072	Phase 1	Basilea Pharmaceuticals	Multidrug resistant gram negatives	✓	-	-
CRS3123	Phase 1	Crestone Inc.	Clostridium *difficile* infection	✓	-	-
LCB01 – 0371	Phase 1	Legochem Biosciences Inc.	Bacterial infection	✓	-	-
TD – 1607	Phase 1	Theravance Biopharma Inc.	Acute skin infection, HAP, VAP, bacteraemia	✓	-	-
WCK 2349	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-
WCK 771	Phase 1	Wockhardt Ltd.	Bacterial infection	✓	-	-

Zidebactam+Cefepime	Phase 1	Wockhardt Ltd.	cUTI, HAP, VAP	✓	-	-
TP – 271	Phase 1	Tetraphase Pharmaceuticals Inc.	CAP	✓	-	-
Aztreonam – Avibactam	Phase 2	Astrazeneca PLC Allergan PLC	cIAI	✓	-	-
MRX – 1	Phase 2	MicuRx Pharmaceuticals Inc.	Acute skin infection (systemic)	✓	-	-
Debio 1450	Phase 2	Debiopharm International SA	Acute skin infection, Staphylococcus *spp*. associated osteomyelitis	✓	-	-
ETX0914	Phase 2	Entasis Therapeutics Inc.	Uncomplicated gonorrhoea	✓	-	-
P0L7080	Phase 2	Polyphor Ltd.	Pseudomonas spp. associated VAP, lower respiratory tract infection, bronchiectasis	✓	-	-
Brilacidin	Phase 2	Cellceutix Corporation	Acute skin infection (systemic)	✓	-	-
Ceftaroline+Avibactam	Phase 2	AstraZeneca PLC Allergan PLC	Bacterial infection	✓	-	-
CG400549	Phase 2	Crystal Genomics Inc.	Acute skin infection, osteomyelitis	✓	-	-
Finafloxacin	Phase 2	MerLion Pharmaceuticals Pte Ltd.	cUTI, cIAI, acute skin infection, pyelonephritis	✓	-	-

Geptidacin	Phase 2	GlaxoSmithKline PLC	cUTI, CAP, uncomplicated urogenital gonorrhoea	✓	-	-
Nemonoxacin	Phase 2	TaiGen Biotechnology Co. Ltd.	CAP, acute skin infection, diabetic foot	✓	-	-
Ramoplanin	Phase 2	Nanotherapeutics Inc.	Prevent recurrent Clostridium *difficile* infection	✓	-	-
Ridinilazole	Phase 2	Summet Therapeutics Inc.	Clostridium *difficile*	✓	-	-
Zabofloxacin	Phase 3	Dong Wha Pharmaceuticals Co. Ltd.	CAP	✓	-	-
S – 649266	Phase 3	Shionogi Inc.	HAP, VAP, cUTI, bloodstream infection	✓	-	-
Omadacycline	Phase 3	Paratek Pharmaceuticals Inc.	CAP, cUTI, acute skin infection	✓	-	-
Lefamulin	Phase 3	Nabriva Therapeutics AC	CAP, HAP, VAP, acute skin infection, osteomyelitis, prosthetic joint infections	✓	-	-
Imipenem / Cilastatin+Relebactam	Phase 3	Merck & Co. Inc.	cUTI, cIAI, HAP, VAP, acute pyelonephritis	✓	✓	-
Iclaprim	Phase 3	Motif Bio PLC	HAP, acute skin infection	✓	-	-
Cadazolid	Phase 3	Actelion Pharmaceuticals Ltd.	Clostridium *difficile*	✓	✓	-
Taksta (fusidic acid)	Phase 3	Cempra Inc.	Acute skin infection, prosthetic joint infection	✓	-	-

Carbavance (Meropenem+Vaborbactam)	Phase 3	Rempex Pharmaceuticals Inc.	cUTI, cIAI, HAP, VAP, febrile neutropenia, bacteraemia, acute pyelonephritis[a]	✓	✓	1
Delafloxacin (Baxdela)	Phase 3	Melinta Therapeutics Inc.	Acute skin infections, CAP, cUTI	✓	Waiver granted	-
Eravacycline	Phase 3	Tetraphase Pharma Inc.	cIAI and cUTI	✓	✓	-
Plazomicin	Phase 3	Achaogen Inc.	cUTI, HAP, VAP, cIAI, catheter-associated bloodstream infection[a]	✓	-	-
Solithromycin	Phase 3	Cempra Inc.	CAP, uncomplicated urogenital gonorrhoea, urethritis	✓	✓	2

HAP, hospital-acquired pneumonia; VAP, ventilator-acquired pneumonia; cUTI, complicated Urinary Tract Infection; CAP, Community-acquired pneumonia; cIAI, complicated Intra-abdominal Infection.

[a] target carbapenem resistant enterobacteriaceae

DISCUSSION

Our search identified 76 clinical trials investigating one or more antibiotics recruiting children between 0 and 18 years of age. This is low in comparison to the number of on-going trials in adults, despite children representing around a quarter of the global population.[14, 15] A review of completed CTs in the U.S. between 2000 and 2010 identified a total of 4078 adult trials compared to just 294 that had recruited children.[16] In our study, the lack of trials recruiting neonates is striking. Just 23 of the 76 trials identified were recruiting neonates, and remarkably just 8 CTs globally were recruiting preterm neonates. There are broadly two types of pediatric trials conducted globally. Either pharmaceutical-led Phase 1/2 PK and safety trials (n=17) being conducted in the HIC setting, or investigator led, often pragmatic, late phase efficacy trials in the LMIC setting (n=34), with a greater proportion of on-going trials being sponsored by non-profit organisations over industry (66% compared to 34%).. As of April 2016, there were 17 antibiotic PIPs agreed by the EMA,[8] covering a range of indications, most commonly cSSTI, complicated IAI (cIAI), and complicated UTI (cUTI).[13] In contrast, treatments for respiratory and systemic infections, the most common clinical indications for antibiotics in pediatrics, are not currently being evaluated.[14] Thirty-seven antibiotics are currently being developed in adults, yet to our knowledge just 2 of these are being studied in children. Some classes of antibiotics that may be of higher risk for children (tetracyclines and fluoroquinolones) may not be pursued as aggressively for pediatric approvals due to well-recognized issues of toxicity, particularly when safer alternatives are widely available. Given that Gram-negative sepsis is a growing problem in neonates, with a significant increase in the proportion of multi-resistant Gram-negative pathogens,[15] the substantial lag time between the submission date (for PIP or waiver) and declared completion date of PK studies in adults is a real concern; although, there is value in generating substantial safety data in adults prior to exposing children and newborns to potentially toxic new agents.

In 2013, a similar review of European pediatric clinical trials identified 31 trials of antibiotics approved for adults by the EMA in 2000 that were recruiting children in Europe (compared to the 22 trials we found recruiting in Europe). They included both published and ongoing trials, which likely accounts for the higher number of trials reported. They similarly found a very small proportion of neonatal trials (2 of 31), as well as a greater proportion of efficacy-based trials.[9] A review of interventional trials registered with *ClinicalTrials.gov* between 2007 and 2010 found that only 17% had recruited children below 18 years of age.[17] A similar review of antimicrobial CTs conducted in the U.S. between 2000 and 2012 reported that just 5% had recruited only children compared to 74% that recruited only adults, and that, as we have found, the trials were sponsored primarily by non-profit organisations (60% versus 30% by industry).[14] In our search of global trials, 39% of registered CTs reported collection of PK data in comparison to a 2009 paediatrc PK research review that reported 24% of registered CTs would be collecting PK data.[18]

The search strategy used has some limitations. Since the search was limited to clinical trials registered with *ClinicalTrials.gov*, it is possible other open or on-going trials registered with alternative platforms (for example, the WHO International Clinical Trials Registry Platform [ICTRP]) will have been missed. Together with *ClinicalTrials.gov* these could help to establish the entirety of current clinical research in this field. We did however search EudraCT, and found no further studies beyond those captured on *ClinicalTrials.gov*. Our search was also limited to open CTs, thereby missing active but not yet recruiting trials, and those that had already closed to recruitment. The information recorded for each trial registered with *ClinicalTrials.gov* is updated by the trial investigators, and therefore relies on them to periodically update the registry. Occasionally, information such as recruitment status might not be updated in real time.

