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Implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review

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Abstract

Background: Antibiotics are the most common medicines prescribed to children in hospitals and the community, with a high proportion of potentially inappropriate use. Antibiotic misuse increases the risk of toxicity, raises healthcare costs, and selection of resistance. The primary aim of this systematic review is to summarize the current state of evidence of the implementation and outcomes of pediatric antimicrobial stewardship programs (ASPs) globally.

Methods: MEDLINE, Embase and Cochrane Library databases were systematically searched to identify studies reporting on ASP in children aged 0–18 years and conducted in outpatient or in-hospital settings. Three investigators independently reviewed identified articles for inclusion and extracted relevant data.

Results: Of the 41,916 studies screened, 113 were eligible for inclusion in this study. Most of the studies originated in the USA (52.2%), while a minority were conducted in Europe (24.7%) or Asia (17.7%). Seventy-four (65.5%) studies used a before-and-after design, and sixteen (14.1%) were randomized trials. The majority (81.4%) described in-hospital ASPs with half of interventions in mixed pediatric wards and ten (8.8%) in emergency departments. Only sixteen (14.1%) studies focused on the costs of ASPs. Almost all the studies (79.6%) showed a significant reduction in inappropriate prescriptions. Compliance after ASP implementation increased. Sixteen of the included studies quantified cost savings related to the intervention with most of the decreases due to lower rates of drug administration. Seven studies showed an increased susceptibility of the bacteria analysed with a decrease in extended spectrum beta-lactamase producers *E. coli* and *K. pneumoniae;* a reduction in the rate of *P. aeruginosa* carbapenem resistance subsequent to an observed reduction in the rate of antimicrobial days of therapy; and, in two studies set in outpatient setting, an increase in erythromycin-sensitive *S. pyogenes* following a reduction in the use of macrolides.

Conclusions: Pediatric ASPs have a significant impact on the reduction of targeted and empiric antibiotic use, healthcare costs, and antimicrobial resistance in both inpatient and outpatient settings. Pediatric ASPs are now widely implemented in the USA, but considerable further adaptation is required to facilitate their uptake in Europe, Asia, Latin America and Africa.

Keywords: Antibiotic stewardship, Antimicrobial stewardship, Infectious diseases, Pediatrics

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Background

Antimicrobials are the most commonly prescribed medicine in pediatrics [1–3], with some estimates showing that between 37 and 61% of hospitalized infants and children receive antibiotics [4–8]. It has been demonstrated that between 20 to 50% of these prescriptions are potentially unnecessary or inappropriate [9–13], and that many children still receive broad-spectrum antibiotics for viral infections or antibiotic courses that are significantly longer than needed [14–18].

This unnecessary exposure increases the risk of serious side effects, raises healthcare costs, and contributes significantly to the global emergency of antimicrobial resistance [7, 19].

Although antimicrobial resistance occurs naturally and can be acquired through gene transfer, antimicrobial misuse promotes the selection of resistant organisms [20, 21]. The emergence of resistant pathogens and their global spread has rapidly become a major threat to public health around the world, constituting a substantial burden for patients, prolonging hospital stays, and leading to increases in both healthcare costs and mortality [22–27]. This is particularly urgent due to the steady reduction in the number of new antibiotic drugs approved over the last few decades, particularly for children [28, 29].

The World Health Organization and the United Nations at the General Assembly of 2016 identified the development of country-level and institutional antimicrobial stewardship programs (ASPs) as key instruments to tackle this concern [30, 31].The concept of an ASP was formally introduced in 2007 by the Infectious Disease Society of America (IDSA) and defined as a set of coordinated interventions designed to improve antimicrobial use in terms of selecting the appropriate agent, dose, route of administration, and therapy duration without compromising patient outcomes [32]. The Pediatric Infectious Diseases Committee on Antimicrobial Stewardship has defined the development of ASPs in three different settings: inpatients, special populations (e.g. oncology), and outpatients. Indeed, the characteristics of specific ASPs may vary to best fit the needs of different settings [33]. The primary aim of this review is to summarize the current state of evidence on how ASPs are conducted in pediatrics inpatients and outpatients globally, informing practice in the field.

Materials and methods

Study design and search strategy

A review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34]. Working with a medical librarian, we conducted a systematic search of the MEDLINE, Embase, and Cochrane Library databases, including citations from January 1, 2007, to November 21, 2018, with a strategy combining Medical Subject Heading (MeSH) and free-text terms for 'children' AND 'antimicrobial' AND 'stewardship.' The full strategy is provided in the Additional file 1.

