Antibiotic use in ambulatory care for acutely ill children in high-income countries: a systematic review and meta-analysis

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ABSTRACT

Objective To determine the rate and appropriateness of antibiotic prescribing for acutely ill children in ambulatory care in high-income countries.

Design On 10 February 2021, we systematically searched articles published since 2000 in MEDLINE, Embase, CENTRAL, Web Of Science and grey literature databases. We included cross-sectional and longitudinal studies, time-series analyses, randomised controlled trials and non-randomised studies of interventions with acutely ill children up to and including 12 years of age in ambulatory care settings in high-income countries. Pooled antibiotic prescribing and appropriateness rates were calculated using random-effects models. Meta-regression was performed to describe the relationship between the antibiotic prescribing rate and study-level covariates.

Results We included 86 studies comprising 11 114 863 children. We found a pooled antibiotic prescribing rate of 45.4% (95% CI 38.2% to 52.8%) for all acutely ill children, and 85.6% (95% CI 73.3% to 92.9%) for acute otitis media, 37.4% (95% CI 30.9% to 44.3%) for respiratory tract infections, and 40.4% (95% CI 29.9% to 51.9%) for other diagnoses. Considerable heterogeneity can only partly be explained by differences in diagnoses. The overall pooled appropriateness rate is 68.5% (95% CI 55.8% to 78.9%, I^2=99.8%; 19 studies, 119 995 participants). 38.3% of all prescribed antibiotics were aminopenicillins.

Conclusions Antibiotic prescribing rates for acutely ill children in ambulatory care in high-income countries remain high. Large differences in prescription rates between studies can only partly be explained by differences in diagnoses. Better registration and further research are needed to investigate patient-level data on diagnosis and appropriateness.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ambulatory care is where most antibiotics are prescribed and children are often inappropriately prescribed antibiotics.
⇒ Recent data on the use of antibiotics for acutely ill children presenting to ambulatory care in high-income countries are lacking.
⇒ These data can provide insights into the illnesses for which antibiotics are mainly prescribed and support decisions on the conditions to which antibiotic stewardship interventions could be most usefully applied.

WHAT THIS STUDY ADDS

⇒ Antibiotic prescribing rates for acutely ill children in ambulatory care in high-income countries are estimated to be around 45.4%, with large differences between diagnoses.
⇒ About one-fifth to one-half of these antibiotic prescriptions are estimated to be inappropriate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More comparable antibiotic prescription data for acutely ill children in ambulatory care are needed as heterogeneity in the existing literature is omnipresent.
⇒ Adequate antibiotic stewardship programmes focusing on policy, regulatory and clinical strategies are required to minimise inappropriateness of antibiotic prescribing.

INTRODUCTION

Due to antimicrobial resistance (AMR), common diseases might become untreatable and patients with resistant infections are sicker for longer and use more antibiotics.[1] In 2019, about 1.27 million deaths were attributable to bacterial AMR.[2] By 2050, costs are projected to be US$100 trillion worldwide if no action is taken.[3] Access to vaccines (eg, pneumococcal conjugate vaccines (PCVs)) could reduce the burden of infectious diseases and AMR.[1]

In high-income countries, most acute childhood infections are viral and self-limiting. Nevertheless, primary care accounts for 80%–90% of all antibiotic prescriptions.[4] Diagnostic uncertainty can lead to inappropriate antibiotic prescribing[5] and clinician characteristics (eg, specialism and age) influence prescribing.[6] Clinicians can also be influenced by consultation time restraints, and they can perceive pressure from day-care providers, employers or parents who believe antibiotics are required to treat their ill child.[7] Furthermore, physicians may incorrectly assume the patient or parent expects antibiotics.[7] A clinician's uncertainty about the social, health, or legal consequences of not prescribing can also negatively influence antibiotic prescribing.[7]