Concerns around the growing threat of antimicrobial resistance have prompted several new initiatives. In 2016, the EMA published a draft Concept Paper to propose the development of an Addendum to the guideline on the evaluation of new anti-bacterial products for treatment of bacterial infections in children.[19] At the same time, the Clinical Trials Transformation Initiative (CTTI) is currently focused on the identification of key barriers in the conduct of pediatric antibacterial CTs, which hamper their successful implementation into clinical practice.[20] Recent evidence states that overall, antibiotic CTs make up less than 1% of all registered pediatric CTs, and that trial completion is slow, with an average time to completion of around two years.[21] There are specific areas where the design and conduct of pediatric antibiotic CTs can be harmonized and simplified, such as the standardisation of the inclusion and exclusion criteria for specific Clinical Infection Syndromes, and improved bridging of safety and efficacy data from other age groups; these advances could improve trial conduct and efficiency in children.[22]

CONCLUSIONS

This review highlights that very few pediatric antibiotic CTs are being conducted globally, particularly in neonates. There is a marked disparity between antibiotic drug development programmes in adults and children. Many issues contribute to the difficulties in conducting pediatric antibiotic clinical trials. The lack of regulatory guidance, vulnerability of this population, issues with informed consent and assent, and lack of research-experienced hospital personnel all present challenges in study design, delivery and recruitment. Delays in the initial start-up of CTs in pediatrics due to pediatric-specific protocol issues and complicated ethical approval continue to discourage both academic and pharmaceutical interest. The limited data presented here suggest that the dismal state of pediatric antibiotic research continues. Earlier collaboration between global academic research networks and pharmaceutical companies is now vital to accelerate progress.

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Conflict of interest None declared.

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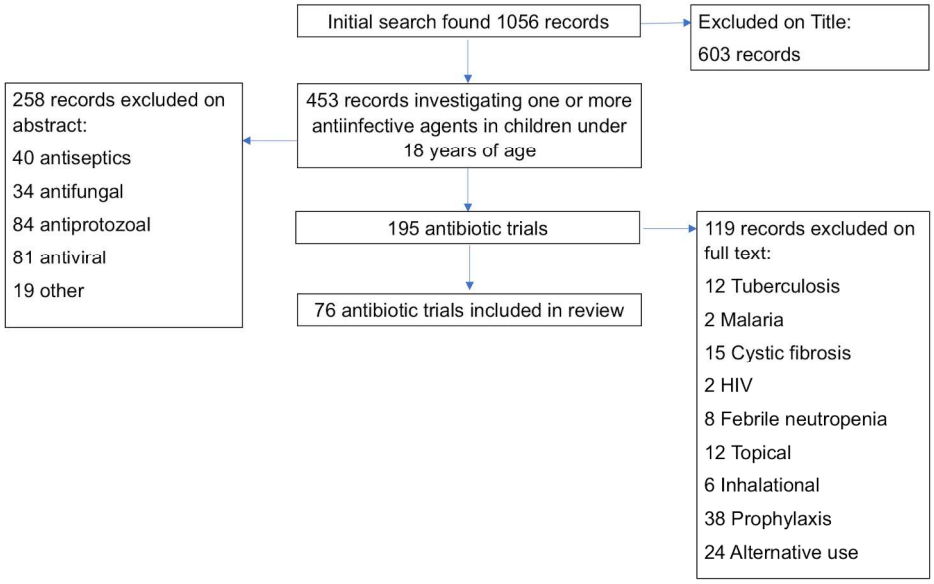

Figure 1. Flow Chart. Clinical trial selection process.

254x190mm (300 x 300 DPI)

DATASET

	A	B	C	D
1	**NCT Number**	**Title**	**Recruitment**	**Study Results**
2	NCT02539407	Population Pharmacokinetics of Anti-infectives in Critically Ill Children	Recruiting	No Results Available
3	NCT02935374	Effect of Antimicrobial Treatment of Acute Otitis Media on the Intestinal Microbiome in Children	Not yet recruiting	No Results Available
4	NCT02899143	Short-course Antimicrobial Therapy in Sepsis	Recruiting	No Results Available
5	NCT01595529	The SCOUT Study: Short Course Therapy for Urinary Tract Infections in Children	Recruiting	No Results Available
6	NCT02380352	Short-course Antimicrobial Therapy for Paediatric Respiratory Infections	Not yet recruiting	No Results Available
7	NCT02891915	Trial to Evaluate Beta-Lactam Antimicrobial Therapy of Community Acquired Pneumonia in Child	Recruiting	No Results Available
8	NCT02746276	Optimising Antibiotic Treatment for Sick Malnourished Children	Recruiting	No Results Available
9	NCT02917551	BALANCE on the Wards: A Pilot RCT	Not yet recruiting	No Results Available
10	NCT01243437	A Clinical Trial to Evaluate the Safety and Efficacy of Ciprofloxacin in the Treatment of Plague in	Recruiting	No Results Available
11	NCT02635191	Tailored Therapy for Helicobacter Pylori in Children	Recruiting	No Results Available
12	NCT01522105	Daptomycin in Pediatric Patients With Bacterial Meningitis	Recruiting	No Results Available
13	NCT02456974	Antibiotic Dosing in Pediatric Intensive Care	Recruiting	No Results Available
14	NCT00579956	A Randomized Double Blinded Comparison of Ceftazidime and Meropenem in Severe Melioidosis	Recruiting	No Results Available
15	NCT00545961	Middle Meatal Bacteriology During Acute Respiratory Infection in Children	Not yet recruiting	No Results Available
16	NCT01431326	Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care	Recruiting	No Results Available
17	NCT02475876	PK of Clindamycin and Trimethoprim-sulfamethoxazole in Infants and Children	Recruiting	No Results Available
18	NCT01420341	Co-trimoxazole as Maintenance Therapy for Meliodosis	Recruiting	No Results Available
19	NCT02266706	Pharmacokinetic and Safety Study of Ceftolozane/Tazobactam in Pediatric Participants Receiving	Recruiting	No Results Available
20	NCT00867789	Antibiotics Versus Placebo in the Treatment of Abscesses in the Emergency Department	Recruiting	No Results Available
21	NCT02879981	A Safety Study of Balsamic Bactrim in Pediatric Participants With Acute Bronchitis	Not yet recruiting	No Results Available
22	NCT01269541	MESS-study MRSA Eradication Study Skl´ne	Recruiting	No Results Available
23	NCT02276482	Study of Tedizolid Phosphate in Adolescents With Complicated Skin and Soft Tissue Infections (cS	Recruiting	No Results Available
24	NCT02663596	Safety and TDM of Continuous Infusion Vancomycin Through Continuous Renal Replacement Th	Not yet recruiting	No Results Available
25	NCT02555059	Special Drug Use Investigation of Ciproxan Injection in Pediatrics	Recruiting	No Results Available
26	NCT02297815	Comparative Effectiveness of Antibiotics for Respiratory Infections	Recruiting	No Results Available
27	NCT02224040	Typhoid Fever: Combined vs. Single Antibiotic Therapy	Recruiting	No Results Available
28	NCT02775968	Population Pharmacokinetics of Cephalosporins and Macrolides in Chinese Children With Comm	Not yet recruiting	No Results Available
29	NCT02687906	Dose-finding, Pharmacokinetics, Safety, and Tolerability of Meropenem-Vaborbactam in Pediatr	Recruiting	No Results Available
30	NCT02783859	Hospitalised Pneumonia With Extended Treatment (HOPE) Study	Recruiting	No Results Available
31	NCT01994993	Antibiotic Safety (SCAMP)	Recruiting	No Results Available

