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REGULAR ARTICLE

Antibiotic usage, dosage and course length in children between 0 and 4 years

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Abstract

Aim: Antibiotic drugs are most frequently used by 0- to 4-year-old children. We performed a cross-sectional study in the Netherlands using a pharmacy prescription database to investigate the use, dose and course length of antibiotic drugs in 0- to 4-year-olds.

Methods: We used a database with pharmacy drug-dispensing data. We investigated all prescriptions of systemic antibiotics prescribed in the years 2002–2006 for children of 0–4 years of age. Prescriptions for children under the age of 3 months were excluded.

Results: Children of 9–12 months of age received more antibiotics than children in other age groups. In the 3- to 6-month-olds, amoxicillin was prescribed in 75.2% of the cases. This percentage was 50.4% in the 4-year-olds. The contribution of other broad-spectrum antibiotics increased with age (clarithromycin and amoxicillin/clavulanic acid). Small-spectrum penicillins were prescribed less often than the broad-spectrum antibiotics. From the prescriptions of the five most used drugs, 97.6% were within the recommended dose range. Most course lengths corresponded with the guidelines. Of the prescriptions, 3.9% were unlicensed or off-label.

Conclusion: Within the group of 0- to 4-year-old children, most antibiotics were used by 9- to 12-month-olds. The doses and course lengths were mostly correct, but the choice of antibiotics was not according to the guidelines. Young children received unlicensed and off-label prescribed antibiotics.

INTRODUCTION

Antibiotics are the drugs most commonly prescribed in children (1–3). The age group of 0- to 4-year-olds uses the most antibiotic drugs: yearly, 29% has at least one antibiotic drug prescribed (4). This youngest age group could cause problems in prescribing, because not all drugs are tested and licensed for this age group, and differences in dosing may result from metabolism, weights and diseases (5).

There are few studies about antibiotic drug use in the youngest children. Several European studies found that the highest use of antibiotics is in 1- to 6-year-olds (6–9). The kinds of antibiotic drugs varied per country.

Not all antibiotics are registered for use in young children. Some are unlicensed (e.g. a formulation prepared in the pharmacy) or are prescribed off-label (e.g. a licensed drug not registered for use under a certain age). A Dutch study investigating unlicensed and off-label use of drugs found that, out of all the prescriptions for children, 16.6% were unlicensed, and 20.6% were off-label. The 0- to 1-year-old age group had the highest chance of receiving unlicensed or off-label drugs (10). Comparable figures are found in a second Dutch study investigating general practitioner (GP) prescriptions (11). Obviously, this means that prescribing outside the marketing authorization takes place, but it is not known to what extent this concerns antibiotic drugs.

In young children, the dosage is usually calculated by weight or body surface area (12,13). It is not known whether this is common practice. A Scottish study found that 11.8% of children aged 0–4 years were prescribed an antibiotic in lower doses than recommended (14). In daily practice, an antibiotic course could be repeated after a few months or half a year, without taking into account that the child has grown.

We performed a cross-sectional study, using a pharmacy prescription database, to find answers to the following questions:

How many and what kinds of antibiotic drugs are used by 0- to 4-year-olds, and what are the differences between the ages within this group?

Do the types of drugs, the dosages and the course lengths correspond with the Dutch guidelines, and how often are unlicensed and off-label antibiotics prescribed to this group?

Abbreviations

ATC, Anatomical Therapeutical Chemical classification; DDD, defined daily dose; WHO, World Health Organization; OTC, over the counter; SD, standard deviation; NHG, Nederlands Huisartsen Genootschap (Dutch College of General Practitioners); NKFK, Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (Netherlands Expertise Centre of Pharmacotherapy in Children); GP, general practitioner.

METHODS

In this study, information on drug use was obtained from the IADB.nl database (University of Groningen, the Netherlands). The database contained pharmacy-dispensing data from 55 community pharmacies in the Netherlands. Dutch patients usually register at a single

community pharmacy; therefore, these pharmacies are able to provide an almost complete listing of the subject's prescribed drugs (15). Pharmacy data contain, among other data, information on the name of the drug dispensed, Anatomical Therapeutical Chemical (ATC) classification, date of prescription, number of days the drug was prescribed and number of defined daily doses (DDDs) based on the definition by the World Health Organization (WHO) (16). The use of over-the-counter (OTC) drugs and in-hospital prescriptions are not included. The database covers a population of 500 000 people since 1999, of whom 120 000 are individuals younger than 19 years of age, and is representative for the Dutch population in terms of drug use.

