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Factors associated with inappropriateness of antibiotic prescriptions for acutely ill children presenting to ambulatory care in high-income countries: a systematic review and meta-analysis

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Background: Acutely ill children are at risk of unwarranted antibiotic prescribing. Data on the appropriateness of antibiotic prescriptions provide insights into potential tailored interventions to promote antibiotic stewardship.

Objectives: To examine factors associated with the inappropriateness of antibiotic prescriptions for acutely ill children presenting to ambulatory care in high-income countries.

Methods: On 8 September 2022, we systematically searched articles published since 2002 in MEDLINE, Embase, CENTRAL, Web of Science, and grey literature databases. We included studies with acutely ill children presenting to ambulatory care settings in high-income countries reporting on the appropriateness of antibiotic prescriptions. The quality of the studies was evaluated using the Appraisal tool for Cross-Sectional Studies and the Newcastle–Ottawa Scale. Pooled ORs were calculated using random-effects models. Meta-regression, sensitivity and subgroup analysis were also performed.

Results: We included 40 articles reporting on 30 different factors and their association with inappropriate antibiotic prescribing. 'Appropriateness' covered a wide range of definitions. The following factors were associated with increased inappropriate antibiotic prescribing: acute otitis media diagnosis [pooled OR (95% CI): 2.02 (0.54–7.48)], GP [pooled OR (95% CI) 1.38 (1.00–1.89)] and rural setting [pooled OR (95% CI) 1.47 (1.08–2.02)]. Older patient age and a respiratory tract infection diagnosis have a tendency to be positively associated with inappropriate antibiotic prescribing, but pooling of studies was not possible.

Conclusions: Prioritizing acute otitis media, GPs, rural areas, older children and respiratory tract infections within antimicrobial stewardship programmes plays a vital role in promoting responsible antibiotic prescribing. The implementation of a standardized definition of appropriateness is essential to evaluate such programmes.

Introduction

Acutely ill children are at risk of unwarranted antibiotic prescribing.[1] Qualitative studies describe several factors that may influence antibiotic prescribing for children presenting to ambulatory care.[2,3] First of all, physicians themselves may experience certain attitudes and feelings, including anxiety or fear, concerning prescribing.[2,3] For instance, they might experience diagnostic uncertainty regarding the seriousness of the child's illness,[2–4] or prescribe an antibiotic to satisfy the patient or their parent.[2] Secondly, patients or their parents can express a certain pressure, concern or expectation.[2,3] For example, some parents believe that antibiotics are effective for their child's current illness[3] due to a lack of education or awareness of antibiotic use.[2] Third, external factors such as time pressure and financial issues might also drive antibiotic overprescribing, since it might be easier to write the prescription for an antibiotic than to have the discussion about why antibiotics are not needed.[2]

Inappropriate antibiotic prescribing raises healthcare costs, needlessly exposes patients to adverse drug events such as allergic reactions, and increases the prevalence of antibiotic-resistant bacteria.[5,6] Antimicrobial resistance (AMR) has emerged as one of the leading public health threats of the 21st century.[7] In 2019, there were an estimated 1.27 million deaths attributable to bacterial AMR globally.[7] By 2050, associated costs are projected to be as high as 100 trillion US dollars worldwide if no action is taken.[8]

To the best of our knowledge, no review to date summarizes literature on factors associated with inappropriate antibiotic prescriptions for acutely ill children in high-income countries. These data may provide insights into potential antibiotic stewardship interventions, which are essential to tackle AMR. A recent systematic review demonstrated that, in high-income countries, about one-fifth to one-half of antibiotic prescriptions for acutely ill children are inappropriate.[9] The specific risk factors associated with the inappropriateness of antibiotic prescriptions were not evaluated in that review.[9] Other reviews on inappropriateness of antibiotic prescriptions did not investigate children separately,[10–12] or concentrated on low- and middle-income countries.[13,14] We aimed to collate all available evidence on factors associated with inappropriate antibiotic prescriptions for acutely ill children presenting to ambulatory care in high-income countries. Secondly, we examined the relationship between inappropriateness of antibiotic prescriptions and safety outcomes (i.e. adverse events, hospital admission or death).

Methods

We performed a systematic review according to the methods as described by Cochrane[15] and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist (Tables S1–3, available as Supplementary data at *JAC* Online).[16]

Search strategy

We systematically searched MEDLINE (PubMed), Embase (Elsevier), Web-of-Science Core Collection (Clarivate) and Cochrane CENTRAL (Wiley). The following grey literature databases were searched: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), National Health Service (NHS) Health Technology Assessment (HTA), International Network of Agencies for Health Technology Assessment (INAHTA), ECDC and CDC. For the latter two, due to the high number of results, we only checked the first 100 results for their relevance. We restricted the search to studies published from the last two decades, from the year 2002 onwards. There were no language restrictions. If needed, the full text was translated with DeepL software or Google Translate. The search string was based on the following key terms: 'antibiotics', 'appropriateness' and 'ambulatory care'. Due to a lack of specificity, we decided to add some Boolean NOT-operator terms to reduce the number of retrieved irrelevant articles. This was done prudently with assistance from a biomedical librarian. Search strings for all databases are included in the Supplementary data (pages 13–22). Hand searching was not performed.

Inclusion and exclusion criteria

References reporting on the appropriateness or inappropriateness of antibiotic prescriptions for acutely ill children presenting to ambulatory care in high-income countries were eligible for this review. There were no restrictions on how 'appropriateness of antibiotic prescriptions' was defined. We included cross-sectional studies, prospective and retrospective cohort studies, and reports from health organizations and HTA agencies. Randomized controlled trials, non-randomized studies of interventions, and case–control studies were included as well, but only data on the control group were extracted if representative of usual care. (Systematic) reviews, editorials, letters, comments, posters, oral presentations, book chapters, conference abstracts, qualitative studies, purely economic analyses, and mathematical modelling studies were excluded. Studies that included patients of any age in the range of zero up to and including 18 years of age were eligible. Authors reporting pooled data on participants up to and older than 18 years of age were contacted via e-mail. We requested data of only the participants up to and including 18 years of age. If the authors did not reply after one e-mail and at least two reminders, each with an interval of at least 1 week, the article was excluded. Studies targeting children with specific comorbidities or chronic diseases (e.g. cystic fibrosis, immunodeficiency) were excluded. There were no restrictions in terms of race or gender. Participants had to present to ambulatory care (also called 'outpatient care'), which includes doctor's offices, clinics, ambulatory surgery centres, emergency departments and outpatient departments, but not any setting related to dental care. Studies conducted solely in an inpatient setting, those evaluating prophylactic antibiotic regimens, or those examining veterinary use of antibiotics were excluded. Only studies assessing results from high-income countries were included. We used the definition of the World Bank for high-income countries.[17]