	A	B	C	D
32	NCT02258763	Trial on the Ideal Duration of Oral Antibiotics in Children With Pneumonia	Recruiting	No Results Available
33	NCT02688790	Study Evaluate the PK Profile of Dalbavancin in Hospitalized Infants and Neonates Patients With	Recruiting	No Results Available
34	NCT00323219	Oral Moxifloxacin Versus Cefazolin and Oral Probenecid in the Management of Skin and Soft Tiss	Recruiting	No Results Available
35	NCT02750761	A Study of Oral and Intravenous (IV) Tedizolid Phosphate in Hospitalized Participants, Ages 2 to	Recruiting	No Results Available
36	NCT02466438	Safety and Pharmacokinetics of Piperacillin-tazobactam Extended Infusion in Infants and Childre	Recruiting	No Results Available
37	NCT02260102	Temocillin Pharmacokinetics in Paediatrics	Not yet recruiting	No Results Available
38	NCT02694458	Comparison of Two Dosage Adjustment Strategies of Vancomycin in Children	Recruiting	No Results Available
39	NCT01540838	Slow Initial beta-lactam Infusion With High-dose Paracetamol to Improve the Outcomes of Child	Recruiting	No Results Available
40	NCT00368498	A Trial to Evaluate the Loading Dose Required to Achieve Therapeutic Serum Teicoplanin Concer	Recruiting	No Results Available
41	NCT01785641	Single Versus Combined Antibiotic Therapy for Bacterial Peritonitis in CAPD Patients	Recruiting	No Results Available
42	NCT02554383	Efficacy of Antibiotics in Children With Acute Sinusitis: Which Subgroups Benefit?	Recruiting	No Results Available
43	NCT01265173	Comparison of Efficacy of Cefotaxime, Ceftriaxone, and Ciprofloxacin for the Treatment of Spont	Recruiting	No Results Available
44	NCT02335905	Ceftaroline for Treatment of Hematogenously Acquired Staphylococcus Aureus Osteomyelitis in	Recruiting	No Results Available
45	NCT02922686	Penicillin for the Emergency Department Outpatient Treatment of CELLulitis	Not yet recruiting	No Results Available
46	NCT02848820	Initial Non-operative Treatment Strategy Versus Appendectomy Treatment Strategy for Simple A	Not yet recruiting	No Results Available
47	NCT02475733	Evaluation of Safety,Pharmacokinetics and Efficacy of CAZ-AVI With Metronidazole in Children A	Recruiting	No Results Available
48	NCT02372461	Randomized Trial of Amoxicillin Versus Placebo for (Fast Breathing) Pneumonia	Recruiting	No Results Available
49	NCT01553006	Study of Cefditoren Pivoxil in Treatment of Childhood With Acute Rhinosinusitis	Recruiting	No Results Available
50	NCT02527681	Pharmacokinetics and Safety of Ceftobiprole in Neonates and Infants up to 3 Months Treated W	Recruiting	No Results Available
51	NCT02210169	RCT of Continuous Versus Intermittent Infusion of Vancomycin in Neonates	Recruiting	No Results Available
52	NCT02497781	Evaluation of Safety, Pharmacokinetics and Efficacy of Ceftazidime and Avibactam (CAZ-AVI) Co	Recruiting	No Results Available
53	NCT02814916	Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections in Children,	Not yet recruiting	No Results Available
54	NCT02210325	Efficacy and Safety Study of Oral Solithromycin Compared to Intramuscular Ceftriaxone Plus Ora	Recruiting	No Results Available
55	NCT02801370	Phase 3 Study of OTO-201 in Acute Otitis Externa	Recruiting	No Results Available
56	NCT02760420	3 Days Amoxicillin Versus Placebo for Fast Breathing Childhood Pneumonia in Malawi	Recruiting	No Results Available
57	NCT02678195	3 Days Versus 5 Days Amoxicillin for Chest-indrawing Childhood Pneumonia in Malawi	Recruiting	No Results Available
58	NCT02605122	Safety and Efficacy of Solithromycin in Adolescents and Children With Community-acquired Bact	Recruiting	No Results Available
59	NCT02570490	Oral Sodium Fusidate (CEM-102) Versus Oral Linezolid for the Treatment of Acute Bacterial Skin	Recruiting	No Results Available
60	NCT02443285	Is Spontaneous Bacterial Peritonitis Still Responding to 3rd Generation Cephalosporins?	Recruiting	No Results Available
61	NCT02334124	Comparing the Intravenous Treatment of Skin Infections in Children, Home Versus Hospital	Recruiting	No Results Available
62	NCT02218372	A Study to Investigate the Safety and Efficacy of Fidaxomicin (Oral Suspension or Tablets) and Va	Recruiting	No Results Available

	A	B	C	D
63	NCT01032499	Open and Comparative Study to Measure Tolerability and Efficacy of Taro Elixir	Not yet recruiting	No Results Available
64	NCT02598362	Pharmacokinetics of Ciprofloxacin in Pediatric Patients	Recruiting	No Results Available
65	NCT02878031	Community Case Management of Chest Indrawing Pneumonia	Recruiting	No Results Available
66	NCT02790996	Neonatal Vancomycin Trial	Not yet recruiting	No Results Available
67	NCT02712307	Study of 5 and 10 Days Treatment With Penicillin Against Sore Throat Caused by Streptococci	Recruiting	No Results Available
68	NCT02424734	Safety, Tolerability and Efficacy of Ceftaroline in Paediatrics With Late-Onset Sepsis	Recruiting	No Results Available
69	NCT02134301	Open-Label, Dose-Finding, Pharmacokinetics, Safety and Tolerability Study of Oritavancin in Ped	Recruiting	No Results Available
70	NCT02013141	An Open-Label Study of the Pharmacokinetics of a Single Dose of Telavancin in Pediatric Subject	Recruiting	No Results Available
71	NCT01427842	Dose Enhancement of Vancomycin IN Everyday Patients	Recruiting	No Results Available
72	NCT01278017	The Role of Short-course Ceftriaxone Therapy in the Treatment of Severe Nontyphoidal Salmone	Recruiting	No Results Available
73	NCT00988026	Safety and Efficacy Comparison of Minocycline Microgranules Versus Lymecycline in the Treatm	Recruiting	No Results Available
74	NCT02288234	Telavancin Observational Use Registry (TOUR)	Recruiting	No Results Available
75	NCT01304459	Vancomycin Serum Concentrations in Pediatric Oncology Patients Under Intensive Care	Recruiting	No Results Available
76	NCT01173575	Assessment of the Efficacy of FOSFOMYCIN in Patients With Bacterial Infection	Recruiting	No Results Available
77	NCT01778634	Trial of Intravenous Azithromycin to Eradicate Ureaplasma Respiratory Tract Infection in Preterm	Recruiting	No Results Available

