The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001324

Using Prescription Patterns in Primary Care to Derive New Quality Indicators for Childhood Community Antibiotic Prescribing

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Abbreviated Title: Quality of Outpatient Childhood Antibiotic Prescribing

Running Head: Quality of Childhood Antibiotic Prescribing

Sources of funding: This work has received co-funding from the European Union in the framework of the Health Programme. ARPEC Project A 2009-11-01

Conflicts of interest: The authors have no conflicts of interest to disclose.

Abstract

Background: To describe patterns of antibiotic outpatient use in three European countries, including two new pediatric-specific quality indicators (QIs).

Methods: A cohort study was conducted, 2001-2010, using electronic primary care records of 2,196,312 children up to 14 (*Pedianet*, Italy) or 18 years (*THIN*, UK; *IPCI*, the Netherlands) contributing 12,079,620 person-years. Prevalence rates of antibiotic prescribing per year were calculated and antibiotics accounting (drug utilization) for 90% of all antibiotic prescriptions were identified (DU90% method). The ratio between users of broad to narrow-spectrum penicillins, cephalosporins and macrolides (B/N ratio) and two pediatric-specific quality indicators (QIs): the proportion of amoxicillin users (amoxicillin index, AI) and the ratio between users of amoxicillin to broad-spectrum penicillins, cephalosporins and macrolides (A/B ratio) were determined.

Results: The overall annual prevalence of antibiotic prescriptions was 18.0% in the Netherlands, 36.2% in the UK and 52.0% in Italy. Use was maximal in the first years of life. The number of antibiotics accounting for the DU90% was comparable. The B/N ratio varied widely from 0.3 to 74.7. The AI was highest in the Netherlands and the UK (50-60%), lowest in Italy (30%) and worsened over time in the UK and Italy. The A/B ratio in 2010 was 0.3 in Italy, 1.7 in the Netherlands and 5.4 in the UK.

Conclusions: The patterns of antibiotic prescribing varied highly with age and country. The pediatric-specific QIs combined with the total prevalence rate of use provide a clear picture of

the trends of community childhood antibiotic prescribing, allowing monitoring of the impact of policy interventions.

Keywords: outpatient, pediatrics, antibiotic, quality, pharmacoepidemiology

Introduction

Despite clear evidence that poorly targeted antibiotic use contributes to the major health problem of antimicrobial resistance, outpatient antibiotic prescribing in Europe remains high with a strong north-south gradient. [1-3]. Children are high consumers of antibiotics especially in the first years of life [4, 5]. Indeed, high rates of antibiotic prescribing in primary care, often for acute respiratory tract infections (RTIs) [6], warrant close monitoring of childhood prescribing patterns. Yet, there have been few initiatives so far to assess quality of outpatient antibiotic prescribing in children [7]. Quality indicators (QIs) have already been developed within the context of the European Surveillance of Antimicrobial Consumption (ESAC) project [8] based on outpatient use data. However, these QIs are not directly applicable to pediatric antibiotic use because of the absence of age-specific pediatric defined daily dosages (DDDs) and age-related differences in the prevalence of infections and patterns of drug use between adults and children.

The Antibiotic Resistance and Prescribing in European children (ARPEC) project, aimed to improve antimicrobial prescribing in hospitals and in the community, by obtaining up-to-date, relevant data on variation in clinical management and antimicrobial resistance rates. Within this sub-project of ARPEC, we sought to describe patterns of antibiotic use in pediatric primary care in three European countries using, amongst others, two newly proposed pediatric-specific quality indicators.

Patients and Methods

Study design and Data sources

This study is a retrospective cohort study. Data were collected from three population based primary care databases in the Netherlands (NL), the United Kingdom (UK) and Italy (IT). In NL and UK, general practitioners (GPs) are responsible for the primary care of children. The *Integrated Primary Care Information database (IPCI)* from NL comprises electronic medical records from more than 400 Dutch GPs since 1996 [9, 10]. *The Health Improvement Network (THIN)* is a database of primary care medical records from UK, prospectively collecting data since September 2002 and containing retrospective data since the late 1980's [11]. In Italy, family pediatricians (FPs) are the gatekeepers of primary care for children less than 14 years of age. The *Pedianet* database contains exclusively pediatric electronic medical records from 150 FPs in IT since 2000 [12]. These databases contain the complete automated patient files, with detailed information on population, diagnoses and drug prescriptions. Their use has been proven valid for pharmacoepidemiologic research and data are representative of national pediatric populations with regard to gender and age distribution [11, 13]. Details about their structure have been described elsewhere [9, 10, 12, 14].