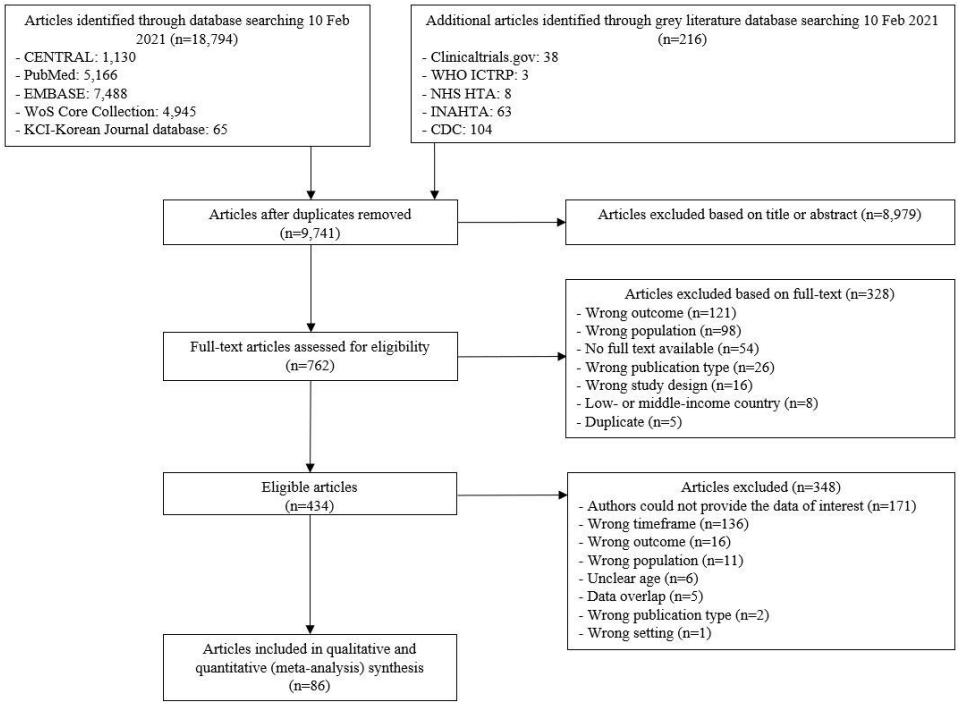

Figure 1 PRISMA flow chart. Study identification and process for selection of studies included in the review. 'Authors could not provide the data of interest': this occurred when the authors did not reply after one email and at least two reminders, or when the authors were not able to provide data of only children up to and including 12 years of age. 'Wrong time frame' means that data were collected entirely before the introduction of pneumococcal vaccination in the country where the research was conducted. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data on antibiotic prescribing rates by diagnosis and appropriateness provide an overall framework for studies in this field and inform clinicians on their prescribing practices. These data also provide insights into potential interventions to combat inappropriate prescribing, which is essential to tackle AMR. Recent reviews of these data are lacking. Records on antibiotic use for various infections are still fragmented and difficult to retrieve.[8] Previous reviews on prescribing rates for children are outdated and survey based,[9] examine drug prescriptions in general,[10 11] are either performed in an inpatient or very specific setting,[11 12] or do not address acutely ill children specifically.[9 10] In this systematic review, we aim to collate all available evidence on the proportion of acutely ill children being prescribed antibiotics in ambulatory care in high-income countries and evaluate the appropriateness of these prescriptions.

METHODS

This systematic review follows the Meta-analysis of Observational Studies in Epidemiology reporting checklist (online supplemental material)[13] and was prospectively registered on PROSPERO.[14]

Search strategy

On 10 February 2021, we systematically searched MEDLINE, Embase, Cochrane-CENTRAL, Web Of Science, and grey literature from 2000 onwards without language restrictions (online supplemental file). To achieve as much homogeneity in our case-mix as possible, we opted to only include studies conducted after the implementation of PCVs, with the first implementation occurring in the USA in October 2000. Hand searching was not performed.

Inclusion and exclusion criteria

References reporting on the antibiotic prescribing rate for acutely ill children presenting to ambulatory care (ie, outpatient care) in high-income countries[15] were eligible.