	E	F
1	**Indication**	**Infection category**
2	Proven or suspected infection (in patients on PICU)	9
3	Acute Otitis Media	3
4	Sepsis	8
5	Urinary Tract Infections (UTI)	7
6	Community-acquired Pneumonia (CAP)	4
7	Pneumonia	4
8	Proven or suspected infection in patients with malnutrition	9
9	Bacteremia	8
10	Plague	8
11	Helicobacter Pylori Infection	7
12	Meningitis	1
13	Proven or suspected bacterial infection (Pharmacokinetics)	9
14	Melioidosis	8
15	Acute Respiratory Infection|Sinusitis	3
16	Various infections (including nosocomial Pneumonia, CAP, Acute Bac	Various
17	Bacterial Infections	9
18	Meliodosis	8
19	Proven or Suspected Gram-negative Bacterial Infection	9
20	Abscess	1
21	Bronchitis	4
22	Throatcarriers of MRSA	3
23	Acute Skin and Soft Tissue infections (aSSTIs)	2
24	Proven or suspected bacterial infection (in CRRT patients)	9
25	Cystitis / Pyelonephritis	7
26	Acute Upper Respiratory Tract Infections (ARTIs)	3
27	Typhoid Fever	8
28	Community Acquired Pneumonia (CAP)	4
29	Bacterial Infections	9
30	Pneumonia	4
31	Complicated Intra Abdominal Infections (cIAIs)	6

	E	F
32	Pneumonia	4
33	Bacterial Infections	9
34	Cellulitis	2
35	Gram-Positive Bacterial Infections	9
36	Infection	9
37	Urinary Tract Infection or suspected Cholangitis	7
38	Methicillin-resistant Staphylococcal Infections	9
39	Bacterial Meningitis	1
40	Staphylococcal Infections	9
41	Peritonitis (in CAPD patients)	6
42	Acute Sinusitis (Respiratory Tract Infections)	3
43	SBP in patients with Liver Cirrhosis	6
44	Hematogenously Acquired Staphylococcus Aureus Osteomyelitis	5
45	Cellulitis or Wound Infection	8
46	Appendicitis	6
47	Complicated Intra-abdominal Infections (cIAIs)	6
48	Pneumonia (fast-breathing)	4
49	Rhinosinusitis	3
50	Bacterial Infections	9
51	Sepsis	8
52	Complicated Urinary Tract Infections (cUTIs)	7
53	Methicillin-Resistant Staphylococcus Aureus Skin Infection	2
54	Uncomplicated Urogenital Gonorrhea	7
55	Acute Otitis Externa	3
56	Pneumonia	4
57	Pneumonia	4
58	Community-acquired Bacterial Pneumonia	4
59	Acute Bacterial Skin and Skin Structure Infections	2
60	Primary Bacterial Peritonitis	6
61	Cellulitis	8
62	Clostridium Difficile-associated Diarrhea (CDAD)	6

	E	F
63	Acne Vulgaris II or III Degree	2
64	Urinary Tract Infection or Pyelonephritis	7
65	Pneumonia	4
66	Late Onset Neonatal Sepsis	8
67	Tonsillitis	3
68	Late-onset Sepsis	8
69	Gram Positive Bacterial Infections	9
70	Gram-Positive Bacterial Infections	9
71	Vancomycin Therapy	9
72	Diarrhea	6
73	Mild to Moderate Acne	2
74	Hospital Acquired Bacterial Pneumonia (HAP), Complicated Skin and	Various
75	Infection	9
76	Bacterial Infection	9
77	Eradicate ureaplasma respiratory tract infection from preterm infant	4

	G	H	I	J
1	**Interventions**	**Antibiotic class (J01 code)**	**Gender**	**Age**
2	Antiinfectives (beta-lactam, aminoglycoside, glycopeptide, fluoroquinolone,	Various	Both	Up to 18 Years
3	Amoxicillin, Amoxicillin-Potassium Clavulanate, Macrolide	Various	Both	6 Months to 7 Years
4	Antibiotic	J01	Both	Up to 18 years
5	Trimethoprim sulfamethoxazole, cefixime, or cephalexin	Various	Both	2 Months to 10 Years
6	Amoxicillin	J01C	Both	6 Months to 10 Years
7	Amoxicillin, Amoxicillin-clavulanate, Cefdinir	Various	Both	6 Months to 71 Months
8	Ceftriaxone, Metronidazole	J01D	Both	2 Months to 59 Months
9	7 days vs 14 days of adequate antibiotic treatment	J01	Both	Up to 18 years
10	Ciprofloxacin, doxyxcycline	Various	Both	8 Years and older
11	Tailored vs standard therapy (Amoxicillin, Clarithromycin, Metronidazole, Ra	Various	Both	4 Years to 18 Years
12	Daptomycin	J01X	Both	3 Months to 16 Years
13	Amoxicillin-clavulanate, Piperacilline-tazobactam, Vancomycin	Various	Both	Up to 16 Years
14	Meropenem, Ceftazidime	J01D	Both	15 Years and older
15	Amoxicillin clavulanate acid	J01C	Both	6 Years to 13 Years
16	Various drugs (Ceftazidime, Ciprofloxacin, Clindamycin, Doxycycline, Levoflo	Various	Both	Up to 18 years
17	Clindamycin, Trimethoprim-sulfamethoxazole	Various	Both	1 Month to 16 Years
18	Co-trimoxazole	J01E	Both	15 Years and older
19	Ceftolozane/Tazobactam	J01D	Both	Up to 17 Years
20	Trimethoprim-sulfamethoxazole	J01E	Both	3 Months to 17 Years
21	Guaifenesin, Sulfamethoxazole trimethoprim	J01E	Both	4 Years to 14 Years
22	Systemic Rifampin and Clindamycine/Trimehoprimsulfa, or Topical mupiroci	Various	Both	5 Years and older
23	Tedizolid Phophate	J01X	Both	12 Years to 18 Years
24	Vancomycin	J01X	Both	Up to 18 years
25	Ciprofloxacin	J01F	Both	Up to 14 Years
26	Antibiotics (Amoxicillin-clavulanate, azithromycin, cefdinir, cefprozil, cefurox	Various	Both	6 Months to 18 Years
27	Ceftriaxone, Ceftriaxone/azithromycin, Azithromycin, Azithromycin/cefixime	Various	Both	2 Years to 80 Years
28	Cephalosporins and Macrolides	Various	Both	1 Year to 18 Years
29	Carbavance	J01D	Both	Up to 17 Years
30	Amoxicillin-clavulanic Acid	J01C	Both	3 Months to 5 Years
31	Ampicillin/metronidazole/gentamicin/clindamycin/Piperacillin-tazobactam c	Various	Both	Up to 120 Days

