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Systematic Review

The impact of Antimicrobial Stewardship Programmes in paediatric emergency departments and primary care: a systematic review

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Abstract

Background: Antibiotics remain the most prescribed medicine in children worldwide, but half of the prescriptions are unnecessary or inappropriate, leading to an increase in antibiotic resistance. This study aims to systemically review the effects of different Antimicrobial Stewardship Programmes (ASPs) on reducing the rates of both antibiotic prescriptions and changes in antimicrobial resistance, and on the economic impact in paediatric emergency departments (PED) and primary care settings.

Materials and methods: Embase, MEDLINE, and Cochrane Library were systematically searched, combining Medical Subject Heading and free-text terms for 'children' and 'antimicrobial' and 'stewardship'. The search strategy involved restrictions on dates (from 1 January 2007 to 30 December 2020) but not on language. Randomized controlled trials, controlled and non-controlled before and after studies, controlled and non-controlled interrupted time series, and cohort studies were included for review. The review protocol was registered at the PROSPERO International Prospective Register of Systematic Reviews: Registration Number CRD42021270630.

Results: Of the 47,158 articles that remained after removing duplicates, 59 were eligible for inclusion. Most of the studies were published after 2015 (37/59, 62.7%) and in high-income countries (51/59, 86.4%). Almost half of the studies described the implementation of an ASP in the primary care setting (28/59, 47.5%), while 15 manuscripts described the implementation of ASPs in EDs (15/59, 25.4%). More than half of the studies (43/59, 72.9%) described the implementation of multiple interventions, whereas few studies considered the implementation of a single intervention. Antibiotic prescriptions and compliance with guidelines were the most frequent outcomes (47/59, 79.7% and 20/59, 33.9%, respectively). Most of the articles reported an improvement in these outcomes after implementing an ASP. Meanwhile, only very few studies focused on health care costs (6/59, 10.2%) and antimicrobial resistance (3/59 5.1%).

Conclusion: The implementation of ASPs has been proven to be feasible and valuable, even in challenging settings such as Emergency Departments and Primary care.

Keywords: antibiotics, antimicrobial resistante, antimicrobial Stewardship programs, pediatric emergency department

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Background

Antibiotics are the most prescribed medicines in children worldwide, especially in outpatient settings.[1,2]

In the United States, 41% of all outpatient prescriptions were written by family practice doctors, paediatricians, and internal medicine physicians, as reported by Zetts *et al.* in their review. Of these,

at least 30% were considered unnecessary, with the majority prescribed for patients with acute respiratory tract infections.[3]

Data from the United States reported that emergency departments (EDs) receive around 30 million paediatric visits annually, with about 7 million associated antibiotic prescriptions; half of these are unnecessary or inappropriate.[4]

A cross-sectional observational study in 28 European EDs reported that 19–64% of children receive antibiotics inappropriately, especially broad-spectrum ones.[5] Antibiotic overprescribing and misuse has led to an increase in antibiotic resistance rates. Indeed, although resistance can occur naturally, antibiotic overuse plays a key role in selecting multi-drug-resistant organisms.[6]

The concept of Antimicrobial Stewardship Programmes (ASPs) was formally introduced in 2007 by the Infectious Disease Society of America (IDSA).[7] ASP is defined as a set of coordinated interventions designed to improve antimicrobial use in selecting the appropriate agent, dose, route of administration, and therapy duration without compromising patient outcomes.

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.

However, these standard stewardship approaches recommended for the hospital setting are challenging to implement in the ED or primary care settings.

Significant challenges for the implementation of ASP in primary care settings consist in a lack of funding resources to support a programme; identifying a clinical leader who has the time and interest to commit; engaging outpatient prescribers in a quality improvement initiative; obtaining data to identify high impact targets, tracking process improvements; and sustaining these improvements over time.[8]

Paediatric EDs (PEDs) are uniquely positioned at the interface of inpatient and outpatient settings and remain a hybrid in which elements of both inpatient and outpatient stewardships are generally merged. Indeed, PED physicians could influence prescribing trends in patients discharged to home and those admitted to the ward.

As reported by Mistry *et al.*, reducing inappropriate antibiotic use in PEDs is not easy because of unique operational, provider-level, and system-level barriers native to paediatric, general, and community ED environments. Challenges in antibiotic prescribing in this setting include high patient and practitioner turnover rates and rapid decision-making. Furthermore, this makes the development of ASP interventions, like prospective audits and feedback or formulary restriction, quite difficult.[9]

However, APSs in the outpatient settings are clearly necessary. In 2019, a survey on National Paediatric Antibiotic Stewardship Programmes, Networks and Guidelines was conducted in 23 European Countries. This survey reports a fragmented implementation of Paediatric Antibiotic Stewardship Programmes (PASPs) in Europe, a lack of established PASP competencies, an almost complete lack of national PASP networks, and an absence of dedicated funding to support the implementation of PASPs at a national level.[10]

Given the high rates of antimicrobial resistance documented in Europe, developing a robust and committed PASP strategy has become critical. In order to identify the best available strategies, we systematically reviewed published studies that evaluated the different types of ASPs by assessing their impact on three aspects:

- The antibiotics prescription rate, especially of broad-spectrum antibiotics.
- The antimicrobials resistance rate.
- The health care costs in the PED and primary care settings.

Materials and methods

Search strategies and study design

This systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11] A systematic search was conducted in Embase, MEDLINE, and Cochrane Library database. The search strategy combined Medical Subject Heading (MeSH)

and free-text terms for 'children' and 'antimicrobial' and 'stewardship'. To identify all possible interventions recognized as stewardship, we expanded the search strategy to also include specific intervention MeSH terms.

The search strategy involved restrictions on dates (from 1 January 2007 to 30 December 2020) but not on language. Additional studies were identified through reference checking. The full search strategy is provided in the Supplementary Material.

The review protocol was registered at the PROSPERO International Prospective Register of Systematic Reviews: Registration Number CRD42021270630.

Inclusion and exclusion criteria

Studies were eligible for full-text review if they included patients younger than 18 years of age with suspected infections attending a PED or primary care where an ASP was implemented.

Randomized controlled trials (RCTs), controlled and uncontrolled before and after studies, interrupted time series, and cohort studies were included for review.

Studies about children admitted to a paediatric hospital ward where an ASP was implemented were excluded.

Review articles, case series, notes and letters, conference abstracts, opinion articles, and studies from which it was not possible to extract paediatric data were also excluded. Studies published before 2007 were excluded because the concept of ASP was formally introduced that year. Studies about ASP on malaria, HIV, viral, and fungal treatment were also excluded.

Studies selection

Identified references were downloaded into Rayyan software for further assessment and handling. In line with the PRISMA guidelines for systematic reviews, titles, and abstracts, identified through an electronic database, were independently screened by two investigators (GB and SR), and any references which did not meet the inclusion criteria were excluded. For all remaining references, full-text copies were obtained and were examined in detail to determine whether they met all the inclusion criteria for the review. Discussion with a third reviewer (DD) resolved any disagreement regarding selection of studies.

Data collection

Data were extracted using a standardized data collection form which summarized information about the study characteristics (authors, year of publication, study design, study location, and country), the patient characteristics, the type of ASP, and the main results with accuracy measures (health outcomes – e.g. rate of prescription, days of therapy – and economic outcomes).

Studies were grouped by setting (PED and primary care) and intervention type.

Each country's income level was defined according to the World Bank List of economies published in July 2021.[12]

Quality assessment (risk of bias)

The quality of each eligible study was evaluated depending on the study design. Clinical trials were assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2),[13] while non-randomized studies were assessed using the Risk of Bias in Non-randomized studies – of Interventions (ROBINS-I) assessment tool.[14] The overall risk of bias judgements of each study did not affect the inclusion in this review. It was not possible to conduct a meta-analysis as the disparity in types of interventions and study setting prevented the combining of data from different studies.

Results

After removing duplicates, a total of 47,158 articles remained for the screening. Of these, 59 were eligible for inclusion in this review. The selection process is summarized in Figure 1.

Authors, title, publication year, study design, country, study period, setting, type of ASP, and quality assessment are summarized in Table 1.

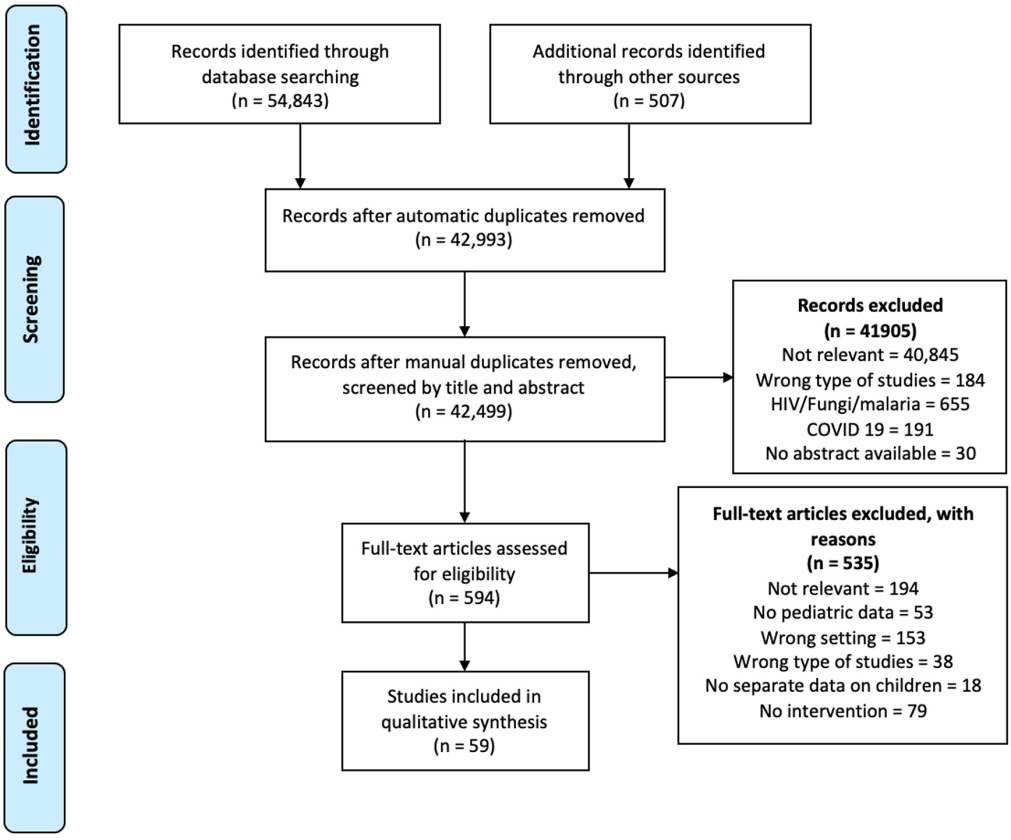

Figure 1. Flowchart of the study selection process (PRISMA).

