Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review

Laura Folgori, Julia Bielicki, Beatriz Ruiz, Mark A Turner, John S Bradley, Daniel K Benjamin Jr, Theoklis E Zaoutis, Irja Lutsar, Carlo Giaquinto, Paolo Rossi, Mike Sharland

There is no global consensus on the conduct of clinical trials in children and neonates with complicated clinical infection syndromes. No comprehensive regulatory guidance exists for the design of antibiotic clinical trials in neonates and children. We did a systematic review of antibiotic clinical trials in complicated clinical infection syndromes (including bloodstream infections and community-acquired pneumonia) in children and neonates (0–18 years) to assess whether standardised European Medicines Agency (EMA) and US Food and Drug Administration (FDA) guidance for adults was used in paediatrics, and whether paediatric clinical trials applied consistent definitions for eligibility and outcomes. We searched MEDLINE, Cochrane CENTRAL databases, and ClinicalTrials.gov between Jan 1, 2000, and Nov 18, 2015. 82 individual studies met our inclusion criteria. The published studies reported on an average of 66% of CONSORT items. Study design, inclusion and exclusion criteria, and endpoints varied substantially across included studies. The comparison between paediatric clinical trials and adult EMA and FDA guidance highlighted that regulatory definitions are only variably applicable and used at present. Absence of consensus for paediatric antibiotic clinical trials is a major barrier to harmonisation in research and translation into clinical practice. To improve comparison of therapies and strategies, international collaboration among all relevant stakeholders leading to harmonised case definitions and outcome measures is needed.

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Paediatric Infectious Disease Research Group, Institute for Infection and Immunity, St George's University of London, London, UK (L Folgori MD, J Bielicki MD, B Ruiz MD, Prof M Sharland MD); **Paediatric Pharmacology, University Children's Hospital Basel, Basel, Switzerland** (J Bielicki); **University of Liverpool, Institute of Translational Medicine, Department of Women's and Children's Health, Crown Street, Liverpool, UK** (M A Turner MD); **Department of Pediatrics, University of California San Diego, and Rady Children's Hospital San Diego, San Diego, CA, USA** (Prof J S Bradley MD); **Duke Clinical Research Institute, Duke University, Durham, NC, USA** (Prof D K Benjamin Jr MD); **Department of Pediatrics, University of Pennsylvania School of Medicine, Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, PA, USA** (Prof T E Zaoutis MD); **Institute of Medical Microbiology, University of Tartu, Tartu, Estonia** (Prof I Lutsar MD); **Department of Women's and Children's Health, University of Padova, Padova, Italy** (Prof C Giaquinto MD); **and University Department of Pediatrics (DPUO), Bambino Gesù Children's Hospital, Rome, Italy** (Prof P Rossi MD)

Correspondence to: Prof Mike Sharland, Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's University of London, London SW17 0RE, UK **mike.sharland@stgeorges.nhs.uk**

See Online for appendix

Introduction

Antimicrobial resistance is a major health threat. Increasing numbers of neonates and children with serious bacterial infections due to resistant bacteria are being reported, associated with substantial morbidity and mortality.[1] Optimised use of existing antibiotics is essential to improve management of serious bacterial infections in children and reduce selection pressure.[2] The prevalence of multidrug-resistant pathogens is likely to be under-reported in many areas of the world. To address this issue, a substantial number of new antibiotics are under development and might enter the licensing process.[3]

The pathophysiology of many infections differs between adults and neonates or children, including differences in clinical presentation, natural history, and underlying comorbidities between age groups. Clinical trials in children are necessary for registration of new antibiotics and for optimum use of older antibiotics. The number of regulatory clinical trials of antibiotic efficacy reported or ongoing in paediatrics is low compared with the number of adult clinical trials.[4,5] As a result, approval and marketing authorisation of new antibiotics for children is often delayed, resulting in drugs being used off-label, without proper information about dosing across age-groups, potential toxicity, and evidence of clinical safety and efficacy.[6,7]

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have developed standardised guidance for assessment of medicinal products indicated for treatment of bacterial infections (appendix p 15).[8–15] For each clinical infection syndrome, these guidelines include the core elements of trial design that should be included to support efficacy assessment (eg, inclusion and exclusion criteria and primary and secondary endpoints). Use of consistent definitions for key features of regulatory clinical trial design enables assessment of efficacy. Clinical trials can later be compared and outcomes pooled. Conversely, absence of harmonised trial design can lead to difficulties in interpretation, which could reduce the efficiency of antibiotic licensing and delay collection of data needed to support applications for marketing authorisation.

The aim of this systematic review is to assess the extent of harmonisation in clinical trials addressing efficacy and effectiveness of antibacterial drugs in children and neonates. The specific objectives were to systematically review the extent to which antibiotic trials of efficacy in children apply consistent definitions for participant selection and endpoints, and use the standardised inclusion and exclusion criteria and endpoints for the complicated major clinical infection syndromes, as defined by the FDA and EMA for adults (described in full in appendix p 15). For the purpose of this systematic review, we assumed that clinical trials used the optimum dose of antibiotics and therefore we did not consider pharmacokinetic and safety assessments.

Methods

Search strategy and selection criteria

This systematic review was done according to PRISMA guidelines.[16] We searched MEDLINE and Cochrane CENTRAL databases between Jan 1, 2000, and Nov 18, 2015, combining MeSH and free-text terms for the following: "bloodstream infections", "community-acquired pneumonia", "hospital-acquired pneumonia and ventilator-associated pneumonia", "complicated urinary tract infections", "complicated intra-abdominal infections", "acute bacterial skin and soft tissue infections", and "antibiotics in children (age range

0–18 years)". We searched ClinicalTrials.gov from Jan 1, 2000, to Nov 18, 2015, with the above terms for ongoing, completed, and unpublished trials. The search was limited from 2000 onwards because the aim of this review was to demonstrate how the lack of regulatory guidance was a barrier to study quality. To achieve this point a timeframe of 15 years was considered sufficient. Studies published in English, German, Italian, French, Polish, Greek, Dutch, Hungarian, Portuguese, and Spanish were considered for inclusion. The full search strategy is in the appendix.

