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Use of Antibiotics in children: A Danish Nationwide Drug Utilization Study

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Background

We aimed to describe the use of systemic antibiotics among children in Denmark.

Methods

National data on drug use in Denmark were extracted from the Danish National Prescription Database. We used prescription data for all children in Denmark aged 0-11 years from January 1, 2000 to December 31, 2012.

Results

We obtained data on 5,884,301 prescriptions for systemic antibiotics issued to 1,206,107 children. The most used single substances were phenoxymethylpenicillin (45%), amoxicillin (34%) and erythromycin (6%). The highest incidence rate of antibiotic treatment episodes was observed among children under two years of age at 827 per 1,000 children in 2012. Incidence rates were relatively stable throughout the study period. One-year prevalences in 2012 were 485, 363 and 190 per 1,000 children among children aged 0-1, 2-4 and 5-11, respectively. A gradual shift from narrow-spectrum penicillin V to the broader-spectrum amoxicillin was found among children below the age of 5 years. The use of macrolides decreased slightly, especially among those aged 0-1 years. Minor regional differences were noted, with a somewhat higher use in the Capital Region. Skewness in use was most notable among those aged 0-1 years. There was little evidence of heavy users.

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Conclusion

Prescribing rate of antibiotic to children in Denmark remained stable at a high level from 2000 to 2012. An increase in the use of broad-spectrum beta-lactam penicillin was noted, but otherwise the prescribing pattern adhered well to National guidelines with respect to choice of antibiotics.

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Introduction

Antibiotics are the most commonly prescribed drugs in children with the highest incidence rates in pre-schoolers (1). The issue of antibiotic resistance is of global concern and considered a threat to modern health care, rendering patients at risk of ineffective treatment regimens and societies strained by increasing health care costs (2). Antibiotic consumption is directly related to the antibiotic resistance rates of common bacteria (3,4). The World Health Organization emphasizes the role of antimicrobial stewardship in their antimicrobial resistance strategy (5,6). As new medicinal entities within antibiotics are far and few between in the pharmaceutical pipeline (7), promotion of judicious use of antibiotics is essential to limit antibiotic resistance rates.

Prescribing antibiotics for common non-serious or inaccurately diagnosed infections in childhood is a common and controversial issue in primary care (8). In the case of acute respiratory tract infections, the majority will be of viral origin (9) in which case antibiotics are of no benefit and potentially harmful due to side effects. A general practitioner will on average have to treat 20 children with otitis media for one of them to benefit from treatment (10). It is known that treatment with antibiotics is heavily influenced by individual prescribing patterns, which does not always follow relevant guidelines (11), and furthermore that differences in guidelines leads to patients being managed differently (12,13).

Detailed knowledge on actual prescribing patterns is necessary to plan relevant activities that limit excessive use of antibiotics in general as well as of particular types of antibiotics. We therefore conducted an antibiotic utilization study in children (0-11 years)

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from 2000-2012 characterizing patterns of antibiotic prescribing in relation to age, gender and region. We also looked for evidence of skewed use.

Materials and Methods

In this study, we described the use of systemic antibiotics obtained at community pharmacies among children in Denmark. We obtained prescription data for all children in Denmark 0 to 11 years of age during the period January 1, 2000 to December 31, 2012. On average per year, 804,000 children of this age resided in Denmark during the study years.

Data source

National data on drug use in Denmark was extracted from the Danish National Prescription Database (14). The registry contains complete information, from 1 January 1995 and onwards, on all prescriptions redeemed by Danish residents at outpatient pharmacies. For each redeemed prescription, the registry contains information on the following variables relevant for this study: type of antibiotic, date of purchase, age, gender and region of residence. Registered drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the World Health Organization (WHO) for purposes of drug use statistics (15). The registry is reported to have a high completeness and validity (14).

The Danish Civil Registration System (16) contains data on vital status (dates of birth and death) and migrations to and from Denmark, which allowed us to keep track of all study subjects.

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Population statistics were obtained from Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.

Study drugs

Systemic antibiotics were defined as all drugs within ATC-group J01 (antibiotics for systemic use).

Analysis

In all analyses, we age-categorized children according to the European Medicines Agency (EMA) (17), i.e. subdivided into <2 years, 2-4 years, and 5-11 years. Age was calculated using the birthdate compared to the date of the filling of a prescription.

The incidence rates of antibiotic treatment episodes were calculated annually from 2000 to 2012 for each age category, using the total number of children within each age category living in Denmark on January 1 of the relevant year as the denominator (as an approximation of the total amount of follow-up in person-years). If two or more prescriptions were redeemed with ≤14 day's interval, we regarded them as one treatment episode. The incidence rate was given per 1,000 person-years. We also calculated the one-year prevalences. This is similar to the incidence rate, except that children that have multiple different courses within a calendar year are only counted once in the numerator. By definition, a one-year prevalence cannot exceed 100% (18).

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We illustrated the age and gender distribution of antibiotics use by estimating the incidence rate of antibiotic treatment episodes (similarly as above) for each age year during 2012 among boys and girls 0 to 11 years of age. Furthermore, to investigate regional differences in the use of antibiotics, we estimated the incidence rate (2012) by age category in each of the five Danish regions: North-, Mid-, South-, Zealand- and Capital Region.

Looking at 2012, we calculated the total number of prescriptions redeemed per 1,000 children for each single class of antibiotics, using the third level ATC-code (e.g. J01C beta-lactam antibacterials, antibiotics), for each age category. We furthermore looked at the temporal trends 2000-2012 for each single class of antibiotics within each age category.

To identify any evidence of skewed use, we categorized children within each age category by the total number of prescriptions they had redeemed during 2012 (using the age at 1 January 2012, excluding those born during 2012).