Outcomes

The antibiotic prescribing rate (primary outcome) had to be specified in the article as the ratio of the number of acutely ill children receiving at least one antibiotic prescription over all acutely ill children, or the ratio of the number of acutely ill children with a certain diagnosis receiving at least one antibiotic prescription over all acutely ill children with a certain diagnosis.

Secondary outcomes included: the appropriateness of antibiotic prescriptions (ie, the proportion of antibiotic prescriptions deemed appropriate by the authors of the respective study) and the type of prescribed antibiotic (ie, which antibiotic classes were prescribed).

Study characteristics

We included cross-sectional and cohort studies, time-series analyses, health agency reports, and control group data (representing usual care) from randomised controlled trials (RCTs) and non-randomised intervention studies. Records were eligible if they included data after introduction of PCVs in the country where the data were collected.

Patient characteristics and setting

Studies including patients of any age were eligible. Authors reporting data on participants up to and older than 12 years of age were requested to provide data of only the participants

Table 1 Characteristics of studies included in the review

Diagnosis (n)	Setting (n)	Studies
AOM (102 967)	ED (3461)	Boatright 2015 (USA), Palma 2015 (Italy), Rothman 2018 (Israel), Balasundaram 2019 (Australia)
	GP (15 545)	Pouwels 2018 (UK), Barrera 2019 (USA), Olsen 2020 (Denmark), van Uum 2020 (the Netherlands)
	Mixed (78 563)	Coco 2010 (USA), Speets 2011 (Sweden), Yang 2016 (Korea)
	Paediatrician (5398)	Levy 2011 (France), Usonis 2016 (Estonia, Lithuania, Poland, Romania, Slovenia)
RTI (10 783 966)	ED (319 832)	Doan 2009 (Canada), Angoulvant 2012 (France), Ouldali 2017 (France), Gotta 2017 (Switzerland), Messina 2019 (Italy), Papenburg 2019 (USA), Van De Maat 2019 (the Netherlands), van Houten 2019 (Israel, the Netherlands), Burrowes 2020 (USA), Flood 2020 (USA), Pulia 2020 (USA), Zipursky 2020 (Australia, Canada, Ireland, New Zealand, Portugal, Spain, UK, USA)
	GP (63 362)	Francis 2009 (UK), Biezen 2015 (Australia), Dallas 2016 (Australia), Magin 2016 (Australia), Blair 2017 (UK), Dallas 2017 (Australia), Freer 2017 (UK), Kraus 2017 (Germany), Lindberg 2017 (Norway), Mehta 2017 (UK), Razai 2017 (UK), Ivanovska 2018 (the Netherlands), Maguire 2018 (Ireland), Redmond 2018 (UK), van Vugt 2018 (the Netherlands), Bernardo 2019 (Australia), Patel 2019 (Australia), van Aerde 2021 (the Netherlands)
	Mixed (10 357 656)	Nadeem Ahmed 2010 (USA), Hebert 2012 (USA), Ebell 2015 (USA), Malo 2015 (Spain), Al-Tawfiq 2017 (Saudi Arabia), Frost 2018 (USA), Havers 2018 (USA), Williams 2018 (UK), Andrade 2019 (Portugal), Kimura 2019 (Japan), Montejo 2019 (Spain), Montejo Fernández 2019 (Spain), Ray 2019 (USA), Teratani 2019 (Japan), Florin 2020 (USA)
	Paediatrician (43 116)	Christakis 2005 (USA), Arnold 2006 (USA), Kjærgaard 2019 (Greece), Zhou 2019 (USA), Kronman 2020 (USA)
GE (4843)	GP (205)	Stefanoff 2013 (Poland)
	Mixed (4638)	Schmutz 2017 (Switzerland), Okubo 2019 (Japan)
Other (223 087)	ED (49 806)	Kharazmi 2012 (USA), Jain 2014 (USA), Khine 2014 (USA), Dumitrascu-Biris 2016 (Ireland), Rebnord 2016 (Norway), Leigh 2019 (UK), Piller 2019 (Switzerland), Hagedoorn 2020 (Austria, Germany, Greece, Latvia, the Netherlands, Spain, Slovenia, UK), Ramgopal 2020 (USA)
	GP (32 726)	Zolaly 2011 (Saudi Arabia), Elshout 2013 (the Netherlands), de Bont 2015 (the Netherlands), O'Brien 2015 (UK), de Bont 2018 (the Netherlands), Dumpis 2018 (Latvia, Lithuania, Sweden), Lemiengre 2018 (Belgium), Howarth 2020 (Australia), Davey 2020 (Australia)
	Mixed (138 338)	Trinh 2020 (France)
	Paediatrician (2217)	van Esso 2020 (Spain)