Table 1. Characteristic of studies included in the review.

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Aronson *et al.*[15]	2015	Association of Clinical Practice Guidelines with Emergency Department Management of Febrile Infants ⩽56 Days	OR, cross-sectional	1 January 2013 to 31 December 2013	USA	ED	+	•	Local clinical practice guideline	Moderate
Hernani *et al.*[16]	2010	Evolution of the antibiotics prescription in a pediatric emergency service	BA	January 2008 December 2008 and January 2009	ESP	ED		•	Educational talks	Serious
Weddle *et al.*[17]	2013	Impact of an Educational Intervention to Improve Antibiotic Prescribing for Nurse Practitioners in a Pediatric Urgent Care Center	BA	NA	USA	ED	+	•	Educational sessions	Serious
Baer *et al.*[18]	2013	Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents (ProPAED): A Randomized Controlled Trial	RCT	1 January 2009 to 28 February 2010	CHE	ED	+	•	Laboratory PCT	Low

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
van de Maat *et al.*[19]	2020	Evaluation of a clinical decision rule to guide antibiotic prescription in children with suspected lower respiratory tract infection in The Netherlands: A stepped-wedge cluster randomised trial	Stepped-wedge cluster RT	1 January 2016 to 30 September 2018	NLD	ED	+	•	Validated clinical prediction model (Feverkidstool)	Some concerns
Angoulvant *et al.*[20]	2014	Impact of unlabeled French antibiotic guidelines on antibiotic prescriptions for acute respiratory tract infections in 7 Pediatric Emergency Departments, 2009-2012	BA	1 November 2009 to 31 October 2011 1 November 2011 to 31 October 2012	FRA	ED	+	••••	Local protocols for antibiotic use with ARTI, implementation of guidelines with scientific discussion, teaching lessons twice per year, pocket guidelines	Serious
Angoulvant *et al.*[21]	2012	Impact of implementing French antibiotic guidelines for acute respiratory-tract infections in a paediatric emergency department, 2005-2009	BA	November 1, 2005 to October 31, 2006 November 1, 2006 to October 31, 2009	FRA	ED		••	Local guideline based on French guidelines on antibiotic prescriptions for ARTI; teaching sessions twice a year; pocket cards	Serious
Crook *et al.*[22]	2020	Impact of clinical guidance and rapid molecular pathogen detection on evaluation and outcomes of febrile or hypothermic infants	BA	January 2011 to December 2014, January 2015 to April 2018, May 2018 to June 2019	USA	ED		••	Clinical guideline during period 2 associated with Rapid testing during period 3	Moderate
Cunney *et al.*[23]	2019	'Start smart': using front-line ownership to improve the quality of empiric antibiotic prescribing in a paediatric hospital	OP	December 2014 to December 2017	IRA	ED		••••	Plan, Do, Study, Act Weekly audit with feedback Front-line ownership Spot quiz App and laminated card Poster	No information
Dona *et al.*[24]	2018	The Impact of Clinical Pathways on Antibiotic Prescribing for Acute Otitis Media and Pharyngitis in the Emergency Department	BA	15 October 2014 to 15 April 2015, 15 October 2015 to 15 April 2016	ITA	ED		••	CPs were delivered as laminated pocket cards and 3 educational lectures were presented to physicians and residents on how to implement these tools in practice	Moderate
Geurts *et al.*[25]	2014	Impact analysis of an evidence-based guideline on diagnosis of urinary tract infection in infants and young children with unexplained fever	BA	January 2008 to January 2009, April 2010 to April 2011	NLD	ED		••	implementation of guideline several group lectures in medical staff meetings, laminated pamphlets of the guideline were available at the ED written instructions were sent three times to all health care professionals working at the ED	Moderate
Malmgren *et al.*[26]	2019	Education, decision support, feedback and a minor reward: a novel antimicrobial Stewardship intervention in a Swedish paediatric emergency setting	BA	October 2015 to January 2017, February 2017 to January 2018	SWE	ED		••	Education, decision support, email-based feedback and a physician-directed reward	Moderate

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Mercurio *et al.*[27]	2020	Clinical Practice Guideline Reduces Evaluation and Treatment for Febrile Infants 0 to 56 Days of Age	BA	1 April 2015 to 1 April 2016, 1 April 2017 to 1 April 2018	USA	ED		••	Education, training, and adoption of clinical practice guideline	Moderate
Powell *et al.*[28]	2015	Appropriate Use of Vancomycin in a Pediatric Emergency Department Through the Use of a Standardized Electronic Guideline	BA	January 2009 to May 2012	USA	ED		•••	Implementation of a standardized treatment guideline + antibiotic order template + individual chart audits	Serious
Walters *et al.*[29]	2019	An Ambulatory Antimicrobial Stewardship Initiative to Improve Diagnosis and Treatment of Urinary Tract Infections in Children	BA	January 2017 to December 2018	USA	ED		•••	PDSA (multiple Plan-Do-Study-Act) cycles	Serious
McDaniel *et al.*[30]	2018	A Multisite Intervention for Pediatric Community-acquired Pneumonia in Community Settings	BA	January 2015 to December 2015, March 2016 to February 2017	USA	ED + inpatient	+	••	Implementation of the CAP pathway occurred between January and February2016: (1) in-person presentation and distribution of electronic copies, (2) display of the printed pathways in provider work areas, (3) an in-person presentation of the pathway to community hospital paediatric hospitalists at site-specific staff meetings. An additional educational session was conducted with both EM providers and paediatric hospitalists at all three sites at the beginning of respiratory season in October 2016.	Moderate
Ambroggio *et al.*[31]	2013	Quality Improvement Methods Increase Appropriate Antibiotic Prescribing for Childhood Pneumonia	BA	May 2011 to July 2012	USA	ED + inpatient		•••	Multiple plan-to-study-act: (1) guideline seminar, grand rounds, antibiotic recommendations in the medical staff update, (2) charge nurse flag cards, (3) index card with appropriate first-line antibiotic information for ED physicians and inpatient residents and resident report, (4) H&P template and order set in EMR and link to PIDS/IDSA guideline	Serious
Dona *et al.*[32]	2018	Effects of clinical pathway implementation on antibiotic prescriptions for pediatric community-acquired pneumonia	BA	October 2014 to April 2015, October 2015 to April 2016	ITA	ED + inpatient		••	Clinical pathway for CAP and educational sessions	Moderate

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Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Rutman *et al.*[33]	2017	A Comprehensive Approach to Pediatric Pneumonia: Relationship Between Standardization, Antimicrobial Stewardship, Clinical Testing, and Cost	BA	1 August 2011 to 31 August 2013	USA	ED + inpatient		•	Clinical pathway for CAP	Moderate
Yeo *et al.*[34]	2020	Knowledge translation in Western Australia tertiary paediatric emergency department: An audit cycle of effectiveness of guideline dissemination on bronchiolitis management	BA	1 July to 31 August 2015, 1 July to 31 August 2017	AUS	ED + inpatient		••	Update local bronchiolitis guideline, education, and email	Serious
Doyon *et al.*[35]	2009	Quantitative evaluation of a clinical intervention aimed at changing prescriber behaviour in response to new guidelines	BA	October 2004 to March 2005, October 2005 to 14 January 2006, 15 January 2006 to March 2006	CAN	ED + inpatient		•	Consultation by email, small group educational sessions, implementation of guideline, pre-printed prescription sheet, educational session	Moderate
Poole *et al.*[36]	2020	Improving Antibiotic Prescribing for Children With Urinary Tract Infection in Emergency and Urgent Care Settings	BA	1 January 2009 to 31 May 2010, 1 June 2010 to 31 December 2014	USA	ED + primary care	+	••	Clinical pathway for uncomplicated UTI. The pathway was implemented through the introduction of a decision-making algorithm and an electronic order set in June 2010 and again in December 2011. Information on the pathway was also included in a newsletter distributed to providers at the start of the intervention. Reminders to utilize the pathway were provided quarterly *via* electronic mail	Moderate
Shaw *et al.*[37]	2020	Improving antibiotic prescribing in the emergency department for uncomplicated community-acquired pneumonia	BA	1 January 2015 to December 2015, December 2015 to 28 February 2017 implementation in December	USA	ED + primary care	+	•	New clinical practice guideline (CPG) was implemented and knowledge of implementation was disseminated *via* email	Moderate
Aoybamroong *et al.*[38]	2019	Impact of an Antibiotic Stewardship Program on Antibiotic Prescription for Acute Respiratory Tract Infections in Children: A Prospective Before-After Study	BA	1 May 2016 to 31 October 2016, 1 May 2017 to 31 October 2017	THA	ED + primary care		••	Education for paediatric faculty staff, residents, and fellows *via* providing guidelines of antibiotic smart use in respiratory tract infections; the guidelines were sent to all relevant physicians *via* email or LINE instant messaging every 2 months. Poster displaying the guidelines were posted in every examination room and active monitoring was conducted by informing physicians of the antibiotic use rate every 2 months *via* email or line	Moderate

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Di Pietro *et al.*[39]	2017	Monitoring adherence to guidelines of antibiotic use in pediatric pneumonia: the MAREA study	BA	February 2013 to December 2013 February 2014 to December 2014	ITA	ED + primary care	+	•	1-day educational intervention and concise written materials	Moderate
Llamas del Castillo *et al.*[40]	2010	Strategy for improving the use of antibiotics in paediatrics	BA	January 2008 to April 2008, January 2009 to April 2009	ESP	ED + primary care		••	Guide on empirical antibiotic therapy was distributed to all paediatricians and emergency services along with training sessions	No information
March-Lopez *et al.*[41]	2020	Impact of a Multifaceted Antimicrobial Stewardship Intervention in a Primary Health Care Area: A Quasi-Experimental Study	BA	January to December 2016, January to December 2017, January to December 2018	ESP	ED + primary care	+	••••	Face-to-face sessions (education) and poster Point of care test for GAS pharyngitis every 3 months, updated report containing qualitative and quantitative indicators on antibiotics consumption. Set of local guidelines on antibiotic usage and preferred regimens for adult and paediatric patients, interactive workshop, workshop material by email	Moderate
Saha *et al.*[42]	2017	Urine Culture Follow-up and Antimicrobial Stewardship in a Pediatric Urgent Care Network	BA	July 2013 to December 2015	USA	ED + primary care	+	•	Standard protocol for urine culture follow-up and discontinuation of unnecessary antibiotics	Serious
Gagliotti *et al.*[43]	2015	A regionwide intervention to promote appropriate antibiotic use in children reversed trends in erythromycin resistance to Streptococcus pyogenes	BA	2007 to 2013	ITA	Primary care	+	•	Guideline for the management of acute pharyngitis	No information
Trinh *et al.*[44]	2020	Association between National Treatment Guidelines for Upper Respiratory Tract Infections and Outpatient Pediatric Antibiotic Use in France: An Interrupted Time–Series Analysis	ITS	January 2009 to December 2017	FRA	Primary care	+	•	Update clinical practice guidelines for managing upper respiratory tract infections (announced on websites and communicated through several oral presentations during conferences and workshops both before and after its official release)	Moderate
Lemiengre *et al.*[45]	2018	Point-of-care CRP matters: normal CRP levels reduce immediate antibiotic prescribing for acutely ill children in primary care: a cluster randomized controlled trial	RCT cluster	15 February 2013 to 28 February 2014	BEL	Primary care		•	Point of care (POC) C-reactive protein (CRP) test	Some concerns
Torres *et al.*[46]	2014	Impact Assessment of a Decision Rule for Using Antibiotics in Pneumonia: A Randomized Trial	RCT	April 2010 to March 2011	ARG	Primary care		•	Prediction rule bacterial pneumonia score	Some concerns