Data from the different databases were pooled using a distributed network approach, in which dataholders maintain control over their original data and only anonymized and aggregated data are shared. This was done through generation of data into a common format followed by local data aggregation using custom-built software, Jerboa© [15]. The respective scientific and ethics committees of each database approved the conduct of the study.

Study period

As the start date for data collection differed between databases, the start of the study period was defined as the 1st January 1995 for the UK, the 1st January 1996 for the Netherlands and the 1st January 2001 for Italy. The study period ended on the 31st December 2010.

Children were followed from the start of entry into the study (start of study period, date of registration plus 6 months (except for newborns) until their 18th (NL and UK) or 14th (IT) birthday, the end of the study period, leaving the practice, death, or latest data recorded, whichever came first.

Patterns and quality of antibiotic use

All antibiotics under the therapeutic subgroup J01 'Antibacterials for systemic use' of the Anatomical Therapeutic Chemical (ATC) classification system [16] were included in the study. The proportion of children being prescribed antibiotics and the number of individual drugs accounting for 90% of drug use, called drug utilization 90% (DU90%), have been proposed as indicators of the quality of antibiotic prescribing [17-19]. Annual prevalence rates were expressed as the number of users per 100 person years (PYs) notated as a percentage to be interpreted as the number of children per 100 who use an antibiotic drug or drug class in one year. For the numerator, the number of children that received at least one prescription for an antibiotic drug or drug class within a calendar year was assessed. Because of the dynamic nature of the population, we used person time rather than total number of individuals as denominator. To account for the large differences in antibiotic use within the pediatric population, ranging from neonates to adolescents, prevalence was stratified in one-year age categories (0-<1 years etc.) and in broader age-categories; 0-<1 years, 1-<5 years, 5-<12 years and 12-<18 years. Similarly, prevalence of use was calculated at ATC 3th (pharmacological subgroup) and 5th (active substance) levels. Also, the number and type of antibiotics that covered 90% of all antibiotic prescriptions (DU90%) were assessed and presented by country, calendar year and age category.

Further, one of the ESAC QIs, the ratio between the number of users of broad-spectrum (J01CR, J01DC, J01DD and J01F [without erythromycin]) to those of narrow-spectrum penicillins, cephalosporins and macrolides (J01CE, J01DB and J01FA01), the B/N ratio, was determined. This ratio gives an estimate of the balance between prescribing of broad- versus narrow-spectrum antibiotics. So the smaller the B/N ratio, the most appropriate the prescribing[8]. Two new QIs more relevant for children were estimated based on amoxicillin use: 1) the proportion of amoxicillin users (J01CA04) among all antibiotic users (J01) - the amoxicillin index (AI), and 2) the ratio between the number of amoxicillin users (J01CA04) and the number of users of broad-spectrum penicillins, cephalosporins and macrolides (J01CR, J01DC, J01DD and J01F [without erythromycin]) - the amoxicillin to broad-spectrum ratio (A/B ratio). This ratio gives an estimate of the use of a first-line and relatively narrower-spectrum penicillin antibiotic to that of broader-spectrum penicillins, cephalosporins and macrolides in children. Thus, the greater the A/B ratio, the most appropriate the prescribing. All three ratios were stratified by country, age categories and calendar year.

Statistical analysis

Data were described in narrative and tabular forms. For each country, a Poisson regression model was applied to determine the influence of increasing calendar year on yearly antibiotic prevalence rates. Statistical analyses were performed using the SAS software version 9.3 software (SAS Inc, Cary, North Carolina).

Results

In this population-based cohort study a total of 2,195,312 children were included: 239,293 from NL (10.9%), 1,725,798 from UK (78.6%), and 230,275 from IT (10.5%) who altogether contributed 12,079,620 PYs of follow up.

Overall antibiotic use

The overall annual prevalence of antibiotic prescriptions for NL, UK and IT was 18% (18 users/100PYs), 36% and 52%, respectively. The time trends for the three countries are shown in

Figure 1. The prevalence of antibiotic prescription in the UK and IT slightly decreased with increasing calendar years (RR=0.995, *p-value* <0.001 and RR=0.997, *p-value* <0.001), whereas it remained stable in NL (RR=0.999, *p-value* =0.42).