AOM, acute otitis media; ED, emergency department; GE, gastroenteritis; GP, general practitioner; n, sample size; RTI, respiratory tract infection.

up to 12 years. Studies targeting children with comorbidities or chronic diseases were excluded.

Study selection

Search results were imported into EndNote and duplicates were removed.[16] Two reviewers independently screened all studies by title and abstract and by full text.

Data extraction

Data were extracted by one reviewer and checked by another. Disagreements were resolved through discussion or by a third reviewer. If additional study information, data or documents were required, authors were contacted. In addition to study population characteristics, we extracted the number of acutely ill children with a certain diagnosis receiving at least one antibiotic prescription, and all acutely ill children with a certain diagnosis. We extracted the number or percentage of prescriptions deemed appropriate by the authors and the total number of prescriptions. Countries were classified according to their geographical region. Settings were categorised as 'General Practitioner', 'Emergency Department', 'Paediatrician', or 'Other'. Diagnoses were coded as 'Respiratory Tract Infection', 'Acute Otitis Media', 'Gastroenteritis', and 'Other'.

Risk of bias assessment

The risk of bias was evaluated independently by two reviewers. We used the Appraisal tool for Cross-Sectional Studies (AXIS)[17] for cross-sectional studies, cohort studies and time-series analyses (omitting questions 8 and 9), and the Cochrane Risk of Bias Assessment Tool 2.0 (RoB 2.0) for RCTs.[18]

Data analysis

The logit-transformed antibiotic prescribing rates and appropriateness of prescriptions were pooled using random-effects meta-analysis models to calculate pooled rates with 95% CIs and 95% prediction intervals (PIs).[19] The results were transformed back to proportions (inverse logit). We used the restricted maximum-likelihood estimator method to estimate the heterogeneity variance tau^2.[20] The Hartung-Knapp-Sidik-Jonkman adjustments were used to calculate the CIs.[21 22] Cochran's Q, H^2, I^2 and tau^2 were used to quantify heterogeneity.[23] For 'Type of Prescribed Antibiotic', we calculated percentages per antibiotic type and constructed bar charts using Excel.

Subgroup analyses were performed for each diagnosis group with at least four studies.

Multivariable meta-regression on logit-transformed data was performed to describe the relationship between the antibiotic prescribing rate and study-level covariates (diagnosis, region, setting, age, and midpoint of data collection).

For all studies and subgroups containing at least 10 studies, funnel plots were constructed and Egger's regression test was used to detect small study biases.[24 25] We computed various outlier and influential case diagnostics by calculating leave-one-out diagnostics for each case.

Sensitivity analyses were performed by excluding studies with a high risk of bias, small studies (sample size <500), and studies with influential outlying values.

We used R V.4.0.2[26] and the Metafor[20] and Meta[27] packages.

RESULTS

From the database search, 19 010 records were identified (figure 1). After removing duplicates and screening, 434 articles

remained. During data extraction, we excluded 348 articles, mostly because authors could not provide the data of interest (n=171) or because the study was conducted entirely before the introduction of PCVs of the respective country (n=136). Finally, 86 articles were included.

Characteristics and quality of the studies

Study characteristics

Study characteristics are summarised in table 1, details are shown in the online supplemental file. Most studies were observational: 59 longitudinal and 17 cross-sectional studies, and 1 time-series analysis. Nine studies were RCTs. The most common data sources were medical records (n=36). Most of the studies were conducted in Western Europe (n=29) and general practice offices (n=32). Most studies evaluated antibiotic prescriptions for respiratory tract infections (RTIs) (n=50) and 13 articles examined acute otitis media (AOM) separately. Three studies investigated gastroenteritis (GE). The 'Other' group contained one study on urinary tract infections and one on skin and soft tissue infections; the remaining 18 studies investigated multiple diagnoses relating to several organ systems. Study participants were equal to or younger than 5 years in 30 studies.