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Chowdhury *et al.*[47]	2018	Effectiveness of an educational intervention to improve antibiotic dispensing practices for acute respiratory illness among drug sellers in pharmacies, a pilot study in Bangladesh	BA	June 2012 to December 2013	BGD	Primary care	+	••	Educational intervention to drug sellers, laminated poster with ARI management algorithm to hang in pharmacies	Serious
Bourgeois *et al.*[48]	2010	Impact of a Computerized Template on Antibiotic Prescribing for Acute Respiratory Infections in Children and Adolescents	RT	October 2006 to April 2007	USA	Primary care	+	•	Acute respiratory interactive template (ARI-IT) within an electronic health record (EHR) to manage paediatric ARIs	High risk
Hersh *et al.*[49]	2018	Impact of Antimicrobial Stewardship for Pediatric Outpatient Parenteral Antibiotic Therapy	BA	May 2013 to April 2014, May 2014 to May 2015	USA	Primary care		•	(1) stewardship team review/ recommendations included input regarding discharge with OPAT prescription, (2) the peripherally inserted central catheter team paged the stewardship team before line placement if the designated purpose was OPAT, (3) care coordinators paged the stewardship team when arranging home care for OPAT, (4) discharge planning software was modified to generate an electronic alert *via* text message to the stewardship team when discharge medications included OPAT	No information
Noorani *et al.*[50]	2011	Use of a pneumonia management tool to manage children with pneumonia at the first level health care facilities	OP	October 2000 to April 2001	PAK	Primary care	+	••	Application of ARI SCM guidelines at the FLHC facilities by using a simplified Pneumonia Management Tool (PMT); monthly meetings were held at the district level with health workers, supervisors and paediatricians to interact and share learning, experiences and qualitative information	Serious
Al-Tawfiq *et al.*[51]	2017	A multifaceted approach to decrease inappropriate antibiotic use in a pediatric outpatient clinic	OP	December 2012 to December 2013	SAU	Primary care		••	Educational grand round, academic detailing and prospective audit and feedback and peer comparison	Serious

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Clegg *et al.*[52]	2019	Impact of Education and Peer Comparison on Antibiotic Prescribing for Pediatric Respiratory Tract Infections	BA	January to June 2014, July 2014 to December 2017	USA	Primary care	+	●●●●	Educational materials, clinical guidelines in June 2014. For the collaborative clinics, a 1-h, in-person educational visit was held with each clinic's lead clinician and clinic administrator to discuss the clinical guidelines, measure definitions, baseline performance scores and improvement methods in September 2014. Performance feedback since September 2014. Non-productive compensation, tip sheet emailed monthly for all clinics with clinic-specific feedback	Moderate
Di Mario *et al.*[53]	2018	Observational pre–post study showed that a quality improvement project reduced paediatric antibiotic prescribing rates in primary care	BA	2005 to 2007, 2007 to 2016	ITA	Primary care	+	●●●●	Developing guidelines and updates, disseminating evidence, audits, and feedback, public information campaigns, engaging health managers, and performance incentives	No information
Diaz *et al.*[54]	2020	Impact of a Personalized Audit and Feedback Intervention on Antibiotic Prescribing Practices for Outpatient Pediatric Community-Acquired Pneumonia	RCT	August 2016 to February 2017	USA	Primary care	+	●●	Educational webinar personalized audit and feedback monthly only for intervention group	High risk
Fernandez *et al.*[55]	2019	An initiative to reduce the use of unnecessary medication in infants with bronchiolitis in primary care	BA	1 October 2015 to 31 March 2016, 1 October 2016 to 31 March 2017	ESP	Primary care	+	●●	Distribution through the mail system of the protocol recommended for management of bronchiolitis, distribution in poster format through all the clinics, interactive informational sessions	Serious
Fiks *et al.*[56]	2015	Adoption of Electronic Medical Record-Based Decision Support for Otitis Media in Children	RCT	February 2009 to August 2010	USA	Primary care	+	●●	CDS and performance feedback	High risk
Finkelstein *et al.*[57]	2008	Impact of a 16-Community Trial to Promote Judicious Antibiotic Use in Massachusetts	RCT	1 September 2009 to 31 March 2004	USA	Primary care	+	●●●●	Guideline dissemination, small group education, frequent updates, and educational materials and prescribing feedback; parents received educational materials by mail and in primary-care practices, pharmacies, and child care settings	Some concerns

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Forrest *et al.*[58]	2013	Improving Adherence to Otitis Media Guidelines With Clinical Decision Support and Physician Feedback	RCT	December 2007 to September 2010	USA	Primary care	+	••	CDS and performance feedback	Some concerns
Francis *et al.*[59]	2009	Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial	RCT	October 2006 to April 2008	GBR	Primary care	+	••••	Booklet for clinician and parents	Some concerns
Gerber *et al.*[60]	2013	Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians A randomized trial	RCT	October 2008 to June 2011	USA	Primary care	+	••	One 1-h on-site clinician education session followed by 1 year of personalized, quarterly audit and feedback of prescribing for bacterial and viral ARTIs or usual practice	High risk
Gulliford *et al.*[61]	2019	Effectiveness and safety of electronically delivered prescribing feedback and decision support on antibiotic use for respiratory illness in primary care: REDUCE cluster randomised trial	RCT	11 November 2015 to 9 August 2016 follow-up on 9 August 2017	GBR	Primary care	+	••	AMS intervention comprised a brief training webinar, automated monthly feedback of antibiotic prescribing and electronic decision support tools to inform appropriate prescribing over 12 months.	Some concerns
Hurlimann *et al.*[62]	2015	Improvement of antibiotic prescription in outpatient care: a cluster-randomized intervention study using a sentinel surveillance network of physicians	RCT	1 January 2011 to 31 December 2012	CHE	Primary care	+	••	Providing guidelines on treatment of RTIs and UTIs coupled with sustained regular feedback on individual antibiotic prescription behaviour during 2 years	Some concerns
Huynh *et al.*[63]	2019	Impact of expanding a paediatric OPAT programme with an antimicrobial stewardship intervention	OP (prospective longitudinal study)	1 August 2021 to 31 July 2013, 1 August 2013 to 31 July 2014	AUS	Primary care		••	OPAT-specific guidelines Active review of OPAT prescription and input by paediatric infectious diseases	Moderate
Jindrák *et al.*[64]	2008	Improvements in antibiotic prescribing by community paediatricians in the Czech republic	BA	1998 to 2003	CZE	Primary care	+	••	Feedback based on the results of the repeats surveys. Dissemination of printed survey results to individual doctors. Final conference and local seminars	No information
Mainous *et al.*[65]	2013	Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental trial	BA	October 2009 to December 2009, January 2010 to March 2011	USA	Primary care	+	••	Quarterly HER-based audit and feedback, "best practice" dissemination during meetings of practice representatives and practice site visits for academic detailing, performance review and CDSS training	No information

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Norton *et al.*[66]	2018	Improving Guideline-Based Streptococcal Pharyngitis Testing: A Quality Improvement Initiative	BA	October 2013 to September 2014, 1 October 2014 to 31 October 2016	USA	Primary care		●●●	Face-to-face meeting, Provider education, modification of existing office procedure, email update, communication strategies, and patient and family education	Serious
Osterholt *et al.*[67]	2009	Improving pneumonia case-management in Benin: a randomized trial of a multi-faceted intervention to support health worker adherence to Integrated Management of Childhood Illness guidelines	RCT	1999, 2001, 2002, 2004	BEN	Primary care	+	●●●	Training plus either study supports (job aids, non-financial incentives, and supervision of workers and supervisors) or "usual" supports	High risk
Papaevangelou *et al.*[68]	2012	Decrease of Antibiotic Consumption in Children with Upper Respiratory Tract Infections after Implementation of an Intervention Program in Cyprus	BA	November 2005 to March 2006, November 2007 to March 2008	CYP	Primary care	+	●●	1 day workshop on antibiotic misuse in children with URTIs, lectures on antibiotics use and therapeutic algorithms To educate parents: invitations to participate in educational lectures, instructive pamphlets at paediatric offices and emergency rooms, educational video in waiting rooms and a 30-min discussion was broadcasted through the radio and an article was published in the local newspaper	No information
Regev-Yochay *et al.*[69]	2011	Reduction in Antibiotic Use Following a Cluster Randomized Controlled Multifaceted Intervention: The Israeli Judicious Antibiotic Prescription Study	RCT	April 2000 to March 2006	ISR	Primary care	+	●●●	Physicians focus group meetings, workshops, seminars, practice campaigns, evidence-based guidelines, pamphlets, posters, colouring booklets	Some concerns
Stille *et al.*[70]	2008	Physician Responses to a Community-Level Trial Promoting Judicious Antibiotic Use	RCT	2000 to 2004	USA	Primary care	+	●●●	Locally endorsed guidelines, group educational sessions and biweekly newsletters	Some concerns
Wei *et al.*[71]	2017	Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care	RCT	July 2015 to March 2016	CHN	Primary care + inpatient	+	●●●●	Evidence-based prescribing guideline, training, and monthly prescribing peer-review meetings for doctors, brief educational for caregiver during consultations and an educational waiting room video for caregivers	Some concerns

(Continued)

Table 1. (Continued)