Penicillins with extended spectrum (J01CA) were the most frequently prescribed antibiotics particularly in the first years of life (Figure 2). Overall, the most commonly prescribed antibiotic was amoxicillin: 9.2 % in NL, 19.7% in the UK and 18% in IT. Amoxicillin prescriptions peaked at the age of one to two years with a maximum of 30.5% in NL, 46% in the UK and 31.3% in IT. Prescriptions for the class 'combinations of penicillins, incl. beta-lactamase inhibitors' (J01CR) were frequent in NL and IT, while in the UK beta-lactamase sensitive penicillins were very frequently prescribed (J01CE).

In the macrolides class (J01FA), erythromycin was the main antibiotic prescribed in the UK, with a prevalence rate of 4.5%, peaking at one to two years of age (8.7%). In NL, clarithromycin (1.1%; maximal 3.3% at one to two years) and azithromycin (1.6%; maximal 3.4% at one to two years) were predominant. In IT, the prevalence rate of clarithromycin was 7.1% (maximal 11.1% at three to four years) and that of azithromycin was 7.6% (maximal 12.8% at three to four years). The prevalence of second and third generation cephalosporins (J01DC-DD) was high in IT, up to 4.1% and 6.8% at three to four years of age (Figure 2), while in the UK and NL prevalence of cephalosporin use (J01D) was low (2.3%) and very rare (0.02%), respectively. In IT, third-generation cephalosporins made up a large proportion of cephalosporin prescribing: cefixime (2.8% at three to four years), cefpodoxime (2% at three to four years) and ceftibuten (1.1% at one to two years).

Ninety per cent of all antibiotic prescriptions (DU90%) in this population were covered by 9 drugs in NL and by 8 drugs in both UK and IT. In NL and UK, the number of drugs accounting for the DU90% increased with age, while this number was stable in Italy (table 1 a-c).

Quality Indicators

The B/N ratio was highest in IT for all ages and all calendar years. Across all three countries, the B/N ratio was highest in the youngest children: 5.7 in infants aged below one year in NL and 0.4 and 100.1 in children aged one to four years in the UK and IT, respectively. When comparing calendar years 2001, 2006 and 2010, the B/N ratio increased slightly in the UK and in NL whereas it multiplied by 10 between 2001 and 2010 in IT (table 2).

The AI was highest in infants aged less than 1 year: 80% in NL and the UK and approximately 50% in IT (figure 3.1). Overall, this percentage remained stable between 2001 and 2010 in NL whereas it slightly decreased in the UK and in IT (figure 3.2).

The UK had the highest A/B ratio in all age categories (Table 3). In NL, the A/B ratio was also high however, the ratio decreased with increasing age; in adolescents between 14 and 18 years of age, users of broad-spectrum antibiotics were nearly twice those of amoxicillin. In IT, broad-spectrum antibiotics were more commonly prescribed than amoxicillin in all age categories, though again the difference increased with increasing age. Over the years, the overall number of users of amoxicillin compared to that of broad-spectrum antibiotics increased in NL whereas it decreased in the UK and in IT.

Discussion

In this cohort study we describe patterns of primary care prescribing of antibiotic agents in children in three European countries. More than 2 million children aged 0-<18 years were included, contributing over 12 million PYs of follow up through a period of 10 to 16 years. Based on this large cohort, we were able to demonstrate the application of two new QIs of pediatric community-based antibiotic prescribing, the AI and the A/B ratio.

Expectedly, we found that the antibiotic prescribing prevalence rates were lowest in NL (18% per year), 36% per year in the UK and highest in IT (52% per year) [4, 5, 20]. Antibiotic prescribing tended to slightly decrease over time in all countries, though this decrease was not statistically significant in NL. Although there was considerable variability in the type of antibiotics that were most commonly prescribed, amoxicillin was the most commonly prescribed antibiotic in all three countries. However, the number of antibiotics making up the DU90% was similar across the three countries, demonstrating the limited repertoire of antibiotics making up the bulk of community-based antibiotic prescribing for children. These findings are in line with recent European data also placing IT and NL at the two extremes of antibiotic use and Germany, UK and Denmark between those extremes, at decreasing prevalence rates [21, 22].

Broad-spectrum antibiotic prescribing increased in all countries in the studied period and was highest in IT. The B/N ratio was highest in the youngest children. The overall ratios for children were somewhat lower than the ESAC findings for adults in 2004 for the UK (0.3 vs. 0.56) and NL (3.2 vs. 5.12), and higher in Italy (74.7 vs. 50.9) [8]. For pediatric patients, this ratio is highly variable and hard to interpret especially as certain drugs, such as penicillin V (phenoxymethylpenicillin), are not available in specific countries.

