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

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

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Abstract

Importance: There are very few options to treat multidrug resistant bacterial infections in children. A major barrier is the duration and complexity of regulatory trials of new antibiotics. Extrapolation of safety data from adult trials could facilitate drug development for children.

Objective: We performed a systematic review on safety of antibiotic clinical trials (CTs) in children (0-18 years) to evaluate the overall quality of safety trials conducted in children and to determine if age-specific adverse events (AEs) could be identified for specific antibiotic classes.

Data Sources: We searched MEDLINE, Cochrane CENTRAL, and ClinicalTrials.gov for trials conducted between 2000-2016.

Study Selection: All trials in which safety was declared as a primary or secondary endpoint were included. Exclusion criteria were (i) topical or inhalational route of administration, (ii) non-infectious conditions, (iii) administration for prophylaxis rather than treatment, (iv) selected population (i.e. cystic fibrosis, malignancies, HIV and tuberculosis) and (v) design other than randomized-controlled trials. Trials reporting data on both adults and children have been included only if paediatric results were reported separately.

Data Extraction and Synthesis: Two authors independently extracted the data. To assess the quality of published trials, the Extension for harms for Consolidated Standards of Reporting Trials (CONSORT) Statement 2004 was used.

Main Outcome and Measure: In order to quantitatively assess the rate of developing AEs by drug-class, the numbers of overall and body-system-specific AEs were collected for each study arm. Overall and body-system-specific AEs were collected and calculated per single drug class as median and interquartile range (IQR) of the proportions across CTs. The AEs most frequently reported were compared in the meta-analysis by selecting the CTs on the most represented drug classes.

Results: 83 CTs were included, accounting for 27,693 children. Overall, 69.7% of CONSORT items were fully reported. The median proportion of children with any AE was 22.5%, but did not exceed 8% in any single body-system. Serious drug-related AEs and drug-related discontinuation were very

rare (median 0.3% and 0.9%, respectively). Limitations included inability to stratify by age-group, particularly neonates.

Conclusions and Relevance: Overall AEs in paediatric antibiotic CTs were predictable and class-specific; no unexpected (age-specific) side effects were identified. Smaller open-label dose-finding high-quality single-arm pharmacokinetic trials seem potentially sufficent for certain common antibiotic classes, extrapolatimg well-established safety profiles determined from large adult efficacy trials. This approach could reduce duration and enhance subsequent registration of urgently needed new antibiotics. This will need to be combined with enhanced methods of pharmacovigilance for monitoring of emerging AEs in routine clinical practice.

Key points

- Data reported for the antibiotic classes most commonly used in children showed that adverse events in paediatrics were class-specific and broadly predictable.
- Within the limitations of the lack of neonatal data, no age-specific or unexpected toxicity has been identified.
- For common antibiotic classes, with well-established safety profiles in adults, it is potentially possible to simplify the safety assessments if combined with enhanced post-marketing approval pharmacovigilance for monitoring emerging adverse events in routine clinical practice.

1 Introduction

Drug development for children remains challenging, with nearly half of paediatric medicines in Europe prescribed off-label [1, 2]. The introduction of new antibiotics to routine paediatric care is a particularly urgent issue due to the global challenge of antimicrobial resistance. The barriers to conducting clinical trials (CTs) of antibiotics in children have been previously reported [3]. Several initiatives have been put in place to bridge this gap to improve the efficiency and feasibility of paediatric CTs [4-6].

Recruiting children into antibiotic CTs is challenging and trials need to be made as efficient as possible. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) encourage modelling and simulation for dose finding and to extrapolate data on efficacy from adult studies [7, 8]. Although the concept of extrapolation of efficacy endpoints in paediatric trials is well established, the extrapolation of safety has not been accepted generally by regulators. The overall aim is to improve the efficiency of trials in children and maximise the amount of information extracted from adults, without compromising the quality of evidence for regulatory decisions [8]. However, age stratification showed that some safety signals may be detected only in specific age groups [9]. Therefore, the collection of safety data to identify unexpected (age-specific) adverse events (AEs) may be required in the target population when a drug use is age-specific or an age-specific risk is expected [10]. On the other hand, the reporting of pharmacovigilance data on antibiotics in neonates and children is currently limited. Pharmaceutical companies conduct a comprehensive assessment of drug safety following marketing approval and then submit this data to the drug regulatory authority. However, this process requires a significant amount of resources, with the result that AEs are often under-reported, especially in case of uncomplicated non-serious events [11].