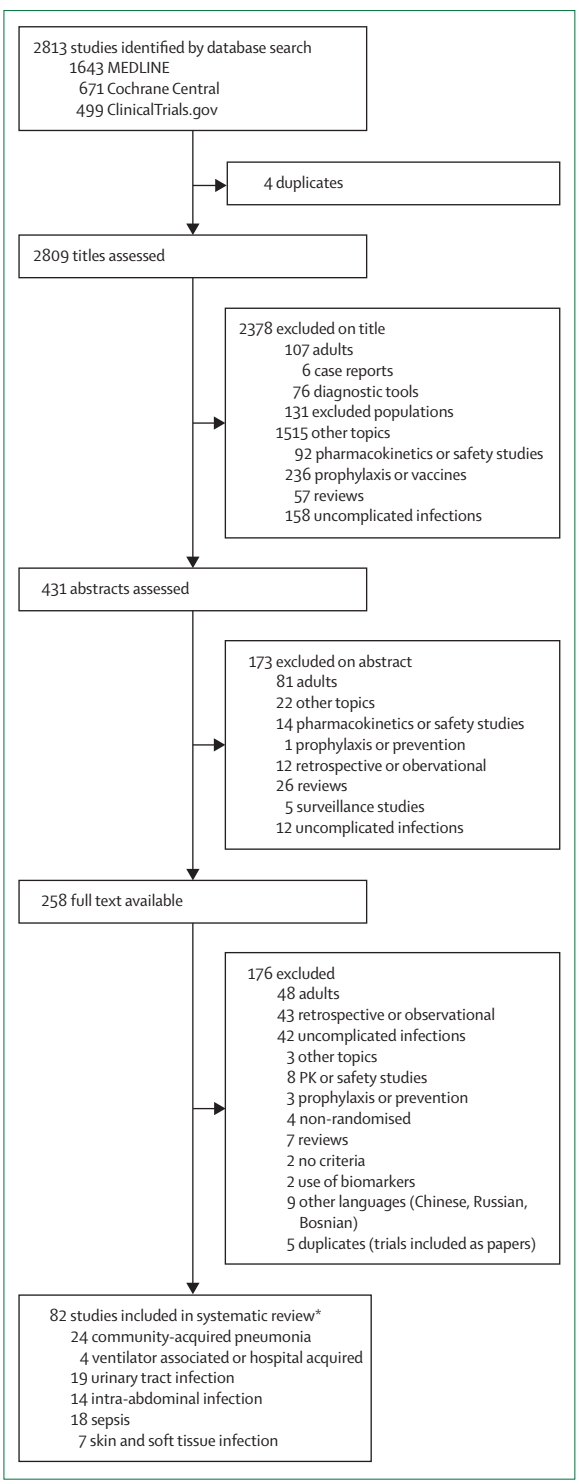

Figure 1: **Study selection**
*Three studies reported data for more than one clinical infection syndrome and were counted separately for each disorder, so 86 datasets were included in total.

We included randomised clinical trials that reported on the efficacy and effectiveness of antibacterial drugs in children and neonates. Studies were only included if age-related information could be identified. We defined children as aged 0–18 years, including neonates. We included trials on the following complicated clinical infection syndromes only: bloodstream infections, community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, complicated urinary tract infections, complicated intra-abdominal infections, and acute bacterial skin and soft tissue infections. The search was limited to these syndromes because adult regulatory guidance was available for all of them; we did not include complicated infections for which EMA or FDA guidance was not available. We included trials reporting participant inclusion and exclusion criteria and primary or secondary endpoints. We excluded studies reporting data on uncomplicated or non-severe infections, antibiotic prophylaxis, topical or inhalational treatments, diagnostic or prognostic markers, and selected patient subgroups whose diagnostic criteria might be different (eg, patients with febrile neutropenia or cystic fibrosis).

For each included study, two authors (LF and BR) independently extracted the following data according to prespecified criteria: study design, study population, inclusion and exclusion criteria, and primary and secondary endpoints. Disagreements were resolved in discussion with a third author (JB).

To score the quality of reporting, we used the Consolidated Standards of Reporting Trials (CONSORT) Statement 2010 for reporting parallel-group randomised trials.[17] We calculated the proportion of items of the CONSORT 2010 checklist adequately reported for each study (appendix p 4). We did not exclude any studies based on quality. We could not assess quality of trials identified through ClinicalTrials.gov against the CONSORT statement because full protocols were not accessible.

We obtained FDA and EMA adult inclusion and exclusion criteria and outcome measures (primary and secondary endpoints) from the respective guidelines assessment of medicinal products for the selected clinical infection syndromes and used these as a reference standard (appendix p 15).[8–15] In neonates and children, bloodstream infections with no primary focus occur more frequently than in adults. Because we were unable to identify an official FDA definition of sepsis, we used the US Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) surveillance

definition of health-care-associated infections as reference for bloodstream infections.[18]

We used two-tailed Mann-Whitney *U* tests for two independent samples to compare CONSORT scores for papers according to their year of publication (up to and including 2001, or after 2001 [publication of the first CONSORT statement]) to determine changes in reporting after the publication of the revised criteria. We did statistical tests with Stata, version 13.0. We considered $p<0·05$ to be statistically significant.