Author	Publication year	Title	Study design	Study period	Country	Setting	MC	Type of ASP		Quality assessment
Wei *et al.*[72]	2019	Long-term outcomes of an educational intervention to reduce antibiotic prescribing for childhood upper respiratory tract infections in rural China: Follow-up of a cluster-randomised controlled trial	RCT	July 2015 to March 2016, January 2016 to March 2017	CHN	Primary care + inpatient	+	••••	Evidence-based prescribing guideline, training and monthly prescribing peer-review meetings for doctors, brief educational for caregiver during consultations and an educational waiting room video for caregivers only for the first 6 months	Some concerns
Zhang *et al.*[73]	2018	Cost-effectiveness analysis of a multi-dimensional intervention to reduce inappropriate antibiotic prescribing for children with upper respiratory tract infections in China	RCT	July 2015 to March 2016	CHN	Primary care + inpatient	+	••••	Concise evidence-based clinical guidelines on URTI management, monthly peer-review meetings assessing providers' antibiotic prescription rates. Patients and caregivers received information on appropriate antibiotic use, both verbally and *via* an educational leaflet. A video with key messages on appropriate use of antibiotics was played daily in the waiting rooms and public areas of the town-ship hospital	Some concerns

ASP, Antimicrobial Stewardship Programme; AMS, Antimicrobial Stewardship Programme; CAP, community-acquired pneumonia; CDS, clinical decision support; CG, clinical guideline; ED, emergency department; Edu, Education; EMR, Electronic Medical Record; FLHC, First level health care; GAS, Group A Streptococcal; IDSA, Infectious Disease Society of America; ITS, Interrupted Time Series; MC, multicenter; OP, observational Prospective; OPAT, Outpatient Parenteral Antibiotic Therapy; PCT, Procalcitonin; PDSA, Plan-Do-Study-Act; PIDS, Paediatric Infectious Diseases Society; RCT, randomized controlled trial; RT, Randomized Trial; SCM, Standard Care Management; UTI, urinary tract infection; URTI, upper respiratory tract infections.
Intervention legend: • = Guidelines, •=Audit and feedback, • = Physicians education, • = Parents education, • = Pre-authorization, • = CDS tool, • = CP, • = Other ASP intervention

Most of these studies (51/59, 86.4%) were conducted in high-income countries. Twenty-three articles (39.0%) described ASPs implemented in Europe (5 in Italy,[24,32,39,43,53] 4 in Spain,[16,40,41,55] 3 in France,[20,21,44] 2 in the Netherlands,[19,25] United Kingdom,[59,61] and Switzerland[18,62] respectively, one each in Sweden,[26] Belgium,[45] Cyprus,[68] Ireland[23] and the Czech Republic[64]); 24 studies were set in North America (40.7%, 23 in the United States,[15,17,22,27–31,33,36,37,42,48,49,52,54,56–58,60,65,66,70] 1 in Canada,[35] 8 studies (13.6%) were set in Asia [3 in China,[71–73] 1 in Saudi Arabia,[51] 1 in Israel,[69] 1 in Pakistan,[50] 1 in Thailand,[38] 1 in Bangladesh[47]), and two studies (3.4%) in Australia.[34,63] Only one study was conducted in South America (Argentina[46]) and one in Africa (Benin[67]). Figure 2 shows the geographical distribution of articles.

Thirty-seven studies were published between 2015 and 2020 [37/59, 62.7%;[15,19,22–24,26–30,32–34,36–39,41–45,47,49,51–56,61–63,66,71–73] 15/37 (40.5%) from the United States, 14/37 (37.8%) from Europe, 6/37 (16.2%) from Asia, 2/37 (5.4%) from Australia], four times more than during the 2007–2010 period [9/59, 15.2% in total,[16,35,40,48,57,59,64,67,70] 4/9 (44.4%) from Europe, 3 (33.3%) from United States, 1 (11.1%) from Canada, 1 (11.1%) from Benin].

Thirty-six (36/59, 61.0%) were multicentre studies: 15/36 (41.7%) were set in North America,[15,17,30,36,37,42,48,52,54,56–58,60,65,70] 14/36 (38.9%) in Europe,[9,18–20,41,43,44,53,55,59,61,62,64,68] 6/36 in Asia (16.6%)[47,50,69,71–73] and 1/6 (2.8%) in Africa.[67]

More than a half of the studies were before-and-after studies (34/59, 57.6%),[16,17,20–22,24–43,47,49,52,53,55,64–66,68] and more than a quarter of the total studies were randomized control studies (19/59, 32.2%).[18,19,45,46,48,54,58–62,67,69–73] The remaining were se studies [4 observational prospective

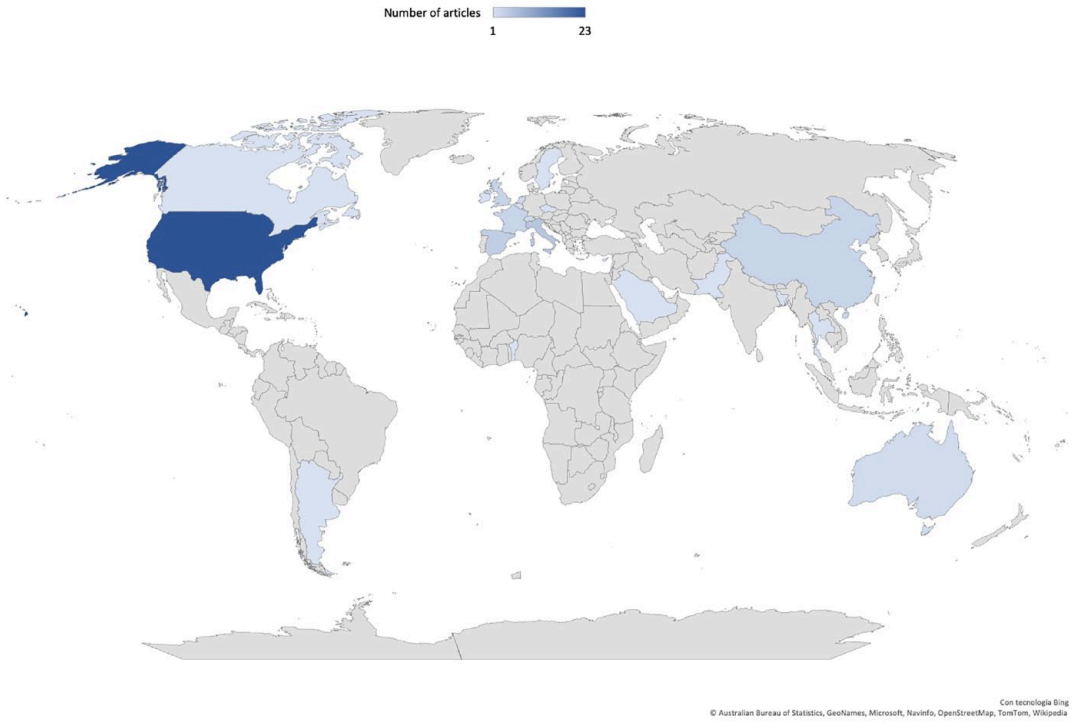

Figure 2. Geographical distribution of articles included in this review.

studies (6.8%),[23,50,51,63] as well as 1 retrospective study (1.7%),[15] and 1 was an interrupted time series study (1.7%)[44]].

ASPs setting and type of intervention

More than half of the studies (43/59, 72.9%) described the implementation of multiple interventions, like clinical pathways or clinical guidelines, combined with education or rapid test, or a combination of prescribers' or parents' education, clinical guideline, or clinical pathways, audit, and rapid test [Figure 3(a)].[20–32,34,36,38,40,41,47,50–73]

More than half of the studies included in this review (38/59, 64.4%) regarded the implementation of multiple interventions for managing respiratory tract infections, both upper and lower.[18–21,24,26,30–35,37–39,43,44,46–48,50–52,54–56,58,59,61,62,65–68,70–73] Of these, eleven articles regarded the implementation of intervention for community-acquired pneumonia (CAP),[30–33,35,37,39,46,50,54,67] two for acute otitis media (AOM),[56,58] two for pharyngitis,[43,66] two for both AOM and pharyngitis,[24,26] and two for bronchiolitis. The other articles considered, in general, upper and lower respiratory tract infections. Ten studies (10/59, 17.0%) regarded the implementation of interventions for the management of children with fever both in ED or primary care,[16,23,40,41,53,57,60,64,69,74] while three articles (3/59, 5.1%) considered specific interventions for febrile infants with less than 56 days of age.[15,22,27] Four studies (4/59, 6.8%) considered the implementation of intervention for the management of urinary tract infection (UTI),[25,29,36,42] and two articles are about parenteral antibiotic therapy in outpatients.[49,63] One article considered the implementation of educational interventions for both UTIs, skin and soft-tissue infections, and upper and lower respiratory tract infections.[17] All the specific syndromes targeted by each intervention are specified in the table in the Supplementary material.

Almost half of the studies described the implementation of an ASP in the primary care setting (28/59, 47.5%) [Figure 3(b)]. Ten of these studies were conducted in Europe (10/28, 35.7%),[43–45,53,55,59,61,62,64,68] 11 in the United States (11/28, 39.2%),[48,49,52,54,56–58,60,65,66,70] and the remaining seven studies in South America (1/28, 3.6%),[46]

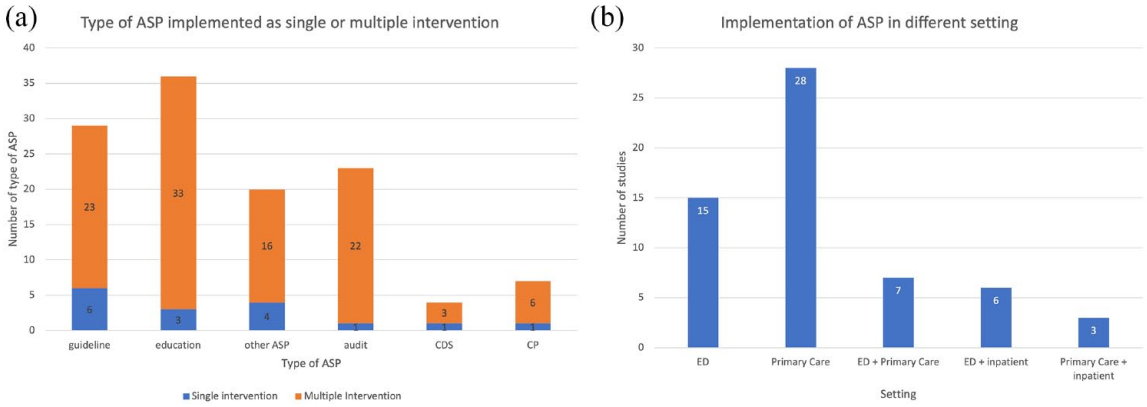

Figure 3. (a) Different type of ASP implemented as single intervention and multiple intervention and (b) number of studies for each different settings.
ASP, Antibiotic Stewardship Programme; CDS, clinical decision support; CP, clinical pathway; ED, emergency department.