The overall aim of this systematic review was to provide a summary overview on the appropriateness of safety data reported in CTs of antibacterial agents in children and neonates. The

specific objectives were (i) to evaluate the overall quality of safety trials conducted in children and (ii) to determine if age-specific AEs could be identified for different antibiotic classes.

2 Methods

Medline (Ovid MEDLINE® without Revisions 1996) and Cochrane CENTRAL (Issue 6 of 12, June 2016) databases were systematically searched on 2 June 2016, using a strategy combining MeSH and free-text terms that included "antibiotic" AND "randomized controlled trial" AND "safety" in children (0–18 years). The search was limited to CTs published after 2000. *Clinicaltrial.gov* register was systematically searched on the 2 June 2016 for registered CTs using the same strategy. The search was limited to ongoing trials and trials closed in the last 5 years (2011-2016) in order to cover the publication gap. No language restriction was applied. The full strategy is available in the Online resource.

All trials in which safety was declared as a primary or secondary endpoint were included. Exclusion criteria were (i) topical or inhalational route of administration, (ii) non-infectious conditions, (iii) administration for prophylaxis rather than treatment, (iv) selected population (i.e. cystic fibrosis, malignancies, immunodeficiencies, HIV and tuberculosis) and (v) study design different from randomized controlled trial (RCTs). Trials reporting data on both adults and children have been included only if paediatric results were reported separately.

Two authors (PP and LF) independently reviewed and extracted the data. Disagreements were resolved by discussion with a third author (JB). Data on trial design, population, inclusion and exclusion criteria, primary and secondary endpoints, intervention, safety parameters (clinical, laboratory or hearing test), and timing of safety assessment were extracted. For each randomized arm, the number of overall and body-system-specific AEs (classified according to DAIDS (Division of AIDS) recommendations [12]), treatment discontinuations due to AEs and mortality, were also collected. We collected serious AEs (SAEs) [13] and serious drug-related AEs (SDR-AEs) as defined by

the authors. Laboratory-related AEs were included if assessed as a measure of safety evaluation in the trial design or if defined as pathological by the investigators.

To assess the quality of published trials, the *Extension for harms for Consolidated Standards of Reporting Trials* (CONSORT) Statement 2004 was used [14]. The proportion of CONSORT items adequately reported was calculated for each CT.

This review complies with the PRISMA guidelines [15].

Statistical analysis

Proportions have been calculated based on the total number of trials or patients reported as the safety population. Overall and body-system-specific AEs were calculated per single drug class as median and interquartile range (IQR) of the proportions across CTs. AEs reported in less than three CTs in single drug classes were summarised by means. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for overall and body-system-specific AEs were calculated. To determine statistical differences between groups the Chi-square (χ^2) test was used.

The two-tailed Mann-Whitney *U*-test for two independent samples was used to compare the CONSORT score among CTs having safety as a primary vs secondary endpoint, published before or after the publication of the CONSORT statement (2000-2004 vs 2005-2016), and to compare the proportions of reported AEs between non-profit and industry-funded trials. A *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were carried out using STATA version 14.0 (StataCorp).

The meta-analysis included CTs investigating those drug classes that were most represented in our sample (i.e. involving the great majority of children) and whose arms had different antibiotics to be compared. Among them, we compared the AEs that were most frequently reported. The meta-analyses were performed with Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We used a random effect model because of the high potential heterogeneity across trials (different conditions, different comparators), which

was assessed with the I^2 measure of inconsistency. Publication bias was assessed with funnel plots.

