Antibiotic prescription for febrile children in European emergency departments: a cross-sectional, observational study

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Summary

Background Prevalence of serious bacterial infections in children in countries in western Europe and the USA is low. Antibiotic stewardship aims at a more rational use of antibiotics but information on the frequency of antibiotic prescription to children in emergency departments is scarce. We aimed to quantify and explain variability in antibiotic prescription in children attending European paediatric emergency departments.

Methods We did a cross-sectional, observational study of children aged between 1 month and 16 years who presented with fever to one of 28 European emergency departments on one random sampling day per month between Nov 1, 2014, and Feb 28, 2016. The surveyed sites were spread across 11 countries and included 17 academic hospitals with 3000 to up to 80 000 annual visits to their paediatric emergency departments. We determined the proportion of children without comorbidities who received antibiotic prescriptions by country, focus of infection, and type of antibiotic. We then did a detailed analysis of the same population, using a multilevel logistic regression analysis, into the variability in prescriptions across hospitals, focusing particularly on respiratory tract infections and correcting for a combination of result-dependent factors. Random group assignment was done by computer randomisation.

Findings Of 5177 children in total, 617 children had comorbidities. Of the 4560 children without comorbidities, 1454 (32%) received antibiotics. This percentage varied from 19% to 64% across countries. Of these 1454 prescriptions issued, 893 (61%) were second-line antibiotics. Antibiotic prescription for respiratory tract infections, the most common infection type, in children without comorbidities was most variable across countries (15–67% for upper respiratory tract infections and 24–87% for lower respiratory tract infections) and was associated with age (odds ratio [OR] 1·51, 95% CI 1·08–2·13), fever duration (OR 1·45, 1·01–2·07), blood concentrations of C-reactive protein (OR 2·31, 1·67–3·19), and chest x-ray results (OR 10·62, 5·65–19·94, for focal abnormalities; OR 3·49, 1·59–7·64, for diffuse abnormalities). After correcting for patient characteristics, diagnostic assessment, and hospital characteristics, antibiotic prescription for respiratory tract infections remained highly variable across emergency departments (standardised antibiotic prescription ratio 0·49–2·04).

Interpretation Antibiotic prescription in European emergency departments is highly variable, with frequent use of second-line antibiotics. To ensure successful antibiotic stewardship initiatives in Europe aimed at reducing unnecessary prescription of antibiotics, variability of prescription across hospitals should be considered, drivers of suboptimal antibiotic prescription at the local level need to be identified, and European guidelines need to be devised.

Funding None.

Introduction

Fever is one of the most frequent reasons for children to visit the emergency department.[1] A small proportion (5–15%) of these children have a serious bacterial infection, of which respiratory tract infections cause the highest mortality.[2] Variability in the management of respiratory tract infections suggests that there is overdiagnosis of bacterial infections and overtreatment with antibiotics,[3–5] fuelling antibiotic resistance.[6]

To reduce inappropriate antibiotic use, antibiotic stewardship programmes have been launched worldwide[7] but few of them include the emergency department.[8] Studies on antibiotic prescription in febrile children often focus on primary care or in-hospital settings.[9,10] Information about antibiotic prescription in emergency department settings is mostly derived secondarily from studies of selected populations, and it is not supported by primary studies.[11] To implement effective interventions for antibiotic stewardship, having access to data from emergency departments on antibiotic prescription and understanding the factors that influence antibiotic prescription in this setting is then crucial.

This cross-sectional, observational study aims to fill this gap by answering the following questions: (1) what is the current proportion of antibiotic prescriptions given to febrile children visiting European paediatric emergency departments; and (2) can differences in patient characteristics, diagnostic assessment, or hospital setting explain the variability in antibiotic prescription?

Research in context

Evidence before this study

Evidence on antibiotic prescription in febrile children attending emergency departments is inconclusive. We searched Embase, MEDLINE, Web of Science, Scopus, CINAHL, Cochrane, PubMed, and Google Scholar for studies on antibiotic prescription in febrile children in emergency departments, published between Jan 1, 2000, and Nov 1, 2018. We used the keywords "fever", "antibiotics", "emergency department", "children", and "antibiotic prescription" and checked references for additional relevant articles. We assessed the risk of bias using the methodological index for non-randomised studies (MINORS) criteria. There is evidence for the effectiveness of reducing antibiotic prescription to children with respiratory tract infections or acute otitis media by delaying prescription. Determinants of antibiotic prescription in children in emergency departments are unknown. The available studies are highly heterogeneous, reducing the possibility to pool their results and to draw firm conclusions.

Added value of this study

This international, prospective, observational study shows that most antibiotics prescribed to children in European emergency departments target respiratory tract infections, with high variability across hospitals and countries. Determinants of antibiotic prescription for respiratory tract infections are age, duration of fever, blood concentrations of C-reactive protein, and chest x-ray results. Differences in antibiotic prescription across paediatric emergency departments cannot be explained only by patient characteristics, diagnostic assessment procedures, or hospital characteristics.