Results

Study selection and description

We identified 2813 published studies or registered clinical trials, which included the abstracts for 499 registered trials. Of the 258 full-text studies assessed, we excluded 171 (66%; figure 1). 82 individual studies fulfilled the inclusion criteria and were included in the final analysis (figure 1). Of these, 24 studies focused on childhood community-acquired pneumonia (ClinicalTrials.gov, numbers NCT01312792, NCT01399723, NCT01386840, NCT00372541, NCT00227331, NCT01110421, NCT 00968370, NCT01669980, NCT01530763, NCT 02258763),[19–32] four on childhood hospital-acquired or ventilator-associated pneumonia (NCT01110421),[33–35] 19 on urinary tract infection (NCT00161330, NCT01110408, NCT00136656, NCT02497781),[36–50] 14 on intra-abdominal infections (NCT01110382, NCT01994993, NCT01069900, NCT00462020, NCT02561117, NCT01678365, NCT 02475733),[51–57] 18 on sepsis (NCT01867138, NCT00844337, NCT01728376, NCT02503761),[33,34,58–69] and seven on acute bacterial skin and soft tissue infections (NCT01498744, NCT02276482, NCT01400867, NCT00711802, NCT 02024867).[34,70] Three studies reported data for more than one clinical infection syndrome and were counted separately for each disorder (NCT01110421).[33,34]

Of the 82 included studies, according to the 2015 World Bank Classification,[71] 35 were carried out in high-income countries (NCT00161330, NCT00136656, NCT01994993, NCT00462020, NCT02561117, NCT01678365, NCT01867138, NCT01498744, NCT02024867),[21,33,34,36,37–41,43,44–47,49,52–57,62,63,70] 37 in low-income or middle-income countries (NCT01312792, NCT01399723, NCT01386840, NCT00372541, NCT00968370, NCT02258763, NCT00844337, NCT02503761), and 13 studies (NCT01669980, NCT01530763, NCT01110421, NCT01110408, NCT02497781, NCT01110382, NCT01069900, NCT02475733, NCT01728376, NCT02276482, NCT01400867, NCT00711082)[19,20,22–24,26–32,35,42,48,50,51,58–61,64–69] were done in both settings; two studies (NCT00227331 and NCT01110421) did not provide their setting (appendix p 6). Only one study was placebo controlled.[70] 24 (29%) of 82 studies were directly funded by pharmaceutical companies—15 (63%) among high-income countries *vs* 9 (38%) among low-income or middle-income countries. All studies had been designed for children, 38 (46%) of which were for registration purposes and 44 (54%) were led by academic investigators. We identified only ten paediatric clinical trials as ongoing (NCT02258763, NCT02497781, NCT01994993, NCT01069900, NCT02561117, NCT02475733, NCT01728376, NCT02276482).[61,68] Only 20 (24%) of 82 studies, mainly involving sepsis, included neonates (NCT01994993, NCT01867138, NCT00844337, NCT02503761; table 1).[33,34,58–69]

Quality assessment of included studies

We identified substantial variation in study design, population, inclusion and exclusion criteria, classification of infections (mild, moderate, or severe), and endpoints in paediatric antibiotic clinical trials. Overall, the published

	ClinicalTrials.gov, numbers	Number of studies	Enrolled patients	CONSORT items reported*	Pharma-led studies	Including neonates	Ongoing trials
Community-acquired pneumonia[19–32]	NCT01312792, NCT01399723, NCT01386840, NCT00372541, NCT00227331, NCT01110421, NCT00968370, NCT01669980, NCT01530763, NCT02258763	24	19 985	74%	5	0	1
Ventilator-associated or hospital-acquired pneumonia[33–35]	NCT01110421	4	116	61%	3	2	0
Urinary tract infection[36–50]	NCT00161330, NCT01110408, NCT00136656, NCT02497781	19	3948	61%	5	0	1
Intra-abdominal infections[51–57]	NCT01110382, NCT01994993, NCT01069900, NCT00462020, NCT02561117, NCT01678365, NCT02475733	14	1706	65%	3	1	4
Sepsis[33,34,58–69]	NCT01867138, NCT00844337, NCT01728376, NCT02503761	18	1829	65%	2	16	3
Acute bacterial skin and soft tissue infections[34,70]	NCT01498744, NCT02276482, NCT01400867, NCT00711802, NCT02024867	7	1489	73%	4	1	1
Totals	..	86†	29 073	66%	22 (26%)	20 (23%)	10 (12%)

*Expressed as mean of included studies. †82 individual studies. CONSORT=Consolidated Standards of Reporting Trials.

Table 1: **Basic characteristics of included studies**

studies reported on a mean of 66% (range 30–97) of CONSORT items, with slight differences between the various clinical infection syndromes (table 1; appendix). Because the first revision of the CONSORT statement was published in 2001, we assessed the effect of the revised guideline on trial reporting. Grouping papers according to their year of publication, studies published up to and after 2001 showed a significant difference in the percentage of CONSORT items reported (49% before 2001 *vs* 70% after 2001; Mann-Whitney *U* p=0·004).

Patient inclusion criteria

The studies that provided specific inclusion and exclusion criteria varied widely in their definitions. Diagnosis of a severe infection was mainly based on individual study definitions of combinations of clinical signs and laboratory tests. Exceptionally, 12 (50%) of 24 community-acquired pneumonia studies (NCT01399723, NCT01386840, NCT00372541, NCT00227331)[19,20,22,24,27–29,32] referred to a single definition for childhood acute respiratory infections provided by WHO.[72] Except for studies of intra-abdominal infections, clinical findings were most commonly used as inclusion criteria for all clinical infection syndromes (table 2). Microbiological tests were used only in studies of urinary tract infections, for which urine culture positivity was mandatory for patient inclusion in 15 (79%) of 19 clinical trials (NCT00161330, NCT01110408, NCT00136656, NCT02497781).[36–39,41–43,46,48–50] The hospital-acquired or ventilator-associated pneumonia group was the only one for which imaging was required in all the included studies. For intra-abdominal infections, diagnosis of complicated appendicitis during surgery was an eligibility criterion in 11 (79%) of 14 included studies (NCT01994993, NCT01069900, NCT00462020, NCT02561117, NCT02475733);[51–57] an invasive procedure was not required in studies of any other clinical infection syndrome.