Other

All calculations were performed using STATA Release 12.0 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency and Statistics Denmark's Scientific Board. According to Danish law, purely registry-based studies do not require approval from an ethics committee.

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Results

We obtained data on 5,884,301 prescriptions for systemic antibiotics issued to 1,206,107 children. The most used single substances were phenoxymethylpenicillin (2,671,843 prescriptions, 45.4%), amoxicillin (1,980,420 prescriptions, 33.7%) and erythromycin (339,193 prescriptions, 5.8%).

The highest incidence rate of antibiotic treatment episodes was observed among children under two years of age (827 per 1,000 years of follow-up in 2012, figure 1) with reasonably stable incidences throughout the study period. When estimating one-year prevalence (i.e. only including each child once per year despite multiple treatment episodes within a calendar year) we saw a similar picture, with prevalences in 2012 of 485, 363 and 190 per 1,000 children among children 0 to 1, 2 to 4 and 5 to 11 years of age respectively. The incidence rate peaked at one year of age among boys and girls (figure 2). Treatment was slightly more common among boys than girls until the age of four years, after which the opposite pattern was seen (figure 2).

Small regional differences in incidence rates of treatment episodes within each age group were identified. For 2012, the regional incidence rate varied from 691, 469 and 233 in the Mid Region to 1,041, 675 and 300 per 1,000 person-years in the Capital Region among children 0 to 1, 2 to 4 and 5 to 11 years of age respectively (table 1).

By far, the most commonly used antibiotic drugs were the beta-lactam antibacterials penicillins (J01C), although the use of macrolides (J01F) was also noticeable. For a

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more detailed distribution see table 2. This pattern was stable throughout the study period except for a few antibiotics. Among the penicillins, we saw a slight decrease in the use of phenoxymethylpenicillin (figure 3) and an increase in the use of amoxicillin (figure 3 and 4), most notably among those <2 years old. The incidence rate of amoxicillin with an enzyme inhibitor, increased substantially over the study period (figure 4). In children below the age of 1 year the incidence rate rose from about 7/1000 to about 30/1000 person-years. The overall use of macrolides declined slightly, especially among those 0 to1 years of age, with a decrease in the use of erythromycin and an increase in the use of clarithromycin (figure 5). The incidence rates of trimethoprim alone and in combination with sulphanomides are illustrated in figure 6.

Table 3 shows the percentile distribution of total number of prescriptions redeemed per child by age group. The skewness in use of antibiotics was most pronounced among <2 year olds where 7.1% had used four or more prescriptions during 2012 (table 3). Generally, however, there was little evidence of skewed use.

Discussion

We demonstrate a relatively stable high overall incidence rate of antibiotic use in all three age groups of children studied in Denmark from 2000-2012. Penicillin dominates prescribing, with the pattern shifting from the narrow-spectrum penicillin V towards an increase in the prescribing of the more broad-spectrum amoxicillin in the children below the age of 5. Macrolide prescribing was modest compared to other countries, and changed from erythromycin to clarithromycin during the study period.

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Unfortunately, it is not possible from our data to provide a meaningful assessment of the appropriateness of the prescription pattern observed. The vast majority of antibiotics prescribed to children are prescribed by general practitioners and, despite an extensive documentation of health-care related issues in Denmark, there is no nation-wide database with relevant information on the indications for prescribing antibiotics as related to general practice. Specific diagnoses or proxy indicators such as C-reactive protein, white blood cell count or results from microbiological diagnostic procedures remain elusive for the period studied. Such a database is under development and implementation thus allowing for a reasonable level of qualification of such prescriptions on a nation-wide basis in the future (19,20). In the European Surveillance of Antimicrobial Consumption (ESAC) study the total (including adults) use of outpatient antibiotics in Denmark was low (about 14 DDD per 1000 inhabitants daily) compared to most other countries (3), and the described utilization may be viewed as an example of a relatively low prescription rate pattern.

An important strength of the study is that it is based on a registry with full coverage of the entire Danish nation (14). In Denmark, antibiotics are available on prescription only, and apart from a very small proportion dispensed in hospitals (see below), we could therefore account for all users. Our study is thus unlikely to be affected by selection bias. We also had data from a wide period in time, which allowed us to describe temporal trends in use. Among the limitations are that we did not have data on the indications for antibiotic prescribing, nor on the diagnostic procedures whereby the indications were established. Our data does not cover antibiotics provided by hospitals, but prescriptions written at hospitals and filled at community pharmacies were included.

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Finally, it may be argued that our description of antibiotic use applies to a setting that is somewhat unusual. Compared to other countries in Europe, Denmark has a low overall rate of antibiotic prescribing, with a high proportion of narrow-spectrum use (3). However, given that this position is regarded as desirable, a description of antibiotic use in Denmark may impact other health care systems in promoting a rational use of antibiotics in primary care.

The rate was highest in the age group <2 years with an incidence rate of about 800-900 per 1,000 children as compared to roughly 600 and 300 per 1,000 children for the age groups from 2-4 and 5-11 years, respectively. This is in accordance with other, albeit incomplete, Danish data from 1999 and 2006 (11,21). The prescribing rate is comparable to recent population based German and Norwegian data (22,23), and somewhat lower than previous data from Sweden (24). However, a recent study from the Netherlands found markedly lower prescribing rates of about 250/1,000 in children below the age of 5 (25). In France, a reduction of about 50% in the absolute number of prescriptions of antibiotics to children between 2000 and 2010 were recently reported (26). Our data are also rather close to U.K. data from 2007 where prescribing rates were about 750, 900 and 450 per 1,000 children in at ages <2, 2-4 and 5-9 years, respectively. In the U.K., the overall prescribing rate has increased substantially by 41% from 2000 to 2007 (27). In the US, one year prevalence rates of antibiotic use around 23-28% in persons below the age of 19 have been reported in some settings (28,29) and rates in the late 1990's were reported at about 900 per 1,000 children (30); but this data are not directly comparable due to the substantial differences in health care organization between the US and Denmark.