We developed and assessed two new simple QIs to evaluate the quality of community-based antibiotic prescribing, the AI and the A/B ratio, which revealed important differences in antibiotics prescribed, both between age groups and countries. The AI was highest in the UK and NL (50%) and lowest in IT (30%), which is compatible with the much higher annual exposure of

Italian children to macrolides, to penicillins with beta-lactamase inhibitors and to $3^{rd}/4^{th}$ generation cephalosporins. The A/B ratio provided further detail. This ratio was highest for the UK (A/B ratio of 6, that is 6 amoxicillin users observed for one broad-spectrum antibiotic user in a given calendar year) followed by NL (A/B ratio of 2). Together with the AI, this can be interpreted as greater prescribing preference for narrower-spectrum antibiotics, such as beta-lactamase susceptible penicillins, as alternatives to amoxicillin in the UK compared to NL. Thus, although overall prescribing in NL is lower than in the UK, children receiving antibiotics are more likely to be prescribed broader-spectrum agents than in the UK. In IT, the A/B ratio is reversed (<1), indicating that prescriptions of broad-spectrum agents are altogether more common than amoxicillin prescriptions.

The selection of amoxicillin as the reference standard to evaluate the quality of antibiotic prescribing may seem somewhat arbitrary. However, upper and lower respiratory tract infections remain by far the most common indications for childhood antibiotic prescribing in community practice [5, 23]. Many guidelines recommend amoxicillin as the first-line choice for suspected bacterial respiratory tract infections, including pneumonia and otitis media.[24-27] Several patterns in our data support the role of amoxicillin in assessing antibiotic prescribing quality in the childhood population. In all three countries, seasonal variation with peak prescribing in winter, in line with the seasonal trend of the incidence of acute respiratory infections, was observed (data not shown) [28]. The high AI in NL and the UK as well as the substantial contribution of macrolides and penicillins combined with beta-lactamase inhibitors in IT support the interpretation that a large proportion of childhood community-based antibiotic prescribing targets acute respiratory infections. The AI was highest in the youngest children, who are also most frequently treated with antibiotics for respiratory infections [29, 30]. Equally a drop in the A/B ratio from infancy to preschool age may be partially explained by the increasing use of macrolides with increasing age due to the unresolved questions about the need to cover for atypical pathogens in older children [31] .

As many prescriptions are likely to be issued to children with viral respiratory infections, efforts are needed to reduce prescribing in this setting [32]. Amoxicillin consumption could reflect the part of antibiotic use in children that has the greatest potential for reduction [5]. In the 15 years covered by this study considerable effort has been put in reducing inappropriate prescriptions of antibiotics in Europe [7, 33, 34]. Despite these efforts, the overall change in prevalence rates observed in this study over time was very small. Yet, major interventions can effectively reduce inappropriate antibiotic prescribing [35]. In France, national campaigns focusing on inappropriate antibiotic prescribing for respiratory tract infections of viral origin in children aged 0 to 6 years reported a 35.8% reduction in antibiotic prescriptions[36].

However, beyond aiming to achieve an overall reduction in antibiotic prescribing, it may also be necessary to improve the quality of antibiotic selection. In the UK, narrow-spectrum penicillins were the second most commonly prescribed antibiotic class after amoxicillin whereas in NL amoxicillin with enzyme inhibitor and macrolides were preferred. In IT, third-generation oral cephalosporins and macrolides were very commonly used together with amoxicillin with or without enzyme inhibitor, a pattern that has already been described in previous drug utilization studies [37]. Likewise, use of broad-spectrum antibiotics, oral cephalosporins and macrolides, in Germany has been noted as comparable to that of IT whereas antibiotic prescriptions in Denmark concern almost exclusively narrow-spectrum agents[21, 22]. Differences in prescribed antibiotics among the countries can partly be explained by availability of antibiotics and differences in guidelines. For example, penicillin V is not available in Italy whereas it is widely used in the

UK. For the treatment of acute pharyngitis, amoxicillin is the first choice in IT with second generation cephalosporins considered second line, while in other countries use of narrow-spectrum penicillins is more strongly recommended[38-40]. To improve community-based antibiotic prescribing, antibiotic stewardship should target both volume of antibiotic use and agent selection. While such interventions have been successfully implemented in the US, on-going activities are required to sustain any improvements[41].