	G	H	I	J
32	Amoxicillin-Potassium Clavulanate	J01C	Both	3 Months to 59 Months
33	Dalbavancin	J01X	Both	Up to 28 Days
34	Cefazolin/Moxifloxacin	Various	Both	Up to 18 Years
35	Tedizolid Phosphate	J01X	Both	2 Years to 11 Years
36	Piperacillin-tazobactam	J01C	Both	2 Months to 6 Years
37	Temocillin	J01C	Both	6 Months to 3 Years
38	Vancomycin	J01X	Both	1 Month to 16 Years
39	Beta-lactam	J01C	Both	2 Months to 15 Years
40	Teicoplanin	J01X	Both	16 Years and older
41	Ceftazidime/ciprofloxacin, Ceftazidime, Cefazolin/gentamicin, Cefazolin	Various	Both	15 Years and older
42	Amoxicillin-clavulanate	J01C	Both	2 Years to 11 Years
43	Cefotaxime, Ceftriaxone, Ciprofloxacin	Various	Both	16 Years and older
44	Ceftaroline Fosamil	J01D	Both	1 Year to 17 Years
45	Flucloxacillin, Phenoxymethylpenicillin	J01C	Both	16 Years and older
46	Augmentin/Gentamicin, Appendectomy	J01C	Both	7 Years to 17 Years
47	Ceftazidime-avibactam, Meropenem, Metronidazole	Various	Both	3 Months to 18 Years
48	Amoxicillin	J01C	Both	2 Months to 59 Months
49	Cefditoren pivoxil	J01D	Both	1 Year to 15 Years
50	Ceftobiprole	J01D	Both	Up to 3 Months
51	Vancomycin	J01X	Both	Up to 90 Days
52	Ceftazidime-avibactam, Cefepime	J01D	Both	3 Months to 18 Years
53	Dalbavancin single dose	J01X	Both	3 Months to 17 Years
54	Solithromycin, Ceftriaxone, Azithromycin	Various	Both	15 Years and older
55	Ciprofloxacin	J01M	Both	6 Months and older
56	Amoxicillin	J01C	Both	2 Months to 59 Months
57	Amoxicillin	J01C	Both	2 Months to 59 Months
58	Solithromycin	J01F	Both	2 Months to 17 Years
59	Sodium fusidate, Linezolid	J01X	Both	12 Years and older
60	Cefotaxime, Ceftriaxone	J01D	Both	Up to 18 Years
61	Ceftriaxone, Flucloxacillin	Various	Both	6 Months to 18 Years
62	Fidaxomicin, Vancomycin	J01X	Both	Up to 17 Years

	G	H	I	J
63	Taro Elixir	J01A	Both	14 Years and older
64	Ciprofloxacin	J01M	Both	3 Months to 17 Years
65	Amoxicillin	J01C	Both	2 Months to 59 Months
66	Vancomycin	J01X	Both	Up to 90 Days
67	Phenoxymethylpenicillin	J01C	Both	6 Years and older
68	Ceftaroline Fosamil	J01D	Both	Up to 59 Days
69	Oritavancin	J01X	Both	Up to 18 Years
70	Telavancin	J01X	Both	1 Year to 17 Years
71	Vancomycin	J01X	Both	16 Years and older
72	Ceftriaxone	J01D	Both	3 Months to 18 Years
73	Minocycline, Lymecycline	J01A	Both	14 Years to 30 Years
74	Telavancin	J01X	Both	Up to 18 Years
75	Vancomycin	J01X	Both	Up to 18 Years
76	Fosfomycin	J01X	Both	Up to 18 Years
77	Azithromycin	J01F	Both	0 to 72 hours

	K	L	M	N	O
1	**Age group**	**Estimated enrollment**	**Location**	**Income class**	**Geographic region**
2	8	1850	France	High income	Europe
3	9	150	Finland	High income	Europe
4	8	320	Italy	High income	Europe
5	9	746	United States	High income	North America
6	9	270	Canada	High income	North America
7	9	400	United States	High income	North America
8	9	80	Kenya	Lower middle income	Africa
9	8	50	Canada	High income	North America
10	11	200	Uganda	Low income	Africa
11	11	200	China	Upper middle income	Asia
12	10	5	Switzerland	High income	Europe
13	8	200	Belgium	High income	Europe
14	5	750	Thailand	Upper middle income	Asia
15	11	120	Finland	High income	Europe
16	8	3000	Various (United States, Canad	High income	International
17	10	54	United States	High income	North America
18	5	800	Thailand	Upper middle income	Asia
19	8	36	United States	High income	North America
20	10	200	United States	High income	North America
21	11	50	Peru	Upper middle income	Latin America
22	11	69	Sweden	High income	North America
23	5	162	Various (United States, Argent	Upper middle to High income	International
24	8	10	United States	High income	North America
25	8	45	Japan	High income	Asia
26	10	117000	United States	High income	North America
27	11	120	Nepal	Low income	Asia
28	10	750	China	Upper middle income	Asia
29	8	56	United States	High income	North America
30	9	314	Various (Australia, Malaysia)	High income	Oceania
31	6	284	Various (United States, Canad	High income	North America

	K	L	M	N	O
32	9	300	Malaysia	Upper middle income	Asia
33	2	24	United States	High income	North America
34	8	390	Canada	High income	North America
35	4	32	United States	High income	North America
36	9	141	Canada	High income	North America
37	9	45	Belgium	High income	Europe
38	10	100	France	High income	Europe
39	10	400	Angola	Upper middle income	Africa
40	5	20	Taiwan, China	High income	Asia
41	5	300	Thailand	Upper middle income	Asia
42	4	688	United States	High income	North America
43	5	261	Republic of Korea	High income	Asia
44	10	18	United States	High income	North America
45	5	414	Ireland	High income	Europe
46	11	334	Netherlands	High income	Europe
47	10	102	Various (United States, Argent	Upper middle to High income	International
48	9	2500	Pakistan	Lower middle income	Asia
49	10	120	Thailand	Upper middle income	Asia
50	6	45	Various (Belgium, Germany, Li	High income	Europe
51	6	200	Australia	High income	Oceania
52	10	102	Various (United States, Czech	Upper middle to High income	International
53	10	300	United States	High income	North America
54	5	300	Various (United States, Austra	High income	International
55	10	500	Various (United States, Canad	High income	North America
56	9	2000	Malawi	Low income	Africa
57	9	2000	Malawi	Low income	Africa
58	10	400	Various (United States, Bulgar	High income	International
59	5	712	Various (United States, Puerto	High income	International
60	8	100	Egypt	Lower middle income	Africa
61	10	188	Australia	High income	Oceania
62	8	144	Various (United States, Belgiu	High income	International

	K	L	M	N	O
63	5	120	Brazil	Upper middle income	Latin America
64	10	20	Belgium	High income	Europe
65	9	308	Nigeria	Lower middle income	Africa
66	6	300	Various (United Kingdom, Fra	High income	Europe
67	11	432	Sweden	High income	Europe
68	7	24	Various (United States, Hunga	High income	International
69	8	60	United States	High income	North America
70	10	32	United States	High income	North America
71	5	100	Australia	High income	Oceania
72	10	200	Taiwan, China	High income	Asia
73	5	168	Mexico	High income	North America
74	8	1000	United States	High income	North America
75	8	50	Brazil	Upper middle income	Latin America
76	8	200	Various (Austria, Germany)	High income	Europe
77	1	180	United States	High income	North America