Inclusion criteria

Studies were eligible for full-text review if they included both patients younger than 18 years and were conducted in outpatient or in-hospital settings. Randomized controlled trials, controlled and non-controlled before-and-after studies, controlled and non-controlled interrupted time series, and cohort studies were included.

Exclusion criteria

Review articles, case series, letters, notes, conference abstracts, and opinion articles were excluded. Papers on both adults and children where extraction of pediatric data was not possible were also excluded. We excluded studies published before 2007, as the concept of antimicrobial stewardship was formally introduced that year. We did not include articles about malaria, HIV, viral and fungal treatments.

Study selection

Assessments of the titles, abstracts, and full texts were conducted independently by two investigators (EB and MD). Any disagreement regarding study selection was resolved by discussion with a third reviewer (DD). The selection process is summarized in Fig. 1.

Data collection

Data were extracted using a standardized data collection form which summarized information about authors, year of publication, study design, country, study period, setting, multicentric involvement, type of intervention, and main results**.**

Results

Of 41,916 titles and abstracts, 113 were eligible for inclusion in this review. Most of the studies (98/113, 86.7%) originated from high-income countries (defined according to the World Bank list of economies in September 2018) [35] and a slight majority described ASPs implemented in the USA (59/113, 52.2%). Only 28/113 (24.7%) papers describe the implementation of an ASP in Europe (Ireland, Cyprus, Czech Republic, Germany, Greece, Spain, France, Netherlands, Switzerland, UK, and Italy); 20/113 (17.7%) describe the implementation of an ASP in Asia (India, Indonesia, Israel, Philippines, Russia, Saudi Arabia, Singapore, South Korea, Pakistan, Bangladesh, Japan, and China), with the remainder describing ASPs implemented in Benin, Argentina, and Canada.

Fifty studies were published between 2016 and 2018 [50/113, 44.5% in total; 28/50 (56%) from USA, 11/50 (22%) from Asia, and 11/50 (22%) from Europe], three times more than during the 2007–2009 period [16/113, 14.2% in total; 6/16 (37.5%) from the USA, 5/16 (31.3%) from Asia, 4/16