3 Results

3.1 Trial selection and description

Our search generated a total of 4,044 records of which 1,157 were registered trials. 290 papers were assessed on full-text, 207 (71.4%) of which were excluded, as shown in **Figure 1**. The main reasons for exclusion were trials conducted only in adults or conducted in adults and children with safety assessment not reported by age group, non-randomized design, topic different from safety, administration for prophylaxis purpose, and excluded languages (Chinese, Japanese, Russian, Serbian). Overall, 83 RCTs were included in the final analysis, with 62 published trials and 21 trials registered in *clinicaltrials.gov.* All the included trials accounted for 29,134 children. Trial characteristics are reported in **eTable 1.** Due to the lack of available results, the 21 trials registered in *clinicaltrials.gov* were only analysed in a descriptive way and for quantitative information on trial design (e.g. sample size per investigated drug class). Different levels of performed analyses are show in **Figure 2**. 17 (21%) of the included trials assessed safety as a primary endpoint [16-32], 64 (77%) as a secondary endpoint [33-96], and two (2%) as both primary and secondary endpoint [97, 98]. Two trials were placebo-controlled [92, 94]. 45 (53%) trials were open-label [16-20, 23, 24, 29, 30, 33, 34, 39-41, 44-50, 55, 56, 60-65, 67, 68, 70, 72, 75-78, 80, 81, 83, 88, 89, 93, 95, 96], 28 (34%) were double-blind [21, 22, 35-38, 42, 43, 51, 52, 54, 58, 59, 69, 71, 73, 74, 79, 82, 84-87, 90-92, 94, 98], and ten (13%) were single-blind [25-28, 31, 32, 53, 57, 66, 97]. Overall, 34 (41%) of the 83 trials were funded by pharmaceutical companies [18, 26-32, 34-38, 42, 43, 45, 51-53, 57, 58, 62, 63, 65, 66, 68, 71, 72, 82, 84, 86, 89, 90, 98]. The included CTs investigated various infectious conditions, with respiratory tract infections assessed most frequently (**Table 1**). Five CTs (6%) did not restrict the study population to paediatric age but included adult patients as well [47, 48, 67, 70, 83]. 1,441/29,134 children (4.9%) were not included in the quantitative analyses because it was not

possible to define the administered drug (i.e. only defined as standard of care, or different comparator per different age group). Overall, 27,693/29,134 children were included and stratified by drug class according to the assigned treatment (**eTable 2**). Penicillins were the most frequently studied drug-class (11,408 children), followed by aminoglycosides and cephalosporins (**eTable 2**). A single antibiotic was administered to 18,398 children, with a combination of two or more antibiotics used in 9,295 children. Among the latter, 77.3% (7,186 children) were treated with a combination of penicillin and aminoglycoside.

3.2 Quality assessment

The 62 published RCTs were assessed for quality, according to the number of CONSORT Statement's items adequately reported. An overall mean of 69.7% items was reported (range 33.3-100) properly. There was no evidence of difference between trials reporting safety as a primary (77.4%) or secondary (68.2%) endpoint (p=0.05). The most frequent recommendation that trials did not report on (45/62, 72.6%) was item number three ("List addressed AEs with definition for each"), that should be reported in the methods section. Only 20 (32%) of 62 trials clearly defined their safety parameters in the publication providing details about expected vs unexpected AEs, mode of data collection (spontaneously reported or assessed by investigator), pathologic values defining toxicity (e.g. "nephrotoxicity was defined as doubling in serum creatinine concentration compared with baseline"), grading and timing of evaluation of each AE [19-23, 33-36, 42, 46, 54, 55, 60, 62-66, 80]. Just six trials provided a reference for the definitions of AEs (two DAIDS [63, 82], two COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) [66, 84], and two WHO (World Health Organization) coding system [35, 53]). The justification for sample size and definition of safety population were provided only by two of the ten published trials including safety as a primary endpoint [24, 98].

3.3 Quantitative analysis of reported AEs

Published RCTs in which the number of body-system-specific AEs was recorded were included in the quantitative analysis **(Table 2, eTable 3)**. Only 33 trials reported the number of children experiencing at least one AE [20, 24, 34-40, 42, 44, 45, 52, 53, 57, 60, 62, 63, 66, 68, 69, 71, 73, 75-79, 81-84, 98]. Statistical analyses were performed on those randomized arms with a single drug intervention, including a total of 15,716 children. The combination penicillin/aminoglycoside was considered as aminoglycoside single drug when well-recognised class specific AEs (nephrotoxicity and ototoxicity) were reported [99].

The median proportion of children with reported AEs across the trials was 22.5% (IQR 7.7–44.6), while the median rate of discontinuation of therapy due to AEs was less than 1% (0.9 %, IQR 0–3). There was no evidence of difference in the proportion of reported AEs between trials funded by industry and non-profit CTs (p=0.05).