Patient exclusion criteria

Chronic or underlying disorders was an exclusion criterion in 69 (84%) included trials (NCT01399723, NCT01386840, NCT00372541, NCT00227331, NCT01110421, NCT01669980, NCT01530763, NCT02258763, NCT00161330, NCT01110408, NCT00136656, NCT02497781, NCT01110382, NCT01994993, NCT01069900, NCT00462020, NCT02561117, NCT01678365, NCT02475733, NCT00844337, NCT01728376, NCT02503761, NCT01498744, NCT00711802, NCT02024867)[19–39,41,43–48,50,51,53–56,58–62,64–68,70] and a history of a recent infection or antibiotic use was an exclusion criterion in 42 (51%) included trials (NCT01399723, NCT01386840, NCT00372541, NCT01110421, NCT00227331, NCT01669980, NCT01530763, NCT02258763, NCT00161330, NCT01110408, NCT00136656, NCT02497781, NCT01110382, NCT019949930, NCT02561117, NCT01678365, NCT02475733, NCT01498744, NCT02276482, NCT01400867, NCT00711802, NCT02024867, NCT02503761; table 2).[19–21,23,26,28–31,34–38,41,43,45–48,50,51,53–55,57,70] Potential drug allergy, defined as a previously reported reaction to the study drug, was stated as an exclusion criterion in only 51 (62%) included studies. Imaging findings were relevant for exclusion only in trials of urinary tract infections, for which the presence of a structural urinary tract abnormality was an exclusion criterion in 14 (74%) of 19 studies of urinary tract infections (NCT00161330, NCT01110408, NCT00136656, NCT02497781).[36–39,41,44,45,47,48,50] Laboratory tests (ie, haematological or biochemical) were used as exclusion criteria in only 17 (21%) studies, mainly because of exclusion of patients with renal or hepatic failure (NCT01110421, NCT01110408, NCT02497781, NCT01110382, NCT01994993, NCT01069900, NCT02475733, NCT01728376, NCT00711802).[29,35,38,41,43,48,53,55]

Primary and secondary endpoints

A clear primary endpoint was not defined properly in 39 (48%) included trials (NCT00968370, NCT01530763, NCT01669980, NCT00227331, NCT01312792, NCT00161330, NCT02497781, NCT01110382, NCT01069900, NCT02475733, NCT00844337, NCT01728376, NCT01498744, NCT02276482, NCT01400867, NCT00711802).[21,22,26,29,33,34,41,43,45,48–54,56,57,60,65,66] In some of these, we were able to deduce the endpoint from the reported results. Clinical efficacy or effectiveness (clinical improvement, clinical cure rate, treatment failure, or clinical deterioration) was the most frequently used outcome (table 2). Microbiological efficacy (including bacterial eradication and sensitivity of the isolate) was assessed as an endpoint in 27 (33%) studies (NCT01110421, NCT01530763, NCT01994993, NCT01069900, NCT01867138, NCT02503761).[20,25,33–36,40–45,48,53,59,60,62,65] Infection-related mortality was reported as a primary endpoint in 15 (18%) studies (NCT01867138, NCT02503761, NCT01994993, NCT00372541)[19,20,27,28,32,35,61,62,64,68,69] and as a secondary endpoint in nine (11%) studies (NCT01399723, NCT00968370, NCT02503761)[19,20,27,28,32,35,61,62,64,68,69] mainly in sepsis and community-acquired pneumonia trials. Except for studies NCT00372541 and NCT01994993, in all the other 13 clinical trials in which death was reported as primary endpoint it was used as composite endpoint. Infection sequelae were primary endpoints in 26 studies (NCT01399723, NCT02503761, NCT00161330, NCT00136656, NCT00462020, NCT02475733).[19,20,23,28,30,31,37–39,46,47,49–52,54,56] Other measured endpoints were reports of severe adverse events (stated by 17 trials [NCT01069900, NCT00462020, NCT02475733, NCT01386840, NCT02258763, NCT02503761][19,20,25,28,34,38,42,59,62,68,69]), and process outcomes (ie, assessment of hospital *vs* outpatient management) in four community-acquired pneumonia studies (NCT01312792, NCT01386840, NCT00968370),[24] one urinary tract infection study,[49] and one intra-abdominal infection study.[56]

Timing of endpoints

Of the 86 included studies, 75 (87%) reported the exact time for assessment of study endpoints. Endpoint assessments varied widely, even when studies were grouped by clinical infection syndromes. Some studies

	FDA	EMA	Number of studies that used the criteria	Number of studies that did not use the criteria
Ventilator-associated or hospital-acquired pneumonia (4 studies)*				
Inclusion criteria				
Clinical findings	Yes	Yes	4 (100%)	0
Timing of infection	No	Yes	2 (50%)	2 (50%)
Haematological tests	Yes	No	4 (100%)	0
Microbiology	No	No	1 (25%)	3 (75%)
Increase in mechanical ventilation requirement	Yes	Yes	3 (75%)	1 (25%)
Imaging	Yes	Yes	4 (100%)	0
Exclusion criteria				
Clinical findings	No	No	1 (25%)	3 (75%)
Haematological tests	No	No	2 (50%)	2 (50%)
Biochemical tests	No	No	2 (50%)	2 (50%)
Microbiology	Yes	Yes	2 (50%)	2 (50%)
Imaging	No	No	1 (25%)	3 (75%)
Underlying conditions	No	No	3 (75%)	1 (25%)
History of recent infection	No	No	3 (75%)	1 (25%)
History of recent antibiotics	Yes	No	2 (50%)	2 (50%)
Allergy to study drugs	No	No	2 (50%)	2 (50%)
Endpoints				
Clinical improvement	Yes	Yes	4 (100%)	0
Microbiological efficacy	No	No	4 (100%)	0
Mortality	Yes	Yes	1 (25%)	3 (75%)
Severe adverse events	No	No	1 (25%)	3 (75%)
Comorbidities or sequelae	Yes	No	0	4 (100%)
Acute bacterial skin and soft tissue infections (7 studies)†				
Inclusion criteria				
Clinical findings	Yes	Yes	6 (86%)	1 (14%)
Haematological tests	No	No	2 (29%)	5 (71%)
Imaging	No	No	1 (14%)	6 (86%)
Exclusion criteria				
Clinical findings	No	No	5 (71%)	2 (29%)
Haematological tests	Yes	No	1 (14%)	6 (86%)
Microbiology	No	No	2 (29%)	5 (71%)
Underlying disorders	Yes	Yes	6 (86%)	1 (14%)
History of recent infection	No	No	6 (86%)	1 (14%)
History of recent antibiotics	Yes	No	5 (71%)	2 (29%)
Allergy to study drugs	No	No	7 (100%)	0
Endpoints				
Clinical improvement	Yes	Yes	7 (100%)	0
Community-acquired pneumonia (24 studies)‡				
Inclusion criteria				
Clinical findings	Yes	Yes	23 (96%)	1 (4%)
Haematological tests	No	No	3 (12%)	21 (88)
Biochemical tests	No	No	2 (8%)	22 (92%)