Implications of all the available evidence

Interventions to reduce antibiotic prescription in emergency departments should target children with respiratory tract infections. The unexplained variability of antibiotic prescription across emergency departments emphasises the need for a multicentre and international approach in future studies and interventions. To ensure that antibiotic stewardship initiatives are successful internationally, factors associated with suboptimal antibiotic prescription in individual hospitals and nationally need to be identified and international guidelines for antibiotic prescription for respiratory tract infections need to be developed.

Methods

Study design and participants

We did a cross-sectional, observational study at European paediatric emergency departments (figure 1, appendix). 28 hospitals participating in the Research in European Pediatric Emergency Medicine (REPEM) network were invited.[12] We included children aged between 1 month and 16 years who visited the emergency department with fever as the reason for consultation, irrespective of additional symptoms, between Nov 1, 2014, and Feb 28, 2016. We excluded patients if they repeatedly visited the emergency department for the same problem within 7 days, if they had used antibiotics 7 days before their visit to the emergency department, and if they had an antibiotic allergy.

This study was approved by the medical ethics committee of the Erasmus Medical Center (MEC-2014–419) and local feasibility was approved by the ethics committees of all participating hospitals. The need for obtaining written informed consent was waived, except by the ethics committee of Cruces Hospital, Bilbao, Spain. These local researchers obtained written informed consent from all their participants. The protocol development and conduct of the study was done without collaboration with patient groups.

Procedures

Each month, hospitals were randomly assigned one sampling day. Hospitals were divided into ten groups, and each group was randomly assigned to one calendar day each month via computer randomisation. All hospitals participated in data collection for 12 consecutive months. A sampling day ran from 0730 h to 0730 h (24 h) and there was a period of 2–6 weeks between sampling days. To avoid inclusion bias, we collected data from all children who met our inclusion criteria and visited the emergency department on the random sampling days. Data were prospectively collected via an electronic questionnaire (appendix) that included general characteristics of the patient, method of referral, triage level, clinical signs and symptoms, additional diagnostics (table 1), presumed focus of infection at time of discharge from the emergency department, treatment, and disposition. All questionnaire items were mandatory but always included the option "not known". Each hospital had one or two physicians dedicated to data collection. 1 week before each sampling day, the responsible physician for each hospital was informed of the date, and a reminder email with instructions for data collection was sent by the principal investigator on the sampling day. After a sampling day, data integrity was evaluated by the principal investigator and the local physicians who collected the data were provided with feedback on completeness and potential errors, in order to optimise the data collection process. Information on immunisation coverage for 2014–16 was retrieved from the WHO UNICEF Review of National Immunization Coverage 1980–2017 database. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report this study.

See Online for appendix

For the **WHO UNICEF Review of National Immunization Coverage 1980–2017 database** see http://apps.who.int/immunization_monitoring/globalsummary/wucoveragecountrylist.html#S

Outcome measures

Our primary analysis was the proportion of children who received an antibiotic prescription on discharge from the emergency department. We grouped the prescribed antibiotics into first-line and second-line antibiotics. The first-line antibiotics were amoxicillin, narrow-spectrum penicillins (benzylpenicillin and flucloxacillin), first-generation cephalosporins, and erythromycin. The second-line antibiotics were doxycycline, broad-spectrum penicillins (ampicillin, coamoxiclav, and piperacillin plus tazobactam, excluding amoxicillin), second-generation and third-generation cephalosporins (cefuroxime, cefotaxime, and ceftriaxone), sulfonamide plus trimethoprim, macrolides excluding erythromycin, aminoglycosides, fluoroquinolones, vancomycin, and metronidazole.[13]

Statistical analysis

In the descriptive analyses, we compared children with and without comorbidities. Relevant comorbidities were defined as cardiovascular, respiratory, renal, haematological or immunological, neuromuscular, genetic defects, malignancy, and multiple comorbidities. When information about comorbidities was missing, we assumed that no relevant comorbidity was present. In addition, we evaluated the proportion of children who were prescribed antibiotics by country and by focus of infection in children without comorbidities. In these and further analyses, children with comorbidities were excluded because of an increased risk for serious infections or a more serious disease course.

We used a multilevel logistic regression model (clustered by hospital) to calculate the influence of patient-level determinants, diagnostic assessment, and specific hospital determinants on antibiotic prescription