Australia (1/28, 3.6%),[63] Africa (1/28, 3.6%),[67] and Asia (4/28, 14.3%).[47,50,51,69] Most of the ASP implemented were multiple interventions (22/28, 78.6%).[47,50–67,69,70,74] Single interventions were constituted by the implementation of clinical practice guidelines (2/28, 7.1%),[43,44] audit (1/28, 3.6%),[49] clinical decision support (CDS; 1/28, 3.6%)[48] and other ASP (2/28, 7.1%, rapid C-reactive protein test and prediction rule for bacteria pneumonia).[45,46]

Fifteen manuscripts described the implementation of ASPs in ED (15/59, 25.4%) and were conducted in the United States (6/15, 40.0%)[15,17,22,27–29] and Europe (9/15, 60.0%).[16,18–21,23–26] Among these, 10 were focused on multiple interventions like clinical practice guidelines or clinical pathways combined with education (10/15, 66.7%).[20–29] Single interventions implemented were educational interventions (2/15, 13.3%),[16,17] other types of ASP (2/15, 13.3%, rapid procalcitonin and validated clinical prediction model for pneumonia),[18,19] and clinical practice guidelines (1/15, 6.7%).[15]

The remaining 16 studies were conducted in multiple settings simultaneously (16/59, 27.1%), 7 both in the ED and primary care setting (7/16, 43.8%),[36–42] 6 both in the ED and inpatient setting (37.5%),[30–32,34,35,75] and 3 both in primary care and inpatient settings (18.8%).[71–73] Eleven of these studies described the implementation of multiple interventions like clinical pathways or clinical practice guidelines combined with education and sometimes audit (11/16, 68.8%).[30–32,34,36,38,40,41,71–73] Single interventions implemented were clinical practice guidelines (3/16, 18.8%),[35,37,42] educational sessions [1/16, 6.3%[39]], and clinical pathways [1/16, 6.3%[33]].

ASPs outcomes and types of intervention

The different outcomes considered in this review are reported in Figure 4, stratified by the successful or unsuccessful intervention [Figure 4(a)] as reported in each article and by the country's income level [Figure 4(b)].

Forty-seven studies reported changes in antibiotic prescriptions rate (47/59, 79.7%) as their main outcome. These studies were mainly conducted in Europe (20/47, 42.6%)[16,18–21,24,26,32,39–41,43–45,53,55,59,61,62,68] and North America [19/47, 40.4%, 18 in the United States,[15,17,22,27–31,33,36,37,42,48,49,57,60,65,70] 1 in Canada[35]]. Of the eight remaining studies, six were conducted in Asia (12.8%),[38,47,51,69,71,72] one in Australia (2.1%)[34] and one in South America (Argentina, 2.1%).[46] Thirty-one of these (31/47, 66.0%)[20–22,24,26–32,34,36,38,40,41,47,51,53,55,57,59–62,65,68–72] were studies focused on multiple interventions, above all on the implementation of clinical practice guidelines or clinical pathways combined with educational talks and sometimes audit. The remaining 16 studies (16/47, 34.0%) focused on the implementation of a single intervention (which differed as follows: six articles on clinical guidelines,[15,35,37,42–44] three on educational sessions,[16,17,39] one on audits,[49] one on clinical pathways,[33] one on CDS tools,[48] and four on other types of ASP, like clinical prediction models or rapid tests).[18,19,45,46]

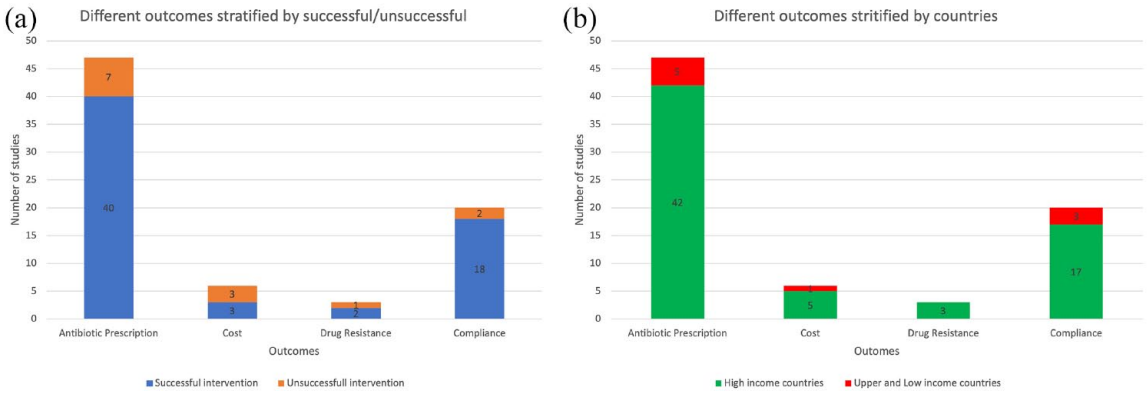

Figure 4. Different type of outcomes stratified by (a) the successful or unsuccessful of the intervention and (b) by the country's income level.

Forty articles (40/47, 85.1%)[15–17,20–22,24,26,27,29–33,35,36,38–49,51,53,55,57,59,60,65,68–72] described a statistically significant reduction of inappropriate prescribing that could regard both the unnecessary administration of antibiotics and the selection of the narrow-spectrum instead of the broad-spectrum ones. Regarding the prescription of broad-spectrum antibiotics, only 14 studies reported the variation in total antibiotics prescription rates and the difference between narrow-spectrum and broad-spectrum, usually identified as the second- and third-generation cephalosporins and macrolides.[20,21,24,32,36,39,40,44,48,53,60,65,69,72] Of these 14 studies, 13 reported a significant reduction in prescribing these antibiotics after the different interventions were analysed.[20,24,32,36,39,40,44,48,53,60,65,69,72] The remaining seven articles did not show any statistically significant change in antibiotic prescribing after implementing an ASP.[18,19,28,34,37,61,62]

Twenty articles (20/59, 33.9%) considered the main outcome of compliance to clinical guidelines or clinical pathways. More than half of these studies are conducted in North America [11/20, 55.0%, 10 in the United States,[27,29,30,37,52,54,56,58,60,66] 1 in Canada[35]], 5 in Europe (5/20, 25%),[23,25,26,40,41] and the remaining four in Asia (2/20, 10%),[38,50] Africa (1/20, 5%),[67] and Australia (1/20, 5%).[63] Of these studies, 18 articles described increased compliance among prescribers (18/20, 90%).[23,25–27,29,30,35,38,40,41,50,52,54,56,58,60,63,67] Most of these studies (18/20, 90.0%) focused on implementing clinical practice guidelines or clinical pathways alone or in combination with educational sessions or audit and feedback.[23,25–27,29,30,38,40,41,50,52,54,56,58,60,63,66,67] Some of these studies have also evaluated the sustainability of these interventions over time. Two of these studies reported using CDS tools in combination with audit and feedback.

Only six of the included studies (6/59, 10.2%) described the change in health care cost associated with the intervention; three were conducted in the United States (3/6, 50.0%),[15,30,33] two in Europe (2/6, 33.3%),[23,24] and 1 in Asia (1/6, 16.7%).[73] Three [3/6, 50.0%, 1 in the United States[30] and two in Europe[23,24]] reported a statistically significant reduction in health care costs, mainly due to the reduction in prescription, above all in broad-spectrum antibiotics. Half of these papers (3/6, 50.0%[24,33]) were focused on implementing clinical pathways alone or in combination with educational sessions, one on implementing a clinical practice guideline,[15] and the remaining two studies on the implementation of multiple interventions.[23,73] Five of these studies (5/6, 83.3%) were set in ED (three only in ED,[15,23,24] 2 both in ED and inpatient settings[30,33]).

Only three articles described the change in drug resistance (3/59 5.1%, 1 in the United States,[36] and 2 in Europe[43,64]). Two out of three articles reported a reduction in erythromycin resistance after the fall of the use of macrolides.[43,64]

All the details regarding study outcomes are reported in Table S1 in the Supplementary material.

Risk of bias assessment for Randomized Controlled Trial

The risk of bias assessment for RCT is summarized in Figure 5(a). Selection, detection, performance, attrition, and other bias have been assessed for all the studies. The assessment of each specific bias is reported in Table 2 in the Supplementary Material. Most of them (13/19) presented some concerns as overall judgements.[19,45,46,57–59,61,62,67,69–73] Five studies were considered at overall high risk of bias.[48,54,56,60,67] Only one study has been considered overall at low risk of bias.[18]

As it can be seen from Figure 1A in the Supplementary Material that shows the different types of bias, all the studies are at low risk of the bias arising from the randomization process and the bias due to missing outcome data.

Almost all the studies have been considered as having a risk of attrition bias. One study has been considered at high risk of bias because most of its analysis was based on the per-protocol analysis instead of the intention to treat analysis; the other studies have been considered as having some concerns. More than three-quarters of the studies have been classified as having some concerns in the section of bias in measuring the outcome due to the absence of the blinding. A quarter of the studies have been classified as having some transparency bias concerns because the published analyses were not always pre-planned.

Risk of bias assessment for observational studies

The risk of bias assessment for non-RCT is summarized in Figure 5(b). Bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result were assessed. The assessment of each specific bias is reported in Table 3 in the Supplementary Material. All of them were considered in the overall judgement as moderate risk of bias (18/40, 45.0%)[15,22,24–27,30,32,33,35–39,41,44,52,63] or high risk of bias (14/40, 35.0%).[16,17,20,21,28,29,31,34,42,47,50,51,55,66] No studies were considered at low risk of bias. Eight studies[23,40,43,49,53,64,65,68] were classified as 'No information' because there were no described characteristics of the population of interest.

Figure 1B in the Supplementary Material shows the different types of bias. All or nearly all the studies were considered at low risk of bias due to deviations from the intended interventions and the selection of the reported results. All the studies were considered at moderate risk of bias in the measurement of the outcomes because, in all these studies, the outcome assessors were aware of the intervention received by study participants. Most of the studies were considered at moderate or high risk of bias due to confounding or selection of participants because many studies did not consider a lot of the confounding domain that we considered necessary. In almost a quarter of the studies, we did not find any information about the confounding domains that authors could have considered about selecting participants and, potentially, the missing data.

Discussion

Although IDSA has recommended implementing ASPs since 2007, the effort to implement ASPs in paediatric settings is still limited.