(Table 2 continues in next column)

	FDA	EMA	Number of studies that used the criteria	Number of studies that did not use the criteria
(Continued from previous column)				
Microbiology	Yes	No	1 (4%)	23 (96%)
Imaging	Yes	Yes	10 (42%)	14 (58%)
Exclusion criteria				
Clinical findings	No	No	19 (79%)	5 (21%)
Haematological tests	No	No	2 (8%)	22 (92%)
Biochemical tests	No	No	5 (21%)	19 (79%)
Microbiology	Yes	Yes	12 (50%)	12 (50%)
Imaging	No	No	4 (17%)	20 (83%)
Underlying conditions	Yes	Yes	21 (88%)	3 (12%)
History of recent infection	No	No	10 (42%)	14 (58%)
History of recent antibiotics	No	No	10 (42%)	14 (58%)
Allergy to study drugs	No	No	16 (67%)	8 (33%)
Endpoints				
Clinical improvement	Yes	Yes	16 (67%)	8 (33%)
Treatment failure or changed antibiotic	Yes	No	13 (54%)	11 (46%)
Microbiological efficacy	No	No	4 (17%)	20 (83%)
Mortality	Yes	No	7 (29%)	17 (71%)
Severe adverse event	No	No	6 (25%)	18 (75%)
Comorbidities or sequelae	No	No	7 (29%)	17 (71%)
Process outcome	No	No	4 (17%)	20 (83%)
Sepsis (18 studies)§				
Inclusion criteria				
Clinical findings	Yes	Yes	14 (78%)	4 (22%)
Haematological tests	Yes	Yes	5 (28%)	13 (72%)
Biochemical tests	Yes	Yes	7 (39%)	11 (61%)
Microbiology	Yes	No	6 (33%)	12 (67%)
Exclusion criteria				
Clinical findings	No	No	14 (78%)	4 (22%)
Biochemical tests	No	No	3 (17%)	15 (83%)
Microbiology	No	No	2 (11%)	16 (89%)
Underlying disorders	No	No	13 (72%)	5 (28%)
History of recent infection	No	No	4 (22%)	14 (78%)
History of recent antibiotics	No	No	7 (39%)	11 (61%)
Allergy to study drugs	No	No	2 (11%)	16 (89%)
Endpoints				
Clinical improvement	No	No	8 (44%)	10 (56%)
Treatment failure or changed antibiotics	No	No	12 (67%)	6 (33%)
Microbiological efficacy	No	No	8 (44%)	10 (56%)
Mortality	No	Yes	7 (38%)	11 (62%)
Severe adverse events	No	No	5 (28%)	13 (72%)
Comorbidities or sequelae	No	Yes	4 (22%)	14 (78%)

(Table 2 continues on next page)

	FDA	EMA	Number of studies that used the criteria	Number of studies that did not use the criteria
(Continued from previous page)				
Urinary tract infection (19 studies)¶				
Inclusion criteria				
Clinical findings	Yes	Yes	18 (95%)	1 (5%)
Indwelling catheter	Yes	Yes	0	19 (100%)
Haematological tests	No	No	2 (11%)	17 (89%)
Biochemical tests	Yes	Yes	14 (74%)	5 (26%)
Microbiology	No	Yes	15 (79%)	4 (21%)
Imaging	No	No	10 (53%)	9 (47%)
Exclusion criteria				
Clinical findings	No	No	8 (42%)	11 (58%)
Haematological tests	No	No	3 (16%)	16 (84%)
Biochemical tests	No	No	5 (26%)	14 (74%)
Microbiology	No	No	5 (26%)	14 (74%)
Imaging	Yes	Yes	11 (58%)	8 (42%)
Underlying disorders	Yes	No	17 (89%)	2 (11%)
History of recent infection	No	No	6 (32%)	13 (68%)
History of recent antibiotics	Yes	No	11 (58%)	8 (42%)
Allergy to study drugs	No	No	14 (74%)	5 (26%)
Endpoints				
Clinical improvement	Yes	Yes	9 (47%)	10 (53%)
Treatment failure or changed antibiotic	No	No	5 (26%)	14 (74%)
Microbiological efficacy	Yes	Yes	7 (37%)	12 (63%)
Severe adverse events	No	No	3 (16%)	16 (84%)
Comorbidities or sequelae	No	No	10 (53%)	9 (47%)
Process outcome	No	No	1 (5%)	18 (95%)
Intra-abdominal infection (14 studies)‖				
Inclusion criteria				
Clinical findings	Yes	No	5 (36%)	9 (64%)
Haematological tests	Yes	No	2 (14%)	12 (86%)
Microbiology	No	No	1 (7%)	13 (93%)
Imaging	No	No	6 (43%)	8 (57%)
Surgical procedure	Yes	Yes	11 (79%)	3 (21%)
Exclusion criteria				
Haematological tests	No	No	6 (43%)	8 (57%)
Biochemical tests	No	No	8 (57%)	6 (43%)
Microbiology	No	No	2 (14%)	12 (86%)
Imaging	No	No	3 (21%)	11 (79%)
Underlying disorders	Yes	No	12 (86%)	2 (14%)
History of recent infection	Yes	No	2 (14%)	12 (86%)
History of recent antibiotics	Yes	No	7 (50%)	7 (50%)
Allergy to study drugs	No	No	11 (79%)	3 (21%)
Endpoints				
Clinical improvement	Yes	Yes	11 (79%)	3 (21%)
Treatment failure or changed antibiotic	No	No	7 (50%)	7 (50%)
Microbiological efficacy	No	No	5 (36%)	9 (64%)
Mortality	Yes	No	1 (7%)	13 (93%)
Severe adverse events	No	No	6 (43%)	8 (57%)
Comorbidities or sequelae	Yes	No	5 (36%)	9 (64%)
Process outcome	No	No	1 (7%)	13 (93%)