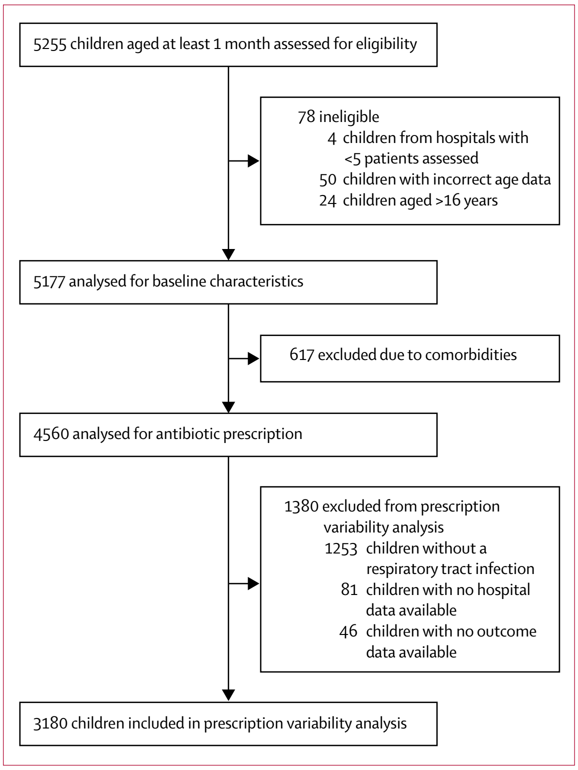

Figure 1: **Study profile**

for respiratory tract infections in more detail. For this analysis, we excluded children with another focus of infection, children with missing data on the outcome of antibiotic prescription, and children from hospitals with missing information on hospital determinants. The null model included an intercept only. Model 1 included patient-level risk factors for serious bacterial infections, based on clinical prediction rules and guidelines[14–16] from the UK National Institute for Health and Care Excellence: age, sex, fever duration, ill appearance, temperature, tachycardia, tachypnoea, oxygen saturation, capillary refill time, decreased consciousness, work of breathing, petechiae, meningeal signs, focus of infection, referral method, and the season of the emergency department visit. In model 2, diagnostic assessment was added to the analysis, which included the performance and results of C-reactive protein tests and chest x-rays. We tested the linearity of the associations of continuous predictors with the main outcome of antibiotic prescription using splines. Potentially meaningful interactions were included in the model if they improved the model fit.

For the final model, we considered hospital characteristics that have been suggested in previous publications to influence antibiotic prescription,[17–19] namely: national health-care system, hospital type (academic, teaching, or non-teaching), crowding (number of emergency department visits on sampling days), specialist responsible in the emergency department, first doctor evaluating the child, mode of supervision, availability of guidelines for respiratory tract infections, and vaccine coverage. We considered paediatric health-care systems (where >75% of children are under the primary care of a paediatrician), general practice systems (general practitioners offer primary care to >75% of children), or combined systems.[19] Supervision could be direct (supervising specialist is physically present at the emergency department), indirect (supervising specialist is not at the emergency department but can be reached by phone and come to the emergency department if needed within 20–30 min), or a combination of direct and indirect supervision.[20] We selected hospital variables for our final model on the basis of the validity of the data, the plausibility of the predictor influencing antibiotic prescription, and the added value of the predictor in our model. We calculated the standardised antibiotic prescription ratio (between observed and expected number of antibiotic prescriptions in a hospital) on the basis of the null model (crude prescription) and the final model (adjusted prescription), illustrated by a bar plot. A number of 1 indicates the average prescribing hospital based on the model, a number above 1 indicates excess prescriptions, and a number below 1 means fewer prescriptions than expected on the basis of the model predictions.

For regression analysis, missing data were imputed ten times using the mice package in R (version 3.3.2). An imputation model was used to draw plausible data values from a distribution specifically designed for each missing data point, including all available variables, general

	Without comorbidity (n=4560)		With comorbidity (n=617)	
	Proportion of patients (n [%])*	Patients with missing data (n [%])	Proportion of patients (n [%])*	Patients with missing data (n [%])
General characteristics				
Male sex†	2451 (54%)	3 (<1%)	387 (63%)	··
Mean age (years)†	2·4 (1·1–4·7)	1 (<1%)	3·2 (IQR 1·5–5·9)	··
Season†				
Spring	1110 (24%)	··	127 (21%)	··
Summer	766 (17%)	··	86 (14%)	··
Autumn	1024 (23%)	··	160 (26%)	··
Winter	1660 (36%)	··	244 (40%)	··
Method of referral†	··	36 (1%)	··	10 (2%)
General practitioner	395 (9%)	··	57 (9%)	··
Self	3966 (87%)	··	509 (83%)	··
Other	163 (4%)	··	41 (7%)	··
Triage level†	··	710 (16%)	··	34 (6%)
Immediate or very urgent	197 (4%)	··	59 (10%)	··
Urgent	1042 (23%)	··	246 (40%)	··
Standard	1866 (41%)	··	192 (31%)	··
Non-urgent	745 (16%)	··	86 (14%)	··
Signs and symptoms				
Ill appearance†	431 (10%)	60 (1%)	88 (14%)	14 (2%)
Median duration of fever in days (IQR)	1 (0·5–2·1)	58 (1%)	1 (0·5–2)	13 (2%)
Mean temperature in °C (SD)	38 (1)	125 (3%)	38·1 (1)	18 (3%)
Mean oxygen saturation in %† (SD)	98 (2·5)	1993 (44%)	97 (3·4)	165 (27%)
Tachycardia†	1138 (25%)	1219 (27%)	185 (30%)	147 (24%)
Tachypnoea†	665 (15%)	2227 (49%)	128 (21%)	301 (49%)
Increased work of breathing†	352 (7%)	40 (1%)	128 (21%)	7 (1%)
Prolonged capillary refill time	67 (2%)	650 (14%)	11 (2%)	100 (16%)
Decreased level of consciousness†	23 (1%)	17 (>1%)	13 (2%)	4 (1%)
Petechiae present†	41 (1%)	62 (1%)	11 (2%)	9 (1%)
Meningeal signs present	10 (>1%)	84 (2%)	3 (>1%)	8 (1%)
Additional diagnostics				
Median concentration of blood C-reactive protein in mg/L (IQR)	16·2 (5·4–51·8)	3820 (84%)	25·3 (5·4–51·8)	457 (74%)
Leucocyte count ($\times10^9$/L)	11·8 (7·8–16·3)	3855 (85%)	12 (1–16·7)	469 (76%)
Median concentration of procalcitonin in ng/mL (IQR)	0·21 (0·10–0·78)	4422 (97%)	0·26 (0·14–0·20)	582 (94%)
Blood culture†	224 (5%)	··	56 (9%)	··
Urinalysis†	841 (18%)	··	140 (23%)	··
X-ray done†	431 (8%)	··	131 (21%)	··
Lumbar puncture done	34 (1%)	··	7 (1%)	··
Treatment				
Antibiotic prescription	1454 (32%)	61 (1%)	206 (33%)	7 (1%)
Disposition†	··	6 (>1%)	··	1 (>1%)
Discharged	4035 (88%)	··	471 (76%)	··
Observation unit <24 h	187 (4%)	··	48 (8%)	··
Admitted to ward	321 (7%)	··	90 (15%)	··
Admitted to intensive care unit	11 (>1%)	··	6 (1%)	··