3.3.1 Clinical AEs

Systemic AEs, including fever, allergic reactions and Red Man Syndrome, were most frequently reported in children on glycopeptides (glycopeptides vs others: OR 14.3; 95% CI 10.0-20.2; p<0.0001). Among them, 40/48 (83%) were clearly class-specific (e.g. Red Man Syndrome) [100]. Anaphylaxis was only reported in children on amoxicillin (3/1,261; 0.002%).

Ten trials reported mortality during the study period, with a rate of 66/15,716 children (0.4%), none of which was attributed to the intervention drug by the investigator [16, 20, 24, 35, 44, 45, 53, 55, 63, 84].

19 trials reported SAEs separately from AEs, in 1.8% of children (137/7,760) [20, 24, 35-37, 44, 45, 53, 59, 60, 65, 68, 69, 71, 74, 79, 82-84]. Among them, eight trials further specified how many SAEs were considered drug-related (11 SDR-AEs/4,171 children; 0.3%) [20, 24, 35, 37, 45, 59, 71, 79]. All the reported SDR-AEs occurred in five drug classes (fluoroquinolones, penicillins+beta-lactamase inhibitors, penicillins, carbapenems, glycopeptides) with the highest rate reported in children treated with glycopeptides (1/19 children reported abnormal kidney function; 6%) and carbapenems

(1/81 children experienced severe diarrhoea; 1%). None of the trials conducted on macrolides investigated or reported cardiotoxicity.

Nearly half of the reported AEs (2,254/5,189) involved the gastrointestinal (GI) system (7.7%; IQR 0.0–20.5). Among them, diarrhoea and vomiting accounted respectively for 49.0% and 22.3% (1,104 and 502 of 2,254 children, respectively). Children on amoxicillin had a significantly higher risk of developing antibiotic-associated diarrhoea than children on macrolides (OR 2.3; 95% CI 1.6–3.1; p<0.0001), a lower but not statistically significant risk compared with cephalosporins (OR 0.8; 95% CI 0.6–1.0; p=0.06) and significantly lower risk compared to penicillin+beta-lactamase inhibitors (BLI) (OR 0.3; 95% CI 0.3–0.4; p<0.0001). Two studies further specified how many diarrhoea adverse events were diagnosed as *Clostridium difficile*-associated diarrhoea [24, 56]. Specifically, only one child out of 13 (7.7%) treated with a low-dose course of cefuroxime axetil experienced *Clostridium difficile*-associated diarrhoea after completing the treatment [56].

Among neurological AEs, 42 of 47 (89%) were reported as headache and five of 47 (11%) as convulsions. The latter were all reported in the same trial and were classified by authors as SAEs [60]. Musculoskeletal AEs were reported only for fluoroquinolones (56/78; 72%) and penicillins+BLI (22/78; 28%). Among them, 39/78 (50%) were arthralgia and 28/78 (36%) were myalgia.

3.3.2 Laboratory AEs

Laboratory AEs, including biochemical and haematological parameters, were evaluated in 15 trials [20, 24, 42, 44, 45, 60, 63, 70-72, 76, 82-84, 98]. The highest proportions were reported in children on linezolid (linezolid vs others OR 8.1; 95% CI 6.5-10.0; p<0.0001) and glycopeptides (glycopeptides vs others OR 5.6; 4.2–7.5; p<0.0001). For both classes, most laboratory AEs were haematological (linezolid 169/215 (78.6%), glycopeptides 63/84 (75%)). Comparing these two antibiotics, the risk of developing laboratory AEs was not statistically different (p=0.948). However, the risk of overall AEs was higher with glycopeptides than linezolid (OR 1.9; 95% CI 1.4–2.6; p=0.0001).

3.4 Meta-analysis

26 RCTs (7,305 children) were included in the meta-analysis. The most frequently reported AEs were compared through forest plots. The risk of antibiotic-associated diarrhoea was significantly higher with penicillins+BLI (Risk ratio (RR) 2.4; 95% CI 1.8–3.2) and lower in cephalosporins (RR 0.6; 95% CI 0.4–1.0) compared to other beta-lactams. There was no evidence of differences between penicillins and other beta-lactams (RR 1.1; 95% CI 0.9–1.2) (**Figure 3**).