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Gender pattern was in accordance with similar data from Sweden, Norway, The Netherlands, U.K. and Germany (22–25,27). A slightly higher use in young boys may to some extent reflect that acute otitis media is more frequent among boys in this age group (31). About 50% of children below the age of 2 years received at least one prescription in 2012, comparable to recent German data (22). Regional differences were minor, except for a strikingly higher use in the Capital (Copenhagen) Region. However the Danish regional differences are considerably less marked than in for example Italy (32), likely reflecting the relative uniformity of the Danish healthcare system. We did not find evidence suggesting a substantial proportion of skewed use.

The use of beta lactam antibiotics dominates the prescribing pattern throughout the period accounting for about 88% of all prescriptions. However a gradual shift from narrow-spectrum penicillin V to a broader spectrum amoxicillin is apparent in children below the age of 5 years. In 2000, the incidence rates for amoxicillin in the three age groups were about 400, 200 and 40 per 1,000 children per year, while in 2012 the numbers were 450, 225 and 40 per 1,000, respectively. Coincidentally, the rate for penicillin V changed from 375, 300 and 200 in 2000 to 300, 225 and 150 per 1,000 children. This is despite the fact that recommendations generally remained unchanged and explicitly discouraged the use of broad-spectrum antibiotics as first line treatment (33). A vaccine against pneumococci was introduced in the Danish Children Vaccine Programme in 2007 (34). This vaccine programme has coverage rate of 80-90% of all Danish children from 2007-2012 (35). The introduction of this vaccine is not obvious in the prescribing pattern of antibiotics.

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Children prefer amoxicillin to phenoxymethylpenicillins, a preference likely related to taste (36), which may partly explain the prescribing pattern. This pattern is of some concern. Unwarranted use of broad spectrum antibiotics promotes the emergence of multi resistant bacteria in the community, now recognised as a worldwide challenge (2,3,7,37–42). Thus, adherence to restrictive prescribing practice with respect to indication and choice of drug is of outmost importance. Of note, in otitis media, tonsillitis and pneumonia, comprising the vast majority of diagnoses for which antibiotic treatment is indicated in children, narrow-spectrum penicillin is the best choice both in terms of microbiological efficacy and ecological considerations (43).

A substantial increase in prescribing rate of amoxicillin and clavulanic acid is apparent (figure 4); this concurs with treatment guidelines suggesting this combination in cases of initial treatment failure from around 2007 (33).

The prescribing rate of macrolide use was low compared to other countries (1,34), and it has decreased slightly during the study period. There are some fluctuations in the prescription incidence rate of macrolides during the study years; perhaps explained by periodical epidemics of mycoplasma pneumonia or bordetella pertussis. In Denmark, there was a relative high incidence of mycoplasma pneumonia in 2005-2006 while historically few cases were reported for 2007-2009. A high incidence was again reported for 2010 and 2011 followed by at steep drop-off for 2012. The bordetella pertussis pattern showed a high incidence from 2004-2005; a very low to moderate incidence for 2006-2011 and a high incidence for 2012 (44) These observations corresponds reasonably well to the overall prescription pattern for the study period. Even so, the level of macrolide prescribing for upper respiratory infections is too high in

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Denmark (45). Inappropriate prescribing of macrolides promotes the development of treatment resistant bacteria (3,46). Erythromycin dominated the macrolide prescribing pattern with a slightly decrease until a sudden drop-off in mid-2012 (figure 5B). From 2011-2012, a corresponding increase in the prescribing rate of clarithromycin was observed (figure 5C). Until 2004, erythromycin was the recommended second line choice of drug or treatment of acute tonsillitis, otitis and pneumonia in children. In 2005, the recommendation shifted briefly to roxithromycin, but from 2006 on, clarithromycin was the recommended second-line choice of drug (33). This corresponds well to the gradual shift in prescribing from erythromycin to clarithromycin from 2004-2012. The sudden drop to virtually no erythromycin prescribing in mid-2012 is probably related to reimbursement regulations. A "dear doctor" letter was distributed from the Danish Health and Medicines Authority in mid-October 2012, warning that the general reimbursement for erythromycin would cease from March 2013 (46). This is unlikely to be the main explanation though; we suspect that manufacturer supply be a major contributor to this observation. However, this could not be objectively confirmed. The prescription incidence rate of azithromycin appears to fluctuate somewhat throughout the study years, with a noticeable temporary drop in 2009 (figure 5D). In Denmark, azithromycin is licensed to the use in children > 45 kg only. Azithromycin has not been recommended in guidelines as primary or secondary treatment for other than chlamydia trachomatis infection (33,47), and we have not been able to identify a plausible explanation for this observation.

The use of pivmecillinam and trimethroprim (figures 3F and 6B) shows a pattern of low, but gradually increasing prescription incidence rate, especially for pivmecillinam from

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around 2006. Antibiotic treatment guidelines for childhood urinary tract infections in Denmark changed recommendations from sulphamethizol or trimethroprim to pivmecillinam in 2006 as first line regimen (33).

Other antibiotics, including cephalosporines and sulphonamides, were rarely prescribed as the aggregate incidence rate was below 20/1,000 person years in 2012 (Table 2). This is significantly below other countries (1,3) and suggests a high degree of adherence to antibiotic treatment guidelines in Denmark in this respect.