Comorbidities are cardiovascular, respiratory, renal, haematological or immunological, neuromuscular, genetic defects, malignancy, or multiple comorbidities. *Unless stated otherwise. †Significantly different between children with and without comorbidities (p<0·05).

Table 1: **Baseline characteristics of the enrolled population**

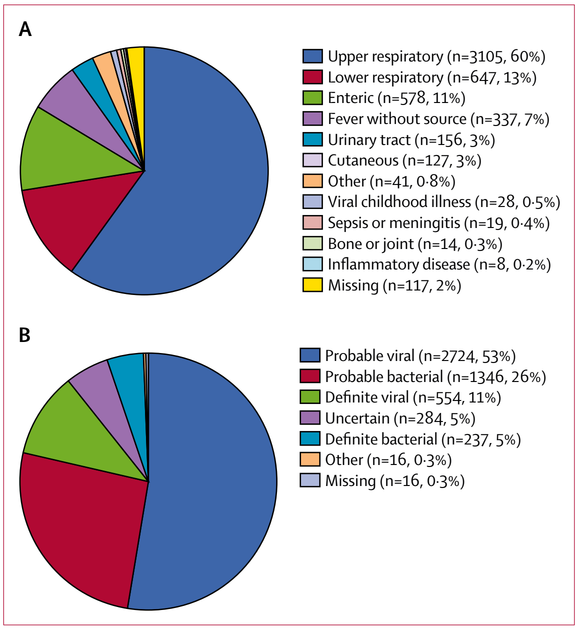

Figure 2: **Frequency of probable focus (A) and cause (B) of infection in all 5177 children studied**
For full data, see appendix.

	Proportion of children prescribed antibiotics	Proportion of prescriptions for second-line antibiotics	Children with missing data
Total population	1454/4560 (32%)	893/1454 (61%)	61/4560 (1%)
Per country			
Turkey	450/708 (64%)	363/450 (81%)	46/708 (6%)
UK	57/145 (39%)	45/57 (79%)	1/145 (1%)
Hungary	41/111 (37%)	29/41 (71%)	4/111 (4%)
Italy	149/446 (33%)	120/149 (81%)	6/446 (1%)
Romania	87/282 (31%)	81/87 (93%)	2/282 (1%)
Spain	161/631 (26%)	68/161 (42%)	..
Portugal	177/698 (25%)	56/177 (32%)	2/698 (<1%)
Denmark	6/24 (25%)	2/6 (33%)	..
France	208/926 (22%)	70/208 (34%)	..
Netherlands	37/161 (23%)	18/37 (49%)	..
Switzerland	81/428 (19%)	41/81 (51%)	..

Countries are ordered from high to low percentage of antibiotic prescriptions. Second-line antibiotics are represented as percentage out of the total number of antibiotic prescriptions per country.

Table 2: **Antibiotic prescriptions per country in children without comorbidities**

information, clinical signs and symptoms, diagnostics, treatment, and disposition. Analyses were done on all ten datasets and results were pooled.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors approved the final version of the manuscript submitted for publication.

Results

A total of 5177 children from 28 emergency departments in 11 countries were included in the analysis of baseline characteristics (figure 1, table 1, appendix). Their median age was 2·5 years (IQR 1·1–4·9) and 2838 (55%) were male. 256 (5%) children were triaged as needing immediate or very urgent care and most children were self-referred. 17 hospitals were academic and the other 11 were teaching or non-teaching hospitals. 17 hospitals were in city centres and the rest were regional or mixed (serving a region incorporating both rural and urban areas) hospitals. The capacities of the hospitals ranged from fewer than 5000 paediatric annual emergency department visits (six hospitals) to more than 25 000 (12 hospitals). In most hospitals, a paediatrician-in-training was the first doctor to evaluate febrile children, supervised by a fully trained paediatrician or a paediatric emergency physician.