Risk of bias

Of the 77 studies evaluated with the AXIS tool, 9 had potential selection bias. The Cochrane RoB 2.0 tool was used for nine studies. One had an overall high risk of bias, four had some concerns and four had low risk of bias (online supplemental material).

Primary outcome: antibiotic prescribing rate

The pooled antibiotic prescribing rates in the diagnosis subgroups are: 'AOM' 85.6% (95% CI 73.3% to 92.9%, 95% PI 25.5% to 99.0%, I^2=99.9%; 13 studies, 102 967 participants), 'RTI' 37.4% (95% CI 30.9% to 44.3%, 95% PI 7.6 to 81.2, I^2=100%; 50 studies, 10 783 966 participants) and 'Other' 40.4% (95% CI 29.9% to 51.9%, 95% PI 8.2 to 83.8, I^2=99.9%; 20 studies, 22 3087 participants). The overall pooled antibiotic prescribing rate is 45.4% (95% CI 38.2% to 52.8%, 95% PI 5.3 to 92.6, I^2=100%; 86 studies, 11 114 863 participants) (figure 2).

The multivariable meta-regression model including all studies (adjusted R^2=47.6%, I^2=99.9%) was significant for the diagnoses covariates: 'AOM' (intercept)=1.77 (95% CI −0.50 to 4.04, p=0.125), 'RTI'=−2.41 (95% CI −3.09 to −1.74, p<0.0001), GE=−3.47 (95% CI −4.93 to −2.01, p<0.0001), 'Other'=−2.14 (95% CI −2.92 to −1.36, p<0.0001). The other covariates (ie, region, setting, age and midpoint of data collection) were not significant. Egger's regression test for the 'Overall' group was significant (p=0.0004). P values in the diagnosis subgroups were 0.1502, 0.0145, and 0.0081 for 'AOM', 'RTI', and 'Other', respectively. One influential outlier was identified in the 'Overall' group (online supplemental material).

Secondary outcomes

Appropriateness of antibiotic prescriptions

Nineteen papers reported this outcome, which was assessed by guideline concordance (n=12), indication appropriateness (n=6) or European Surveillance of Antimicrobial Consumption Network (ESAC-Net) quality indicators (n=1). The overall pooled appropriateness rate is 68.5% (95% CI 55.8% to 78.9%, 95% PI 18.4 to 95.4, I^2=99.8%; 19 studies, 119 995 participants). For the 'RTI' diagnosis group, the pooled appropriateness rate is 68.0% (95% CI 49.6% to 82.1%, 95% PI 12.5 to 96.9, I^2=99.7%; 13 studies, 106 397 participants) (figure 3).

Egger's tests were not significant and no influential outliers were identified for either groups (online supplemental material).

Type of prescribed antibiotic

Thirty-nine papers reported this outcome (figure 4 and online supplemental file). Aminopenicillins were prescribed the most often (38.3% of all antibiotics), followed by other penicillins (17.5%), cephalosporins (11.8%), amoxicillin-clavulanate (13.5%), macrolides (10.6%), other (combinations of) antibiotics (6.5%), sulfamethoxazole and/or trimethoprim (1.4%), and quinolones (0.5%). Out of all diagnoses, penicillins were most often prescribed for AOM (n=10) and least often for GE (n=1): 54.1% vs 31.8%. Conversely, both macrolides and cephalosporins were prescribed most frequently for GE and least frequently for AOM: 18.2% and 18.2% vs 11.3% and 10.2%, respectively. In Scandinavia (n=2), children are prescribed notably less amoxicillin(-clavulanate) compared with other types of penicillins: 16.6% and 64.9%, respectively. Amoxicillin-clavulanate is prescribed most often in Southern Europe (n=3): 36.1% (online supplemental file).