In summary, prescribing rate of antibiotic to children in Denmark remained overall stable at a high level during 2000 and 2012. A disturbing increase in use of broad-spectrum beta-lactam penicillin was noted, but otherwise the prescribing pattern adheres well to National guidelines with respect to *choice* of antibiotics. Whether the *indications* for prescribing justify the high use of antibiotics in children should be subject to future studies.

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Figure legends

Figure 1: Incidence rate of antibiotic treatment episodes

Figure 2: Incidence rate of antibiotic treatment episodes specified by age (in 2012)

Figure 3A: Incidence rate of treatment with penicillins (J01C)

Figure 3B: Incidence rate of treatment with phenoxymethylpenicillin (J01CE02)

Figure 3C: Incidence rate of treatment with amoxicillin (J01CA04)

Figure 3D: Incidence rate of treatment with ampicillin (J01CA01)

Figure 3E: Incidence rate of treatment with pivampicillin (J01CA02)

Figure 3F: Incidence rate of treatment with pivmecillinam (J01CA0)

Figure 3G: Incidence rate of treatment with dicloxacillin (J01CF01)

Figure 4: Incidence rate of treatment with amoxicillin and enzyme inhibitor (J01CR02)

Figure 5A: Incidence rate of treatment with macrolides (J01FA)

Figure 5B: Incidence rate of treatment with erythromycin (J01FA01)

Figure 5C: Incidence rate of treatment with clarithromycin (J01FA09)

Figure 5D: Incidence rate of treatment with azithromycin (J01FA10)

Figure 6A: Incidence rate of treatment with sulphanomides and trimethoprim (J01E)

Figure 6B: Incidence rate of treatment with trimethoprim (J01EA01)

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Table 1: Regional differences in use of antibiotics, expressed as average incidence rate of antibiotic treatment episodes (per 1,000 person years), specified by age category.

Region	Age group <2 years	Age group 2-4 years	Age group 5-11 years
Entire Denmark	880	604	281
North Region	757	541	271
Mid Region	691	469	233
South Region	923	614	269
Zealand Region	959	684	321
Capital Region	1,041	675	300

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Table 2: Number of prescription redeemed during 2012 per 1,000 children per ATC-group.

ATC code	ATC name	Age group <2 years (n= 125,958)	Age group 2-4 years (n= 201,623)	Age group 5-11 years (n= 483,131)
J01A	Tetracyclines	(n<10)	(n<10)	0.2 (0.1%)
J01C	Beta-lactam antibacterials, penicillins	886 (92.2%)	539 (88.8%)	239 (84.8%)
J01CA	Penicillins with extended spectrum	523 (54.4%)	252 (41.5%)	56 (20.0%)
J01CE	Beta-lactamase sensitive penicillins	314 (32.7%)	254 (41.8%)	160 (56.7%)
	Remaining penicillins (J01C)	49 (5.1%)	33 (5.5%)	23 (8.2%)
J01D	Other beta-lactam antibacterials	1 (0.1%)	0.5 (0.1%)	0.3 (0.1%)
J01E	Sulfonamides and trimethoprim	6 (0.6%)	9 (1.5%)	8 (2.8%)
J01F	Macrolides, lincosamid and streptogramins	66 (6.9%)	55 (9.0%)	30 (10.5%)
J01G	Aminoglycoside antibacterials	(n<10)	0.1 (0.0%)	0.1 (0.0%)
J01M	Quinolone antibacterials	0.3 (0.0%)	0.6 (0.1%)	2 (0.5%)
J01X	Other antibacterials	2 (0.2%)	3 (0.4%)	3 (1.1%)
-	TOTAL	961	607	282

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Table 3: Number of prescriptions redeemed per child in 2012, by age category.

Number of prescriptions	**Age group <2 years** (n= 125,958)	**Age group 2-4 years** (n= 201,623)	**Age group 5-11 years** (n= 483,131)
0	50.8%	68.6%	83.7%
1	23.2%	18.7%	11.5%
2	12.5%	7.5%	3.2%
3	6.5%	2.9%	1.0%
4+	7.1%	2.3%	0.6%

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Figure 1: Incidence rate of antibiotic treatment episodes

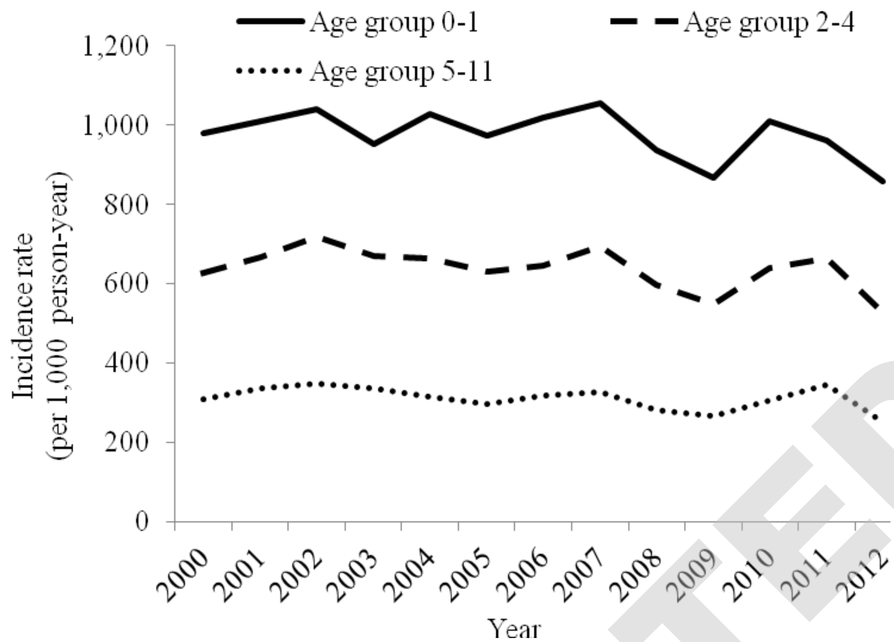

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Figure 2: Incidence rate of antibiotic treatment episodes specified by age (in 2012)