	P	Q	R	S	T
1	**Collaborators**	**Sponsor**	**Study Types**	**Phase**	**Endpoint classification**
2	Assistance Publique - Hopitaux de Paris	Hospital	Observational	Not applicable	Pharmacokinetics
3	University of Oulu|Oulu University Hospital	University	Interventional	Phase 4	Efficacy
4	Ospedale Santa Maria delle Croci	Hospital	Interventional	Phase 2	Safety/Efficacy
5	Children's Hospital of Philadelphia|Children's Ho	Hospital	Interventional	Phase 2	Safety/Efficacy
6	Hamilton Health Sciences Corporation|Children's	Hospital	Interventional	Phase 4	Safety/Efficacy
7	National Institute of Allergy and Infectious Diseas	NIH	Interventional	Phase 4	Efficacy
8	University of Oxford|KEMRI Wellcome Trust Rese	University	Interventional	Phase 2	Pharmacokinetics
9	Sunnybrook Health Sciences Centre	Hospital	Interventional	Not specified	Efficacy
10	Centers for Disease Control and Prevention|MRC	CDC	Interventional	Phase 2	Safety/Efficacy
11	Beijing Children's Hospital	Hospital	Interventional	Phase 4	Safety/Efficacy
12	University Hospital Inselspital, Berne	Hospital	Interventional	Phase 1	Pharmacokinetics
13	University Hospital, Ghent|University Hospital, A	Hospital	Observational	Not applicable	Pharmacokinetics
14	University of Oxford|Mahidol University|Wellcor	University	Interventional	Not specified	Efficacy
15	Oulu University Hospital	University	Interventional	Phase 4	Safety/Efficacy
16	Daniel Benjamin|Eunice Kennedy Shriver Nationa	University	Observational	Not applicable	Pharmacokinetics
17	Michael Cohen-Wolkowiez|Eunice Kennedy Shriv	University	Interventional	Phase 1	Pharmacokinetics
18	Khon Kaen University	University	Interventional	Not specified	Efficacy
19	Cubist Pharmaceuticals LLC	Industry	Interventional	Phase 1	Pharmacokinetics
20	Children's Mercy Hospital Kansas City|Blue Cross	Hospital	Interventional	Not specified	Efficacy
21	Hoffmann-La Roche	Industry	Observational	Not applicable	Safety
22	Region Skane	Hospital	Interventional	Not specified	Efficacy
23	Cubist Pharmaceuticals LLC	Industry	Interventional	Phase 3	Safety
24	Drexel University|The Center for Pediatric Pharm	University	Interventional	Phase 1	Safety
25	Bayer	Industry	Observational	Not applicable	Safety/Efficacy
26	Children's Hospital of Philadelphia	Hospital	Observational	Not applicable	Safety/Efficacy
27	Sheba Medical Center	Hospital	Interventional	Phase 4	Efficacy
28	Beijing Children's Hospital	Hospital	Observational	Not applicable	Pharmacokinetics
29	Rempex Pharmaceuticals (a wholly owned subsid	Industry	Interventional	Phase 1	Safety
30	Menzies School of Health Research|Griffith Univ	University	Interventional	Phase 4	Safety/Efficacy
31	Michael Cohen-Wolkowiez|The EMMES Corporat	University	Interventional	Phase 2-3	Safety

	P	Q	R	S	T
32	University of Malaya|Menzies School of Health R	University	Interventional	Phase 4	Efficacy
33	Durata Therapeutics Inc., an affiliate of Allergan p	Industry	Interventional	Phase 1	Pharmacokinetics
34	University of British Columbia	University	Interventional	Phase 3	Efficacy
35	Merck Sharp & Dohme Corp.	Industry	Interventional	Phase 1	Pharmacokinetics
36	St. Justine's Hospital	Hospital	Interventional	Phase 1	Pharmacokinetics
37	Universitì© Catholique de Louvain	University	Interventional	Phase 4	Pharmacokinetics
38	Assistance Publique - Hì«pitaux de Paris	Hospital	Interventional	Not specified	Pharmacokinetics
39	Helsinki University|Foundation for Paediatric Res	University	Interventional	Phase 4	Safety/Efficacy
40	National Taiwan University Hospital	University	Interventional	Phase 4	Pharmacokinetics
41	Chulalongkorn University	University	Interventional	Not specified	Efficacy
42	University of Pittsburgh|National Institute of Alle	University	Interventional	Phase 3	Safety/Efficacy
43	Korea University	University	Interventional	Phase 4	Efficacy
44	Baylor College of Medicine|Forest Laboratories	University	Interventional	Phase 1-2	Safety/Efficacy
45	Royal College of Surgeons, Ireland|Health Resear	University	Interventional	Phase 4	Efficacy
46	Ramon Gorter|ZonMw: The Netherlands Organis	University	Interventional	Phase 4	Efficacy
47	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2	Safety/Efficacy
48	Aga Khan University	University	Interventional	Not specified	Efficacy
49	Thammasat University	University	Interventional	Phase 4	Safety/Efficacy
50	Basilea Pharmaceutica	Industry	Interventional	Phase 1	Pharmacokinetics
51	Murdoch Childrens Research Institute|Royal Chil	University	Interventional	Not specified	Pharmacokinetics
52	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2	Safety/Efficacy
53	Durata Therapeutics Inc., an affiliate of Allergan p	Industry	Interventional	Phase 3	Safety/Efficacy
54	Cempra Inc|National Institute of Allergy and Infe	Industry	Interventional	Phase 3	Efficacy
55	Otonomy, Inc.	Industry	Interventional	Phase 3	Efficacy
56	Save the Children|University of North Carolina|U	Health Organisat	Interventional	Phase 4	Efficacy
57	Save the Children|University of North Carolina|U	Health Organisat	Interventional	Phase 4	Efficacy
58	Cempra Inc	Industry	Interventional	Phase 2-3	Safety/Efficacy
59	Cempra Inc	Industry	Interventional	Phase 3	Safety/Efficacy
60	Tanta University	University	Interventional	Phase 3	Efficacy
61	Murdoch Childrens Research Institute	University	Interventional	Not specified	Efficacy
62	Astellas Pharma Europe B.V.|Merck Sharp & Doh	Industry	Interventional	Phase 3	Safety/Efficacy

	P	Q	R	S	T
63	Laboratorios Goulart S.A.	Industry	Interventional	Phase 3	Safety/Efficacy
64	University Hospital, Ghent|Universitair Ziekenhu	University	Interventional	Phase 4	Pharmacokinetics
65	Malaria Consortium|World Health Organization	Health Organisat	Interventional	Phase 4	Safety
66	PENTA Foundation|St George's, University of Lor	Health Organisat	Interventional	Phase 2	Safety/Efficacy
67	Sigvard Mì¦lstad|Public Health Agency of Swede	University	Interventional	Phase 4	Safety/Efficacy
68	AstraZeneca|PRA Health Sciences	Industry	Interventional	Phase 2-3	Safety/Efficacy
69	The Medicines Company	Industry	Interventional	Phase 1	Pharmacokinetics
70	Theravance Biopharma Antibiotics, Inc.	Industry	Interventional	Phase 4	Pharmacokinetics
71	The Canberra Hospital	Hospital	Interventional	Phase 2	Pharmacokinetics
72	Chang Gung Memorial Hospital	Hospital	Interventional	Phase 4	Efficacy
73	Darier	Industry	Interventional	Phase 4	Safety/Efficacy
74	Theravance Biopharma Antibiotics, Inc.	Industry	Observational	Not applicable	Safety/Efficacy
75	Grupo de Apoio ao Adolescente e a Crianca com	Hospital	Observational	Not applicable	Pharmacokinetics
76	Infectopharm Arzneimittel GmbH|J&P Medical R	Industry	Observational	Not applicable	Efficacy
77	University of Maryland	University	Interventional	Phase 2	Safety/Efficacy