Looking at PASP's literature evidence, most studies focused on the implementation of ASP in inpatient settings (92/113 studies), with more than a quarter focused on audit and feedback as a single intervention.[76] However, the core strategies proposed by IDSA are challenging to implement in the outpatient settings because of logistical and level barriers. For example, the audit and feedback strategies can be time-consuming and, differently from the inpatient setting, not as useful because of the rapid turnaround time. Nevertheless, despite these difficulties, implementing ASPs in the outpatient setting is necessary, and it is essential to find and adopt the best type of ASP.

To our knowledge, this is the first systematic review that has focused on the implementation of ASPs in paediatrics globally, both in the ED and primary care. In the last 2 years, other systematic reviews about the implementation of PASPs were published, one in premature infants,[77] and the other in PED, but only for respiratory infections.[78] In addition, another recently published review focused on PASP implementation in low- and middle-income countries.[79]

Only 59 articles out of 47,158 were eligible for our review. Our search strategy, also based on the

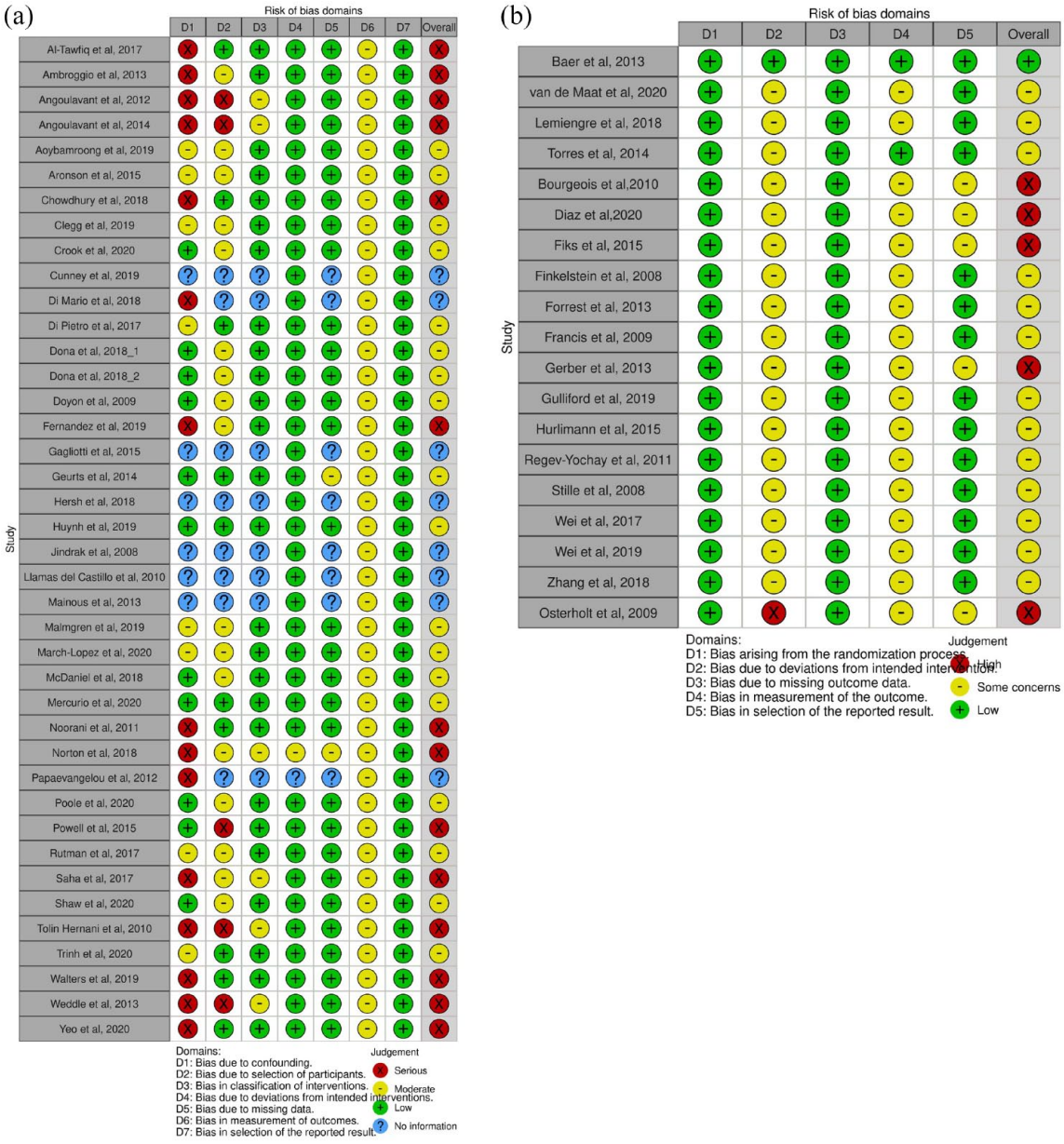

Figure 5. Traffic light plot of the domain-level judgements of (a) observational studies and (b) randomized controlled trials.

scoping review of Donà *et al.*,[76] was extensive because it was not limited to the term 'stewardship', but was also widened to the general terms 'antimicrobial' and 'children'. We decided to expand our search strategy because the interventions we wanted to consider in our review are not always labelled as 'stewardship'. With this comprehensive search strategy, we found and excluded many articles about the use of antibiotics in children but without any interventions.

Due to the high variability of the type of ASPs implemented, it was impossible to conduct a meta-analysis. Only 16 out of 59 focused on a single intervention, such as implementing clinical pathways or clinical guidelines or educational sessions for prescribers and parents.

Articles on a single implementation of clinical pathways and clinical guidelines have proved to change antibiotic prescriptions, reducing and improving

the antibiotic prescriptions rate, with a fall in broad-spectrum prescriptions and a concomitant increase in narrow-spectrum ones. Only one article described unchanged antibiotic prescription rates after implementing a clinical practice guideline.[37] In this before and after trial, the new local clinical guideline was distributed by email without any educational sessions. The authors supposed that combining the in-person training and real-time feedback with the implementation of clinical practice guideline would have had better outcomes, improving adherence to clinical guidelines, as demonstrated by other studies.[25,40]

Forty-three studies focused on multiple interventions in different combinations.

The most widespread, valuable, and feasible type of ASP was represented by educational sessions, both to prescribers and parents or guardians, combined with other types of intervention.

Implementation of PASP must consider many more factors compared to the adult settings. Indeed, it is important to highlight how, above all, the parents' pressure on prescribing is very high in outpatient settings. In addition, prescribers may be conditioned by emotional factors based on fear, uncertainty in the diagnosis, anxiety, risk perception, and difficulty in the doctor–parent communication.[80] Therefore, an important part of ASP interventions in this setting undoubtedly concerns education of the parents.

The second most chosen type of ASP in multiple intervention studies was the implementation of clinical practice guidelines or clinical pathways, combined with educational sessions, audit and feedback or point of care tests.

Studies that described the implementation of audit and feedback were conducted mainly in primary care, with only one study reporting this core strategy in both the ED and primary care. Audit and feedback were often combined with the implementation of clinical practice guidelines, educational sessions, or CDS tools and were proven to reduce unnecessary antibiotic prescriptions. Only one study describing the implementation of multiple interventions (educational sessions, CDS tools and monthly feedback) both in adult and paediatric populations did not show any change in prescribing practice in children.[61] However, it showed a statistically significant change in the adult population. Authors hypothesized that this could be due to the greater difficulty in changing antibiotic prescription behaviour when dealing with children because of higher concerns for the youngest.

Most of the articles included in this review were conducted in high-income countries, with only a few studies in South America and Africa. This is in line with our previous findings[76] and the survey conducted in 2020 both in high- and low-income countries about the implementation of ASPs and infection prevention and control activities.[81] It could be assumed that this is because ASPs are considered part of the new standard of care, and difficult to implement in low-income countries; nevertheless, a Global Action Plan is urgently needed to make ASP feasible and sustainable in resource-limited settings. A recent systematic review on the impact of PASP in low- and middle-income countries found that more than half of the 34 studies included were published after 2015, showing increasing efforts in the implementation of PASPs.[79] In addition, all the articles in this review described a positive impact on antibiotic prescribing and an important reduction of multidrug-resistant organism (MDRO)-related morbidity and mortality in children.

The implementation of ASPs should improve antimicrobial use, reducing antimicrobial resistance, adverse drug events, and health care costs. The most common outcome was a variation in antibiotic prescriptions, meant as both a reduction in total antibiotic prescriptions and a reduction of broad-spectrum antibiotics combined with an increase in narrow-spectrum ones if indicated as first-line therapy. Most of the studies in our review described a statistically significant change in antibiotic prescribing, confirming the results of previous reviews.

A third of the studies focused on compliance and adherence to the implemented guideline. Indeed, an excessively complicated or time-consuming intervention could have a negative impact on the main outcome, leading to an increase in unnecessary antibiotic prescriptions. Therefore, the prescribers must perceive the implemented intervention as a useful tool.

It has been reported that the effect of the ASP implementation and guidelines adherence declined over time in the absence of repeated educational sessions. A study conducted in a

PED in Ireland, implementing a multiple intervention ASP[23] reported that the guideline compliance increased from a median of 30% to 100% after 4 months. The increase was sustained at 100% after 6 months and 90% 1 year after the start of the intervention. Over time, other studies about sustainability are needed to understand how to maintain the positive results obtained after the ASP implementation.

The evaluation of the reduction of antimicrobial resistance is described only in a few studies. This is probably due to the difficulties related to the surveillance of antimicrobial resistance in outpatient settings; indeed, microbiological culture tests, like throat swabs or urine culture, are less frequently prescribed than in the inpatient setting.

A few studies only considered the assessment of the variation of health care costs, and only half of these showed a reduction in costs. Most of the studies focused only on the variation in antibiotic costs due to the reduction of antibiotic prescriptions, without considering the cost of ASPs implementation and the other healthcare costs that could be reduced, such as ancillary tests that could be requested in the ED and infections from multi-drug-resistant bacteria.

As already shown in the literature, the quality of the studies is often very low.[82] Most of the studies included in our review are 'before and after' with a moderate-high risk of bias. Only one of the randomized controlled trials was considered as having a low risk of bias; the others were classified as presenting some concerns or at having of a high risk of bias. In order to support investigations in the design and implementation of the ASP, in 2020, Schweitzer *et al.*[83] published a consensus recommendation about the optimization of the design of studies in this field, with the hope of improving the quality and the impact of the research in this area.

The primary limitation of our review is that only three databases were searched, and it is possible that not all PASP manuscripts were identified. In addition, most of the studies included in our review showed a positive impact on antibiotic prescribing, but we cannot exclude those other studies describing a negative impact that were conducted and not published.