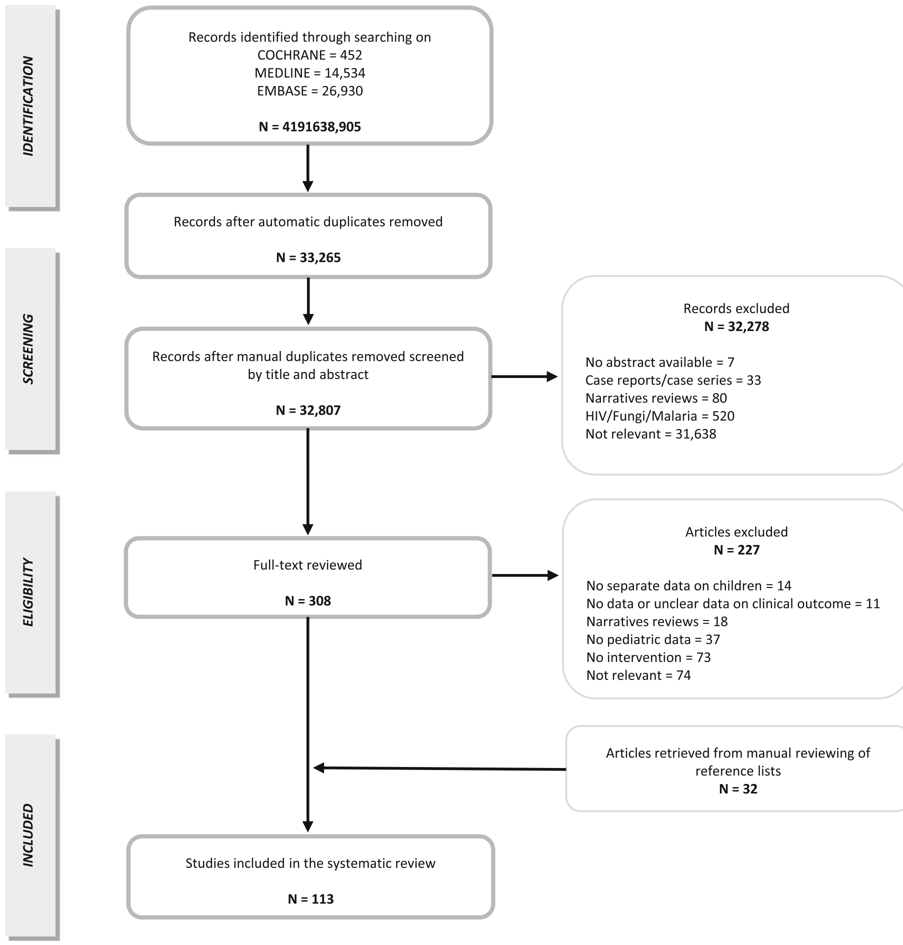

Fig. 1 Flowchart of the study selection process

(25%) from Europe, 1/16 (6.3%) from Africa]. Geographical distribution of articles is shown in Fig. 2.

Author, publication year, study design, country, study period, setting, type of intervention, and main results are summarized in **Table S1** (please see Additional file 2). Thirty-nine (39/113, 34.5%) were multicentre studies: 43.6% (17/39) were set in the USA, 35.9% (14/39) in Europe, and the rest 20.5% in Asia and Africa (8/39).

ASPs setting and type of intervention

Ninety-two studies [92/113, 81.4% in total; 50/92 (54.3%) from the USA and 21/92 (22.8%) from Europe] described ASP implementation in the hospital setting [36–120]. Most of the ASP interventions in this setting were audit and feedback [53, 55–58, 62, 67–71, 74, 76, 78, 79, 82–84, 86, 89, 91, 92, 94, 107, 110, 111, 113, 120–123] guidelines implementation [36, 37, 40, 42, 43, 54, 59, 60, 73, 80, 83–85, 87, 90, 91, 99, 100, 104, 106, 109, 115, 119, 121, 122, 124, 125], and more specific approaches based on laboratory testing and check-lists [38, 42, 51, 52, 54, 61, 65, 75, 77, 81, 87, 91, 95, 96, 98, 99, 101–103, 111, 112, 114, 116–119, 124–131]. Eight interventions conducted in the hospital setting monitored perioperative prophylaxis [3/8 (37.5%) in the USA, 3/8 (37.5%) in Europe the rest in Argentina and Canada (2/8, 25%)]) [51, 54, 59, 69, 87, 91, 98] including one implemented in the NICU ward [115].

Twenty-one papers [21/113, 18.6% in total; 9/21 (42.8%) from USA, 7/21 (33.3%) from Europe, 4/21 (19%) from Asia, and 1/21 (4.7%) from Africa] described ASP in an outpatient setting [126–130, 132–147], among which seven were focused on education combined with audit and feedback [129, 132, 134, 138, 141, 142, 145–147]. ASP interventions stratified for different settings are summarized in Table 1.

ASPs outcomes

Ninety (90/113, 79.6%) studies reported as their main outcome changes in antimicrobial prescribing with a reduction in inappropriate prescriptions [45/90 (50%) from the USA, 23/90 (25.5%) from Europe, and 24.5% from Asia) [36–39, 41, 43–50, 52–62, 64–84, 86, 87, 89–92,

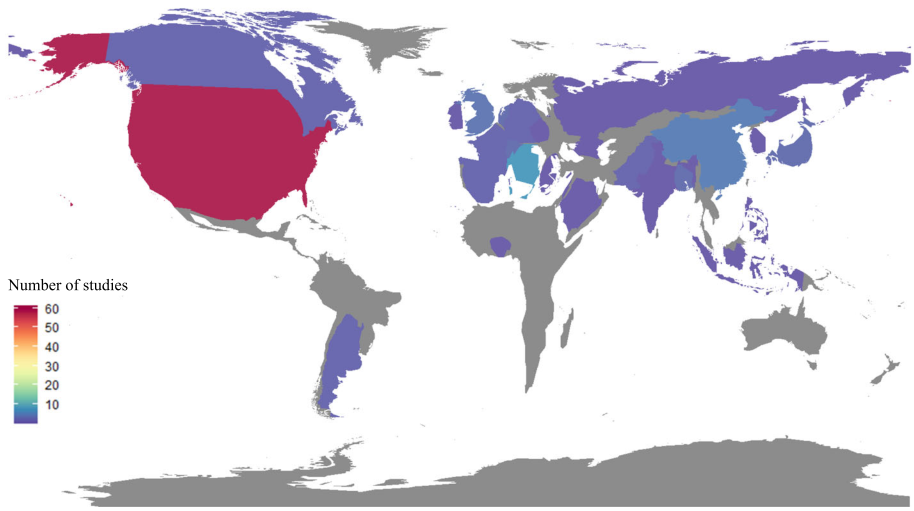

Fig. 2 Area cartogram of the world with each country rescaled in proportion to number of study included in this review (R version 3.5.3)