We selected all prescriptions of systemic antibiotics (ATC code J01) prescribed in the years 2002–2006 for children of 0–4 years of age. Prescriptions for children under the age of 3 months were excluded because of the special indications, low number of prescriptions in this age group and the fact that these children are mostly treated in hospital when they have infections. The age groups are classified in different ways. For determining and comparing the number of prescriptions, we used age groups with 3-month increments.

The types of antibiotics were investigated in the age groups: 3–6 months, 6–12 months, 1 year (that means 12-month-old till the day before the second birthday) and 2, 3 and 4 years.

To examine the length and dose of the courses, we selected all prescriptions of the five most frequently prescribed drugs and excluded injections and prescriptions for which the dose was unknown.

The lengths of the courses were determined by dividing the amount prescribed by the daily dose.

For the dose examination, courses longer than the maximum mentioned in the guidelines were excluded in order to avoid prophylactic multiple continuous antibiotic prescribing. The age groups used here were 3–6 months, 6–12 months, 1 year and 2, 3 and 4 years. To compare the actual prescription with the recommended dose, we used recent figures based on growth change in the Netherlands (17) and calculated for every age group the minimum and maximum dose according to the Dutch guidelines. For the weights, we used a range of 2 standard deviation (SD). Therefore, 95% of all possible weights were included in each age group. The dose of every prescription was examined based on its being within the recommended dose range.

The guidelines used were the Standards of the Dutch College of General Practitioners (NHG) (18), *Blauwdruk Pediatrische Antimicrobiële Therapie* (Blueprint Paediatric Antimicrobial Therapy) (13) and the website http://www.kinderformularium.nl, a website from the Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (NKFK; Netherlands Expertise centre of Pharmacotherapy in Children) (12).

The drug license information was obtained from the summary of product characteristics available on the website of the Dutch Medicines Evaluation Board (http://www.cbg-meb.nl) (19). In this study, we distinguished the following terms to indicate the prescriptions:

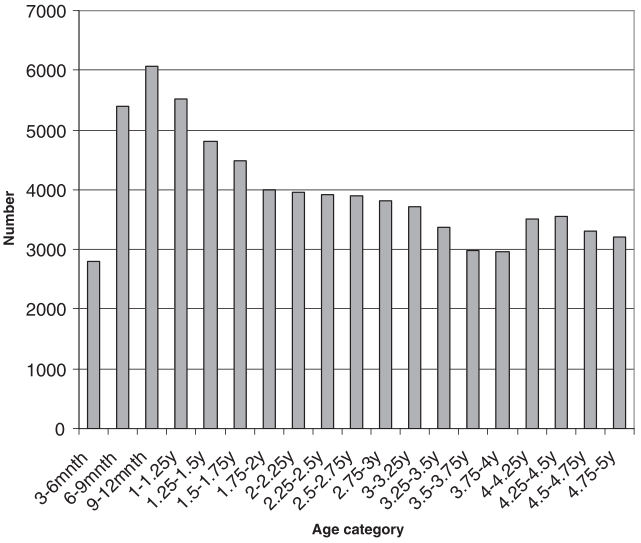

Figure 1 Number of antibiotic prescriptions per age category.

- 'Unlicensed' means that the product has no license in the Netherlands at all: for example, in the pharmacy-prepared formulations.
- 'Off-label' means that the product is licensed but not for this indication or age.
- 'Unregistered' combines both terms: the prescription is not licensed or is off-label.

For the analysis and statistics of the data, Microsoft® Office Excel 2003 (Microsoft® cooperation, Seattle, WA, USA) and R version 2.6.2 (Free Software; Free Software Foundation, Boston, MA, USA) were used.

RESULTS

From the database, 76 212 prescriptions for 30 730 children were selected. After exclusion of the prescriptions for children younger than 3 months, 75 341 remained. Of these, 87.6% were prescribed by GPs, and 12.4% by different specialists, who could not be separately identified by the database. Of the prescriptions, 53.6% were for boys.

Figure 1 shows the number of antibiotic prescriptions per age group. The 9- to 12-month-olds received the most prescriptions. Between 4 and 4.5 years, there was a small peak in the number of prescriptions.