In the absence of pediatric DDDs, we reported total and class specific consumption as prevalence rates, which may also be more explicit for primary care physicians. We also derived two simple new QIs which provide useful information and trends over time, but need to be age-specific since both antibiotic prescribing and the prevalence of infectious diseases are age-dependent. A key limitation of the current study is that we could not stratify our results by clinical indications as the latter were not collected. In future studies, stratification by indication may give more insight in the quantitative and qualitative differences of antibiotic prescribing between countries. It can also provide valuable epidemiological information by drawing inferences on the proportion of children treated for a specific indication. This information is crucial to assess whether antibiotic prescribing policies can be further optimized.

In conclusion, assessment of antibiotic consumption in these three countries identified distinct patterns of use. In the UK, prevalence of antibiotic prescribing remains moderately high with only a slight reduction in global and amoxicillin use over time; however prescribing of broad-spectrum antibiotics is low. Conversely in NL consumption of antibiotics is low and remains stable, but broad-spectrum antibiotic prescribing is progressively increasing compared to narrow-spectrum classes. Finally, antibiotic prescription patterns in IT are dominated by broad-spectrum agents. These patterns were most easily visualised and evaluated using two new simple quality indicators of childhood community-based antibiotic prescribing, the Amoxicillin Index and the Amoxicillin to Broad-spectrum Antibiotic Ratio. Crucially, total antibiotic prevalence of use and the two new pediatric-specific quality indicators may inform the evaluation of existing national interventions to reduce and improve antibiotic prescribing and, most importantly, may help to adequately design future interventions in this area.

Funding:

This work has received co-funding from the European Union in the framework of the Health Programme. ARPEC Project A 2009-11-01.

Contributors:

All authors were responsible for study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, and approval of final manuscript for submission.

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Figures and Tables

Figure 1.

Annual prevalence rate of systemic antibiotic prescriptions by country [J01] (error bars indicate 95% confidence interval)

Figure 2.

Prevalence of prescribed antibiotic classes by age and country

Figure 3.

Figure 3.1 Percentage of children exposed to amoxicillin on the total number of children exposed to antibiotics per database and age group- the amoxicillin index

Figure 3.2 Percentage of children exposed to amoxicillin on the total number of children exposed to antibiotics per database and calendar year - the amoxicillin index

Table 1.

Table 1a. Antibiotics that cover 90% of all antibiotic prescriptions (DU90%) by age categories in the Netherlands (1996-2010)

Table 1b. Antibiotics that cover 90% of all antibiotic prescriptions (DU90%) by age categories in the United Kingdom (1995-2010)

Table 1c. Antibiotics that cover 90% of all antibiotic prescriptions (DU90%) by age categories in Italy (2001-2010)

Table 2.

Ratio of broad to narrow-spectrum penicillins, cephalosporins and macrolides users per database, age category and calendar year

Table 3.

Ratio of users of amoxicillin to users of broad-spectrum penicillins, cephalosporins and macrolides per database, age category and calendar year

Table 1a. Antibiotics that cover 90% of all antibiotic prescriptions (DU90%) by age categories in the Netherlands (1996-2010)

Age 0-<1 years	Age 1-<5 years	Age 5-<12 years	Age 12-<18 years	Overall
Amoxicillin (73.2%)	Amoxicillin (57.8%)	Amoxicillin (43.8%)	Amoxicillin (17.2%)	Amoxicillin (45.1%)
Amoxicillin and enzyme inhibitor (10.4%)	Amoxicillin and enzyme inhibitor (14.0%)	Amoxicillin and enzyme inhibitor (16.5%)	Doxycycline (12.3%)	Amoxicillin and enzyme inhibitor (13.5%)
Clarithromycin (5.7%)	Azithromycin (7.6%)	Azithromycin (8.0%)	Nitrofurantoin (12.1%)	Azithromycin (7.5%)
Azithromycin (3.2%)	Clarithromycin (7.1%)	Clarithromycin (8.0%)	Amoxicillin and enzyme inhibitor (10.2%)	Clarithromycin (7.0%)
	Pheneticillin (4.2%)	Pheneticillin (6.1%)	Pheneticillin (9.0%)	Pheneticillin (5.7%)
		Nitrofurantoin (4.1%)	Azithromycin (8.5%)	Nitrofurantoin (4.4%)
		Flucloxacillin (3.9%)	Minocycline (6.6%)	Doxycycline (3.1%)
			Clarithromycin (6.3%)	Flucloxacillin (3.0%)
			Flucloxacillin (5.2%)	Sulfamethoxazole /trimethoprim (2.8%)
			Trimethoprim (3.5%)	