94–107, 110–114, 116–121, 123–135, 137, 138, 141–143, 147, 148]; sixty-one of these were studies with a single intervention, mainly with an audit and feedback strategy (19/61, 31.1%) [53, 56–58, 62, 64, 67–71, 74, 76, 82–86, 89, 91, 92, 94, 107, 110, 111, 113, 120, 121, 123, 127, 132, 134, 135, 138, 141, 142, 147]. Eighteen papers (18/113, 15.9%) [40–42, 51, 54, 60, 71, 85, 87, 91, 98, 105, 106, 125, 135, 136, 138, 142] showed an increase in compliance among prescribing physicians; half of the papers analysing this outcome were from USA and Canada (10/18, 55.5%), and the main ASPs adopted were guidelines (9/34, 26.5%) [40, 42, 54, 60, 85, 87, 91, 106, 125, 142], doctors education (5/34, 14.7%) [54, 91, 98, 138, 142] and other not common ASPs such as antibiotic order set [42, 51], and checklists [87, 91]. Sixteen of the included studies [16/113, 14.2% in total; 7/16 (43.7%) from USA, 6/16 (37.5%) from Asia and the rest (18.7%) from Europe] quantified cost savings related to the intervention [39, 49, 52, 64, 66, 69, 73, 86, 89, 92, 97, 101, 102, 122–124]. Decreases in costs were most often due to lower rates of drug administration. Twelve papers [12/113, 10.6% in total; 6/12 (50%) from Asia and the rest equally from Europe and USA] took into consideration changes in antimicrobial resistance [52, 58, 66, 67, 72, 106, 112, 115, 124, 137, 141] as an outcome used mostly to analyse audit and feedback ASP [58, 67, 74, 141]. In five cases, no changes were reported [58, 66, 74, 106, 115], while the other seven studies showed an increased susceptibility of the bacteria analysed [52, 67, 72, 112, 124, 137, 141]. The most interesting results were a decrease in extended spectrum beta-lactamase (ESBL) producers *E. coli* and *K. pneumoniae* [72, 112, 124]*;* a reduction in the rate of *P. aeruginosa* carbapenem resistance subsequent to an observed reduction in the rate of antimicrobial days of therapy (DOT) [67, 124]; and, in two studies set in outpatient setting, an increase in erythromycin-sensitive *S. pyogenes* following a reduction in the use of macrolides [137, 141]. See **Table S1** (Additional file 2) for further details regarding study outcomes.

Discussion

Main findings

Since 2007, ASPs have been proven to reduce inappropriate antimicrobial use and resistance, enhance patient safety, and lower drug costs both in adult and pediatric populations. More than 300 studies performed in the adult setting have now been published [149–152], while 113 studies over the last twelve years were performed in pediatric settings.

We conducted this scoping systematic review [153] to provide an easily consultation compendium (divided by country, study period, type of intervention and main outcomes analysed) describing the state of art of ASPs worldwide and to help clinicals to choose wisely which program would fit better in their setting. This is the first systematic scoping review analysing the implementation of ASPs in pediatrics globally, in both inpatient and outpatients settings. Previously, two systematic reviews had been conducted which did not include ASPs intervention in outpatient settings, with Smith et al. [154] limited to inpatient interventions in the USA and Da Silva et al. [155] limited to general pediatric wards and PICU.

It is interesting to notice that the relative number of articles on pediatric ASPs published in Europe and Asia increased between 2016 and 2018, compared to USA where the spike was already observed in 2013–2015. Moreover, there seems to be an ASPs research gaps in certain area of the world, mostly in middle-low or low income countries, that could be due to the fact that

Table 1 Antimicrobial stewardship programs strategies and settings (2007–2018)