In Table 1, the proportions of the different antibiotics are presented. The five most prescribed drugs were amoxicillin, amoxicillin/clavulanic acid, azithromycin, clarithromycin and cotrimoxazole (sulfamethoxazole/trimethoprim). In the first year, amoxicillin was used for 73–75%, but also other antibiotics, mainly clarithromycin and amoxicillin with clavulanic acid, were used. A trend towards less amoxicillin and more of other antibiotic drugs appeared with increase in age. The black cells in the table represent prescriptions that were prescribed unlicensed or off-label. A part of the group 'miscellaneous drugs' is also prescribed unlicensed or off-label, such as ciprofloxacin and tetracycline. In total,

Table 1 Number of prescriptions and percentage of total prescriptions of antibiotic drugs for different age categories

	3–6 months (N = 2800) %	6–12 months (N = 11 499) %	1 year (N = 18 835) %	2 years (N = 15 609) %	3 years (N = 13 025) %	4 years (N = 13 584) %
Amoxicillin	75.25	73.37	62.04	56.44	51.82	50.41
Clarithromycin	7.18	8.84	9.87	10.75	10.74	10.82
Amoxicillin/clavulanic acid	7.11	6.77	9.74	9.94	11.63	11.96
Small-spectrum penicillins	0.64	1.37	2.88	4.70	6.17	7.41
Trimethoprim	3.18	1.56	1.72	1.83	1.64	2.03
Cotrimoxazole	1.54	2.61	4.86	5.82	6.36	6.22
Azithromycin	1.14	1.86	4.35	5.17	5.79	5.51
Erythromycin	1.82	2.00	2.12	2.68	2.49	2.29
Nitrofurantoin	0.86	0.77	0.91	1.03	1.39	1.69
Cephalosporins	0.39	0.22	0.65	0.76	0.78	0.88
Miscellaneous	0.89	0.64	0.86	0.87	1.21	0.78
Beyond registration	7.14	4.64	3.19	3.34	3.76	4.20

Note: Black cells mean that the drugs are prescribed unregistered; grey cells mean that part of the prescriptions are prescribed, not registered.

3.9% was prescribed beyond registration (2.9% unlicensed and 0.9% off-label), mainly nitrofurantoin or trimethoprim (3.0%). The age groups under 1 year of age had the highest percentage of unregistered prescriptions.

For the examination of the doses and course lengths prescriptions of injections and products for respiratory use and for which the daily dose was not known were excluded. The prescriptions with the five most prescribed drugs were selected.

For the dose examination, the courses of amoxicillin and clarithromycin for more than 14 days, of amoxicillin/clavulanic acid and cotrimoxazole for more than 10 days and of azithromycin for more than 5 days were excluded. The doses of the remaining 59 712 courses were examined. Of these prescriptions, 97.6% had a correct dose, 2.0% had a lower dose than recommended and 0.4% had a higher dose. Figure 2 shows that the prescriptions of specialists had more often a too low or a too high dose, but still 93.0% of the prescriptions fell in the recommended dose range. Cotrimoxazole was prescribed more often under the minimum dose than the other drugs.

In Figure 3, the course lengths of the prescriptions of the five most used drugs (n = 66 063) are presented. The graphs show that the most used course length for amoxicillin and amoxicillin/clavulanic acid was 7 days, which is the median. The course length for most azithromycin prescriptions was 3 days; the median was 4 days. The most used course length for clarithromycin was 12 days, and so was the median. For cotrimoxazole, the most used course length was 10 days, with a median of 16 days.

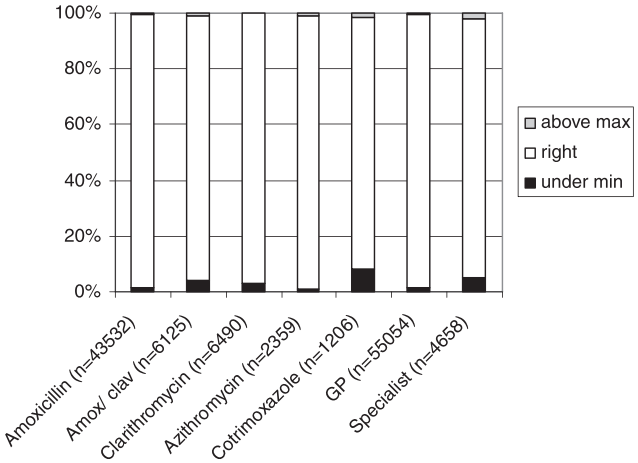

Figure 2 Percentage of prescriptions of the five most used antibiotic drugs with a dose within the recommended dose range ('right'), above the maximum dose ('above max') and under the minimum dose ('under min').