Sensitivity analyses

The sensitivity analyses yielded no different results. When there was funnel plot asymmetry, this was no longer the case when we removed studies with small sample size. Removing studies with high risk of bias only changed the result of Egger's test in the 'RTI' group: no longer significant (p=0.133). Without the outlier study, the funnel plot asymmetry in the 'Overall' group remained (p=0.0003) (online supplemental file 3).

DISCUSSION

Principal findings

We retrieved 86 articles with data from 11 114 863 participants. We found pooled prescribing rates of 85.6% for AOM, 37.4% for RTI and 40.4% for other infections, all with considerable heterogeneity. Overall, we found a pooled antibiotic prescribing rate of 45.4%, but this is of limited clinical value due to heterogeneity. Sensitivity analyses did not lead to different results. Meta-regression showed that only the diagnosis groups can partly explain variability in prescribing rates between studies. Approximately one-third of antibiotic prescriptions were inappropriate. Aminopenicillins were prescribed the most often. Egger's tests suggest small study biases in the 'Overall', the 'RTI' and the 'Other' groups.

Strengths and weaknesses

Our comprehensive search strategy included relevant databases as well as grey literature. We summarised literature across a large number of countries, diagnoses and healthcare settings. We linked antibiotic prescription rates to diagnoses, that is, we know which diagnoses the antibiotics were prescribed for. This is highly valuable information and was mostly unavailable in previous research.[9–11 28] Moreover, we contacted 431 authors at least once and received additional data for 36 articles, allowing a more comprehensive analysis. The main limitation of this study is the high amount of between-study heterogeneity for all outcomes. Hence, these meta-analytical results should be interpreted with caution and no firm clinical conclusions can be drawn from them. Meta-regression analysis showed that heterogeneity could only be explained in part by the diagnosis covariate. However, much residual heterogeneity remained. Q