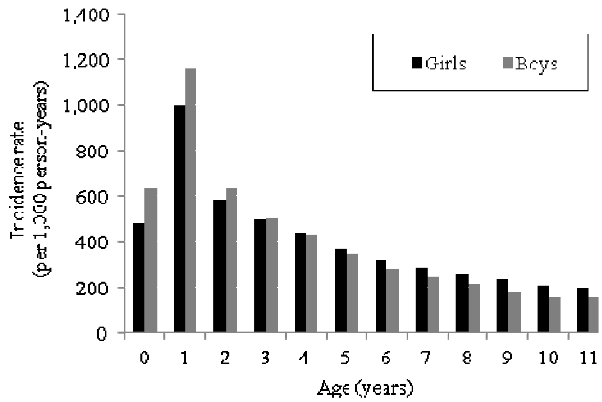

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Figure 3A: Incidence rate of treatment with penicillins (J01C)

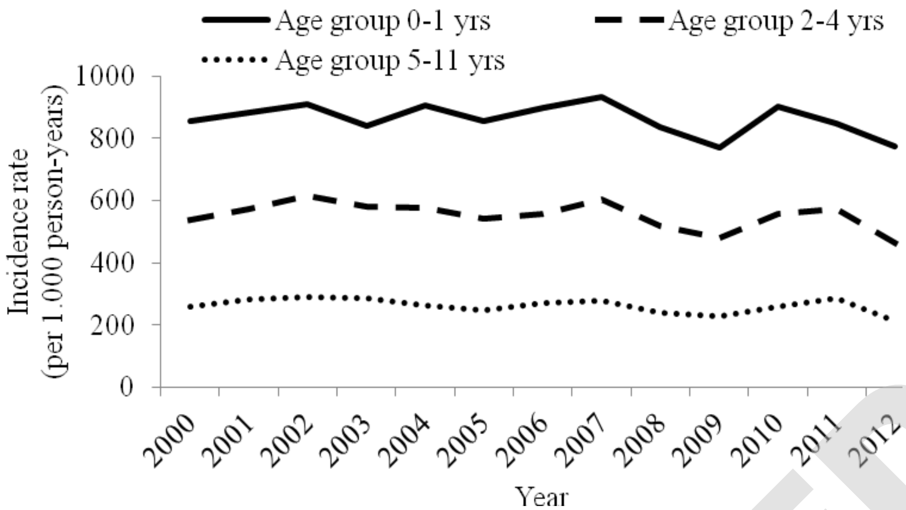

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Figure 3B: Incidence rate of treatment with phenoxymethylpenicillin (J01CE02)

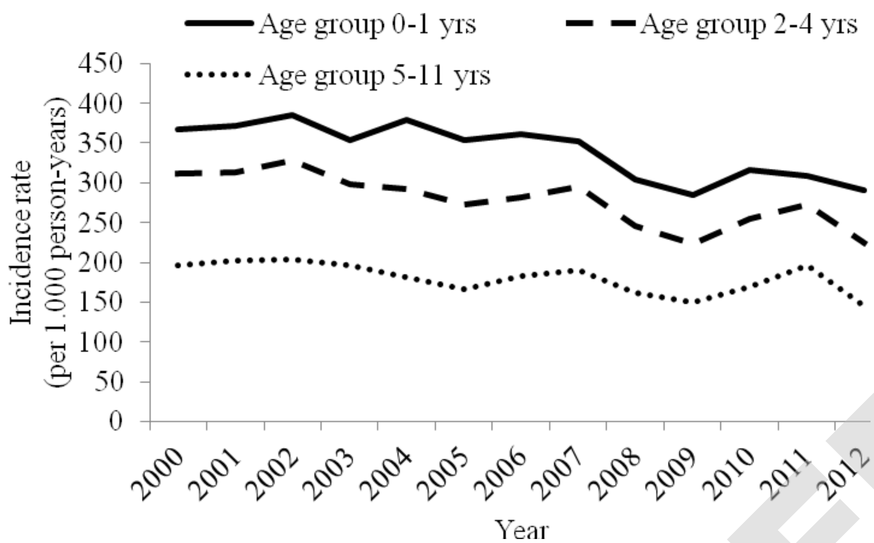

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Figure 3C: Incidence rate of treatment with amoxicillin (J01CA04)

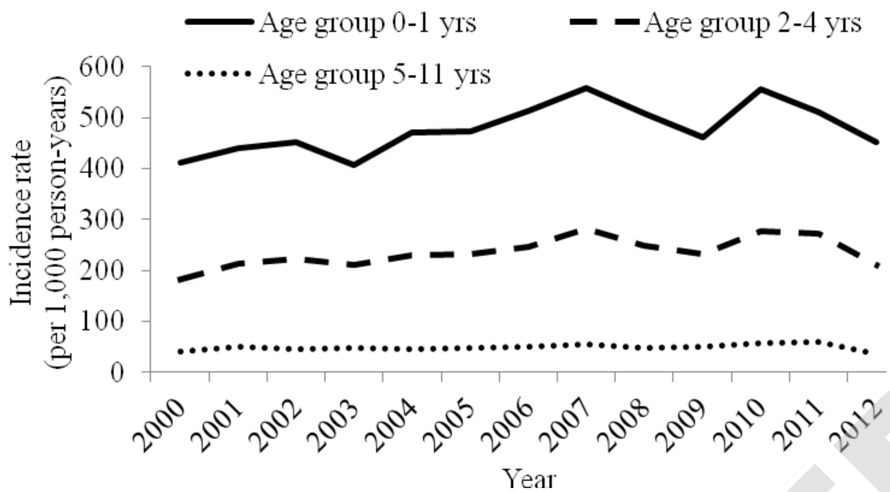

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Figure 3D: Incidence rate of treatment with ampicillin (J01CA01)