DISCUSSION

Main results

For the 0- to 4-year-old group, most antibiotic drugs were prescribed between the age of 9 and 12 months, and the least were prescribed between 3 and 6 months. After reaching the age of 1 year, the use of antibiotics decreased.

In the 3- to 6-month-old group, amoxicillin was prescribed for 75.2%, and its contribution decreased in the other age groups to 50.4% in the 4-year-olds. Clarithromycin and azithromycin were also prescribed in the youngest age groups, as was amoxicillin/clavulanic acid. The proportions of these drugs increased with age.

From the prescriptions of the five most used drugs, 97.6% were within the guidelines' recommended dose range. Most course lengths corresponded with the guidelines, although azithromycin, clarithromycin and cotrimoxazole were often prescribed for a period longer than recommended.

Of the antibiotic prescriptions, 3.9%, mainly nitrofurantoin and trimethoprim, were in discordance with the drug's registration.

Distribution of prescriptions among age groups

We found that most antibiotics were prescribed for children of 9–12 months of age. This differs from the studies by

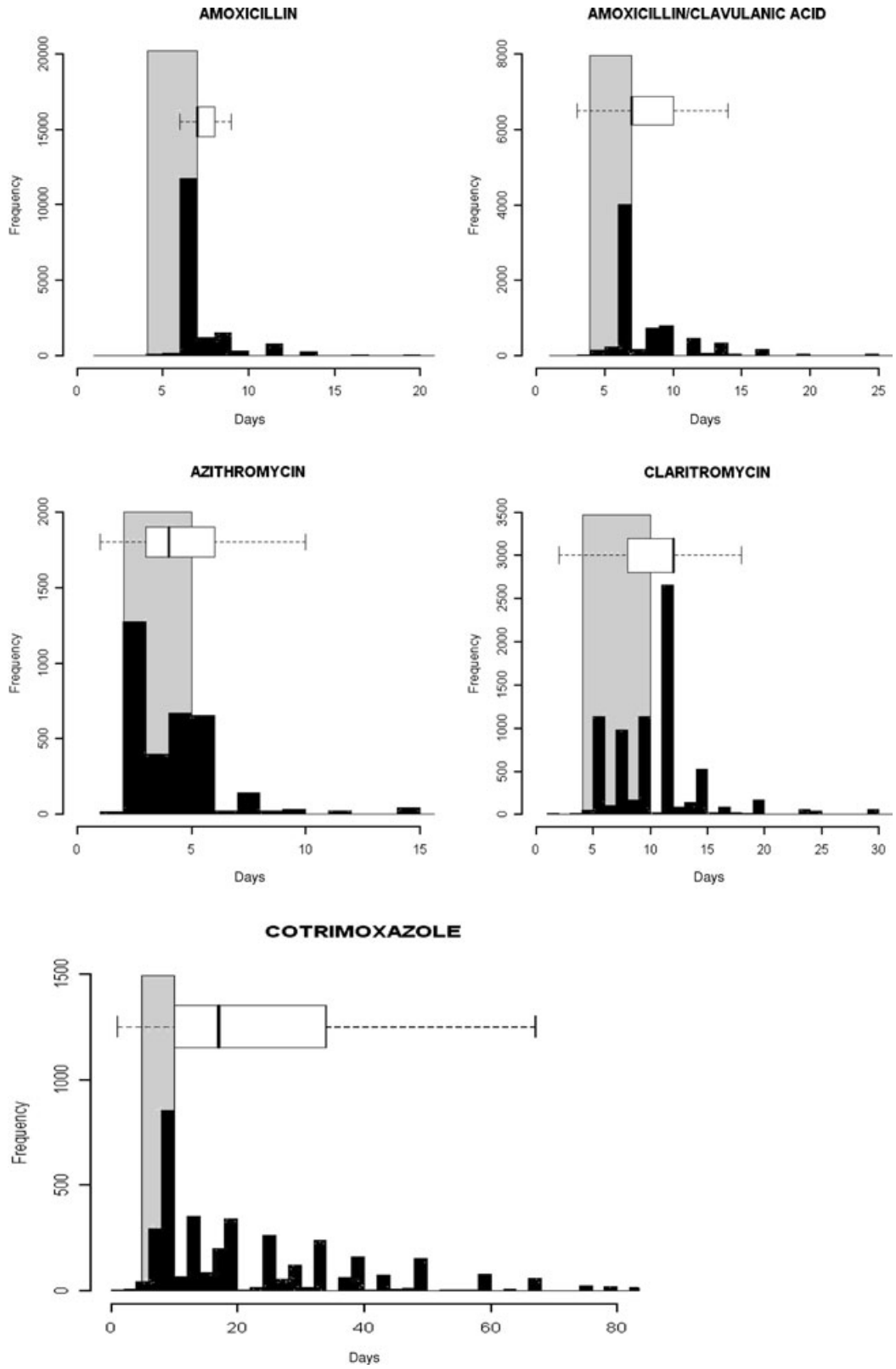

Figure 3 The course lengths of the five most used antibiotic drugs: the grey blocks represent the lengths recommended by the guidelines for the most common indications, the white box plots show the distribution of the prescriptions over the four quartiles and the median and the black histogram shows the distribution over the number of days.

Borgnolo, Thrane and Schindler (6,8,9), who found a peak age at 3–6 years, 1–2 years and 2–3 years, respectively. The explanation for this difference could be that these studies counted the children under 1 year as one group and did not use the 3-month increments, as we did. Counting the prescriptions in the whole group under 1 year, we also found fewer prescriptions than the older groups. This could be attributed to the lack of prescriptions in the group under 6 months, which hides the peak in the number of prescriptions between 9 and 12 months. The other studies are performed in other countries with other health systems. This also could explain the difference.

When we look at prevalence figures from a national Dutch survey of physicians in 2001 (20), infections such as otitis or upper and lower respiratory infections were most common in children under 1 year of age in the Netherlands, which explains the high antibiotic use. The low use of antibiotics in children under 6 months of age was probably because of the fact that those children are treated more often in hospital, and because this treatment is not visible in a prescription database. The small increase we found between 4- and 4.5-year-olds could be explained by the fact that at that age, children begin primary school, which means a change of environment and contact with new germs.