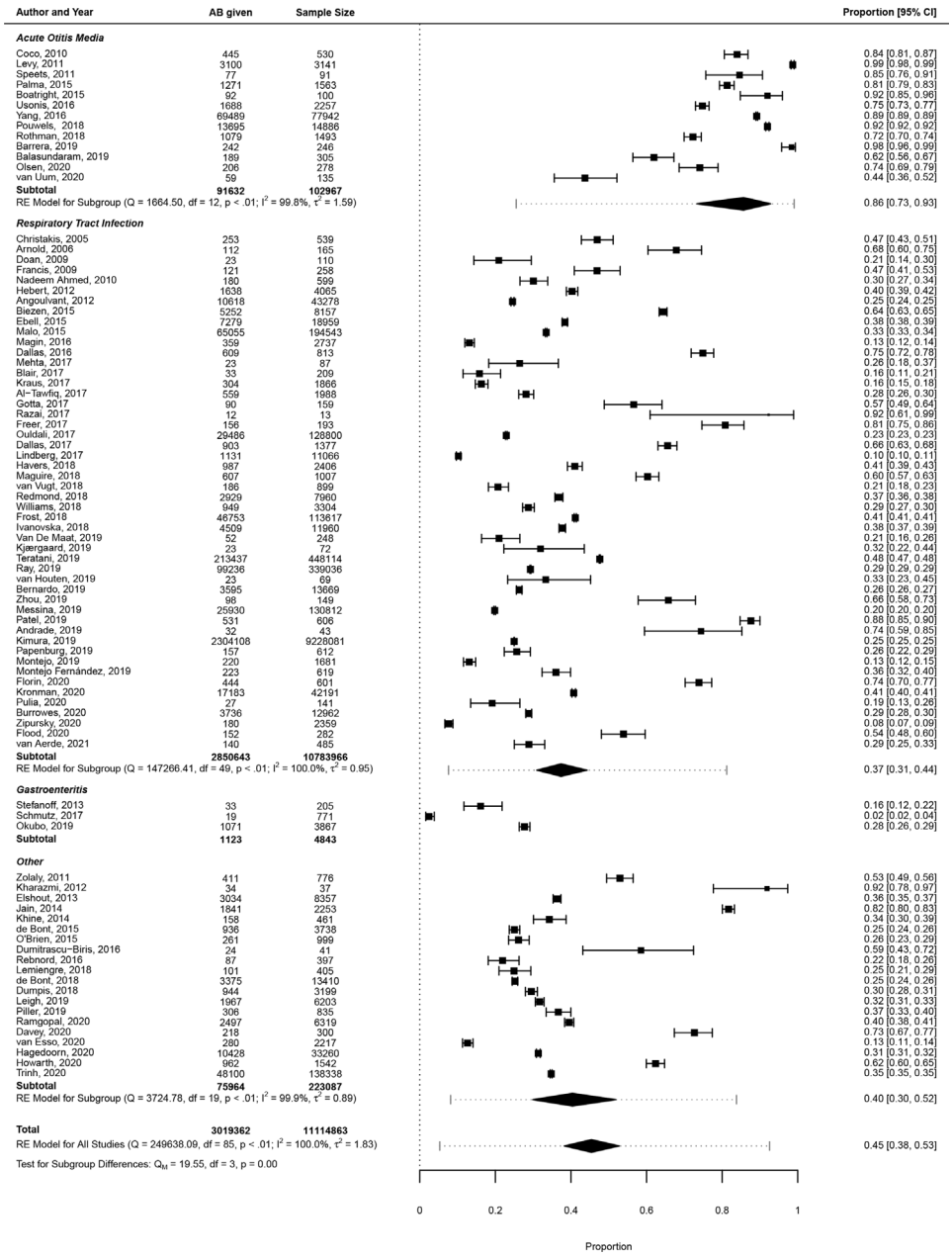

Figure 2 Forest plot for antibiotic prescribing rate (primary outcome). AB, antibiotics; RE, random effects.

and its derivatives I^2 and H^2 rapidly increase with increasing number of studies and increasing sample size,[29] therefore the test has a high power to detect a small amount of heterogeneity that may not be clinically important.[30] Hence, our large number of studies and large sample size generate consistently high values of those measures of heterogeneity. Tau^2 is insensitive to the number of studies and their precision, but its values in our analyses are also high. In order to generate more homogeneous data, we compared studies with the same diagnosis and setting, but still heterogeneity remained. Further, we analysed prescription rates, which makes it impossible to estimate whether the prescription was collected at the pharmacy and appropriately taken by the patient. Another source of bias is the fact that we only included published data or published reports from prescription databases. We did not examine data from those databases directly. Besides, a large proportion of the data in the included studies was collected via health records, which are prone to under-reporting, because not all diagnoses or prescriptions may be registered.

Comparison with existing literature

Our overall antibiotic prescription rate (45.4%) is higher compared with previously reported antibiotic prescription rates for outpatient children, that is, 34% (reported by two systematic reviews in 2007[9] and 2009[10]) and 38% (Belgian report[31]). This is as expected, since the previously reported rates were calculated in relation to the number of inhabitants, whereas our review only considered acutely ill children. This review confirms that heterogeneity is intrinsic to this type of research.[9–12] Compared with similar reviews,[9–12] this review represents a greater number of countries and healthcare settings. Further, we used a more elaborate search strategy.

Implications for clinical practice and further research

Adequate antibiotic stewardship programmes focusing on policy, regulatory and clinical strategies have existed for a while.[32] Nonetheless, prescription inappropriateness rates remain high.