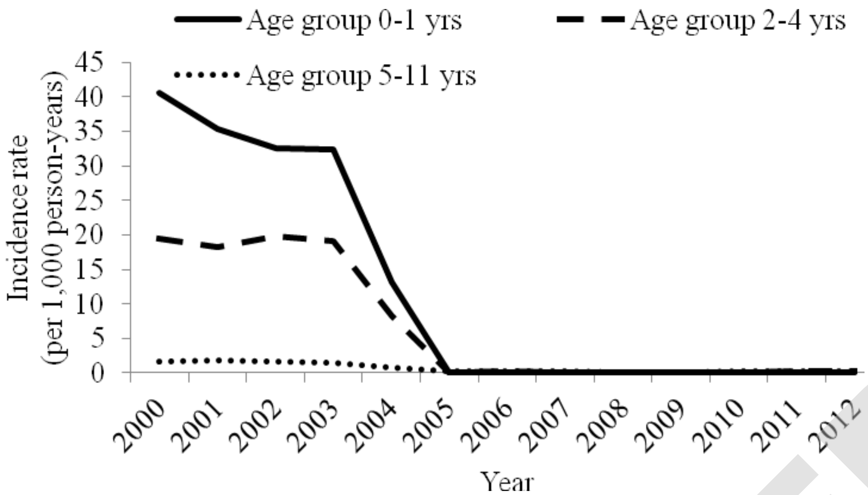

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Figure 3E: Incidence rate of treatment with pivampicillin (J01CA02)

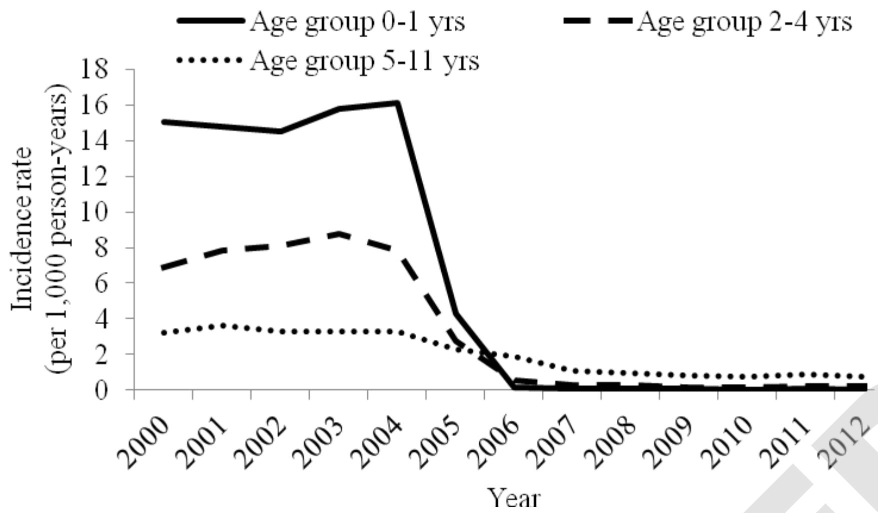

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Figure 3F: Incidence rate of treatment with pivmecillinam (J01CA08)

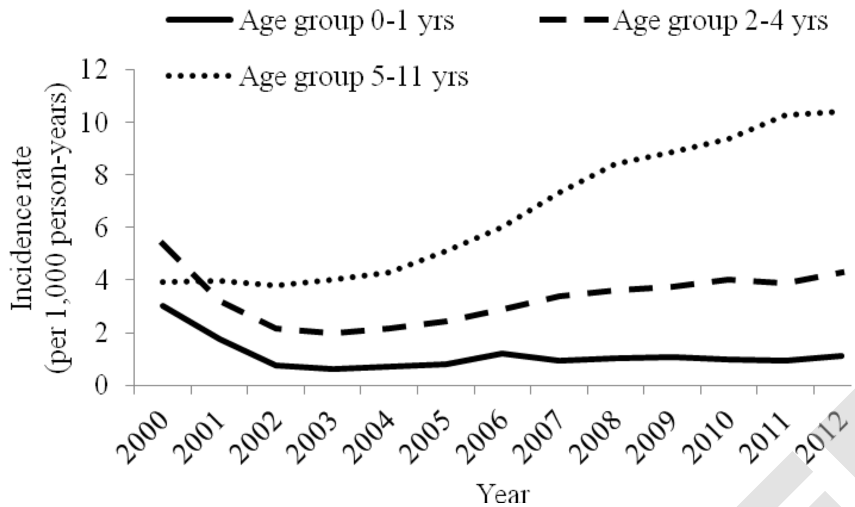

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Figure 3G: Incidence rate of treatment with dicloxacillin (J01CF01)