	U	V	W	X	Y	Z	AA	AB
1	**Primary outcome variable**	**PK data collected**	**First Receive**	**Start Date**	**Completion I**	**Last Updated**	**Last Verified**	**Results First Received**
2	PK	PK study design	July 2, 2015	Sep-15	Dec-18	September 1	Sep-16	No Study Results Posted
3	Efficacy	No PK data	September 2	Oct-16	null	October 12, 2	Oct-16	No Study Results Posted
4	Efficacy	No PK data	September 8	Sep-16	null	September 1	Sep-16	No Study Results Posted
5	Efficacy	No PK data	May 8, 2012	May-12	Apr-18	June 27, 201	Jun-16	No Study Results Posted
6	Efficacy	No PK data	March 2, 201	Mar-16	May-18	March 24, 20	Mar-16	No Study Results Posted
7	Efficacy	No PK data	September 1	Oct-16	Mar-19	October 13, 2	Oct-16	No Study Results Posted
8	PK	PK study design	April 4, 2016	Apr-16	Sep-16	April 25, 201	Apr-16	No Study Results Posted
9	Efficacy	No PK data	September 2	Oct-16	Dec-17	September 2	Sep-16	No Study Results Posted
10	Efficacy	No PK data	November 17	Dec-10	null	September 1	Sep-12	No Study Results Posted
11	Efficacy	No PK data	November 25	Mar-14	Jul-16	December 16	Nov-15	No Study Results Posted
12	PK	Primary PK data	January 26, 2	Apr-12	Apr-18	December 10	Dec-15	No Study Results Posted
13	PK	PK study design	May 18, 2015	May-12	null	November 17	Nov-15	No Study Results Posted
14	Efficacy	No PK data	December 18	Dec-07	Sep-10	June 3, 2008	Aug-07	No Study Results Posted
15	Efficacy	No PK data	October 17, 2	Nov-07	Dec-09	October 18, 2	Oct-07	No Study Results Posted
16	PK	PK study design	August 17, 20	Nov-11	Feb-17	February 4, 2	Feb-16	No Study Results Posted
17	PK	PK study design	June 12, 201	Nov-15	Dec-17	August 1, 201	Aug-16	No Study Results Posted
18	Efficacy	No PK data	August 18, 20	Aug-11	Dec-20	August 30, 20	Aug-16	No Study Results Posted
19	PK	PK study design	September 2	Sep-14	Nov-16	October 31, 2	Oct-16	No Study Results Posted
20	Efficacy	No PK data	March 23, 20	Mar-09	Oct-12	June 21, 201	Jun-11	No Study Results Posted
21	Safety	No PK data	August 23, 20	Aug-16	Dec-16	September 1	Sep-16	No Study Results Posted
22	Efficacy	No PK data	January 3, 20	Mar-11	Jun-15	May 25, 201	May-15	No Study Results Posted
23	Safety	Secondary PK data	October 9, 20	Mar-15	Jan-18	October 31, 2	Oct-16	No Study Results Posted
24	Safety	Primary PK data	January 12, 2	Jan-17	Dec-18	September 8	Sep-16	No Study Results Posted
25	Safety	No PK data	September 1	Jul-16	Sep-18	October 19, 2	Oct-16	No Study Results Posted
26	Efficacy	No PK data	November 17	Jan-14	Jul-17	May 6, 2016	May-16	No Study Results Posted
27	Efficacy	No PK data	August 21, 20	Aug-13	Aug-15	August 26, 20	Aug-14	No Study Results Posted
28	PK	PK study design	May 11, 2016	Aug-16	Oct-22	May 17, 2016	May-16	No Study Results Posted
29	Safety	Primary PK data	February 17,	Jul-16	Sep-19	October 6, 20	Oct-16	No Study Results Posted
30	Efficacy	No PK data	May 5, 2016	Jun-16	Dec-20	October 7, 20	Oct-16	No Study Results Posted
31	Safety	No PK data	November 18	Dec-13	Sep-17	August 1, 201	Aug-16	No Study Results Posted

	U	V	W	X	Y	Z	AA	AB
32	Efficacy	No PK data	September 2	Nov-14	Dec-18	December 20	Dec-15	No Study Results Posted
33	PK	PK study design	February 18,	Apr-16	May-17	October 19, 2	Oct-16	No Study Results Posted
34	Efficacy	No PK data	May 8, 2006	Jan-04	Dec-13	February 6, 2	Feb-12	No Study Results Posted
35	PK	PK study design	April 1, 2016	May-16	Feb-18	October 21, 2	Oct-16	No Study Results Posted
36	PK	PK study design	June 2, 2015	Jan-16	Dec-17	April 18, 201	Apr-16	No Study Results Posted
37	PK	PK study design	October 1, 20	Oct-16	Oct-17	October 24, 2	Oct-16	No Study Results Posted
38	PK	PK study design	February 24,	Feb-16	Feb-17	March 8, 201	Mar-16	No Study Results Posted
39	Efficacy	No PK data	February 23,	Feb-12	Jul-17	February 19,	Feb-16	No Study Results Posted
40	PK	PK study design	August 23, 20	Jun-06	Dec-07	August 23, 20	Aug-06	No Study Results Posted
41	Efficacy	No PK data	January 30, 2	Dec-12	Dec-13	February 6, 2	Feb-13	No Study Results Posted
42	Efficacy	No PK data	September 8	Feb-16	Sep-20	October 3, 20	Oct-16	No Study Results Posted
43	Efficacy	No PK data	December 22	Apr-07	Apr-16	April 8, 2014	Apr-14	No Study Results Posted
44	Safety	Secondary PK data	December 31	Jan-15	Jan-20	June 24, 201	Jun-16	No Study Results Posted
45	Efficacy	No PK data	August 9, 201	Dec-16	Dec-19	September 3	Jul-16	No Study Results Posted
46	Efficacy	No PK data	July 24, 2016	Dec-16	Dec-20	July 26, 2016	Jul-16	No Study Results Posted
47	Safety	Secondary PK data	May 25, 2015	Jul-15	Oct-17	October 21, 2	Oct-16	No Study Results Posted
48	Efficacy	No PK data	November 4,	Nov-14	Jul-17	June 3, 2016	Jun-16	No Study Results Posted
49	Efficacy	No PK data	February 17,	Jan-12	Sep-12	March 13, 20	Mar-12	No Study Results Posted
50	PK	PK study design	August 5, 201	Aug-14	Jun-17	October 20, 2	Oct-16	No Study Results Posted
51	PK	PK study design	August 5, 201	Sep-14	Sep-17	March 17, 20	Mar-16	No Study Results Posted
52	Safety	Secondary PK data	June 16, 201	Sep-15	Oct-17	October 21, 2	Oct-16	No Study Results Posted
53	Efficacy	No PK data	June 8, 2016	Jun-16	Jul-18	June 23, 201	Jun-16	No Study Results Posted
54	Efficacy	No PK data	August 1, 201	Aug-14	Apr-17	September 2	Sep-16	No Study Results Posted
55	Efficacy	No PK data	June 13, 201	Jun-16	Nov-16	June 13, 201	Jun-16	No Study Results Posted
56	Efficacy	No PK data	May 1, 2016	Jun-16	Sep-18	June 10, 201	Jun-16	No Study Results Posted
57	Efficacy	No PK data	February 3, 2	Mar-16	null	June 10, 201	Jun-16	No Study Results Posted
58	Safety	No PK data	November 1(	Mar-16	Jan-18	September 1	Sep-16	No Study Results Posted
59	Efficacy	No PK data	October 5, 20	Nov-15	Feb-17	October 5, 20	Oct-16	No Study Results Posted
60	Efficacy	No PK data	May 11, 2015	Jan-15	Dec-16	May 9, 2016	May-16	No Study Results Posted
61	Efficacy	No PK data	January 4, 20	Jan-15	Jan-17	March 16, 20	Mar-16	No Study Results Posted
62	Efficacy	No PK data	August 11, 20	Oct-14	Feb-17	June 17, 201	Jun-16	No Study Results Posted