1757 (34%) children underwent additional diagnostics, most often urinalysis. The most common focus of infection was the upper respiratory tract (3105 [60%] children; figure 2), and only 19 (<1%) children had sepsis or meningitis. The presumed cause of infection was most often reported as viral (3278 [63%] children).

Children with comorbidities (617 [12%]) were generally older and more ill than those without comorbidities, as evidenced by their higher triage levels and higher number of abnormal signs and symptoms. These children were subjected to more diagnostic tests and were more frequently admitted for hospital treatment or monitoring but received antibiotics just as often as children without comorbidities (1454 [32%] of 4560 children without comorbidities received prescriptions *vs* 206 [33%] children with comorbidities; table 1).

893 (61%) of the prescriptions issued to children without comorbidities were second-line antibiotics (table 2, appendix). The overall proportion of antibiotic prescriptions ranged from 19% to 64% across countries. Overall, countries with high antibiotic prescriptions also prescribed second-line antibiotics more often.

We then analysed the proportion of children without comorbidities who received a prescription by focus of infection (figure 3). The five most common foci of infection were identified in 4247 (93%) of these children. 22 (4%) of 531 children with enteric infections received antibiotics, with low variability between countries. Children with urinary tract infections were prescribed antibiotics most frequently (116 [93%] of 125). Children with respiratory tract infections, comprising 73% (n=3307) of the evaluated patients without comorbidities, accounted for 83% (1208 of 1454) of all antibiotic prescriptions. The mean proportion of prescriptions for lower respiratory tract infections was higher than that for upper respiratory tract infections (227 [47%] of 486 *vs* 981 [35%] of 2821 children respectively), with high variability in prescription between countries for both.

Antibiotics were prescribed for 37% of respiratory tract infections in children without comorbidities (n=1208).

Variation in prescriptions for upper respiratory tract infections was 15–67% across hospitals, and 24–87% for lower respiratory tract infections. We based our multilevel analysis on children with respiratory tract infections from the 26 of 28 hospitals (n=3180) for which information on hospital determinants was available. Figure 4A presents the crude number of antibiotic prescriptions (standardised prescription) based on the null model. An increased standardised prescription ratio indicates that more antibiotics are prescribed than expected and a decreased standardised prescription ratio indicates that fewer antibiotics are prescribed than expected, based on the average prescribing hospital. In the intermediate models (appendix), we added patient characteristics, diagnostic assessment, and hospital characteristics, leading to the final model (table 3).

Older age and longer duration of fever were associated with an increased likelihood of antibiotic prescription. Other significant predictors were high blood concentrations of C-reactive protein and focal or diffuse abnormalities in the chest x-ray. At hospital level, we were limited to two variables: hospital type and national health-care system. Even though these factors did not significantly influence antibiotic prescription individually, they yielded the best model fit.

All factors included in the analysis could only explain part of the variability in antibiotic prescription between hospitals. After adjustment for all factors in the model, the rank of hospitals according to proportion of prescriptions issued changed and the variability in prescription by hospital was slightly decreased (figure 4B). However, substantial variability in prescription remained, ranging from half to twice the number of prescriptions as the average prescribing hospital in our dataset. Even though specific determinants of antibiotic prescription could be identified in the whole population of patients, differences in patient mix, diagnostic assessment, or hospital characteristics could not explain all variability in antibiotic prescription.

Discussion

Our study provides insights into the prescription of antibiotics to febrile children on the basis of a prospective registry across a wide range of European emergency departments. Our results indicate that antibiotic prescription varies substantially between countries and hospitals and that second-line antibiotics are frequently used. We also identified that respiratory tract infections are the most common type of infection with highest variability in antibiotic prescription between paediatric emergency departments. The variability of antibiotic prescription for respiratory tract infections cannot be fully explained by differences in patient characteristics, diagnostic assessment, and measured hospital characteristics.

The main strength of our study is that it provides a prospective European registry of antibiotic prescription