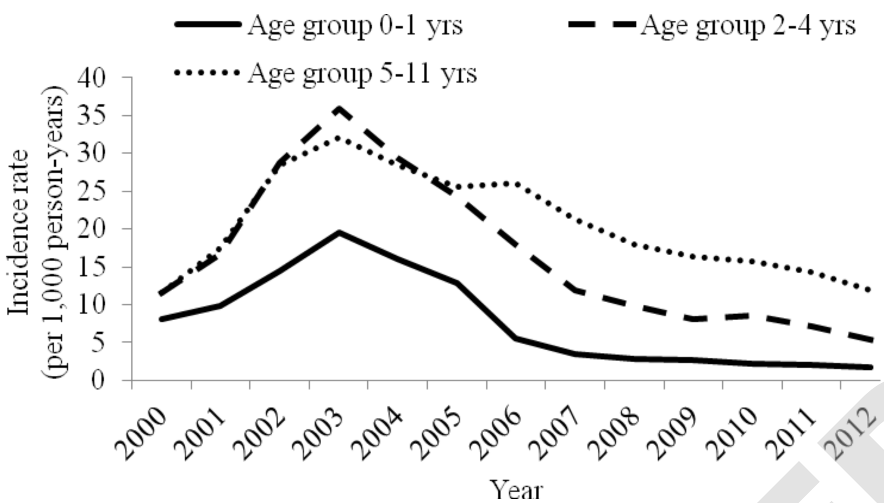

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Figure 4: Incidence rate of treatment with amoxicillin and enzyme inhibitor (J01CR02)

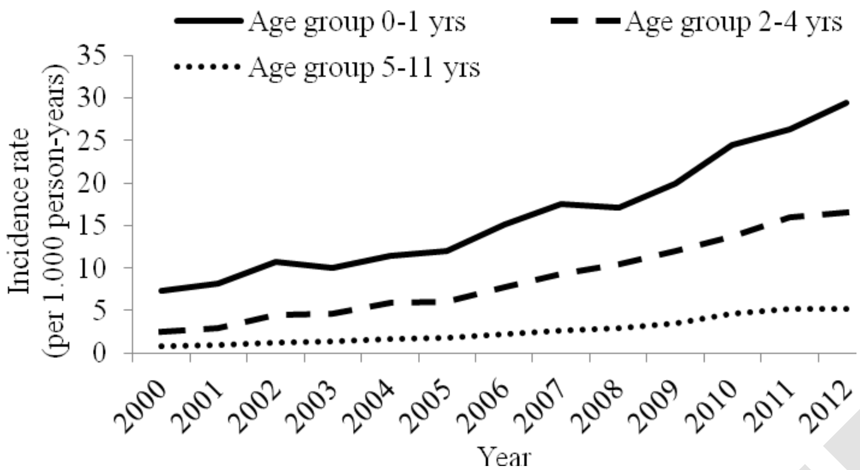

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Figure 5A: Incidence rate of treatment with macrolides (J01FA)

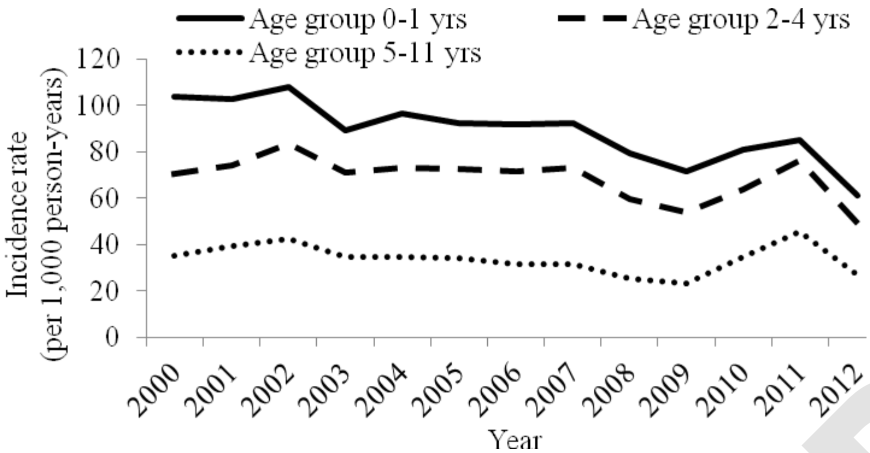

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Figure 5B: Incidence rate of treatment with erythromycin (J01FA01)

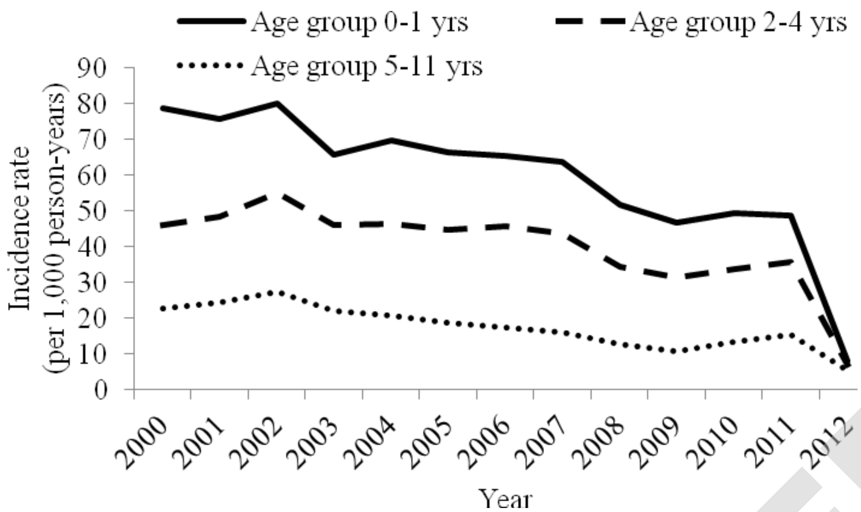

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Figure 5C: Incidence rate of treatment with clarithromycin (J01FA09)