(Table 2 continues in next column)

(Continued from previous column)

EMA=European Medicines Agency. FDA=US Food and Drug Administration. *NCT01110421.[33-35] †NCT01498744, NCT02276482, NCT01400867, NCT00711802, NCT02024867.[34,70] ‡NCT01312792, NCT01399723, NCT01386840, NCT00372541, NCT00227331, NCT01110421, NCT00968370, NCT01669980, NCT01530763, NCT02258763.[19-32] §NCT01867138, NCT00844337, NCT01728376, NCT02503761.[33,34,58-69] ¶NCT00161330, NCT01110408, NCT00136656, NCT02497781.[36-50] ||NCT01110382, NCT01994993, NCT01069900, NCT00462020, NCT02561117, NCT01678365,NCT02475733.[51-57]

Table 2: **Proportion of key study design criteria used in paediatric trials compared with the adult EMA and FDA guidance**

assessed endpoint on an exact day after end of treatment, whereas others considered a range of days. In seven (9%) studies, the timing for assessment of the endpoints was not specified (NCT00968370).[21,23,31,35,49,52,55–58]

Among studies reporting the timing for the clinical endpoints, the days specified for outcome assessment ranged between the first day of treatment and 90 days after the end of treatment. Five (7%) trials assessed the outcome within the first 24 h of treatment (three community-acquired pneumonia studies[28,29,32] and two sepsis studies[60,68]), whereas in ten studies, clinical outcome was assessed at 48 h of treatment (four community-acquired pneumonia studies (NCT01312792),[28,29,32] one urinary tract infection study,[46] one intra-abdominal infection study (NCT01110382), and four sepsis trials[60,63,68] (NCT01867138; figure 2). Several studies assessed clinical endpoints after completion of therapy by counting days after the end of therapy, six within the first 24 h (NCT01069900).[30,42,51,53,67] Only two studies assessed the clinical outcome by counting days after surgery (NCT00462020).[54]

Similarities with, and divergence from, adult EMA and FDA guidelines

Divergence between EMA and FDA guidance is summarised by clinical infection syndrome (appendix p 15), and we reviewed the extent to which standardised inclusion and exclusion criteria and endpoints for the serious clinical infection syndromes identified by the FDA and EMA for adults were used in clinical trials involving neonates and children.

In hospital-acquired or ventilator-associated pneumonia and acute bacterial skin and soft tissue infections trials, criteria established in adult guidelines were broadly

similar to those used in paediatrics (table 2). Adult community-acquired pneumonia guidelines were partly similar to the criteria most often used for children, with the main difference being the absence of mandatory imaging as an inclusion criterion for children. Furthermore, the effect of underlying disorders, such as

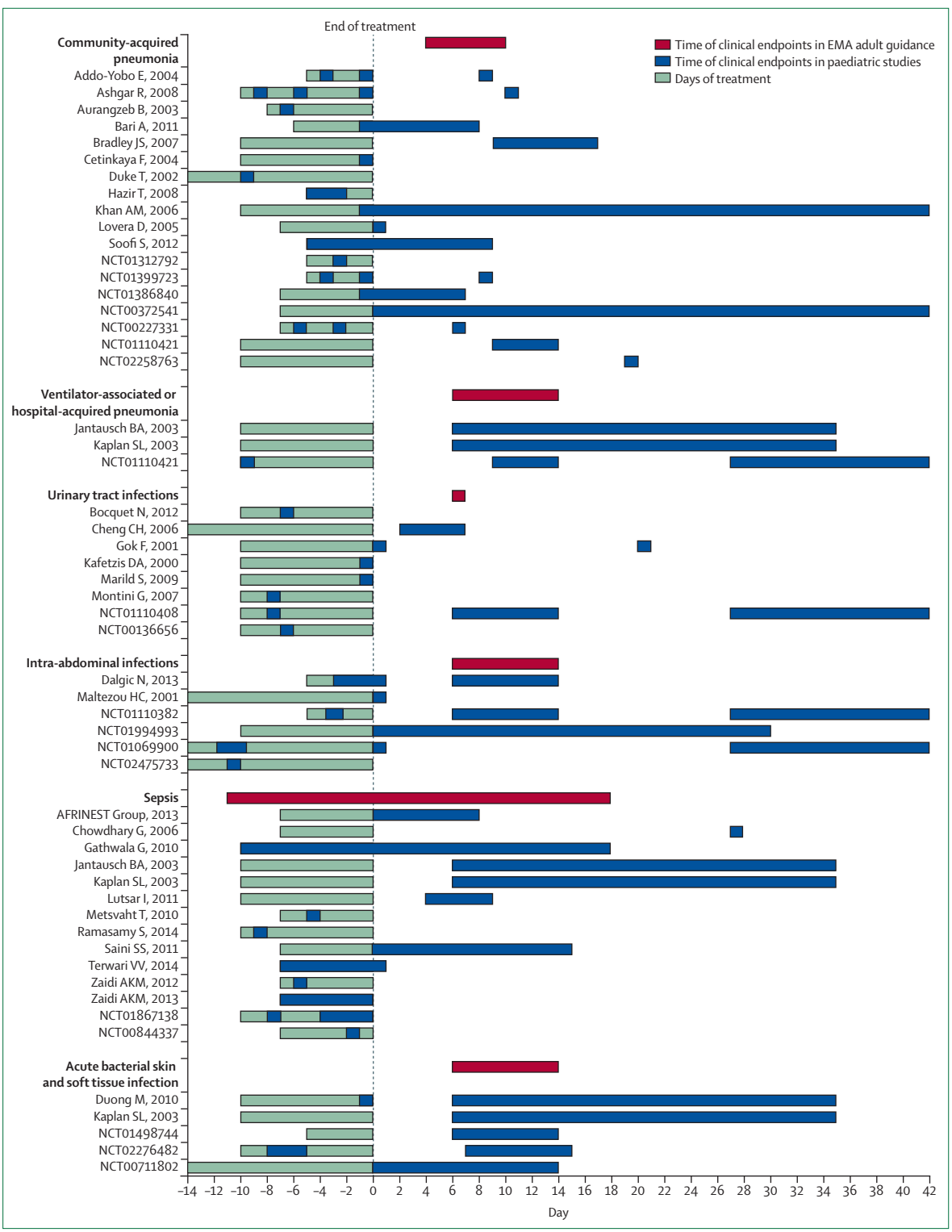

***Figure 2*: Timing of assessment of clinical endpoints in paediatric trials compared with adult European Medicines Agency guidelines**
EMA=European Medicines Agency.