	Audit and feedback	Guidelines	Physician Education	Pre-Authorization	Parents Education	CDS tool	CP	Other
ED (15)		**5**	**4**				**3**	**3**
France		1	1				1	
Italy			1				1	
Netherlands		1						
Switzerland								1
USA		3	1				1	2
Spain			1					
ED + Pediatric ward (4)			**1**				**3**	
Italy			1				1	
USA							2	
Hospital (all wards) (62)	**23**	**11**	**4**	**10**				**14**
Bangladesh			1					
Canada		2	1					1
China	1			1				1
Germany	2							
Greece		1						
Italy		1	1					3
Japan	2			3				
Pakistan		1						
Singapore	1							
South Korea				1				
USA	17	6	1	5				9
Hospital (all wards), ED and PICU excluded (1)				**1**				
USA				1				
Hospital (all wards), PICU excluded (3)			**1**				**1**	**1**
Argentina			1				1	1
Hospital (one ward) (3)		**1**	**1**					**1**
Bangladesh		1	1					1
Hospital (two wards) (1)		**1**						
Russia		1						
NICU (18)	**4**	**3**	**2**			**2**		**7**
France		1						
India								1
Ireland	1		1					1
Netherlands	1							
Philippines								1
USA	2	2	1			2		4
NICU + Hospital nursery (1)								**1**
Netherlands								1
NICU + PICU (2)								**2**
Switzerland								1
UK								1
Oncology ward (3)	**1**	**1**						**1**

Table 1 Antimicrobial stewardship programs strategies and settings (2007–2018) *(Continued)*

	Audit and feedback	Guidelines	Physician Education	Pre-Authorization	Parents Education	CDS tool	CP	Other
UK		1						1
USA	1							
Outpatient (43)	**10**	**6**	**9**		**5**	**4**		**9**
Argentina								1
Bangladesh								1
Benin	1	1						1
Cyprus			1		1			
Czech Republic	1		1					
Israel	1		1		1			
Italy	1	2						2
Saudi Arabia	1		1					
Switzerland		1						
UK			1					1
USA	4	1	3		3	4		3
Spain	1	1	1					
Outpatient + ED (1)			**1**					
Italy			1					
Outpatient + Hospital (8)	**2**	**2**	**2**		**2**			
China	2	2	2		2			
PICU (5)	**1**	**1**	**1**					**2**
China		1	1					1
Pakistan	1							
UK								1
PICU + Pediatric wards (2)		**1**						**1**
Indonesia		1						1
Grand Total	*41*	*32*	*26*	*11*	*7*	*6*	*7*	*42*

Entries in boldface represent total sum of ASP strategies according to setting (eg. ED/Guidelines = 5 it is the sum of France (1), Netherlands (1) and USA (3))

most ASPs program are under development and/or considered as part of new standard of care strategies. An earlier review by Schweitzer et al. [156] found that the overall quality of ASPs studies is low and has not improved over time. Our research confirmed these previous finding with most of the studies having a before-and-after design, most likely because of the low cost, convenience, and simplicity of these designs.

ASPs are mainly based on two core strategies: prospective audit and feedback, which involves interaction and feedback between an infectious disease physician and the prescriber; and formulary restriction and preauthorization requirements for specific agents [32]. Implementation of both core strategies together is strongly recommended by the ASP guidelines, but we found just four studies (3.5%) where both ASPs were implemented. These ASPs were implemented more in the USA, with just seven core interventions implemented in Europe. More accuracy in dosage and better adherence to guidelines were obtained in these studies worldwide, together with an overall decrease in length of therapy and DOT, especially for cephalosporins and fluoroquinolones.

According to the IDSA guidelines, ASPs should improve antimicrobial use, leading to reductions in antimicrobial resistance, adverse drug events, healthcare costs, and rates of *C. difficile* infections. The most commonly reported outcome in this review was a change in the prescribing of antimicrobials, with less emphasis on healthcare costs, safety, and resistance. Almost all the studies we reviewed evaluating antimicrobial consumption showed a significant reduction in inappropriate prescriptions [36–39, 41, 43–50, 52–62, 64–84, 86, 87, 89–92, 94–107, 110–114, 116–121, 123–135, 137, 138, 141–143, 147, 148]. Compliance after ASP implementation reported in eighteen papers (15.9%) was high [40–42, 51, 54, 60, 71, 85, 87, 91, 98, 105, 106, 125, 135, 136, 138, 142], showing that ASP interventions were generally well tolerated despite theoretical concerns about prescriber opposition [82]. It is critical that implementation of these tools be supported by evaluation of compliance, because if the tools are too complicated to use or too time-consuming, physicians will not use them and the likelihood of inappropriate therapy will increase. Papers analysing costs variations mostly included just drug costs, even thought the cost savings of ASPs should also include the reduction due to the shift from intravenous to oral administration, the reduction in length of hospital stays, and reduced rates of infections due to multidrug-resistant bacteria [157]. Only three European studies analysing healthcare costs were published; the other studies were mostly from the USA or other countries, such as China, that do not have universal healthcare coverage. For this reason, formal economic studies are also needed in pediatrics to show how ASP implementation impacts all costs, not just the costs of antimicrobials. Moreover, as Tacconelli et al. strongly advise [158], microbiological analysis of common bacteria such as *S. aureus* and *K. pneumoniae* before and after ASP implementation should be included (just the 11.2% of the papers considered reported microbiological data), as their prevention and control are important potential indicators of program success.