Selection and data extraction

Search results were imported into a reference management programme (Endnote 20.2, Bld 15709, Clarivate Analytics) and duplicate citations were removed.[18] Based on inclusion and exclusion criteria, pairs of two reviewers (six reviewers in total) independently screened all records by title and abstract, using Covidence software.[19] Next, pairs of two reviewers independently reviewed the full text of all potentially relevant records, using the same selection criteria. Data were extracted by one reviewer and checked by another reviewer using Microsoft Excel (version 2208). Any queries or disagreements in either of the steps above were resolved through discussion or, if necessary, another reviewer. The following data items were extracted: title, first author, publication year, journal, country, time frame of data collection, study design, data collection method, sample size, age of the participants (range, median, IQR, mean, standard deviation), number of male participants, diagnoses included, setting, definition of 'appropriateness of antibiotic prescriptions', number of antibiotic prescriptions, number of antibiotic prescriptions deemed appropriate by the authors of the respective study, all studied outcomes (i.e. appropriateness, inappropriateness or safety outcomes) and exposures, the statistical method used, the measures and strength of association between exposure and outcome (i.e. adjusted or unadjusted OR, risk ratio) including their 95% CI, and the set of adjustment factors (in the case of adjusted ORs). If additional study information or data or study documents were required, corresponding authors were contacted via e-mail. Definitions of 'appropriateness of antibiotic prescriptions' were categorized as 'indication' (i.e. appropriate diagnosis to write an antibiotic prescription for), 'class' (i.e. appropriate antibiotic class), 'dose' (i.e. appropriate antibiotic dose), 'duration' (i.e. appropriate duration of antibiotic therapy) or 'mixed' (i.e. a combination of indication, class, dose, frequency and duration).

Risk-of-bias assessment

The methodological quality of the selected studies was evaluated independently by pairs of two authors (four reviewers in total) using the Appraisal tool for Cross-Sectional studies (AXIS tool)[20] for cross-sectional studies and the Newcastle–Ottawa Scale (NOS)[21] for cohort studies. Cross-sectional studies were classified as 'high', 'moderate' or 'low' risk of bias according to the following scores on the AXIS tool: less than or equal to 75%, from 75% up to and including 85%, and more than 85%, respectively. For the AXIS tool, questions 7, 13 and 14 were omitted for

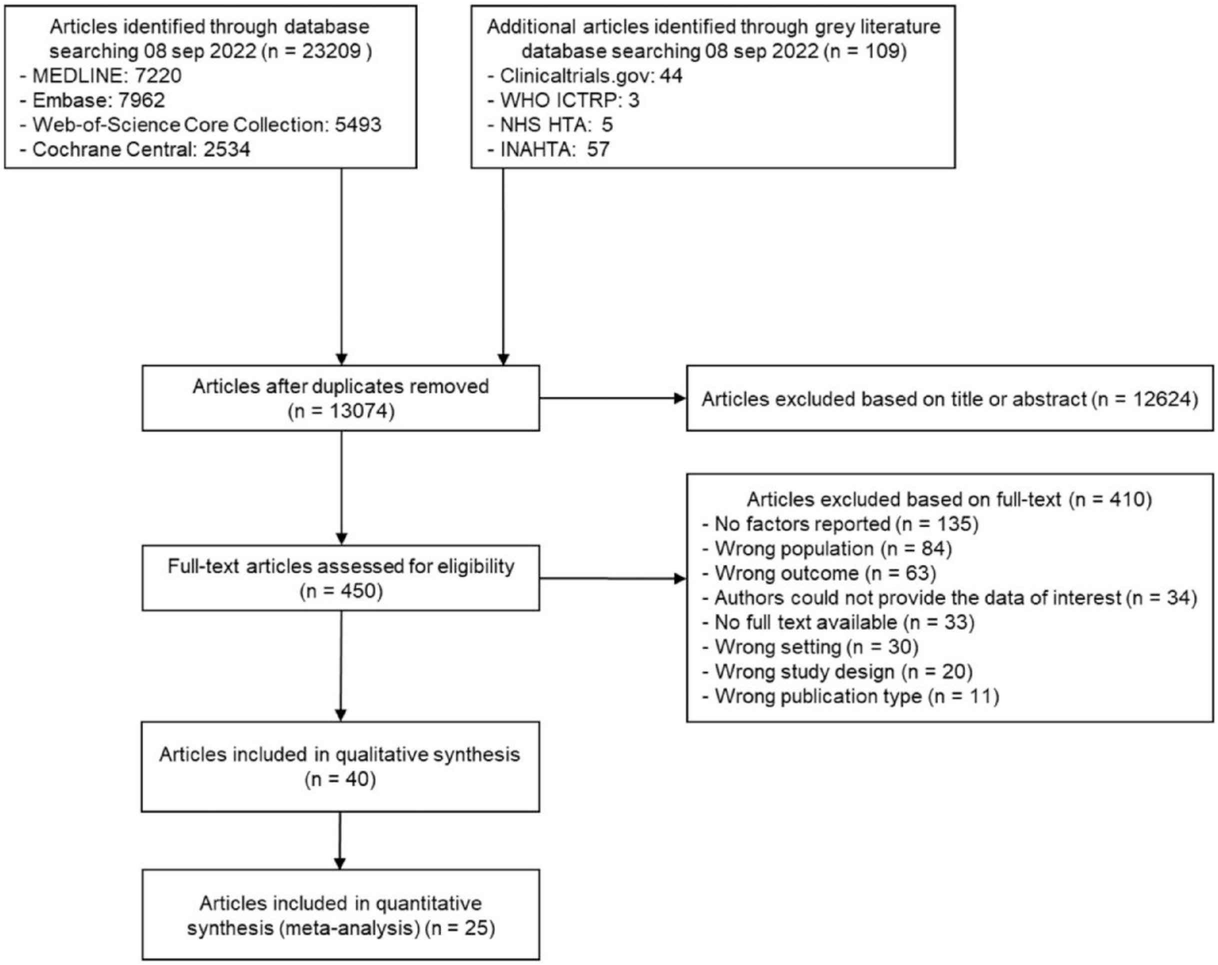

Figure 1. PRISMA flow chart. Study identification and process for selection of studies included in this review.

studies that collected their data retrospectively from databases. Cohort studies were classified as 'high', 'moderate' or 'low' risk of bias according to the following scores on the NOS: 5 or less, 6 or 7, and 8 or 9, respectively.