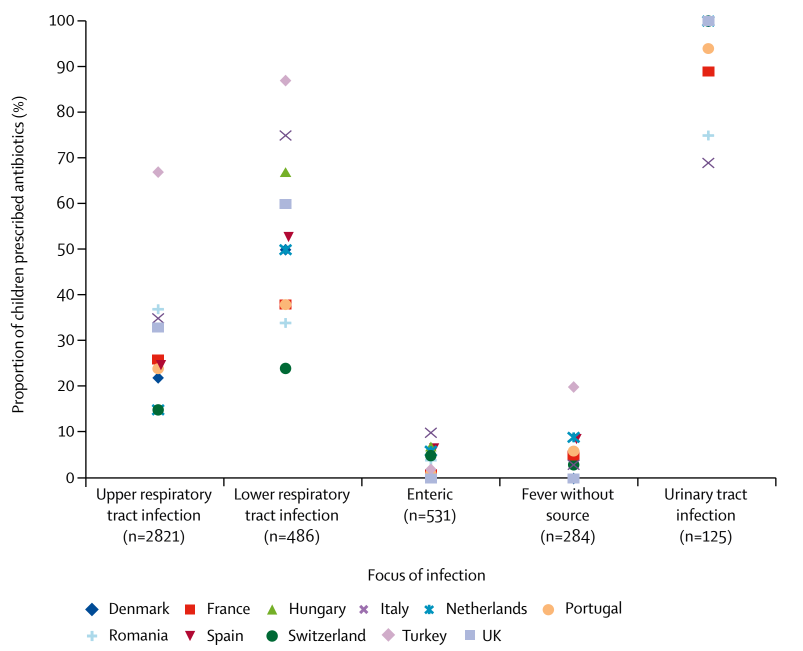

Figure 3: **Variability in antibiotic prescription across countries for the most frequent foci of infection in 4560 children without comorbidities**
For full data, see appendix.

collected in a standardised way in 11 countries, enabling comparisons across a large part of Europe. Hospitals were invited through the REPEM network, which ensured broad European participation and high-quality data. The selected hospitals have an interest in research collaboration and might therefore be more homogeneous in the type of care they provide or have a higher standard of care than hospitals that were not included. The number of included hospitals per country does not match the country's population size.[22] Even though we included very diverse hospitals in terms of type and size, the true antibiotic prescription in European emergency departments might be even higher and more variable than we observed. The size of the hospital largely matches the number of included patients per hospital, suggesting no major selection bias. Hospitals Erasmus Medical Center, Netherlands, and Cukurova, Turkey, sampled on more days immediately before or after the assigned sampling days. Since these extra days were still random, we assume this did not introduce selection bias in our study.

A registry study might be susceptible to the Hawthorne effect but local physicians were only aware of the general scope of this study (registry of febrile children) and not particularly about the monitoring of antibiotic prescription. There are some limitations to this approach. First, four of 11 countries participated with only a single hospital, so we were not able to take clustering at country level into account. Second, some hospitals had small sample sizes (five hospitals included <50 patients),