Table 1b. Antibiotics that cover 90% of all antibiotic prescriptions (DU90%) by age categories in the United Kingdom (1995-2010)

Age 0-<1 years	Age 1-<5 years	Age 5-<12 years	Age 12-<18 years	Overall
Amoxicillin (64.6%)	Amoxicillin (54.9%)	Amoxicillin (41.9%)	Amoxicillin (22.3%)	Amoxicillin (44.0%)
Erythromycin (9.5%)	Erythromycin (10.1%)	Phenoxymethyl -penicillin * (16.6%)	Phenoxymethyl -penicillin * (17.4%)	Phenoxymethyl-penicillin* (12.9%)
Flucloxacillin (6.3%)	Phenoxymethyl -penicillin* (8.8%)	Flucloxacillin (11.3%)	Flucloxacillin (11.8%)	Erythromycin (10.3%)
Trimethoprim (5.2%)	Flucloxacillin (6.7%)	Erythromycin (9.8%)	Erythromycin (11.5%)	Flucloxacillin (9.3%)
Phenoxymethyl -penicillin* (4.2%)	Trimethoprim (5.6%)	Trimethoprim (5.8%)	Oxytetracycline (7.8%)	Trimethoprim (5.5%)
Cefalexin (2.8%)	Amoxicillin and enzyme inhibitor (4.3%)	Amoxicillin and enzyme inhibitor (4.6%)	Trimethoprim (5.0%)	Amoxicillin and enzyme inhibitor (4.0%)
		Cefalexin (3.8%)	Lymecycline (4.8%)	Cefalexin (3.4%)
			Minocycline (4.3%)	Oxytetracycline (1.8%)
			Amoxicillin and enzyme inhibitor (3.0%)	
			Cefalexin (2.8%)	

* Phenoxymethylpenicillin is commonly known as penicillin V.

Table 1c. Antibiotics that cover 90% of all antibiotic prescriptions (DU90%) by age categories in Italy (2001-2010)

Age 0-<1 years	Age 1-<5 years	Age 5-<12 years	Age 12-<14 years	Overall
Amoxicillin (33.5%)	Amoxicillin (25.7%)	Amoxicillin and enzyme inhibitor (24.5%)	Amoxicillin and enzyme inhibitor (25.6%)	Amoxicillin (25.2%)
Amoxicillin and enzyme inhibitor (21.4%)	Amoxicillin and enzyme inhibitor (22.8%)	Amoxicillin (22.9%)	Amoxicillin (21.2%)	Amoxicillin and enzyme inhibitor (23.4%)
Clarithromycin (8.6%)	Cefaclor (10.6%)	Azithromycin (11.6%)	Azithromycin (15.2%)	Azithromycin (10.2%)
Cefaclor (8.4%)	Azithromycin (9.5%)	Clarithromycin (10.2%)	Clarithromycin (12.8%)	Clarithromycin (9.2%)
Azithromycin (6.0%)	Clarithromycin (8.3%)	Cefixime (7.6%)	Cefixime (6.7%)	Cefaclor (8.8%)
Cefixime (5.0%)	Cefixime (7.0%)	Cefaclor (7.2%)	Cefpodoxime (3.5%)	Cefixime (7.1%)
Ceftibuten (3.9%)	Ceftibuten (3.8%)	Cefpodoxime (4.1%)	Cefuroxime (2.3%)	Cefpodoxime (3.6%)
Clofoctol (3.5%)	Cefpodoxime (3.5%)	Ceftibuten (2.9%)	Cefaclor (2.0%)	Ceftibuten (3.4%)
			Ceftibuten (1.4%)	

Table 2. Ratio of broad to narrow-spectrum penicillins, cephalosporins and macrolides users per database, age category and calendar year

Broad/Narrow-spectrum antibiotics (B/N) ratio												
	2001			2006			2010			Overall		
	NL	UK	IT	NL	UK	IT	NL	UK	IT	NL	UK	IT
0-<1 yrs	5.9	0.3	27.1	6.5	0.3	66.8	6.6	0.4	149.5	5,7	0.3	60.8
1-<5 yrs	2.8	0.3	38.2	4.1	0.3	72.5	5.0	0.4	360.7	3,9	0.4	100.1
5-<12 yrs	2.8	0.2	12.9	2.9	0.2	55.9	4.0	0.3	173.3	3,4	0.2	61.0
12-<14 yrs	2.5	0.2	9.4	2.2	0.2	40.8	3.3	0.3	114.5	2,6	0.2	60.3
14-<18 yrs	1.5	0.1	-	2.1	0.2	-	2.4	0.3	-	2.0	0.2	-
All ages	2.6	0.2	19.2	3.1	0.3	62.7	3.2	0.3	217.9	3,2	0.3	74.7

The ratio between the number of users of broad-spectrum penicillins, cephalosporins and macrolides (J01CR, J01DC, J01DD and J01F [without J01FA01]) and the number of users of narrow-spectrum antibiotics (J01CE, J01DB and J01FA01).