Types of antibiotic drugs

Amoxicillin was prescribed mostly, especially in children less than 1 year of age. But even in this age group, other drugs were prescribed, such as clarithromycin and amoxicillin with clavulanic acid. At an older age, the contribution of other drugs increased. The amount of small-spectrum antibiotics, although registered for this young age group, increased, but did not exceed clarithromycin or amoxicillin/clavulanic acid. In Scotland, among 0- to 4-year-olds, erythromycin was used most, followed by amoxicillin (14). In Denmark, 0- to 2-year-olds used mostly broad-spectrum penicillins, but 3- to 6-year-olds used mostly penicillin V (9). In Italy, they used broad-spectrum penicillins, amoxicillin/clavulanic acid and cephalosporins; the contribution of these drugs did not change a lot among the <1-year-olds, the 2- to 4-year-olds and the 3- to 6-year-olds.

So, prescription preferences are quite different between countries, as we found in our former study of 0- to 19-year-olds (4).

Although, in Denmark and Italy, the first choice corresponding to the guidelines was, like in the Netherlands, small-spectrum penicillins for respiratory infections, there also were mainly broad-spectrum antibiotics and macrolides prescribed in this age group.

Dose examination

A dose examination, like in this study, was performed in the Scottish study (14). This study used data from GPs and found that 11.8% of the 0- to 4-year-old children were prescribed a lower than recommended dose, and 2.5% were prescribed a higher than recommended dose. We found that, respectively, 2.0% and 0.4% of the prescriptions had a lower and higher dose than recommended. Apparently, they found more incorrect doses than we did. Because these are data obtained from GPs by questionnaires, there was probably more information available about the real weight of the patient and the indication, which we lacked and which caused in our study an underestimation of the number of incorrect doses. The fact that they found much higher rates of incorrect doses confirms the underestimation we probably made.

Cotrimoxazole was prescribed more often in too low doses, probably because it was prescribed more prophylactically. In the Netherlands, chronic medication is started with a prescription for 14 days, so a 14-day prescription of prophylaxis could be included in the analysis.