The meta-analyses of nephrotoxicity and ototoxicity in aminoglycosides did not find any evidence of differences between one daily dose (OD) and multiple doses (MD) (nephrotoxicity RR 0.8; 95% CI 0.4–1.6; ototoxicity RR 1.5; 95% CI 0.3–6.6) (**eFigure 1**). Overall, there was no evidence of differences in the proportions of reported AEs with macrolides vs penicillins (RR 0.9; 95% CI 0.8–1.2) (**eFigure 2**). There was some suggestion of publication bias based on funnel plots (**eFigure 3**).

4 Discussion

This systematic review included 83 paediatric RCTs on the safety of antibiotics, with the majority of the trials conducted on three antibiotic drug classes (beta-lactams, macrolides, aminoglycosides). Although 21 of the selected CTs included neonates, only 3 were specifically designed to study the neonatal population. The quality of reporting AEs was suboptimal in the great majority of CTs, due to the frequent lack of a detailed definition of both expected and unexpected AEs. Although 10/62 published CTs were designed with safety as the primary endpoint, only two trials provided the justification for the sample size specifically for the safety population. Overall, data reported for those drug classes most commonly used in children demonstrated clearly that AEs in the paediatric antibiotic CTs were both class-specific and predictable. Within the limitations of the lack of neonatal data, we did not identify age-specific or unexpected toxicity, with virtually all AEs graded as non-severe. Discontinuation of treatment due to AEs, including both drug-related and unrelated, was notably low. However, only one of the 83 CTs investigated a new antibiotic (solithromycin), which is included in the Pew Charitable Trusts list [60, 101].

This study represents the first systematic review of the key components of safety in paediatric antibiotic CTs across all clinical infectious syndromes. The aim was to provide a summary overview on both the qualitative and quantitative reporting of AEs. We could identify no similar data available for the adult population, since most reviews on safety in adults have been conducted on patients with specific infectious diseases or on specific antibiotic classes [102-104]. A study conducted on antiretroviral drugs comparing safety between adults and children, based on data provided by the FDA, showed that adult AEs can preliminary inform the safety profile in children, even if specific types and rates in paediatrics cannot exclusively be extrapolated from adults [105].

Similarly to our study, papers targeting the safety of specific drugs in children demonstrated that most of the AEs were classified as non-serious and were generally scarcely reported [106-109]. The poor quality of safety reporting has also been noted in other studies investigating non-infectious conditions in children (e.g. epilepsy) or, collectively, all paediatric drugs [109-110]. In a review evaluating the quality of reporting adverse drug reactions in RCTs performed in children over a 4-year period, only 19 out of 83 CTs had a CONSORT score considered as sufficient by the authors (≥6, range 1–10) [110]. Although our CONSORT assessment noted that 45/83 trials had ≥60% of items adequately reported, this is relatively low considering that we selected only CTs having safety as primary or secondary endpoints. Conversely to one previous study, our overall AE rates did not differ between non-profit and industry-funded CTs [110]. Together, these findings suggest that more emphasis should be placed on the complete reporting of AE methods and definitions in supplementary material, particularly when trial protocols are not available online.

Several initiatives in both the US and the EU aim to improve and facilitate the enrolment of children in antibiotic CTs [4,5]. Paediatric antibiotic safety trials have traditionally included a standard-of-care comparator arm. Variation in the choice of comparator agent internationally and the subsequent complexity of trial design and conduct has led to a high burden on limited paediatric research staff with consequent recruitment difficulties. Other initiatives, such as the Pediatric Health Information System (PHIS) in the US, have been currently put in place to improve the reporting of

pharmacovigilance data on antibiotics in neonates and children following marketing approval [111]. However, these large databases have high costs and require high-level electronic infrastructures to collect the data throughout different centres. A different approach could be the establishment of a network of different stakeholders (academics, physicians, regulators and governments) who share common interests in paediatric pharmacovigilance. The GAIA project represents a good example of how a voluntary network can improve the quality of safety data in a specific population [112]. In an attempt to gather more evidence on efficacy and safety data for antimicrobial drugs in children, some web-based disease-specific drug registries have been put in place in Europe in the last decades to enhance the exchange of information and expertise between centres [113, 114]. Among the other information, these registries prospectively collect toxicity data in children, are generally open access and relatively cheap to maintain.