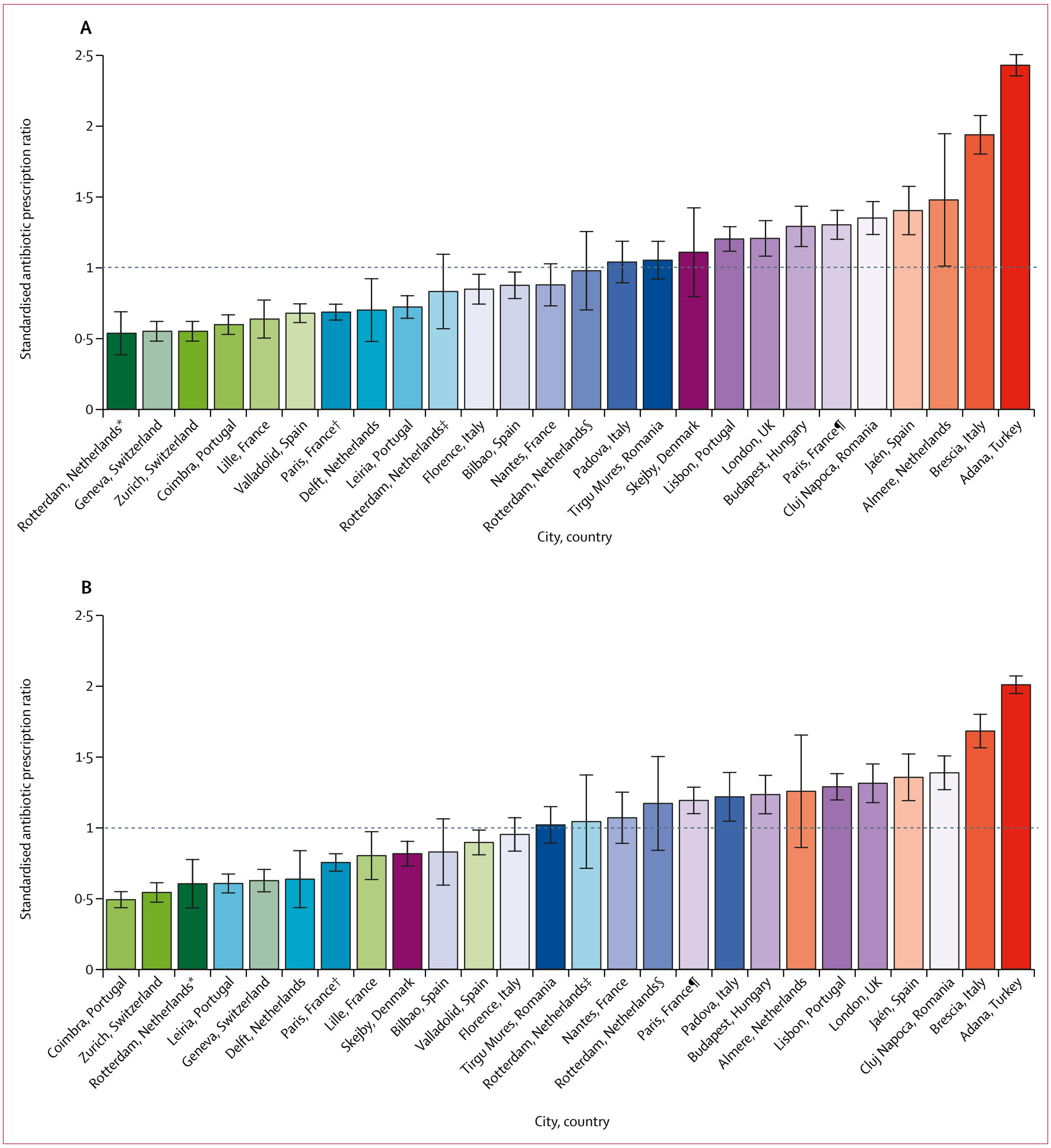

***Figure 4:* Standardised antibiotic prescription for respiratory tract infections per hospital**
(A) Null model (crude standardised antibiotic prescription). (B) Final model (adjusted standardised antibiotic prescription for patient characteristics, diagnostic assessment, and hospital characteristics). Hospital determinants for Hôpital Antoine Béclère (Paris, France) and Hospital de Mendaro (Mendaro, Spain) were not available, so they were not included in this analysis. *Erasmus Medical Center Sophia Children's Hospital. †Hôpital Robert Debré. ‡Maasstad Ziekenhuis. §Sint Franciscus Ziekenhuis. ¶Hôpital Necker–Enfants Malades.

thereby limiting the power to show large differences between hospitals. Nevertheless, our results still showed substantial variability, so this limitation did not hamper our conclusions. Third, we did not include the risk of serious bacterial infection per country in our model because it is already related to clinical signs and symptoms that we did include. Finally, the large proportion of unexplained variability might indicate that there are other contributing factors that we did not include in our model. The statistical limitation of the number of hospital factors that we could include might be one cause of the large remaining unexplained variance. As we have corrected extensively for many known possibly influential factors, we still believe our analysis lead to valid conclusions.

Overall antibiotic prescription variation in our study is consistent with previous reports (27% and 55%),[17,23] in particular for upper respiratory tract infections.[24] Antibiotic prescription for respiratory tract infections and for lower respiratory tract infections is generally reported to be higher than we observed.[25] Studies on fever without a source usually focus on children below 3 months of age, whereas the minimum age of our population was 1 month, explaining why our observed antibiotic prescription was lower than in other studies.[16]

Large variability in antibiotic prescription between European countries has been reported previously but did not focus on paediatric emergency care.[26] The fact that prescription variability was highest for children with respiratory tract infections in our study could have several reasons.

First, respiratory tract infections might include multiple diagnoses, such as acute otitis media, bronchiolitis, or pneumonia, for which there are different specific guidelines and different likelihoods of bacterial or viral origin.[14,27] We had no information available on these specific diagnoses but since we collected data in each hospital throughout a full year, we believe all of these types of respiratory tract infections were represented in our data for all countries. The criteria for diagnoses could have varied between hospitals, hence a standardised diagnostic protocol for presumed focus of infection and confirmed diagnosis (where possible) might assist in future studies. Second, and probably most important, is the lack of a gold standard for the diagnosis of bacterial respiratory tract infections. When a decision on treatment is made, there is often diagnostic uncertainty and bacterial causes can often not be excluded, influencing diagnostic assessment and the likelihood of antibiotic prescription.[5]

Although we found some specific drivers of antibiotic prescription, they could only explain a small proportion of the observed variability between hospitals. Similar results were obtained by a large US observational study, showing broad unexplained variability in antibiotic prescription for respiratory tract infections across primary paediatric practices.[3] The influence of patient characteristics (age and duration of fever) and diagnostic tests on antibiotic prescription we found was generally consistent with previously reported predictors of bacterial infections.[15,16] The effect of different infection foci (lower *vs* upper respiratory tract infection) was strongly correlated with the effect of the chest x-ray result. A notable finding was our observation that focal as well as diffuse abnormalities in the chest x-ray strongly increased the chance of antibiotic prescription, even though their low diagnostic value has been well described.[28] We did not include procalcitonin in our analyses, since this test was only done in isolated cases in less than half of the participating hospitals, reflecting the infrequent use of the biomarker test in routine practice during the study period.

We were particularly interested to ascertain whether hospital characteristics affected antibiotic prescription