It was remarkable that specialists more often prescribed a too low or a too high dose.

Specialists see more patients with special indications or deviant weights. These could be pre-mature children, who need adjusted doses, or children with serious infections or uncommon bacteria, who need higher doses then usually prescribed. This could explain why more doses were not corresponding with the guidelines.

Prescribing outside the marketing authorization

The off-label and unlicensed prescribing in this study were of nitrofurantoin, trimethoprim, azitromycin, tetracycline and ciprofloxacin. In the 0- to 4-year-olds, nitrofurantoin and trimethoprim were mainly used as a pharmacy-based formulation, which means unlicensed. According to the Dutch guidelines for urinary tract infections in such young children (18), the first choice should be amoxicillin/clavulanic acid or cotrimoxazole. These special cases might be treated by paediatricians. According to the prescription database, indeed nitrofurantoin and trimethoprim were less often prescribed by GPs. But, still more than half of the prescriptions were from GPs.

Azithromycin, which is not registered for use in under 1-year-olds, was prescribed 246 times in this age group, even though clarithromycin is a registered alternative. Although the convenient dosage system might contribute to the motivation of prescribing, it is remarkable that 206 (84%) of these prescriptions were prescribed by a GP.

Tetracycline is contra-indicated in children under 8 years of age for oral as well for local use because of binding on teeth and bone and causing bone growth retardation. However, we found 190 prescriptions of pharmacy-based formulations with tetracycline. These were probably drugs for cutaneous use.

Ciprofloxacin is the fifth drug that was prescribed beyond its registration. It is only licensed in children older than 5 years and only with an indication for cystic fibrosis. Therefore, prescribing should be restricted to paediatricians. However, 88 (44%) of our 199 prescriptions were prescribed by a GP.

Nevertheless, it was not known how many prescriptions from GPs are continuations of prescriptions first made by specialists or were prescribed by order of a specialist.

Course lengths

As far as we know, there are no other epidemiological studies of course lengths of antibiotics in children. Figure 3 shows that most course lengths corresponded with the guidelines.

Amoxicillin and amoxicillin with clavulanic acid are mostly prescribed for 7 days.

Azithromycin courses are mainly recommended for 3 days by the guidelines (12,13,18). However, there are also many courses longer than 3 days, even beyond the maximum of 5 days. The content of the packaging could be because of this. This is probably also the explanation why clarithromycin was so often prescribed for 12 days.

For clarithromycin, a dose length of 5–10 days is recommended for most indications. The suspension is packaged in bottles of 60 mL, enough for 6 days, while the usual dosage is 10 mL per day in two doses. It is common practice in the Dutch pharmacies that bottles are not partly delivered, so when a course of, for example, 7 days is needed, two bottles (120 mL) are delivered with the advice to throw away the rest. This wastes medicine and also increases the risk that the child takes by accident a longer course than was meant, which contributes to antibiotic resistance.

Cotrimoxazole was prescribed many times for more than the maximal course length, which is 10 days. It was probably prescribed more often in a prophylactic way than the other antibiotic drugs.

Strengths and limitations

The strength of this study was that data were obtained from daily practice, in which the physician, the pharmacist and the patient were not aware of participation in a study. Also, the large size of the database provided power to the results.

One of the limitations was that the indications for prescription were not known, because this information was not available to the pharmacy. Also, we did not know whether the patient actually used the medication at home.

The number of incorrect doses may be underestimated, as mentioned above. The dose range we used, being calculated for every single age group for the five most used drugs, was quite wide. We did not know the exact weight of the children or the indication or, for example, whether a maximum dose in a certain case was really necessary. So, the prescriptions within the recommended dose range could still contain cases in which an incorrect dose was prescribed.

CONCLUSION

According to this study, most antibiotic courses for children between 0 and 4 years of age have the correct dose (97.6%), the correct length and are registered for this age (96.1%). Nevertheless, the prescriptions do not correspond with the guidelines. Small-spectrum antibiotics, which are recommended for respiratory infections (being one of the common infections) and are registered for this age, are not often prescribed. And although there are enough alternatives, unlicensed and off-label prescribing occurs, especially in the most vulnerable group of under 1 year of age, which uses the most antibiotic drugs.

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FINANCIAL DISCLOSURE

All authors have no financial relationships relevant to this article.

CONFLICT OF INTEREST

None.

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