	U	V	W	X	Y	Z	AA	AB
63	Efficacy	No PK data	December 14	May-10	Oct-10	March 18, 20	Dec-09	No Study Results Posted
64	PK	PK study design	November 4,	Apr-15	Apr-16	November 4,	Nov-15	No Study Results Posted
65	Safety	No PK data	August 17, 2(	Oct-16	Jul-17	October 3, 2(	Oct-16	No Study Results Posted
66	Efficacy	Secondary PK data	April 7, 2016	Jul-16	Mar-18	May 31, 201(	May-16	No Study Results Posted
67	Efficacy	No PK data	March 4, 201	Sep-15	Oct-16	October 4, 2(	Oct-16	No Study Results Posted
68	Safety	Secondary PK data	February 23,	Aug-15	Oct-17	October 14, 2	Oct-16	No Study Results Posted
69	PK	PK study design	May 7, 2014	May-14	Dec-16	November 4,	Nov-15	No Study Results Posted
70	PK	PK study design	December 11	Dec-14	Aug-16	June 24, 201(	Jun-16	No Study Results Posted
71	PK	PK study design	August 31, 2(	Aug-11	Jul-12	September 1	Aug-11	No Study Results Posted
72	Efficacy	No PK data	November 25	Aug-10	Jul-12	January 14, 2	Nov-10	No Study Results Posted
73	Efficacy	No PK data	September 3	Jun-09	Apr-10	September 3	Sep-09	No Study Results Posted
74	Efficacy	No PK data	November 5,	Nov-14	Sep-18	June 29, 201(	Jun-16	No Study Results Posted
75	PK	Primary PK data	February 24,	Jan-11	null	March 21, 20	Mar-12	No Study Results Posted
76	Efficacy	No PK data	July 29, 2010	Aug-10	null	February 5, 2	Feb-16	No Study Results Posted
77	Efficacy	Secondary PK data	January 22, 2	Jul-13	Dec-21	May 28, 201!	May-15	No Study Results Posted

	AC	AD	AE	AF	AG
1	**Primary Com**	**URL**			
2	Jul-18	https://ClinicalTrials.gov/show/NCT02539407			
3	Dec-18	https://ClinicalTrials.gov/show/NCT02935374			
4	Sep-18	https://ClinicalTrials.gov/show/NCT02899143			
5	Apr-18	https://ClinicalTrials.gov/show/NCT01595529			
6	Feb-18	https://ClinicalTrials.gov/show/NCT02380352			
7	Jan-19	https://ClinicalTrials.gov/show/NCT02891915			
8	Sep-16	https://ClinicalTrials.gov/show/NCT02746276			
9	Aug-17	https://ClinicalTrials.gov/show/NCT02917551			
10	Jun-13	https://ClinicalTrials.gov/show/NCT01243437			
11	Mar-16	https://ClinicalTrials.gov/show/NCT02635191			
12	Dec-16	https://ClinicalTrials.gov/show/NCT01522105			
13	Dec-17	https://ClinicalTrials.gov/show/NCT02456974			
14	Sep-10	https://ClinicalTrials.gov/show/NCT00579956			
15	null	https://ClinicalTrials.gov/show/NCT00545961			
16	Feb-17	https://ClinicalTrials.gov/show/NCT01431326			
17	Nov-17	https://ClinicalTrials.gov/show/NCT02475876			
18	Dec-20	https://ClinicalTrials.gov/show/NCT01420341			
19	Nov-16	https://ClinicalTrials.gov/show/NCT02266706			
20	Sep-12	https://ClinicalTrials.gov/show/NCT00867789			
21	Dec-16	https://ClinicalTrials.gov/show/NCT02879981			
22	Jun-15	https://ClinicalTrials.gov/show/NCT01269541			
23	Jan-18	https://ClinicalTrials.gov/show/NCT02276482			
24	Dec-18	https://ClinicalTrials.gov/show/NCT02663596			
25	Sep-17	https://ClinicalTrials.gov/show/NCT02555059			
26	Apr-17	https://ClinicalTrials.gov/show/NCT02297815			
27	Dec-14	https://ClinicalTrials.gov/show/NCT02224040			
28	Aug-22	https://ClinicalTrials.gov/show/NCT02775968			
29	Aug-19	https://ClinicalTrials.gov/show/NCT02687906			
30	Dec-19	https://ClinicalTrials.gov/show/NCT02783859			
31	Apr-17	https://ClinicalTrials.gov/show/NCT01994993			

	AC	AD	AE	AF	AG
32	Dec-17	https://ClinicalTrials.gov/show/NCT02258763			
33	May-17	https://ClinicalTrials.gov/show/NCT02688790			
34	Dec-12	https://ClinicalTrials.gov/show/NCT00323219			
35	Feb-18	https://ClinicalTrials.gov/show/NCT02750761			
36	Dec-17	https://ClinicalTrials.gov/show/NCT02466438			
37	Sep-17	https://ClinicalTrials.gov/show/NCT02260102			
38	Jun-16	https://ClinicalTrials.gov/show/NCT02694458			
39	Feb-17	https://ClinicalTrials.gov/show/NCT01540838			
40	null	https://ClinicalTrials.gov/show/NCT00368498			
41	Dec-13	https://ClinicalTrials.gov/show/NCT01785641			
42	Sep-20	https://ClinicalTrials.gov/show/NCT02554383			
43	Mar-16	https://ClinicalTrials.gov/show/NCT01265173			
44	Jan-17	https://ClinicalTrials.gov/show/NCT02335905			
45	Dec-19	https://ClinicalTrials.gov/show/NCT02922686			
46	Dec-20	https://ClinicalTrials.gov/show/NCT02848820			
47	Oct-17	https://ClinicalTrials.gov/show/NCT02475733			
48	May-17	https://ClinicalTrials.gov/show/NCT02372461			
49	Aug-12	https://ClinicalTrials.gov/show/NCT01553006			
50	Mar-17	https://ClinicalTrials.gov/show/NCT02527681			
51	Sep-17	https://ClinicalTrials.gov/show/NCT02210169			
52	Oct-17	https://ClinicalTrials.gov/show/NCT02497781			
53	Apr-18	https://ClinicalTrials.gov/show/NCT02814916			
54	Apr-17	https://ClinicalTrials.gov/show/NCT02210325			
55	Nov-16	https://ClinicalTrials.gov/show/NCT02801370			
56	Aug-18	https://ClinicalTrials.gov/show/NCT02760420			
57	Aug-18	https://ClinicalTrials.gov/show/NCT02678195			
58	Dec-17	https://ClinicalTrials.gov/show/NCT02605122			
59	Feb-17	https://ClinicalTrials.gov/show/NCT02570490			
60	Dec-16	https://ClinicalTrials.gov/show/NCT02443285			
61	Jan-17	https://ClinicalTrials.gov/show/NCT02334124			
62	Feb-17	https://ClinicalTrials.gov/show/NCT02218372			

	AC	AD	AE	AF	AG
63	Jul-10	https://ClinicalTrials.gov/show/NCT01032499			
64	Feb-16	https://ClinicalTrials.gov/show/NCT02598362			
65	Mar-17	https://ClinicalTrials.gov/show/NCT02878031			
66	Dec-17	https://ClinicalTrials.gov/show/NCT02790996			
67	Oct-16	https://ClinicalTrials.gov/show/NCT02712307			
68	Oct-17	https://ClinicalTrials.gov/show/NCT02424734			
69	Dec-16	https://ClinicalTrials.gov/show/NCT02134301			
70	Aug-16	https://ClinicalTrials.gov/show/NCT02013141			
71	Jul-12	https://ClinicalTrials.gov/show/NCT01427842			
72	Jun-11	https://ClinicalTrials.gov/show/NCT01278017			
73	Feb-10	https://ClinicalTrials.gov/show/NCT00988026			
74	Jun-18	https://ClinicalTrials.gov/show/NCT02288234			
75	null	https://ClinicalTrials.gov/show/NCT01304459			
76	Dec-16	https://ClinicalTrials.gov/show/NCT01173575			
77	Dec-19	https://clinicaltrials.gov/ct2/show/NCT01778634			