Data analysis

Factors and their association with inappropriateness of antibiotic prescriptions were summarized narratively and were categorized as patient-level, prescriber-level, environment-level or 'miscellaneous' factors. Meta-analyses were conducted for factors on which at least four studies reported. The measures of association with inappropriateness were pooled on a natural logarithmic scale, using inverse-variance random effects meta-analysis models, as we anticipated substantial between-studies heterogeneity. We calculated pooled OR, 95% CI and 95% prediction intervals (PIs). We used the restricted maximum-likelihood estimator method to estimate the heterogeneity variance τ^2.[22] For factors on which at least 10 studies reported, multivariable meta-regression was performed to describe the relationship between the strength of association with inappropriateness and study-level covariates (i.e. definition of appropriateness, risk of bias, and whether the study reported adjusted or unadjusted OR).[23] If at least four studies remained, sensitivity analyses were performed by excluding studies based on meta-regression results, studies with a high risk of bias, small studies and studies with influential outlying values (which is based on the following leave-one-out diagnostics: the DFFITS value, the Cook's distance, the hat value and the DFBETAS value).[22] Subgroup analyses were performed based on the definition of appropriateness, if at least four studies per subgroup were available. Forest plots were constructed to visually summarize the results of the meta-analyses. For all analyses containing at least 10 studies, funnel plots were constructed to detect small study biases.[24] Presence of funnel plot asymmetry was assessed through Egger's regression test.[25] We used R version 4.1.3 and the Metafor package.[22] The full R code can be found in the Supplementary data (pages 23–32).

Protocol registration

We published and prospectively registered the protocol for this systematic review on PROSPERO (CRD42022358425).

Results

Identification of studies

From the database search on 8 September 2022, 13 074 unique records were identified and screened for title and abstract. Of these, 450 references were screened based on full text, and 40 unique studies were retained for this review (Figure 1).

Study characteristics are shown in Table 1. We included 33 cross-sectional and 7 cohort studies. The studies were conducted in 15 different high-income countries, with most studies being performed in the USA ($n=13$) and Canada ($n=5$). The vast majority of studies included children up to and including 18 years of age ($n=26$) and only seven studies exclusively included younger children (i.e. up to and including the age of 6 years). Most studies retrieved their data from electronic health records (EHRs; $n=17$), 14 studies collected data from databases (e.g. registries or insurance claims), 8 studies used other data sources (e.g. forms, interviews, discharge reports, questionnaires, video tapes) or a combination of the aforementioned data collection methods, and 1 study did not clearly mention where the data were collected from. More than half of the studies ($n=26$) solely investigated respiratory tract infections (RTIs), three studies examined urinary tract infections (UTIs) and 11 studies included multiple types of infections relating to several organ systems (e.g. a combination of RTIs, UTIs, dermatological infections and gastroenterological infections). The majority of the included studies took place in a general outpatient setting ($n=22$), seven studies were conducted in the emergency department (ED), seven studies were performed in a GP setting, and in four studies the children presented to an ambulatory care paediatrician.

Risk of bias

Of the 33 cross-sectional studies evaluated with the AXIS tool, 14 studies had a low risk of bias, 15 had a moderate score, and four had a high risk of bias. The sample size was not justified in 27 out of 33 studies. Other sources of bias included bias in measurement of the risk factors and outcome variables ($n=12$) and selection bias due to a sample that did not represent the target population under investigation ($n=11$). Of the seven cohort studies evaluated with the NOS, two studies had a low risk of bias, four had a moderate score, and one had a high risk of bias. None of the studies mentioned the adequacy of follow-up of the cohorts and for two studies the follow-up was not long enough for outcomes to occur (i.e. less than 2 days for delivery of a prescription). Full details on the risk of bias assessment can be found in Tables S4 and S5.

Definition of 'appropriateness of antibiotic prescriptions'

The appropriateness of antibiotic prescriptions was assessed by comparing the treatment decision with the (inter)national guidelines or consensus statements ($n=38$) or quality indicators ($n=2$). Twelve studies focused exclusively on whether the class of the prescribed antibiotic was appropriate (e.g. whether a first-line agent was prescribed), nine studies investigated whether the antibiotic was indicated for the illness (e.g. whether the diagnosis justified the antibiotic prescription) and one study examined whether the prescribed dose of the agent was appropriate. The largest group ($n=18$) of the included studies investigated multiple aspects of appropriateness (i.e. a combination of indication, antibiotic class, dose, frequency and duration). An overview of the complete definitions of 'appropriateness of antibiotic prescriptions' can be found in Table S6.

Factors associated with inappropriateness of antibiotic prescriptions

In total, 30 different factors were studied. Twenty-nine studies looked at patient-level factors (e.g. sex, age, ethnicity, diagnosis, symptoms, parent's characteristics), 20 at prescriber-level factors (e.g. specialty, sex, age, experience, number of patients or encounters) and 27 at environmental factors (e.g. type of setting, practice organization, area) (Tables S6–S71).

Factors included in meta-analysis

Boys have 1.06 higher odds of inappropriate antibiotic prescribing compared with girls (95% CI 1.02–1.11; 95% PI 0.94–1.21; $I^2=96.63\%$; 16 studies) (Figure 2a and Figure S1). The diagnosis of acute otitis media, compared with an upper RTI (OR 2.02; 95% CI 0.54–7.48; 95% PI 0.07–59.81; $I^2=100.00\%$; 6 studies) (Figure 2b) and the presence of fever, compared with the absence of fever (adjusted OR 1.13; 95% CI 0.46–2.77; 95% PI 0.17–7.66; $I^2=93.21\%$; 4 studies) (Figure S2) were associated with more inappropriate antibiotic prescriptions, but these were not statistically significant.