One of the main limitations of this review is the high heterogeneity in terms of trial design, population, and data reporting that might reduce the strength of our conclusion. The evaluation of overall instead of drug-related AEs was due to the limited number of trials clearly defining the attribution method to assess the causality between the studied drug and the AE (such as including AEs secondary to the infectious condition rather than the drug itself, possibly leading to an overestimation). Another limitation is that other possible determinants, such as route of administration and dosage, have not been taken into account because of the lack of specific information provided by the investigators. The exclusion criteria applied in the search limit the conclusions of this review to children with an acute infectious disease but otherwise apparently healthy. Immunocompromised children may require longer courses of treatment and/or higher doses of treatment and therefore safety may differ. Rare AEs were essentially not reported, raising concerns about reporting bias and limitations of sample size, considering that most of the included studies were unpowered to detect infrequent AEs. Lastly, it was not possible to stratify safety data by different paediatric age groups because AEs were not reported separately by the authors. Because of the lack of historical data published before than 2000, AEs previously recognised in

literature as specific to children were not detected in this systematic review (e.g. no chloramphenicol-related grey baby syndrome was reported and only one trial on amphenicols including 25 children aged less than 8 years was included) [115].

The implications of this review are that for certain common antibiotic classes, with well-established safety profiles (e.g. beta-lactams, macrolides) determined from large adult efficacy trials, it may be possible to simplify the safety assessments in parallel paediatric trials when drug exposure is similar in children and adults. Smaller open-label dose-finding high-quality single-arm pharmacokenetic trials collecting safety data to confirm no unanticipated child-specific toxicities may be more feasible, enhance recruitment and subsequent registration of needed new drugs. It has been usually considered that extrapolation of safety from adults to children was not possible due to the growth and development characteristics of children and due to the impact that organ maturation has throughout the different stages of childhood (particularly applicable to neonates and young children). Antibacterial agents usually target components of the bacterial cell or selected cellular processes essential for the survival of pathogenic bacteria rather than interacting with human targets. Therefore, extrapolation of safety may be considered as a potential approach to decrease the burden on paediatric patients, i.e., to take advantage of the prior knowledge in adult trials that can be used to streamline the paediatric clinical development. Most of the agreed (between the Paediatric Committee at EMA and Applicants) Paediatric Investigation Plans (PIPs) include, as part of the clinical development, PK studies across all age subsets of the paediatric population (unless safety issues preclude the use in some age group, e.g., the case of tetracycline class of antibiotics and children under 8 years of age) followed by a safety and efficacy study which usually is a randomised, active comparator study in a substantial number of children evenly distributed across the different age groups. This has resulted in a delayed (of around 5 to 7 years) availability of antibacterial agents for the paediatric population when compared to their availability (i.e. regulatory approval) for adult subjects. Once the antibacterial agent is in the market, nothing prevents its off-label use which also makes it difficult the conduct of randomised trials. There is therefore a clear need to speed the

paediatric clinical development. The challenge is to identify in which circumstances the conduct of smaller open-label dose-finding high-quality single-arm pharmacokinetic trials may not be sufficient for regulatory purposes (approval). In this respect, it has been discussed that toxicity data in juvenile animals can inform this decision. Safety concerns that have limited the use of certain antibacterial agents in the paediatric population have been primarily identified in animal studies, such as the case of the quinolone-induced articular toxicity or the permanent dental defects and the delay in ossification processes in foetuses occurring with tetracyclines. A safety study may be unavoidable in the presence of off-target effects identified in the non-clinical setting that are shown (e.g. in adult subjects) thought to have clinical relevance particularly for the paediatric population as a whole or for some age subsets. This can be the case of antibiotics such as fluoroquinolones, linezolid or daptomycin, or for antibacterial agents with new mechanisms of action. Safety studies usually require very large sample sizes and it is questionable whether this can be achieved in the frame of standard clinical trials, particularly when the number of subjects is limited as it is the case of the paediatric population. On the other side, the proposal of a simplified strategy will need to be combined with enhanced methods of pharmacovigilance for monitoring of emerging AEs in routine clinical practice. The institution of a European electronic registry using the well-established PENTA network (www.pentatrials.org) would be a potential option to collect safety and outcome data on both new and old off-patent key antibiotics in children and neonates, including all those antibacterials currently used off-label. The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) is an international network of cohort studies coordinated by PENTA conducting epidemiological research on HIV-infected pregnant women, children and children exposed to HIV in utero, with a programme of work including individual patient data meta-analyses, pharmacovigilance projects and other observational studies. Of note, the EMA launched in September 2015 an initiative which explores ways of expanding the use of patient registries by introducing and supporting a more systematic and standardised approach to their contribution to the benefit-risk evaluation of medicines within the European Economic Area [116]. Such approach

