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%); I² = 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 medical 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 prescribing 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.

In high-income countries, most acute childhood infections are viral and self-limiting. Nevertheless, primary care accounts for 80%–90% of all antibiotic prescriptions. Diagnostic uncertainty can lead to inappropriate antibiotic prescribing and clinician characteristics (eg, specialist and age) influence prescribing. 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. Furthermore, physicians may incorrectly assume the patient or parent expects antibiotics. A clinician’s uncertainty about the social, health, or legal consequences of not prescribing can also negatively influence antibiotic prescribing.
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.

Previous reviews on prescribing rates for children are outdated and survey based, examine drug prescriptions in general, are either performed in an inpatient or very specific setting, or do not address acutely ill children specifically. 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) and was prospectively registered on PROSPERO.

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 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
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 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 tau².20 The Hartung-Knapp-Sidik-Jonkman adjustments were used to calculate the CIs.21 22 Cochran’s Q, H², I² and tau² were used to quantify heterogeneity.21 22 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.4.0.226 and the Metafor20 and Meta27 packages.

**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). The results were transformed back to proportions (inverse logit). We used the restricted maximum-likelihood estimator method to estimate the heterogeneity variance tau². The Hartung-Knapp-Sidik-Jonkman adjustments were used to calculate the CIs. Cochran’s Q, H², I² and tau² were used to quantify heterogeneity. For ‘Type of Prescribed Antibiotic’, we calculated percentages per antibiotic type and constructed bar charts using Excel.

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**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%, I²=99.9%; 13 studies, 102 967 participants), ‘RTI’ 37.4% (95% CI 30.9% to 44.3%, 95% PI 7.6 to 81.2, I²=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, I²=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, I²=100%; 86 studies, 11 114 863 participants) (figure 2).

The multivariable meta-regression model including all studies (adjusted R²=47.6%, I²=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, I²=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, I²=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. 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.

and its derivatives I² and H² rapidly increase with increasing number of studies and increasing sample size, therefore the test has a high power to detect a small amount of heterogeneity that may not be clinically important. Hence, our large number of studies and large sample size generate consistently high values of those measures of heterogeneity. Tau² 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 and 2009) and 38% (Belgian report). 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. Compared with similar reviews, 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. Nonetheless, prescription inappropriateness rates remain high.

Figure 2  Forest plot for antibiotic prescribing rate (primary 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

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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