GPs have 1.38 higher odds of prescribing an antibiotic inappropriately, compared with paediatricians (95% CI 1.00–1.89; 95% PI 0.53–3.59; $I^2=94.32\%$; 10 studies) (Figure 3a and Figure S3). In rural settings, the odds of inappropriate antibiotic prescribing are 1.47 higher compared with urban settings (95% CI 1.08–2.02; 95% PI 0.70–3.11; $I^2=96.08\%$; 5 studies) (Figure 3b). Those studies were performed in the USA ($n=3$) and Canada ($n=2$). We have no evidence that an emergency setting, compared with a non-emergency setting, is associated with inappropriateness of antibiotic prescriptions (OR 0.98; 95% CI 0.69–1.38; 95% PI 0.37–2.59; $I^2=99.89\%$; 9 studies) (Figure S4).

We found that reported ORs differed considerably between studies, and performed meta-regression for the factors 'sex of the patient' and 'specialty of the prescriber'. The heterogeneity could partially be explained by the definition of appropriateness (for both factors), whether the study reported adjusted or unadjusted OR (for both factors), and by risk of bias (only for specialty of the prescriber) (Tables S72 and S73).

The Egger's tests could not demonstrate small study bias (P values of 0.63 for 'sex of the patient' and 0.80 for 'specialty of the prescriber'; Figures S5 and S6).

In the sensitivity and subgroup analyses, the pooled ORs were in line with the main analysis for the factors 'specialty of the prescriber' and 'rurality setting' (Tables S74–S79, Figures S7–S12).

For the factor 'sex of the patient', based on studies reporting unadjusted OR, we have no evidence that the sex of the patient is associated with inappropriateness of antibiotic prescriptions (OR 1.00; 95% CI 0.96–1.04; 95% PI 0.93–1.07; $I^2=94.20\%$; 4 studies). Other sensitivity and subgroup analyses for this factor were similar to the main analysis. For the factor 'diagnosis' (i.e. acute otitis media compared with upper RTI), when we removed one study with an outlying low OR, as per the study protocol, the association with increased inappropriate prescribing became statistically significant (OR 3.24; 95% CI 1.10–9.53; 95% PI 0.26–10.70; $P=0.0329$; $I^2=99.99\%$; 5 studies), which supports the direction of the effect that we saw in the main analysis. Sensitivity and subgroup analyses for the factor 'type of setting' (i.e. emergency compared with non-emergency setting) showed inconsistent directions of effect, without statistical significance: positive associations in the sensitivity analyses (OR 1.14 and 1.19) and a negative association in the subgroup 'definition of appropriateness: class' (OR 0.76).

Table 1. Characteristics of included studies

Author, year	Country	Time frame of data collection (DD/MM/YYYY)	Study design	Data collection method	Age range	Sample size	Diagnoses included	Setting
I. Definition appropriateness 'mixed'								
Abuali, 2019[26]	USA	01/08/2014–31/03/2015	CS	EHR	0–21 years	396	AOM, pharyngitis, sinusitis	Academic paediatric practice, community practice
Alanazi, 2015[27]	Saudi Arabia	01/01/2008–30/03/2008	CS	EHR	6 months–15 years[a]	2258	RTI, UTI, AOM, dermatological infections, gynaecological-related infections, GI infections	ED
Bandell, 2019[28]	The Netherlands	01/01/2015–31/01/2017	CS	EHR	0–18 years	45	URTI, CAP, asthma exacerbation, pertussis, AOM, tonsillitis, Lyme disease, *Helicobacter pylori* eradication, other pulmonary reasons for which azithromycin or clarithromycin was prescribed	Outpatient department, ED, GP[b]
Butler, 2022[29]	USA	01/04/2016–30/09/2018	C	Database	6 months–17 years	2 804 245	AOM, pharyngitis, sinusitis, influenza, viral URTI, bronchiolitis, bronchitis	Outpatient (e.g. ED, office, clinic, UCC)
Croche Santander, 2018[30]	Spain	01/01/2013–31/12/2013	CS	EHR	0–14 years	630	AOM, pharyngitis, wheezing episode, fever without a source, CAP, (un-)infected wound, conjunctivitis, URTI, dog bite, bacterial lymphadenitis, orchiepididymitis, OE, eye injury, bronchiolitis, GE, UTI, laryngitis	ED
Duran Fernandez-Feijoo, 2010[31]	Spain	01/01/2008–31/12/2008	CS	Discharge reports	0–18 years	300	AOM, pharyngotonsillitis, CAP	PED
Etienne, 2015[32]	France	01/10/2012–31/10/2012	CS	Form	0–18 years[c]	45	All diagnoses for which an antibiotic was prescribed	GP
Frost, 2020[33]	USA	01/01/2018–31/12/2018	CS	EHR	2–18 years	926	AOM	Outpatient (PED, UCC, community-based health centres, school-based clinics)
Holm, 2020[34]	Denmark	01/03/2016–31/05/2016	CS	Form	0–18 years[c]	94	UTI	GP
Kozyrskyj, 2004[35]	Canada	01/04/1996–01/04/2000	CS	Database	0–18 years	41 512	Bronchiolitis, bronchitis, RTI, common cold/AOM, pharyngitis, pneumonia, UTI, cellulitis, impetigo	Ambulatory care
LaScala, 2022[36]	USA	01/01/2015–01/08/2018	CS	EHR	0–18 years	7930	AOM, pneumonia, SSTI, streptococcal pharyngitis, UTI	PED
Launay, 2016[37]	France	01/05/2009–01/05/2011[d]	CS	Database	1 month–15 years	3034	CAP	PED