Due to the low quality of the studies and the high variability among the considered interventions, which made the comparison difficult, it is challenging to reach major conclusions.

Many of the interventions included in our review have been proven valuable and feasible, but more studies with better quality are needed to identify the best intervention in each setting.

To help prescribers and researchers, Mistry *et al.*[9] reported in their papers some strategies to enhance the implementation of generalizable, ED-based ASPs.

First, 'collaboration and engagement' with the involvement of frontline providers is crucial for success. To be generalizable, ASPs require input and effort from key stakeholders in paediatric, general, and community EDs. Second, the 'dissemination of best practices': through adapted clinical pathways with locally tailored recommendations for antibiotic prescribing will likely increase guideline uptake. Finally, using 'effort-independent mechanisms methods' to prevent the need for active provider solicitations has been proven effective at curbing inappropriate prescribing in outpatient settings.

To highlight the importance of the ASPs, different organizations both in Europe and in North America have released specific guidelines about the implementation of ASP: the National Institute for Health and Care Excellence (NICE) guideline in 2015[84] and the Centre for Disease Control and Prevention (CDC) guideline in 2016.[85] Four core elements were identified for optimizing outpatient antimicrobial stewardship. First, 'commitment': outpatient prescribers must be engaged to prescribe antibiotics appropriately. Second, 'action for policy and practice': outpatient prescribers have to implement at least one policy or practice to improve antibiotic prescription. Third, 'tracking and reporting': prescribers and leaders of outpatient clinics have to track antibiotic prescriptions and regularly report these data back to prescribers (i.e. audit and feedback) to guide change in practice and assess progress in improving antibiotic prescribing. Finally, 'education and expertise': education on appropriate antibiotic prescription has to involve not only prescribers but patients and caregivers as well in order to improve antibiotic use further.

Conclusion

Implementing ASPs has been proven to positively impact antimicrobial use, healthcare costs, and antimicrobial resistance in inpatient and outpatient settings. Even if the implementation of ASP in the outpatients setting could be more challenging than in inpatient settings, some interventions have shown promising results. Multiple interventions, combining clinical pathways or clinical guidelines with education, audit, and feedback, have been proven valuable and feasible in this specific setting. However, it is difficult to draw strong conclusions from these studies because of their poor/moderate quality and the outcomes' heterogeneity that precludes a meta-analysis. More well-designed studies are needed to reliably assess the implementation of ASPs in paediatric settings, both in high- and low- to middle-income countries.

The implementation in the paediatric settings may be more complicated, but hopefully, it could be improved in the following years. There remains a critical need for National PASP networks to develop and perform uniform interventions. Nowadays, to our knowledge, only two countries have a national PASP network established, Germany and United Kingdom, both of which are not formally funded. It is desirable that all the European countries develop a similar National PASP network, formally funded, to share results intending to promote the more judicious use of antibiotics in children.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Giulia Brigadoi: Conceptualization; Data curation; Methodology; Writing – original draft.

Sara Rossin: Data curation; Writing – original draft.

Davide Visentin: Data curation.

Elisa Barbieri: Methodology; Supervision; Validation; Writing – original draft.

Carlo Giaquinto: Resources; Supervision; Writing – review & editing.

Liviana Da Dalt: Resources; Supervision; Writing – review & editing.

Daniele Donà: Conceptualization; Methodology; Supervision; Validation; Writing – original draft.

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Competing interests

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Supplemental material

Supplemental material for this article is available online.

References

1. Clavenna A and Bonati M. Drug prescriptions to outpatient children: a review of the literature. *Eur J Clin Pharmacol* 2009; 65: 749–755.
2. Muller A, Coenen S, Monnet D, *et al.* European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe, 1998-2005. *Euro Surveill* 2007; 12: 3284.
3. Zetts RM, Stoesz A, Smith BA, *et al.* Outpatient antibiotic use and the need for increased antibiotic stewardship efforts. *Pediatrics* 2018; 141: e20174124.
4. Health C for DC and PNC for, Statistics. Ambulatory health care data, 2018, https://www.cdc.gov/nchs/ahcd/new_ahcd.htm (accessed 17 September 2018).
5. van de Maat J, van de Voort E, Mintegi S, *et al.* Antibiotic prescription for febrile children in European emergency departments: a cross-sectional, observational study. *Lancet Infect Dis* 2019; 19: 382–391.

6. Levy SB. Factors impacting on the problem of antibiotic resistance. *J Antimicrob Chemother* 2002; 49: 25–30.

7. Dellit T, Owens R, McGowan JJ, *et al*. Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44: 158–177.

8. Gerber JS, Jackson MA, Tamma PD, *et al*. Policy statement: antibiotic stewardship in pediatrics. *J Pediatric Infect Dis Soc* 2021; 10: 641–649.

9. Mistry RD, May LS and Pulia MS. Improving antimicrobial stewardship in pediatric emergency care: a pathway forward. *Pediatrics* 2019; 143: e20182972.

10. Kopsidas I, Vergnano S, Spyridis N, *et al*. A survey on national pediatric antibiotic stewardship programs, networks and guidelines in 23 European countries. *Pediatr Infect Dis J* 2020; 39: e359–e362.

11. Page MJ, Moher D, Bossuyt PM, *et al*. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021; 372: 71.

12. New World Bank country classifications by income level: 2021-2022, https://blogs.worldbank.org/opendata/new-world-bank-country-classifications-income-level-2021-2022

13. Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.

14. Sterne JAC, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016; 355: i4919.

15. Aronson PL, Thurm C, Williams DJ, *et al*. Association of clinical practice guidelines with emergency department management of febrile infants ⩽56 days. *J Hosp Med* 2016; 176: 100–106.

16. Hernani MMT, Nuevo VC, Morán ES, *et al*. Evolution of the antibiotics prescription in a pediatric emergency service. *Acta Pediatr Esp* 2010; 68: 541–546.

17. Weddle G, Goldman J, Myers A, *et al*. Impact of an educational intervention to improve antibiotic prescribing for nurse practitioners in a pediatric urgent care center. *J Pediatr Health Care* 2017; 31: 184–188.

18. Baer G, Baumann P, Buettcher M, *et al*. Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial. *PLoS ONE* 2013; 8: e68419.

19. van de Maat JS, Peeters D, Nieboer D, *et al*. Evaluation of a clinical decision rule to guide antibiotic prescription in children with suspected lower respiratory tract infection in the Netherlands: a stepped-wedge cluster randomised trial. *PLoS Med* 2020; 17: e1003034.

20. Angoulvant F, Pereira M, Perreaux F, *et al*. Impact of unlabeled French antibiotic guidelines on antibiotic prescriptions for acute respiratory tract infections in 7 Pediatric Emergency Departments, 2009-2012. *Pediatr Infect Dis J* 2014; 33: 330–333.

21. Angoulvant F, Skurnik D, Bellanger H, *et al*. Impact of implementing French antibiotic guidelines for acute respiratory-tract infections in a paediatric emergency department, 2005-2009. *Eur J Clin Microbiol Infect Dis* 2012; 31: 1295–1303.

22. Crook J, Xu M, Slaughter JC, *et al*. Impact of clinical guidance and rapid molecular pathogen detection on evaluation and outcomes of febrile or hypothermic infants. *Infect Control Hosp Epidemiol* 2020; 41: 1285–1291.

23. Cunney R, Kirrane-Scott M, Rafferty A, *et al*. Start smart': using front-line ownership to improve the quality of empiric antibiotic prescribing in a paediatric hospital. *BMJ Open Qual* 2019; 8: e000445.

24. Dona D, Baraldi M, Brigadoi G, *et al*. The impact of clinical pathways on antibiotic prescribing for acute otitis media and pharyngitis in the emergency department. *Pediatr Infect Dis J* 2018; 37: 901–907.

25. Geurts DH, Vos W, Moll HA, *et al*. Impact analysis of an evidence-based guideline on diagnosis of urinary tract infection in infants and young children with unexplained fever. *Eur J Pediatr* 2014; 173: 463–468.

26. Malmgren A, Biswanger K, Lundqvist A, *et al*. Education, decision support, feedback and a minor reward: a novel antimicrobial Stewardship intervention in a Swedish paediatric emergency setting. *Infect Dis* 2019; 51: 559–569.

27. Mercurio L, Hill R, Duffy S, *et al*. Clinical practice guideline reduces evaluation and treatment for febrile infants 0 to 56 days of age. *Clin Pediatr (Phila)* 2020; 59: 893–901.

28. Powell SL and Liebelt E. Appropriate use of vancomycin in a pediatric emergency department

through the use of a standardized electronic guideline. *J Pediatr Nurs* 2015; 30: 494–497.

29. Walters EM, D'Auria J, Jackson C, *et al*. An ambulatory antimicrobial stewardship initiative to improve diagnosis and treatment of urinary tract infections in children. *Jt Comm J Qual Patient Saf* 2019; 45: 829–837.

30. McDaniel CE, Haaland W, Parlaman J, *et al*. A multisite intervention for pediatric community-acquired pneumonia in community settings. *Acad Emerg Med* 2018; 25: 870–879.

31. Ambroggio L, Thomson J, Murtagh Kurowski E, *et al*. Quality improvement methods increase appropriate antibiotic prescribing for childhood pneumonia. *Pediatrics* 2013; 131: e1623-31.

32. Dona D, Zingarella S, Gastaldi A, *et al*. Effects of clinical pathway implementation on antibiotic prescriptions for pediatric community-acquired pneumonia. *PLoS ONE* 2018; 13: e0193581.

33. Rutman L, Wright DR, OÊ¼Callaghan J, *et al*. A comprehensive approach to pediatric pneumonia: relationship between standardization, antimicrobial stewardship, clinical testing, and cost. *J Healthc Qual* 2017; 39: e59–e69.

34. Yeo YL, O'Brien S, Bear N, *et al*. Knowledge translation in Western Australia tertiary paediatric emergency department: an audit cycle of effectiveness of guideline dissemination on bronchiolitis management. *J Paediatr Child Health* 2020; 56: 1358–1364.

35. Doyon S, Perreault M, Marquis C, *et al*. Quantitative evaluation of a clinical intervention aimed at changing prescriber behaviour in response to new guidelines. *J Eval Clin Pract* 2009; 15: 1111–1117.

36. Poole NM, Kronman MP, Rutman L, *et al*. Improving antibiotic prescribing for children with urinary tract infection in emergency and urgent care settings. *Pediatr Emerg Care* 2020; 36: e332–e339.

37. Shaw R, Popovsky E, Abo A, *et al*. Improving antibiotic prescribing in the emergency department for uncomplicated community-acquired pneumonia. *World J Emerg Med* 2020; 11: 199–205.