Abbreviations: NL=the Netherlands; UK=the United Kingdom; It=Italy; yrs=years

Table 3. Ratio of users of amoxicillin to users of broad-spectrum penicillins, cephalosporins and macrolides per database, age category and calendar year

Amoxicillin/Broad-spectrum antibiotics (A/B) ratio												
	2001			2006			2010			Overall		
	NL	UK	IT	NL	UK	IT	NL	UK	IT	NL	UK	IT
0-<1 yrs	2,0	11,2	1,3	4,0	11,0	0,7	4,7	10,1	0,6	3,6	10,2	0,8
1-<5 yrs	1,6	7,0	0,9	1,9	6,9	0,5	2,3	6,7	0,4	2,0	6,4	0,5
5-<12 yrs	1,0	6,0	0,7	1,4	5,7	0,4	1,5	5,1	0,3	1,4	5,6	0,4
12-<14 yrs	0,8	5,7	0,7	1,2	4,8	0,4	1,1	4,0	0,3	1,1	5,0	0,4
14-<18 yrs	0,6	4,6	-	0,5	3,7	-	0,5	2,9	-	0,6	3,8	-
All ages	1,2	6,6	0,8	1,6	6,1	0,5	1,7	5,4	0,3	1,6	6,0	0,5

The ratio between the number of users of amoxicillin (J01CA04) and the number of users of broad- spectrum penicillins, cephalosporins and macrolides (J01CR, J01DC, J01DD and J01F (without J01FA01])

Abbreviations: NL=the Netherlands; UK=the United Kingdom; It=Italy; yrs=years

Figure 1.

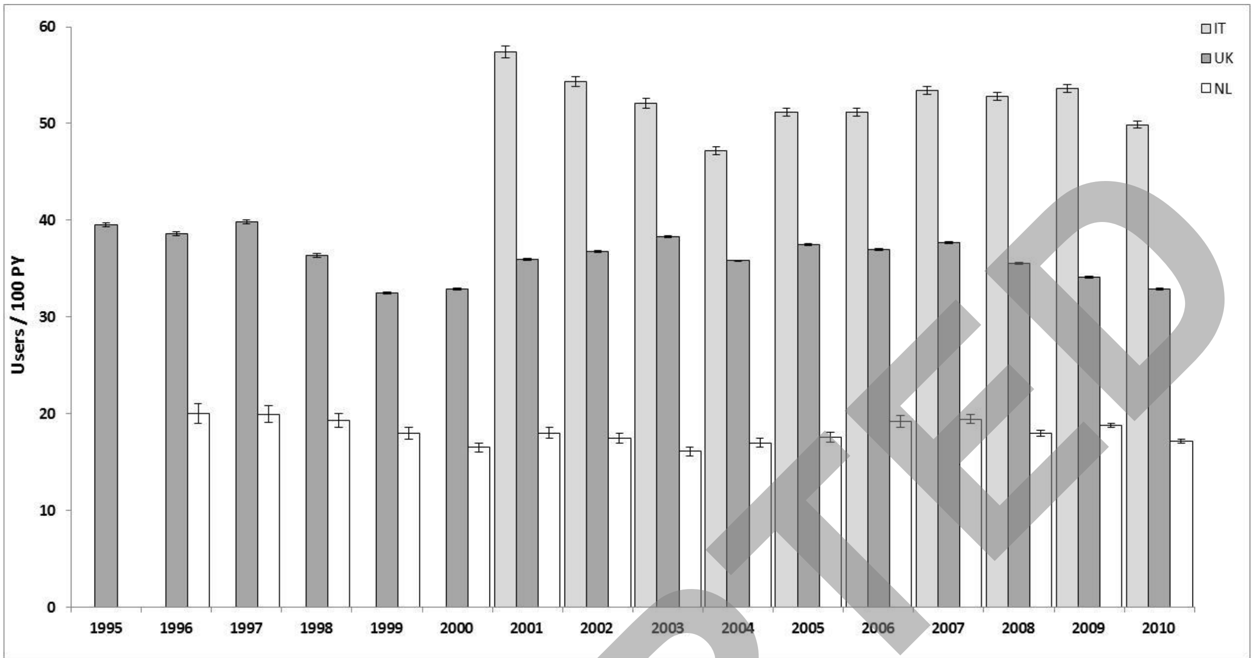
60
50
40
30
20
10
0
Users / 100 PY
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
IT
UK
NL

Figure 2.