Nash, 2002[38]	USA	01/01/1995–31/12/1998	CS	Database	0–18 years	5212	URTI/cold, bronchitis, pharyngitis, sinusitis, AOM	Paediatrician, GP
Otters, 2004[39]	The Netherlands	01/01/2001–31/12/2001[e]	CS	Database, questionnaire, EHR	0–17 years	16 555	Cough, URTI, bronchitis	GP
Ray, 2019[40]	USA	01/01/2015–31/12/2016	C	Database	0–17 years	52 8213[f]	Sinusitis, pneumonia, pharyngitis, AOM, viral URTI, bronchiolitis, OME	Telemedicine care, urgent care, primary care provider visits
Rothman, 2017[41]	Israel	01/01/2014–31/12/2016	CS	EHR	6 months–3 years	1493	AOM	PED
Shetty, 2014[42]	New Zealand	01/04/2012–31/07/2012	CS	Database	3–20 years	423	GAS pharyngitis	School programmes, GP
Shviro-Roseman, 2014[43]	Israel	01/01/2003–31/05/2004	CS	EHR	3 months–3 years	597	AOM	Primary care paediatric clinics (paediatrician, GP)
II. Definition appropriateness ‘class’								
Bradley, 2021[44]	USA	01/10/2013–31/12/2016	C	EHR	0–18 years	1053	AOM	Primary care clinic
Chen, 2011[45]	Taiwan	01/01/2000–31/12/2007	CS	Database	0–18 years	15 468	Pyelonephritis, cystitis, UTI unspecified	Ambulatory care
Fernandez Gonzalez, 2013[46]	Spain	NR	CS	NR	0–14 years	420	AOM	ED, PCP
Ganzeboom, 2018[47]	The Netherlands	01/01/2015–31/12/2015	CS	EHR	0–18 years[c]	104	Cystitis, pyelonephritis, prostatitis	GP
Hayes, 2019[48]	USA	01/10/2013–NR	CS	EHR	0–18 years	2400	Viral illness, croup, fever, upper respiratory illness, viral pharyngitis, cough, AOM, sinusitis, streptococcal pharyngitis, bronchitis, bronchiolitis	General paediatrician
Maguire, 2018[49]	Ireland	01/2015; 01/2016; 01/2017	CS	EHR	0–6 years	1007	URTI	GP
Okubo, 2018[50]	Japan	01/04/2012–31/12/2015	CS	Database	0–18 years	5030	Sepsis due to *Streptococcus* group A, streptococcal sepsis, streptococcal and enterococcal infection unspecified site, streptococcal pharyngitis, streptococcal tonsillitis	Outpatient clinics
Piovani, 2017[51]	Italy	01/01/2011–31/12/2011	CS	Database	1–13 years	1 002 006	All diagnoses for which an antibiotic was prescribed	Community paediatric practice
Quach, 2004[52]	Canada	01/06/1999–30/06/2002	C	Database	3 months–6 years	60 513	AOM	GP, paediatrician, ENT specialist, infectious disease physician; working in private

Continued

Table 1. *Continued*

Author, year	Country	Time frame of data collection (DD/MM/YYYY)	Study design	Data collection method	Age range	Sample size	Diagnoses included	Setting
								offices, ED and outpatient clinics
Shapiro, 2011[53]	USA	01/01/1998–31/12/2007	CS	Database	0–18 years	389	Sinusitis	Offices, hospital outpatient departments, ED
Shetty, 2018[54]	New Zealand	01/04/2016–31/07/2016	CS	Database	3–20 years	1109	GAS pharyngitis	GP
Williams, 2018[55]	UK	07/04/2010–30/04/2012	CS	Form	3 months–5 years	3304	URTI, tonsillitis, AOM/myringitis	GP, PED, walk-in clinic
III. Definition appropriateness 'indication'								
Bianco, 2022[56]	Italy	01/03/2019–31/03/2020	CS	Interview	0–14 years	565	Sinusitis, pharyngotonsillitis, AOM, bronchitis, influenza, common cold, laryngotracheitis	PCP
Clay-Williams 2020[57]	Australia	01/01/2012–31/12/2013	CS	EHR	0–15 years	834	AOM	GP, paediatricians' offices in the community, ED[b]
Heritage, 2010[58] (and Mangione-Smith, 2006[59])	USA	01/10/2000–30/06/2001	CS	Questionnaire, videotape	6 months–10 years	522	AOM, asthma, bronchitis, pneumonia, bronchiolitis, conjunctivitis, croup, *Mycoplasma* infection, OE, OME, streptococcal pharyngitis, sinusitis, viral pharyngitis, viral stomatitis, viral URTI	Community paediatric practice
Mannix, 2022[60]	USA	01/01/2018–31/12/2018	CS	EHR	2 months–18 years	457	AOM, pharyngitis, influenza, pneumonia, sinusitis, URTI	UCC (PCP)
Schwartz, 2020[61]	Canada	01/04/2011–31/03/2016	CS	EHR, database	0–18 years[a]	136 830	Common cold, UTI, asthma, bronchitis, sinusitis, GE, SSTI, eye infection, reproductive tract infection, pharyngitis, pneumonia, AOM, influenza, OE, dental condition, epididymo-orchitis, pyelonephritis, miscellaneous infections	GP
Singer, 2018[62]	Canada	01/04/1999–31/01/2016	C	EHR	1–18 years[c]	31 935	Sinusitis, laryngitis and tracheitis, URTI, bronchitis, rhinitis, nasopharyngitis, influenza	Community-based primary care practices
Singer, 2018[63]	Canada	01/01/2014–31/12/2016	C	EHR	0–18 years[c]	3375	Sinusitis, URTI, bronchitis, rhinitis, laryngitis and tracheitis, nasopharyngitis, influenza	Primary care research network primary care provider
Wattles, 2022[64]	USA	01/01/2017–31/12/2017	CS	Database	0–19 years	328 515	All diagnoses for which an antibiotic was prescribed	Outpatient (GP, NP, paediatrician, physician assistant, other)

Yoshida, 2018[65]	Japan	01/01/2005–30/09/2014	C	Database	0–6 years	1 428 090	URTI		Outpatient
IV. Definition appropriateness 'dose'									
Barstow, 2020[66]	USA	30/06/2014–01/07/2015	CS	EHR	0–18 years	1934	All diagnoses for which an antibiotic was prescribed		ED

NR, not reported; CS, cross-sectional study; C, cohort study; AOM, acute otitis media; GAS, group A streptococcus; GE, gastroenteritis; GI, gastrointestinal; OE, otitis externa; OME, otitis media with effusion; URTI, upper RTI; SSTI, skin and soft tissue infection; (P)ED, (paediatric) emergency department; ENT, ear-nose-throat; NP, nurse practitioner; PCP, primary care paediatrician; UCC, urgent care centre.
[a]We only extracted data for children.
[b]We only extracted data for the outpatient settings (not for inpatient settings).
[c]The data for children separately were made available by the corresponding author.
[d]We only extracted data for the first period.
[e]We only extracted data for the year 2001.
[f]We only extracted data for the matched sample.