asthma and congenital or chronic diseases (apart from cystic fibrosis), often mentioned in paediatric clinical trials, was not commented on in adult guidance (table 2).

Inclusion criteria for sepsis established by the EMA or FDA for adults can be applied to infants and children (considering their age-specific ranges for heart rate, respiratory rate, and white blood cell count).[73] 16 (89%) of 18 included paediatric trials for sepsis enrolled neonates (and used different criteria; NCT01867138, NCT00844337, NCT02503761).[33,58–69] The only study of sepsis involving children (NCT01728376) was done in 2012 and did not apply the available regulatory criteria (table 2).

Adult guidance for complicated urinary tract infections and complicated intra-abdominal infections are poorly applicable in paediatrics, mainly because the pathogenesis, risk factors, and underlying disorders differ by age-group, making inclusion criteria and endpoints difficult to apply (table 2).

Discussion

As the challenges of dealing with antimicrobial resistance become ever more prominent, robust evidence to support optimum use of antibiotics in children is needed. To our knowledge, this is the first systematic review of antibiotic clinical trials in children, including neonates, with complicated clinical infection syndromes. Although such infections continue to account for substantial morbidity and mortality in children worldwide, we identified only a small number of published randomised controlled clinical trials of antibiotic use in children across a wide number of clinical infection syndromes. We also highlight several limitations of the state of published research from clinical trials in this area that ultimately impede translation into clinical practice.

The first striking finding of our Review is the poor adherence of identified publications to CONSORT guidelines for trial reporting. Average completeness of reporting on CONSORT items was only 66%, with little variation between clinical infection syndromes. Quality of reporting was better for clinical trials published in journals with an impact factor of 5 or greater, and for those published after 2001.

The first CONSORT statement was published in 1996, with a revision in 2001, and an explanatory statement with additional elaborations released in 2010.[17,74–76] As we limited our searches to studies published from 2000 onwards, the CONSORT statement would have been available and should have served as guidance for reporting trial findings. Inconsistent and patchy reporting of key trial features substantially affects the ability to assess the quality of studies and therefore restricts clinical application.

This variability in trial reporting needs to be tackled in parallel to addressing harmonisation of trial design. However, we suspect that poor reporting also reflects true and frequently unjustified variation in study design: variability in inclusion and exclusion criteria and choice of primary and secondary endpoints was striking. Specifically, just less than half of the included clinical trials did not define a clear primary endpoint. Furthermore, the type and timing of endpoint assessments was heterogeneous, hindering meta-analyses and comparison between clinical trials.

Neonatal and paediatric antibiotic trials in complicated clinical infection syndromes have two main purposes. Regulatory trials are required to support the licensing process for new antibiotics in children and neonates. Strategic trials aim to generate evidence to support optimum use of older antibiotics in this population.

There is ongoing debate worldwide about the extent to which paediatric drug licensing should include traditional phases of drug development. Generally, the EMA and FDA agree that this is not feasible as a standard approach and that methods to overcome this challenge are required to support introduction of paediatric drug labels.[77–79] At present, optimum design methods focusing on modelling and simulation for assessment of antibiotic pharmacokinetics and obtaining sufficient safety data in this population are being proposed as a key solution. For example, the EMA states that, "in many instances the nature and course of bacterial infections is sufficiently similar between age groups that efficacy data obtained in adults may be used to support use of an antibacterial agent in the same indication in children of various ages provided that there are sufficient safety and pharmacokinetic data available to support age-specific dose recommendations".[9] The FDA Paediatric Study Decision Tree shows largely similar considerations.[79]

Most of the EMA and FDA guidelines we referred to were made available in the past 5 years; some of these guidelines are not yet finalised.[11,15] Furthermore, many of the trials we included were not done to inform paediatric labelling. Nonetheless, it is useful to consider divergence from EMA and FDA guidance. For some clinical infection syndromes, such as community-acquired pneumonia, this divergence from EMA and FDA guidance seems to relate to differing recommendations for clinical management in adults and children (such as chest radiographs not being considered an integral part of clinical assessment in all childhood cases of community-acquired pneumonia). For others, such as complicated urinary tract infections or complicated intra-abdominal infections, EMA or FDA clinical infection syndrome definitions might simply not be reflective of syndromes in neonates and children. Researchers might therefore be concerned that antibiotic treatment response in children could differ from that in adults, therefore placing different requirements on clinical trials. However, adequate explanations for clinical trial designs and their relation to specific research questions or hypotheses were absent in most of the reviewed studies.

Much of the licensing process for paediatric labels will rely on pharmacokinetic studies and early-phase safety trials. Nonetheless, harmonisation of the definitions for target clinical infection syndromes is crucial, in view of

important differences between children and adults (panel). Simple extrapolation from EMA and FDA guidance might miss important clinical infection syndromes and therefore fail to support optimum use of antibiotics in neonates and children. Although definitions of clinical infection syndromes, such as hospital-acquired or ventilator-associated pneumonia, acute bacterial skin and soft tissue infections, and sepsis (apart from neonatal sepsis), are fairly transferable across age groups, others might be missed by current EMA or FDA guidance (such as necrotising enterocolitis).