38. Aoybamroong N, Kantamalee W, Thadanipon K, *et al*. Impact of an antibiotic stewardship program on antibiotic prescription for acute respiratory tract infections in children: a prospective before-after study. *Clin Pediatr* 2019; 58: 1166–1174.

39. Di Pietro P, Della Casa Alberighi O, Silvestri M, *et al*. Monitoring adherence to guidelines of antibiotic use in pediatric pneumonia: the MAREA study. *Ital J Pediatr* 2017; 43: 1–13.

40. Llamas Del Castillo MD, Baró Rodríguez L, Páez Valle Luque Aznar R, *et al*. Estrategia para la mejora del uso de antibióticos en pediatría. *Ars Pharm* 2010; 51: 447–451.

41. March-Lopez P, Madridejos R, Tomas R, *et al*. Impact of a multifaceted antimicrobial stewardship intervention in a primary health care area: a quasi-experimental study. *Front Pharmacol* 2020; 11: 398–397.

42. Saha D, Patel J, Buckingham D, *et al*. Urine culture follow-up and antimicrobial stewardship in a pediatric urgent care network. *Pediatrics* 2017; 139: e20162013.

43. Gagliotti C, Buttazzi R, Di Mario S, *et al*. A regionwide intervention to promote appropriate antibiotic use in children reversed trends in erythromycin resistance to Streptococcus pyogenes. *Acta Paediatr* 2015; 104: e422–e424.

44. Trinh NTH, Bruckner TA, Lemaitre M, *et al*. Association between national treatment guidelines for upper respiratory tract infections and outpatient pediatric antibiotic use in france: an interrupted time–series analysis. *J Pediatr* 2020; 216: 88–94.

45. Lemiengre MB, Verbakel JY, Colman R, *et al*. Point-of-care CRP matters: normal CRP levels reduce immediate antibiotic prescribing for acutely ill children in primary care: a cluster randomized controlled trial. *Scand J Prim Health Care* 2018; 36: 423–436.

46. Torres FA, Pasarelli I, Cutri A, *et al*. Impact assessment of a decision rule for using antibiotics in pneumonia: a randomized trial. *Pediatr Pulmonol* 2014; 49: 701–706.

47. Chowdhury F, Sturm-Ramirez K, Mamun A, *et al*. Effectiveness of an educational intervention to improve antibiotic dispensing practices for acute respiratory illness among drug sellers in pharmacies, a pilot study in Bangladesh. *BMC Health Serv Res* 2018; 18: 1–11.

48. Bourgeois FC, Linder J, Johnson SA, *et al*. Impact of a computerized template on antibiotic prescribing for acute respiratory infections in children and adolescents. *Clin Pediatr (Phila)* 2010; 49: 976–983.

49. Hersh AL, Olson J, Stockmann C, *et al*. Impact of antimicrobial stewardship for pediatric outpatient parenteral antibiotic therapy. *J Pediatric Infect Dis Soc* 2018; 7: E34–E36.

50. Noorani QA, Qazi SA, Rasmussen ZA, *et al*. Use of a pneumonia management tool to manage

children with pneumonia at the first level health care facilities. *J Pak Med Assoc* 2011; 61: 481–485.

51. Al-Tawfiq JA and Alawami AH. A multifaceted approach to decrease inappropriate antibiotic use in a pediatric outpatient clinic. *Ann Thorac Med* 2017; 12: 51–54.
52. Clegg HW, Bean RA, Ezzo SJ, *et al*. Impact of education and peer comparison on antibiotic prescribing for pediatric respiratory tract infections. *Pediatr Qual Saf* 2019; 4: e195.
53. Di Mario S, Gagliotti C, Buttazzi R, *et al*. Observational pre–post study showed that a quality improvement project reduced paediatric antibiotic prescribing rates in primary care. *Acta Paediatr* 2018; 107: 1805–1809.
54. Diaz MCG, Handy LK, Crutchfield JH Jr, *et al*. Impact of a personalized audit and feedback intervention on antibiotic prescribing practices for outpatient pediatric community-acquired pneumonia. *Clin Pediatr* 2020; 59: 988–994.
55. Fernandez M, Benito Manrique I, Montiel Eguia A, *et al*. An initiative to reduce the use of unnecessary medication in infants with bronchiolitis in primary care. *An Pediatr* 2019; 90: 19–25.
56. Fiks AG, Zhang P, Localio AR, *et al*. Adoption of electronic medical record-based decision support for otitis media in children. *Health Serv Res* 2015; 50: 489–513.
57. Finkelstein JA, Huang SS, Kleinman K, *et al*. Impact of a 16-community trial to promote judicious antibiotic use in Massachusetts. *Pediatrics* 2008; 121: e15–e23.
58. Forrest CB, Fiks AG, Bailey LC, *et al*. Improving adherence to otitis media guidelines with clinical decision support and physician feedback. *Pediatrics* 2013; 131: e1071–e1081.
59. Francis NA, Butler CC, Hood K, *et al*. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ* 2009; 339(7717): 374–376.
60. Gerber JS, Prasad PA, Fiks AG, *et al*. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians a randomized trial. *JAMA* 2013; 309: 2345–2352.
61. Gulliford MC, Prevost AT, Charlton J, *et al*. Effectiveness and safety of electronically delivered prescribing feedback and decision support on antibiotic use for respiratory illness in primary care: REDUCE cluster randomised trial. *BMJ* 2019; 364: l236.
62. Hurlimann D, Limacher A, Schabel M, *et al*. Improvement of antibiotic prescription in outpatient care: a cluster-randomized intervention study using a sentinel surveillance network of physicians. *J Antimicrob Chemother* 2015; 70: 602–608.
63. Huynh J, Hodgson KA, Boyce S, *et al*. Impact of expanding a paediatric OPAT programme with an antimicrobial stewardship intervention. *Arch Dis Child* 2020; 105: 1220–1228.
64. Jindrák V, Marek J, Vaniš V, *et al*. Improvements in antibiotic prescribing by community paediatricians In the Czech Republic. *Euro Surveill* 2002; 13: 19040.
65. Mainous AG 3rd, Lambourne CA and Nietert PJ. Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental trial. *J Am Med Inform Assoc* 2013; 20: 317–324.
66. Norton LE, Lee BR, Harte L, *et al*. Improving guideline-based streptococcal pharyngitis testing: a quality improvement initiative. *Pediatrics* 2018; 142.
67. Osterholt DM, Onikpo F, Lama M, *et al*. Improving pneumonia case-management in Benin: a randomized trial of a multi-faceted intervention to support health worker adherence to integrated management of childhood illness guidelines. *Hum Resour Health* 2009; 7: 77.
68. Papaevangelou V, Rousounides A, Hadjipanagis A, *et al*. Decrease of antibiotic consumption in children with upper respiratory tract infections after implementation of an intervention program in cyprus. *Antimicrob Agents Chemother* 2012; 56: 1658–1661.
69. Regev-Yochay G, Raz M, Dagan R, *et al*. Reduction in antibiotic use following a cluster randomized controlled multifaceted intervention: the Israeli judicious antibiotic prescription study. *Clin Infect Dis* 2011; 53: 33–41.
70. Stille CJ, Rifas-Shiman SL, Kleinman K, *et al*. Physician responses to a community-level trial promoting judicious antibiotic use. *Ann Fam Med* 2008; 6: 206–212.
71. Wei X, Zhang Z, Walley JD, *et al*. Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China:

a cluster-randomised controlled trial. *Lancet Glob Health* 2017; 5: e1258–e1267.

72. Wei X, Zhang Z, Hicks JP, *et al*. Long-term outcomes of an educational intervention to reduce antibiotic prescribing for childhood upper respiratory tract infections in rural China: follow-up of a cluster-randomised controlled trial. *PLoS Med* 2019; 16: e1002733.
73. Zhang Z, Dawkins B, Hicks JP, *et al*. Cost-effectiveness analysis of a multi-dimensional intervention to reduce inappropriate antibiotic prescribing for children with upper respiratory tract infections in China. *Trop Med Int Health* 2018; 23: 1092–1100.
74. Lemiengre MB, Verbakel JY, Colman R, *et al*. Reducing inappropriate antibiotic prescribing for children in primary care: a cluster randomised controlled trial of two interventions. *Br J Gen Pract* 2018; 68: e204–e210.
75. Rutman L, Klein EJ and Brown JC. Clinical pathway produces sustained improvement in acute gastroenteritis care. *Pediatrics* 2017; 140: e20164310.
76. Donà D, Barbieri E, Daverio M, *et al*. Implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review. *Antimicrob Resist Infect Control* 2020; 9: 1–12.
77. Rajar P, Saugstad OD, Berild D, *et al*. Antibiotic stewardship in premature infants: a systematic review. *Neonatology* 2021; 117: 673–686.
78. Weragama K, Mudgil P and Whitehall J. Paediatric antimicrobial stewardship for respiratory infections in the emergency setting: a systematic review. *Antibiotics* 2021; 10: 1366.
79. Abo YN, Freyne B, Kululanga D, *et al*. The impact of antimicrobial stewardship in children in low- and middle-income countries: a systematic review. *Pediatr Infect Dis J* 2022; 41: S10–S17.
80. Donisi V, Sibani M, Carrara E, *et al*. Emotional, cognitive and social factors of antimicrobial prescribing: can antimicrobial stewardship intervention be effective without addressing psycho-social factors? *J Antimicrob Chemother* 2019; 74: 2844–2847.
81. Villanueva P, Coffin SE, Mekasha A, *et al*. Comparison of antimicrobial stewardship and infection prevention and control activities and resources between low-/middle- and high-income countries. *Pediatr Infect Dis J* 2022; 41: S3–S9.
82. Schweitzer VA, van Heijl I, van Werkhoven CH, *et al*. The quality of studies evaluating antimicrobial stewardship interventions: a systematic review. *Clin Microbiol Infect* 2019; 25: 555–561.
83. Schweitzer VA, van Werkhoven CH, Rodriguez Bano J, *et al*. Optimizing design of research to evaluate antibiotic stewardship interventions: consensus recommendations of a multinational working group. *Clin Microbiol Infect* 2020; 26: 41–50.
84. National Institute for Health Care Excellence. *NICE medicines and prescribing centre antimicrobial stewardship: systems*. London: National Institute for Health Care Excellence, 2015, 119.
85. Antibiotic Stewardship O and Bell BP. Core elements of outpatient antibiotic stewardship, 2016, https://www.cdc.gov/antibiotic-use/core-elements/outpatient.html#:~:text=The%20four%20core%20elements%20of,reporting%2C%20and%20education%20and%20expertise.