Overall, there was a paucity of literature on other, more specific settings and interventions, resulting in limited conclusions. Just 5.6% of studies were focused on perioperative prophylaxis, 16.8% on EDs, 37.4% on outpatient settings, and 6.5% on parental education activities. It is notable that results from the Weddle et al. study based on education intervention for prescribers in the ED [145] showing a 2% decrease in inappropriate antimicrobial prescribing were consistent with results from a study in the USA based on an adult population, which showed increased consistency of therapy choice from 44.8 to 83% [159]. ASPs implemented in outpatient settings, mainly involving audit and feedback and education, also seemed effective in reducing antimicrobial prescriptions.

The primary limitation of our study is that only three databases were searched, and not all pediatric stewardship studies may have been identified. In addition, available search indices and methods were limited, as unpublished, unreported data and case reports were not included. On the other hand, document such as non peer-reviewed manuscript or report are not assessed for accuracy or validity of the research methodology leaving uncertainties about their quality. Finally, no MeSH term was provided for antimicrobial stewardship, a wide search-term strategy was used to ensure the retrieval of all studies with an intervention on antimicrobial use, even if the intervention was not explicitly defined as antimicrobial stewardship.

Future research – conclusion

Pediatric ASPs have a significant impact on antimicrobial use, healthcare costs, and antimicrobial resistance in both inpatient and outpatient settings. Because of this significant impact, pediatric ASPs are spreading rapidly in the USA. Their implementation in Europe is still limited, possibly due to the fact that guidelines published so far (IDSA/SHEA) are designed for the USA healthcare system and easily adopted in this setting, while the diversity of healthcare systems throughout Europe and Asia implies a wide range of approaches to the same problem. Secondly, across Europe we found a high variability of funding opportunities and availability of specialists with advance training in pediatrics, resources more consistently and easily accessible in the USA.

Further efforts in developing pediatric ASPs are urgently needed, particularly in order to improve the collection of surveillance data regarding antimicrobials use and antimicrobial resistance in pediatric populations. More coordination, harmonization, and sharing of information will lead to a more precise effects on healthcare systems, and, as a result, on patient health as well. This is especially important for pediatric patients, as lack of data represents a greater challenge for pediatricians in their daily practice compared with physicians treating adult patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13756-019-0659-3.

Additional file 1. Search strategy.

Additional file 2. ASPs description according to author, publication year, study design, country, study period, setting, type of intervention, and main results (2007-2018).

Abbreviations

ASP: Antimicrobial Stewardship Program; CAP: Community Acquired Pneumonia; CDS: Computer Decision Support; CP: Clinical Pathway; DDD: Defined Daily Dose; DOT: Days Of Therapy; ED: Emergency Department; EOS: Early Onset Sepsis; ESBL: Extended Spectrum Beta-Lactamase; GAS: Group A Streptococcus; HAI: Hospital Acquired Infection; HSCT: Hematopoietic Stem Cell Transplant; IDSA: Infectious Diseases Society of America; LOT: Length of Therapy; NICU: Neonatal Intensive Care Unit; PCT: Procalcitonin; PICU: Pediatric Intensive Care Unit; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RANIN-KIDS : Reducing Antimicrobial use and Nosocomial INfections in KIDS: A European Network; RCT: Randomized Clinical Trials; RR: Relative Risk

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Authors' contributions

DD conceived the presented idea. EB and MD conduct the assessments of the titles, abstracts, and full texts independently. DD, EB and MD discussed study selection and study details and decided with studies were to be included in the review. DD and EB performed the numerical calculations and wrote the manuscript with input from all authors. RL and MS aided in interpreting the results and revised the manuscript. CG and TZ revised the manuscript.

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Availability of data and materials
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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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