Additionally, strategic trials addressing questions of effectiveness have different requirements. For these trials, strict standardised case definitions might not be as relevant when data from pragmatic trials are required to inform antibiotic use in day-to-day clinical practice. The Infectious Diseases Society of America recognised the importance of considering children separately in aspects of trial design for antibiotics in community-acquired pneumonia.[78]

Even if general guidance for harmonised clinical infection syndrome definitions for neonates and children were to be issued, specific definitions might not be applicable in distinct settings. A notable exception to the otherwise highly variable picture in clinical trials of community-acquired pneumonia were several trials in low-income and middle-income countries that referred to the definition for acute respiratory infections in children designed by WHO for this setting.[72] Standardised definitions are likely to be used to inform trial design, if these are clinically relevant, including for large strategic trials. Equally, findings of these clinical trials might not be generalisable to high-income settings because in low-income and middle-income countries mortality from community-acquired pneumonia is high in otherwise healthy children.[80]

Therefore, for such strategic trials, robust designs and reporting to a high standard becomes central to enable an in-depth assessment of internal and external validity and risk of bias. Differences in availability of, and rapid access to, diagnostic tools, such as chest radiograph, or management approaches might necessitate variations in trial design to increase the relevance of specific clinical trials to specific settings (at the cost of generalisability to other settings).

One major limitation of the clinical trials included in our systematic review was the variability in endpoint definitions and timing of endpoint assessment. Clinical efficacy or effectiveness was the most frequently used outcome, whereas microbiological efficacy and death were assessed less frequently. Outcomes assessed in most clinical trials were based on subjective (patient or clinician) definitions. On the one hand, this reduces opportunities for comparison and could hinder meta-analysis of studies; on the other hand, such pragmatic approaches to trial design might result in clinical trials that are more relevant to clinical practice. Adequate justification for selection of endpoints is crucial to enable health-care professionals to interpret the relevance of trial findings for their patients and setting. Similarly, full justification of the timing for assessment of endpoints on the basis of pathogenesis and clinical infection syndrome course, rather than subjectively selected, arbitrary timepoints is desirable.[81]

Panel: **Reasons why treatment response might differ in children and neonates compared with adults**

- Vaccination
- Reduced or changing immunological competence
- Different clinical range of underlying comorbidities
- Different clinical features of some important infectious syndromes
- Changing microbiome
- Different pathogen and resistance profile of infectious syndromes
- Absence of validated surrogate markers of pharmacodynamic outcomes
- Wide variability of pharmacodynamic indices
- Immature or changing drug metabolism and handling
- Technical issues in formulation and drug delivery

The need to harmonise design and reporting of clinical trial results is a common issue in infectious diseases. Several recent publications address clinical trials in adult clinical infection syndromes, including the key points of superiority or non-inferiority design and sample size calculation, timing for clinical endpoints, and the role of assessing antimicrobial resistance.[82–84] Similar difficulties have been reported to those we observed for paediatric clinical trials; for example, identification of a severe infection required for eligibility being based on clinician observations or patient reports rather than on standardised, reproducible criteria.[83]

The challenges of harmonising design and reporting of clinical trials involving children worldwide and across different paediatric specialties have already been noted for non-infectious diseases.[85–88] Reviews of non-infectious diseases identified similar difficulties to our systematic review, such as reporting of heterogeneous data and the challenges of comparisons across studies.[85,86,89,90] Furthermore, some studies[85,89] have assessed the extent to which information arising from paediatric clinical trials is disseminated in the peer-reviewed literature at a global level or in specific settings. These authors emphasised the limitations in translation of results of clinical trials done in a non-standardised way into clinical practice, even when a clear therapeutic advantage is shown.

Timely, evidence-based use of both new and older antibiotics in children and neonates will be hindered if trials continue to be inadequately reported and to use inconsistent criteria for patient selection and assessment of endpoints. A comprehensive approach involving all the relevant stakeholders, building on existing EMA and FDA initiatives, is required to

improve the design and conduct of paediatric antibiotic clinical trials.[5,77,88,91–95] A closer collaboration between clinicians and the pharmaceutical industry is crucial at the early stages of study design during the pre-competitive stage to ensure rapid and appropriate neonatal and paediatric labelling. Agreed harmonised trial entry criteria and outcome definitions of the most common paediatric complicated clinical infection syndromes would be helpful.

Strategic paediatric trials should use these agreed entry criteria and outcome definitions as a reference point, but divergence would be expected when pragmatic questions about effectiveness are being addressed. A consensus working group involving the main global academic, regulatory, and pharmaceutical partners is central to bringing together all relevant parties in this process. Consensus agreement might help to ensure that high-quality, efficient, and robust clinical trials of both new and old antibiotics done in Europe, the USA, and globally can in the future contribute to improving care for neonates and children with serious and complex infections.

Contributors

MS and JB contributed to the concept and design of the study. MS, JB, and LF designed the search strategy and selection criteria. LF and BR collected the data. All authors contributed to interpretation of the data. LF, JB, 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 had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MS, the Paediatric Infectious Diseases Research Group, and St George's Vaccine Institute at St George's University London receive funding from Pfizer, GSK, and Merck to conduct investigator-led research on vaccine schedules in children. MAT chairs the European Network of Paediatric Research at the European Medicines Agency (EnprEMA) and is academic codirector (Europe) of the Critical Path Institute's International Neonatal Consortium. DKB reports personal fees from Astellas Pharma US, Cempra Pharmaceuticals, GlaxoSmithKline, Janssen Research & Development, Pfizer, The Medicines Company, Shionogi, and Tetraphase Pharmaceuticals. JSB declares no personal competing interests, but his employer, the University of California, receives funding from: the National Institutes of Health, the Biomedical Advanced Research and Development Authority (BARDA) through Duke University, Actavis, and Merck, for the study of antibiotics in paediatric pneumonia. JSB is member of the Foundation of the NIH Biomarkers Consortium (Clinical Trial Design), and the US FDA's Advisors and Consultants Staff (unfunded). TEZ reports grants from Merck, personal fees from Merck, and grants from Cubist. JB's husband is a senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. All other authors declare no competing interests.

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