could potentially allow data to be collected and easily pooled out at a relatively low cost, and help gathering evidence to improve the design and conduct of paediatric CTs. Given the highly concerning rates of antimicrobial resistance that are a rapidly emerging threat to global child health, optimal trial designs to most efficiently bring both new and older re-entry antibiotics into routine clinical care are urgently required.

FIGURE LEGENDS

Fig. 1 Flowchart and study selection

Fig. 2 Inclusion criteria and patients assessed per different level of analysis

Fig. 3 Diarrhoea in β-lactams: Meta-analysis

eFig. 1 Toxicity in Aminoglycosides: one daily dose (OD) versus multiple daily doses (MD) Meta-analysis (A: nephrotoxicity, B: ototoxicity)

eFig. 2 Macrolides vs Penicillins (overall AEs): Meta-analysis

eFig. 3 Funnel plot of: A-B-C: diarrhoea in β-lactams (A: penicillins vs other beta-lactams; B: penicillins+beta lactamase inhibitor vs other beta-lactams; C: Cephalosporins vs other beta-lactams); D-E: Toxicity in one daily vs multiple doses of aminoglycosides (D: Nephrotoxicity; E: Ototoxicity); F: overall AEs in macrolides vs penicillins

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List of contributions

MS and LF contributed to the concept and design of the study. MS, LF and PP designed the search strategy and selection criteria. PP and LF collected the data. All authors contributed to the interpretation of the data. PP, LF and MS wrote the first draft of the manuscript. All authors reviewed and contributed to subsequent drafts and approved the final version for publication. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Compliance with Ethical Standards

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Table 1 Basic characteristics of included trials

	Number (%)[a]
Total trials	83
Total patients	29,134
Study design	
Double blind	28 (34)
Single blind	10 (12)
Open label	45 (54)
Sponsor	
Pharmaceutical company	34 (41)
Not for profit	49 (59)
Ongoing trials	13 (16)
Income[b]	
HIC	36 (43)
LMIC	22 (27)
Both	25 (30)
Condition[c]	
Upper respiratory tract infections	25 (30)
Lower respiratory tract infections	17 (21)
Gastrointestinal infections	11 (13)
Unspecified bacterial infections	10 (12)
Sepsis	8 (10)
Other bacterial infections	8 (10)
Urinary tract infections	6 (7)
Skin and soft tissue infections	5 (6)
CNS infections	1 (1)
Safety outcome	
Primary	19 (23)
Secondary	66 (80)
Age groups	
Neonate (0-28 d)	21 (25)
Infant (29 d-24 mo)	60 (72)
Child (2-12 yr)	67 (81)
Adolescent (12-18 yr)	30 (36)
Study drugs	
Single drug	74 (89)
Multiple drugs	12 (15)

[a]Calculated on 83 included studies; [b]HIC: High-income countries, LMIC: Low and middle-income countries; [c]Upper respiratory tract infections included otitis media; Gastrointestinal infections included complicated intraabdominal infections

Table 2 Median and IQR of overall and body-system-specific reported Adverse Events (AEs) per drug class