Factors not included in meta-analysis

Seventeen studies found a positive association between older patient age and inappropriate antibiotic prescribing (of which 12 were statistically significant); four studies found a negative association (all statistically significant). Meta-analysis to pool ORs was not possible due to the different age group definitions (Table S8, Figure S13).

Three studies showed that the diagnosis of an RTI, compared with a UTI, is positively associated with inappropriate antibiotic prescribing (OR 1.37, 1.54 and 2.04). However, we did not combine these results in a meta-analysis, since there were too few primary studies available (Table S10).

Three studies found a positive association between younger prescriber age and inappropriate antibiotic prescribing (all statistically significant), two studies found a negative association (both statistically significant), and one study could not find any association. Meta-analysis to pool ORs was not possible due to the different age group definitions (Table S42).

A range of patient-level (e.g. ethnicity, presenting symptoms), prescriber-level (e.g. clinical experience, previous training) and environment-level (e.g. type of hospital, geographic region) factors were reported infrequently or comprised different index and reference groups. An overview of reported estimates for these factors per study can be found in Tables S7–S71.

Relationship between inappropriateness of antibiotic prescriptions and safety outcomes

Two studies reported on the relationship between inappropriateness of antibiotic prescriptions and safety outcomes.[29,37] One study showed that prescription non-compliance was significantly associated with a higher risk of hospitalization, but not with admission to the paediatric ICU or death.[37] The other study showed that for children with bacterial infections, inappropriate antibiotic prescriptions were associated with higher risk of *Clostridioides difficile* infection, higher risk of non-*C. difficile* diarrhoea, higher risk of nausea, vomiting or abdominal pain, lower risk of skin rash or urticaria, and lower risk of unspecified allergy.[29] Also, for children with viral infections, inappropriate antibiotic prescriptions were associated with higher risk of skin rash or urticaria and higher risk of unspecified allergy.[29]

Discussion

Main findings

In this systematic review, we identified factors associated with inappropriate antibiotic prescribing for acutely ill children presenting to ambulatory care in high-income countries. We found that the authors of the included studies presented a wide range of definitions for the 'appropriateness of antibiotic prescriptions', comprising aspects such as antibiotic class, indication appropriateness and antibiotic dose, either individually or in combination. A diagnosis of acute otitis media, a GP as prescriber, and a rural area were identified as the main factors that drive inappropriateness of antibiotic prescriptions. Acute otitis media only showed a statistically significant effect in the sensitivity analysis where we excluded one influential outlier. Since the ORs in the main and sensitivity analyses have the same direction and similar magnitude of the effect, we can safely conclude that those results

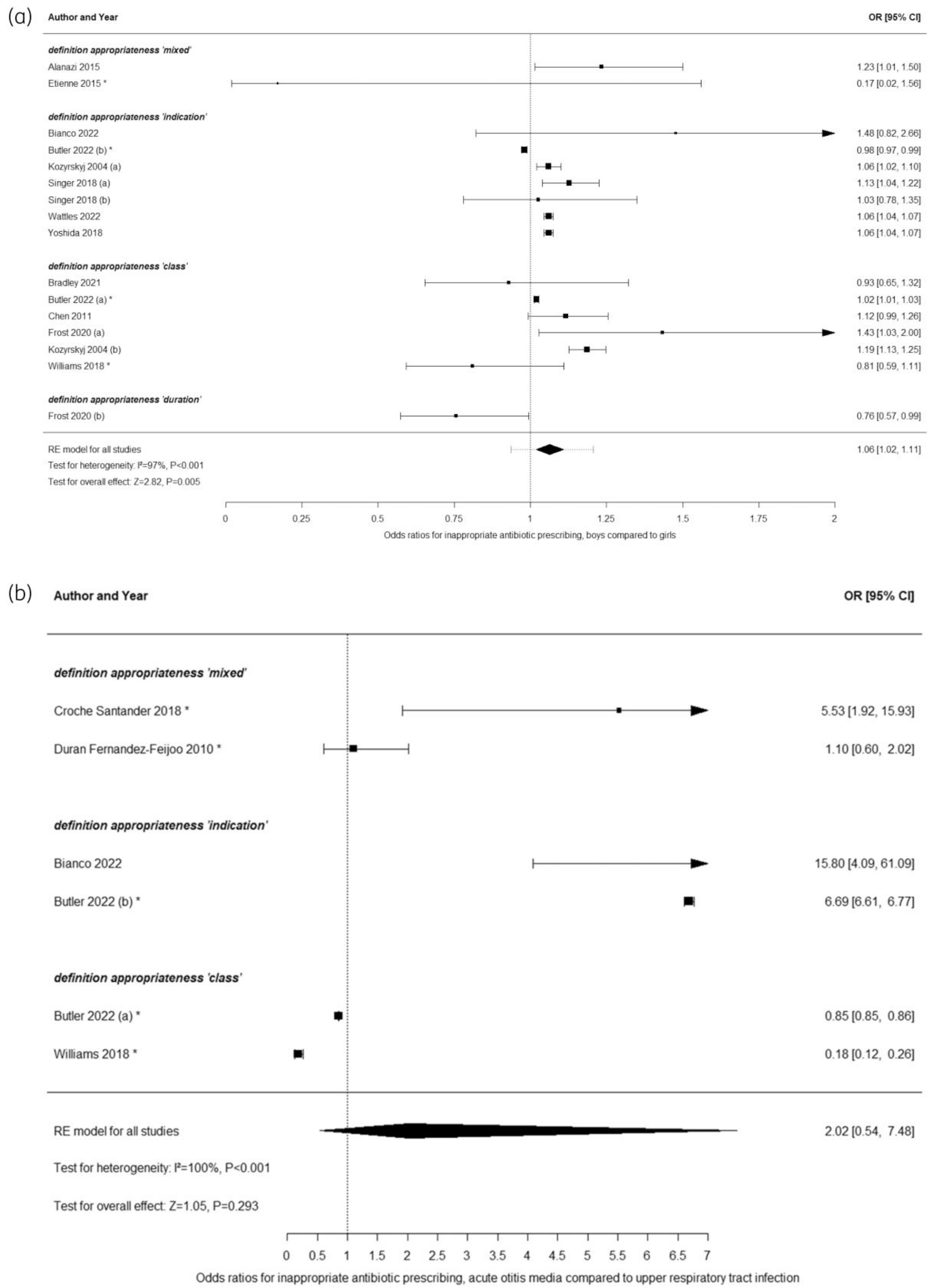

Figure 2. Forest plot of ORs for inappropriate antibiotic prescribing. (a) Boys compared with girls, (b) acute otitis media compared with upper RTI. RE, random effects. All studies report adjusted OR, unless specified otherwise. *Study reports unadjusted OR.