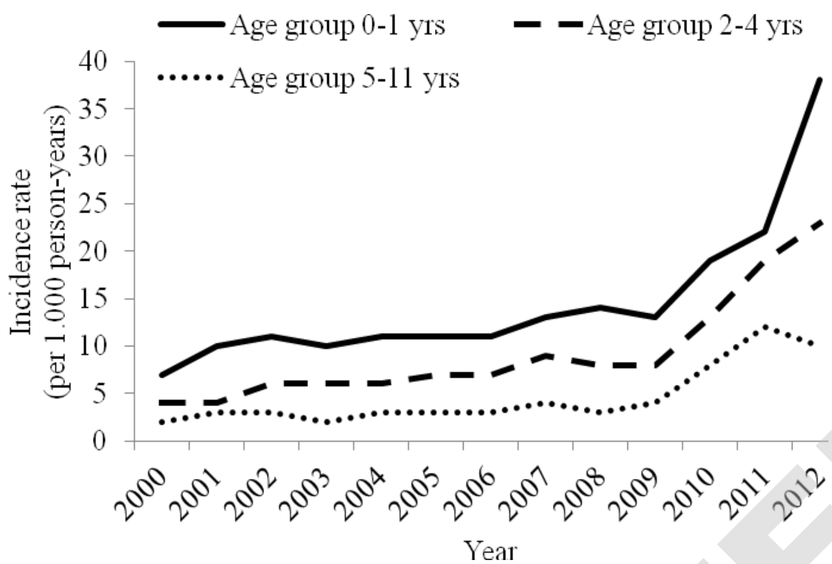

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Figure 5D: Incidence rate of treatment with azithromycin (J01FA10)

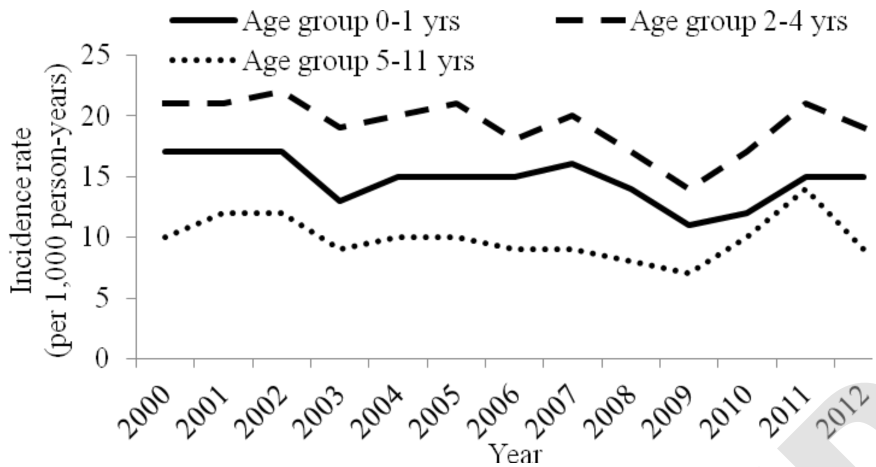

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Figure 6A: Incidence rate of treatment with sulphanomides and trimethoprim (J01E)

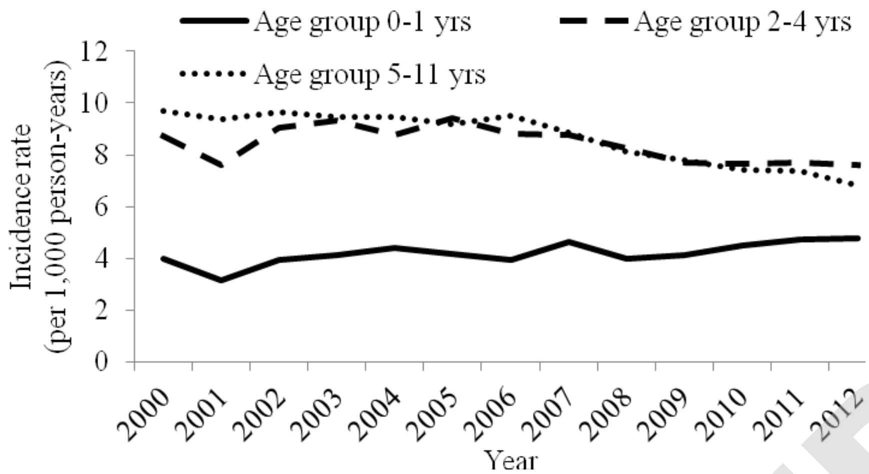

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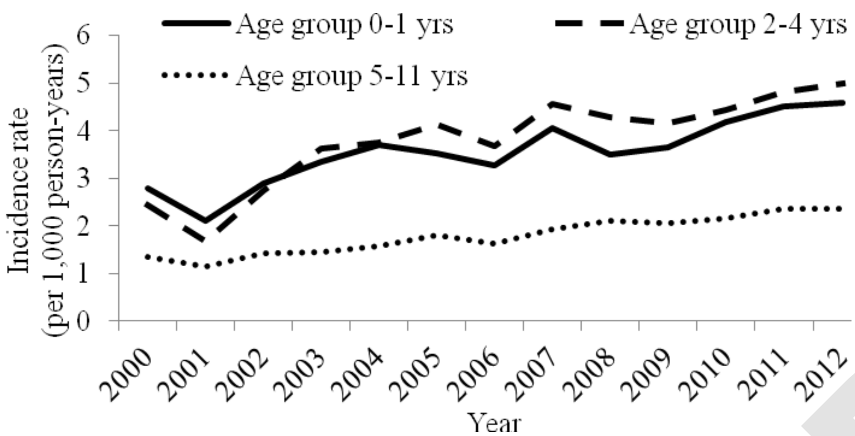
Figure 6B: Incidence rate of treatment with trimethoprim (J01EA01)



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