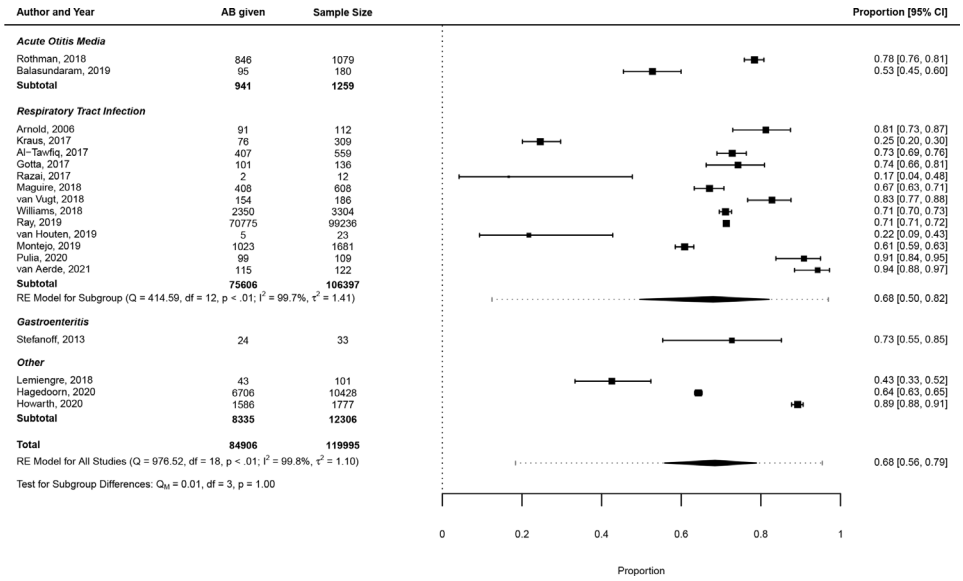

Figure 3 Forest plot for appropriateness of prescriptions (secondary outcome). AB, antibiotics; RE, random effects.

To achieve the reductions in inappropriate antibiotic prescribing necessary to tackle AMR, a paradigm shift in antibiotic stewardship is required to translate policy into clinical practice.

More comparable antibiotic prescription data for acutely ill children are needed as heterogeneity in the literature is omnipresent. Standardisation of antibiotic prescription data by country linked to diagnoses is essential for the evaluation of prescribing practices. It is also critical to collect data for children separately, as this is a population for which antibiotics are often prescribed unnecessarily. Furthermore, we only included studies that reported an antibiotic prescribing rate and we explored appropriateness of prescribing only when this was described. Further research is needed to investigate appropriateness of antibiotic prescriptions for children, in order to provide suggestions for targeted interventions to minimise inappropriate antibiotic prescribing. Similar research is required in low- to middle-income countries, where the rates and inappropriateness of antimicrobial prescribing are even higher.[33 34]

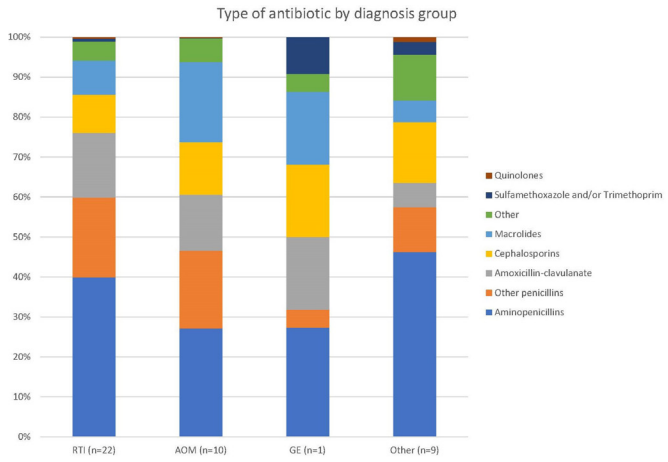

Figure 4 Type of antibiotic as percentage of total antibiotics prescribed for each diagnosis group (secondary outcome). Some authors provided data for multiple diagnoses. In those cases, the data were split up (online supplemental file). Hence, adding up all sample sizes (n) gives a number (42) larger than the number of studies that provided data on type of prescribed antibiotic (39). AOM, acute otitis media; GE, gastroenteritis; RTI, respiratory tract infection.

CONCLUSION

Antibiotic prescribing rates for acutely ill children in ambulatory care in high-income countries remain high. Large differences in prescription rates between studies can partly be explained by differences in diagnosis. About one-fifth to one-half of antibiotic prescriptions are inappropriate, and aminopenicillins are the most prescribed antibiotic. Better registration and further research are needed to investigate patient-level data on diagnosis and appropriateness.

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