Figure 2. Prevalence of prescribed antibiotic classes by age and country

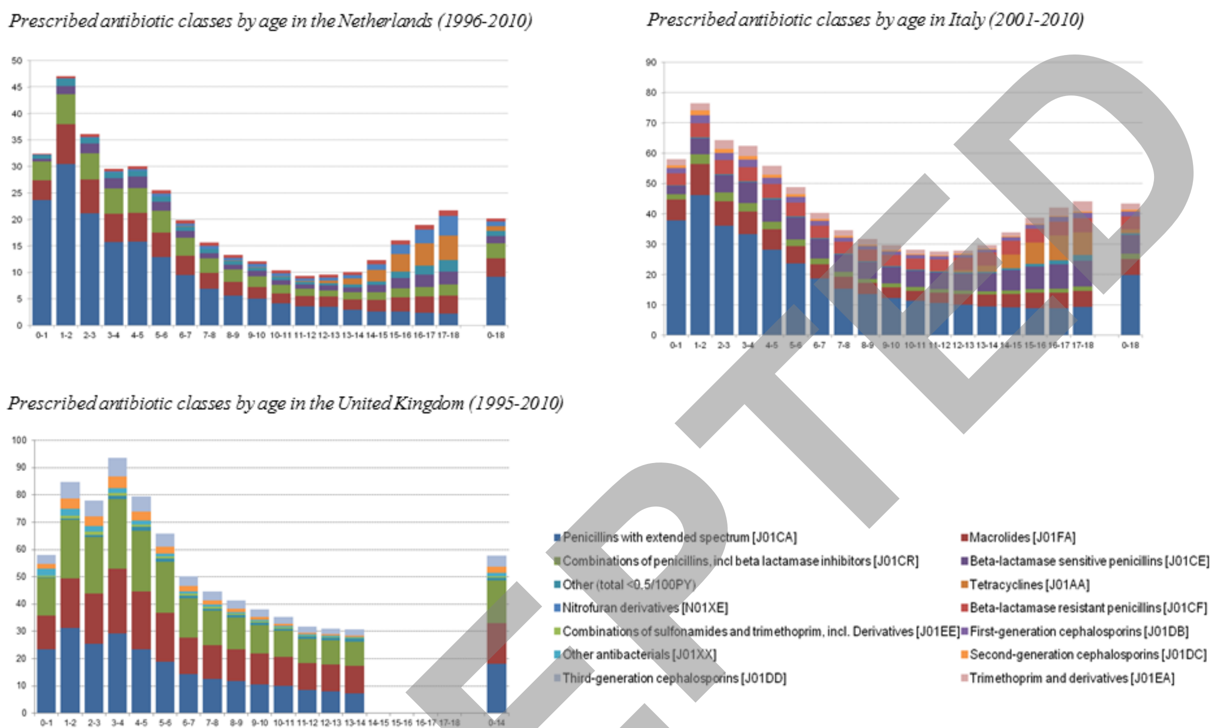

Figure 3.

Figure 3.1 Percentage of children exposed to amoxicillin on the total number of children exposed to antibiotics per database and age group- the amoxicillin index

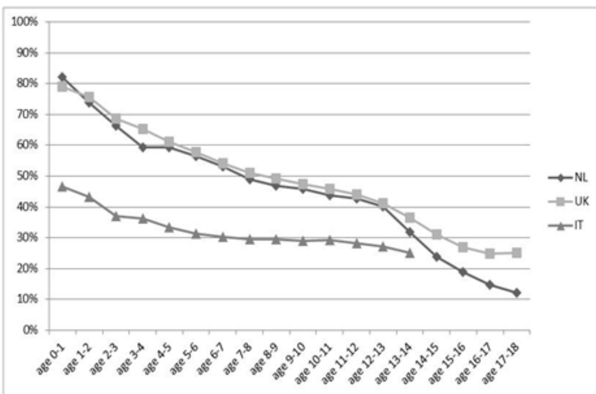

Figure 3.2 Percentage of children exposed to amoxicillin on the total number of children exposed to antibiotics per database and calendar year - the amoxicillin index