	Odds ratio (95% CI)
Final model	
Intercept	0·66 (0·16–2·84)
Patient characteristics	
Age (years)*	1·51 (1·08–2·13)†
Age (years)*‡	0·65 (0·35–1·21)
Female sex	0·88 (0·73–1·07)
Season (spring=reference)	
Summer	0·81 (0·59–1·11)
Autumn	1·13 (0·84–1·53)
Winter	0·87 (0·65–1·15)
Way of referral (general practice=reference)	
Self-referral	1·25 (0·82–1·92)
Other	0·76 (0·39–1·46)
Triage level (very urgent=reference)	
Urgent	0·9 (0·5–1·63)
Standard	0·69 (0·38–1·24)
Non-urgent	0·65 (0·34–1·25)
Ill appearance	0·97 (0·66–1·44)
Duration of fever (days)*	1·45 (1·01–2·07)†
Duration of fever (days)*‡	0·6 (0·27–1·33)
Temperature (°C)*	1·43 (0·99–2·08)
Temperature (°C)*‡	0·69 (0·24–1·94)
Temperature (°C)*§	1·27 (0·02–83·24)
Oxygen saturation (%)*	0·96 (0·86–1·07)
Tachycardia	1·09 (0·85–1·39)
Tachypnoea	0·9 (0·69–1·18)
Increased work of breathing	0·69 (0·43–1·09)
Prolonged capillary refill (>3 s)	1·26 (0·58–2·73)
Decreased level of consciousness	0·3 (0·07–1·34)
Petechiae	1·96 (0·72–5·33)
Meningeal signs	1·75 (0·06–54·57)
Focus (lower RTI *vs* upper RTI)	1·19 (0·8–1·76)
Diagnostic assessment	
C-reactive protein tested	1·04 (0·71–1·54)
C-reactive protein concentration (mg/L)*	2·31 (1·67–3·19)†
X-ray result (not done=reference)	
Normal	0·68 (0·42–1·11)
Focal abnormalities	10·62 (5·65–19·94)†
Diffuse abnormalities	3·49 (1·59–7·64)†
Hospital	
Hospital type (teaching *vs* academic)	1 (0·49–2·04)
Health-care system (paediatric system=reference)	
Combined system	1·28 (0·46–3·6)
General practice system	1·21 (0·4–3·64)

Tachycardia and tachypnoea were defined according to the Advanced Paediatric Life Support guidelines.[21] RTI=respiratory tract infection. *Standardised value. †Significant predictor. ‡Second coefficient (non-linear term: spline with 3 or 4 degrees of freedom). §Third coefficient (non-linear term: spline with 3 or 4 degrees of freedom).

Table 3: **Final multilevel model for antibiotic prescription in children with respiratory tract infections**

and if they could explain variability. We were able to include two specific hospital factors in our model that define differences across local practices in the evaluation of febrile children: hospital type and national health-care system. These factors added most to our model in terms of reducing variance and were assumed to be meaningful. By including health-care system and method of referral in our model, we aimed to cover aspects of the primary care system but we did not have detailed data on primary care in each country because this analysis was beyond the scope of our study. Other potential factors were excluded from the model. Emergency department crowding had a negligible effect on antibiotic prescription and our data were not very consistent for this parameter.[29] All hospitals had guidelines for the diagnosis and treatment of respiratory tract infections but we lacked information on the contents or implementation of these guidelines. There was low variability in immunisation coverage, so we assumed that this factor could not explain any substantial variance in antibiotic prescription. Coverage of vaccination against *Haemophilus influenzae* type B was more than 90% in all participating countries without variation, according to the WHO UNICEF Review of National Immunizaion Coverage 1980–2017 database. Pneumococcal conjugate vaccine coverage was above 75% in all countries with available data, a threshold that has been described as sufficient to uphold herd immunity.[30] Only Romania did not carry out pneumococcal conjugate vaccination at the time of data collection. Children were included throughout the entire 24 h of the sampling day—ie, also in evening and night shifts, both on weekdays and weekends. Choosing sampling days at random aimed to reduce systematic effects introduced by shift schedules, such as variable capacity of supervision.

Our findings that antibiotic prescription for respiratory tract infections is dependent on the hospital and that second-line antibiotics are widely used are crucial for all clinicians, researchers, and policy makers who plan interventions to reduce unnecessary prescription of antibiotics, particularly second-line drugs. Our study was not designed to evaluate the validity of the decision to prescribe an antibiotic; however, the finding of large unexplained variability across hospitals does suggest over-prescription. Given that most antibiotics are prescribed to children with respiratory tract infections but this occurs with high variability, strategies aiming to reduce antibiotic prescription could be most beneficial in this patient group. Particularly, overuse of second-line antibiotics should be addressed as a priority in such strategies. Successful national examples[25] should be extrapolated to a wider setting by international implementation studies and by developing European guidelines. The expected effect of an intervention can nevertheless vary per setting, since not all factors that affect antibiotic prescription have yet been explained and baseline prescription varies between emergency departments. This variation not only affects sample size calculations for different settings but also emphasises the need for multicentre studies on the outcomes of strategies aiming to reduce the inappropriate use of antibiotics. To ensure successful antibiotic stewardship initiatives at the European level, factors associated with suboptimal antibiotic prescription in individual hospitals and nationally need to be identified.

Contributors

All authors contributed to the study design, data analysis, and the writing of the paper. JvdM was responsible for the design of the paper and was the main author of the draft and the revised manuscript. JvdM and DN analysed the data and revised the manuscript. EvdV monitored the data collection, collated the data, and revised the draft. SM, AG, and HM contributed to the design of the study and revised the manuscript. RO is the guarantor for this study; she initiated the study, designed the protocol, and supervised the data collection and the writing of the manuscript. Members of the Research in European Pediatric Emergency Medicine (REPEM) network were responsible for local data collection and revision of the manuscript.

Declaration of interests

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