Drug class	N patients	Overall AEs	Sum of specific AEs	Discontinuation due to AEs	Systemic[a]	Nephro-toxicity	Oto-toxicity	Gastro intestinal	Neurological	Respiratory	Dermatologic	Muscolo-skeletal	Infusional	Laboratory total
Penicillins	3,019	12.8 (9.4–29.7)	9.1 (3.1–29.7)	1.1 (0.0–2.7)	0.0 (0–0.8)	0.6*	nr	4.2 (2.3-8.3)	0.0 (0.0–0.0)	nr	0.7 (0.0 – 5.3)	nr	0.0 (0.0–0.0)	17.7*
Aminoglycosides	1,308	3.3 (1.1–15.8)	2.3 (0.6–15.8)	0.0*	nr	1.8 (1.1–20.0)	1 (0–1.1)	nr	0.0 (0.0–0.0)	nr	nr	nr	nr	nr
Cephalosporins	2,462	16.5 (4.5–42.1)	14.8 (4.5–42.1)	0.3 (0.0–3.0)	0.0 (0.0–0.0)	nr	nr	12.1 (3.6–20.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–4.2)	nr	nr	0.0 (0.0-5.2)
Macrolides	2,931	21.8 (7.7–35.9)	18.8 (6.0–31.6)	0.0 (0.0–3.3)	0.0 (0.0–0.0)	nr	nr	8.6 (3.4–23.3)	nr	0.0 (0.0–0.0)	0.0 (0.0–2.2)	nr	nr	9.8*
Penicillins+β-lactamase inhib	2,566	43.0 (26.6–65.7)	43.0 (19.6–63.0)	1.0 (0.0–2.8)	0.0 (0.0–2.0)	nr	nr	32.6 (13.1–42.8)	nr	0.0 (0.0–0.0)	6.9 (3.8–11.9)	0.0 (0.0–0.0)	nr	0.0 (0.0–0.0)
Fluoroquinolones	1,920	35.7 (24.2–66.7)	31.2 (23.4–61.1)	0.8 (0.0–2.2)	1.1 (0.0–7.5)	nr	nr	17.1 (2.4–23.7)	nr	0.0 (0.0–11.4)	0.0 (0.0–6.2)	3.1 (1.2–3.2)	nr	6.1 (0.4–18.7)
Carbapenems	385	32.7*	25.9*	1.9*	nr	nr	nr	5.8*	nr	nr	nr	nr	10.5*	9.6*
Linezolid	683	60.7 (44.5–70.4)	58.2 (43.7–64.3)	2.0 (0.9–7.0)	0.5 (0.0–1.3)	nr	nr	9.8 (7.6–12.6)	0.0 (0.0–3.9)	0.0 (0.0–2.3)	1.3 (0.0–1.4)	nr	0.0 (0.0–0.0)	45.6 (5.7–52.6)
Glycopeptides	265	75.4 (37.5–90.9)	75.4 (27.6–87.9)	4.3 (1.7–5.7)	18.6 (5.3–27.5)	8.4*	nr	9.3 (0–12.5)	0.0 (0.0–0.0)	nr	6.4 (5.3–9.1)	nr	nr	41.0 (15.8–72.0)
Sulfonamides+ trimethoprim	152	4.6*	4.6*	2.6*	1.3*	nr	nr	2.6*	nr	nr	0.7*	nr	nr	nr
Amphenicols	25	4.0*	4.0*	0.0*	nr	nr	nr	4.0*	nr	nr	nr	nr	nr	nr
Total	**15,716**	**22.5 (7.7–44.6)**	**19.2 (4.6–42.5)**	**0.9 (0.0–3.0)**	**0.0 (0.0–0.5)**	**1.8 (0.8–15.8)**	**1.0 (0.2–1.1)**	**7.7 (0.0–20.5)**	**0.0 (0.0–0.0)**	**0.0 (0.0–0.0)**	**0.0 (0.0–4.0)**	**0.0 (0.0–0.0)**	**0.0 (0.0–0.0)**	**6.1 (0.0–20.3)**

Data are expressed as median proportion and IQR range. *Expressed as mean because reported in < 3 studies; [a]including fever, anaphylaxis and Red Man Syndrome; nr: not reported. Patients on combination of Aminoglycosides/Penicillin were included in Aminoglycosides only when class specific AEs (nephrotoxicity and ototoxicity) were reported. Sum of specific AEs has been calculated as median proportion of the sum of all reported AEs per each RCTs (Nephrotoxicity, Ototoxicity, Gastrointestinal, Systemic, Neurological, Respiratory, Dermatologic, Muscolo-skeletal Infusional and Laboratory-reported AEs).