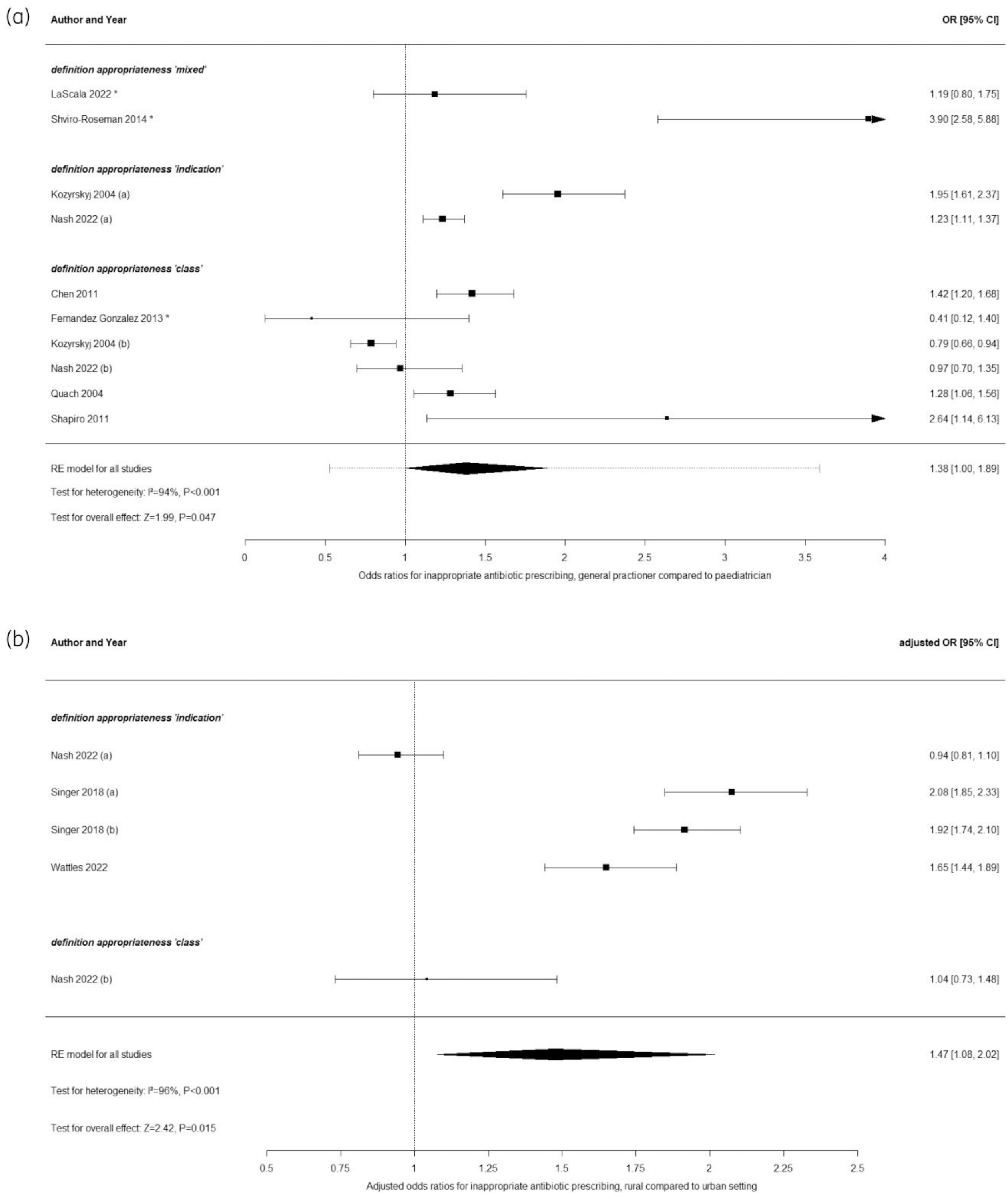

Figure 3. Forest plot of ORs for inappropriate antibiotic prescribing. (a) GP compared with paediatrician, (b) rural compared with urban setting. RE, random effects. All studies report adjusted OR, unless specified otherwise. *Study reports unadjusted OR.

are in agreement. Older patient age and an RTI diagnosis have a tendency to be positively associated with inappropriate antibiotic prescribing, but pooling of studies was not possible. Boys tended to have higher odds of inappropriate prescribing, but this effect disappeared when we only analysed studies reporting unadjusted OR. We remain uncertain about the effects of the presence of fever, an emergency setting and all other factors not included in the meta-analyses. Also, some pooled ORs (e.g. factors 'sex of the patient', 'specialty of the prescriber', 'rurality setting') were close to the value of 1, so their clinical relevance should be questioned. Finally, the relationship between inappropriateness of antibiotic prescriptions and safety outcomes was rarely studied.

Strengths and limitations

Our comprehensive search strategy, which was created in collaboration with a biomedical librarian, allowed us to include studies related to a range of diagnoses, countries and healthcare settings. In addition, we identified diverse factors in their relationship with inappropriate antibiotic prescribing. For six of them, we were able to summarize and quantify the strength of association with inappropriateness across the studies. Further, the reviewers who screened the potentially relevant records had various educational backgrounds (i.e. GP, biomedical scientist, medicine student). Also, we explored between-study heterogeneity, due to both clinical (e.g. different diagnoses) and methodological (e.g. different definitions of 'appropriateness of antibiotic prescriptions') variability, by conducting subgroup analyses and meta-regression.

This systematic review has several limitations. Most of the identified factors were not included in the meta-analysis and some relevant articles were excluded because we could not retrieve the data for children separately. Moreover, included studies were biased because the sample did not represent the target population. The impact of bias was investigated by meta-regression and sensitivity analyses and was generally small. Finally, most of the included studies collected their data from health records, which is prone to underreporting because not all diagnoses or prescriptions may be registered (e.g. during a home visit). Also, health records may not contain sufficient clinical data (e.g. signs and symptoms, comorbidities) to determine whether antibiotics are appropriate in a particular case. In our case, we adhered to the definitions of 'appropriateness of antibiotic prescriptions' provided by the authors of the included studies. In some cases, only the coded diagnosis was taken into account, while in others, the complete health record was considered for this assessment. Moreover, physicians may code the diagnosis based on the intention to prescribe antibiotics, for instance, a physician may classify bronchitis as pneumonia to justify the antibiotic prescription.[67,68]

Comparison with existing literature

Two systematic reviews have indicated that, in ambulatory care, male patients are more likely to receive an antibiotic prescription.[10,11] This is in accordance with the higher rates of inappropriate prescribing observed in boys we found in our review. However, one other systematic review suggests that female patients are more likely to receive an inappropriate prescription,[12] which contradicts the findings of our study. Importantly, these reviews considered prescriptions for both adults and children and did not provide a quantitative summary of the findings. Also, boys can be expected to behave in gender stereotypical ways, namely by avoiding the display of vulnerable emotions such as sadness or fear.[69] This may lead to a tendency among healthcare providers to underestimate the severity of illness in boys in the absence of such emotions, or conversely overestimating the seriousness when they do display negative emotions, potentially resulting in inappropriate treatment decisions. The association we found between sex of the patient and inappropriate prescribing may also be the result of a collider bias, since the majority of studies reporting on this factor mentioned adjusted OR.[70] To avoid this collider bias, we analysed the studies reporting unadjusted OR, in which we observed no evidence of effect.

Additionally, our findings suggest that older children are more likely to receive inappropriate antibiotic prescriptions. When treating younger children, physicians may be more careful about the potential side effects of the prescribed antibiotic, potentially resulting in higher guideline adherence.[45,56] Also, variations in clinical presentation and in liberality of recommendations (e.g. regarding treatment duration) may contribute to the differences in prescribing behaviour across age groups.[43,53]

Further, in accordance with the findings of our study, for RTIs in general, a significant proportion of antibiotic prescribing is considered inappropriate. Indeed, physician visits for RTIs commonly result in an antibiotic prescription, despite the fact that most upper RTIs are caused by viruses.[10,11] Next, some studies have reported that overuse of antibiotics for acute otitis media is widespread,[48,71–73] suggesting inappropriate prescribing behaviour. In our systematic review, the two studies using the antibiotic class as outcome had lower odds of inappropriate prescribing for acute otitis media compared with other RTIs. Indeed, physicians might be well aware that they should prescribe amoxicillin for acute otitis media according to guidelines, but fail to adhere to the guidance that an antibiotic prescription is seldom needed in the case of acute otitis media.[74]

Besides, one systematic review concluded that paediatricians are less likely to prescribe an antibiotic than GPs, indicating that paediatricians have better prescribing practices,[10] which is in line with our review. Paediatricians presumably have greater awareness of clinical guidelines, tend to have better access to continuing medical education and training, and are more experienced in the treatment of paediatric patients.[43,45,46,53] On the other hand, front-line providers such as GPs generally have a busy and high-volume environment, contributing to diagnostic uncertainty and influencing treatment decisions.[10]

Moreover, previous research has consistently shown that, in low-, middle- and high-income countries, antibiotic use and inappropriate antibiotic prescribing are more prevalent in rural areas compared with urban areas.[75–77] Several challenges specific to rural areas contribute to this issue, including widely distributed populations with fewer doctors per capita, resulting in physician fatigue and higher workloads.[75] Moreover, the tendency of rural clinicians to be less inclined towards adopting strategies to reduce antibiotic prescriptions, the poorer health status of the rural population, and limited resource allocations are additional factors influencing inappropriate prescribing behaviour.[75]

Implications for clinical practice and further research

Antimicrobial stewardship can be defined as a coherent set of actions that promote using antimicrobials responsibly.[78] This concept applies to various levels, ranging from individual actions to global initiatives, encompassing human health, animal health and the environment.[78] Responsible use of antimicrobials requires tailored actions that are context-specific.[78] This review showed that, in high-income countries, inappropriate antibiotic prescribing is more common for acute otitis media, by GPs, in rural settings, for older children, and for RTIs. Therefore, it is recommended that antimicrobial stewardship programmes prioritize these specific situations. Several examples of antimicrobial stewardship actions include decision-support tools, audit and feedback, support for adhering to antimicrobial guidelines, fixed pack dispensing, and public awareness campaigns.[78]

Further, this review emphasizes the need for a standardized definition and evaluation of appropriate antibiotic prescribing. According to the WHO, responsible and appropriate use of antimicrobials includes prescribing only when needed, selection of the optimal drug regimen, drug dosing, route of administration and duration of treatment following proper and optimized diagnosis.[79] Adequate monitoring of antimicrobial use enables proper assessment of the effectiveness of antimicrobial stewardship activities.[79]

Besides, further research should investigate the individual-level consequences of inappropriate antibiotic prescribing, since safety outcomes such as adverse events and hospitalizations remain largely unexplored. Lastly, it is critical for future studies to collect data for children separately, as this population is the most vulnerable for inappropriate antibiotic prescribing.[1]

Conclusions

In summary, prioritizing acute otitis media, GPs, rural areas, older children and RTIs within antimicrobial stewardship programmes plays a vital role in promoting responsible antibiotic prescribing. The implementation of a standardized definition of appropriateness is essential to evaluate such programmes.

Acknowledgements

The authors declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. Preliminary results were disclosed at the WONCA Europe conference (9 June 2023).

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Transparency declarations

None to declare.

Supplementary data

Figures S1 to S13 and Tables S1 to S79 are available as Supplementary data at *JAC* Online.

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