

# Age-Specific Antibiotic Prescribing and Adherence to Guidelines in Pediatric Patients in Primary Care

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**Background:** Most antibiotics in children are used to treat viral and self-limiting conditions. This study aims to compare physicians' adherence to guidelines on antibiotic prescribing in fever and in ear and respiratory infections to children in different age groups in the Netherlands.

**Methods:** Data were used from the NIVEL Primary Care Database. For all pediatric episodes of fever, acute otitis media (AOM), streptococcal pharyngitis (strep throat), sinusitis, acute tonsillitis, acute bronchitis/bronchiolitis and pneumonia in 2012, we determined whether national guidelines were followed with regard to whether an antibiotic was prescribed, and the type of antibiotic.

**Results:** For diagnoses that generally do not require antibiotics, more prescriptions were found in adolescents' episodes compared with children 0–4 and 5–11 years of age, respectively, (bronchitis: 52.0% versus 42.4% and 42.7%, and fever: 16.8% versus 9.0% and 14.2%). The same was true for diagnoses that require antibiotics (strep throat: 76.5% versus 55.0% and 49.5%, pneumonia: 71.6% versus 60.2% and 69.8% and tonsillitis: 57.8% versus 54.8% and 49.7%), except for AOM (43.9% versus 52.4% and 39.6%). First-choice amoxicillin was prescribed more frequently in children 0–4 years of age than in age groups 5–11 and 11–17 years (AOM: 88.0% versus 83.2% and 81.8%, and pneumonia: 74.7% versus 57.2% and 53.8%). First-choice narrow-spectrum penicillins were prescribed more often in adolescents than in age groups 0–4 and 5–11 years (strep throat: 72.0% versus 63.6%, and 60.9% and tonsillitis: 67.9% versus 33.1 and 45.9%).

**Conclusions:** Concerning adherence patterns include high antibiotic rates for bronchitis, particularly in adolescents, and underuse of narrow-spectrum penicillins in the 0–4 years group.

**Key Words:** antibiotic prescription, antibiotics, children, guidelines, general practice, respiratory tract infections

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Antibiotics are the most common medicines prescribed for children in primary care.<sup>1</sup> The majority of pediatric antibiotics are used to treat fever, ear and respiratory tract infections (RTI), due to fears of serious bacterial complications, although these conditions are often viral in origin and self-limiting.<sup>2–4</sup>

With antimicrobial resistance on the rise worldwide, it is advised that physicians prescribe antibiotics in accordance with evidence-based guidelines.<sup>5–7</sup> Where relevant, guidelines for antibiotic therapy also consider the age of the patient, along with the illness severity and the presence of underlying diseases. Advice may be age-specific if treatment evidence differs across pediatric age groups. The relationship between age and consultation rates has been reported; children younger than 5 years have respiratory symptoms more frequently and consult their physicians more often than older ones.<sup>8,9</sup> Moreover, RTI etiologies are frequently age-dependent, and different causative organisms, such as bacteria or viruses, can be found in younger and older children.<sup>10</sup> Also, the prevalence of antibiotic prescribing in childhood varies across age, with preschool children being mostly exposed to antibiotics.<sup>11</sup>

Relative to other countries, the Netherlands has low rates of antibiotic use.<sup>12</sup> Yet, despite recommendations for restrictive antibiotic prescribing for RTIs, recent research has revealed potential areas of concern in primary care.<sup>13</sup> Namely, 40% of acute bronchitis episodes in Dutch children were treated with antibiotics contrary to the advice to avoid them, and first-line narrow-spectrum penicillins were used less than recommended.<sup>13</sup>

There is clearly room for improvement, and an analysis of antibiotic prescribing by age may help in identifying age groups with potential inappropriate antibiotic exposure. But, limited knowledge is available on patterns of antibiotic use in children according to both their age and clinical condition.

The purpose of our study was to compare the adherence to guidelines on antibiotic prescribing in fever, ear infections and RTIs between children having different ages. We aimed to determine antibiotic prescribing patterns for children stratified by age, both in terms of degree of prescribing per diagnosis and choice of antibiotics.

## METHODS

Data for 2012 used in this study were derived from the NIVEL Primary Care Database (NIVEL PCD), which collects routine electronic health records from general practitioners (GP) across the Netherlands.<sup>14</sup> The participating GPs constituted a representative sample of the total population of Dutch GPs, and their patients have similar demographic characteristics to the general Dutch population. Practices were included in our study if at least 70% of consultations included a registered diagnosis, and prescription and morbidity data were registered for at least 46 weeks of the year. For the present analysis, 101 practices were available. From these practices, data of all children (0–18 years) with physician-diagnosed fever, ear or respiratory infection (see details below) and a database history of at least one quartile of a year in 2012 were selected.

Our study was carried out according to Dutch legislation on privacy, which instructs that obtaining informed consent and/or

approval by medical ethics committee is not obligatory for observational studies.<sup>15</sup> The NIVEL PCD database includes anonymous information on patients, including their year of birth, dates of consultation, clinical diagnoses (coded with the International Classification of Primary Care version 1 - ICPC-1 scheme) and prescriptions (coded with the Anatomical Therapeutic Chemical - ATC Classification Index).<sup>16,17</sup> Children were grouped into three age categories: 0–4.99 years (early childhood), 5–11.99 years (childhood) and 12–17.99 years (adolescents) according to national and United Nations Children's Fund classification.<sup>18–20</sup>

The latest versions of the Dutch College of General Practitioners (NHG) guidelines for (1) fever; (2) acute otitis media (AOM), (3) acute cough, (4) acute sore throat and (5) rhinosinusitis were used as pertinent national resources to define fever, ear and respiratory infections and provide guidance on their management.<sup>21–25</sup> In line with the guidelines, acute cough was subdivided into diagnoses “pneumonia” and “acute bronchitis/bronchiolitis,” and acute sore throat into diagnoses “strep throat/scarlet fever” and “acute tonsillitis” (bacterial or viral). Overall, seven ICPC codes were considered sufficiently specific to describe our diagnoses of interest: fever (A03), AOM (H71), strep throat/scarlet fever (R72), sinusitis acute/chronic (R75), acute tonsillitis (R76), acute bronchitis/bronchiolitis (R78) and pneumonia (R81). The studied diagnoses and the recommendations on antibiotic prescribing from the NHG guidelines are summarized in Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C832>.

The analysis was based on constructed episodes per ICPC that included all the consultations related to the same health problem within a pre-set time frame. The used algorithm is described elsewhere.<sup>13</sup> To determine whether and which antibiotics were prescribed per diagnosis, antibiotics (ATC code J01) were linked to ICPC using prescription date and episode start and stop date. If more antibiotics were prescribed during an episode, the first prescription was used for the analysis.

Two sets of disease-specific indicators were used to measure the consistency in antibiotic prescribing between guidelines and GPs prescribing patterns for children in 2012. The first set of indicators examined GP adherence to guidelines on whether or not to prescribe antibiotics for the diagnoses. Antibiotics are generally not recommended for fever and bronchitis/bronchiolitis, so less episodes treated with antibiotics (lower indicator values) mean better adherence to guidelines. In contrast, more episodes of pneumonia treated with antibiotics (higher indicator values) mean better adherence to guidelines. For diagnoses with restrictive antibiotic use (AOM, strep throat, sinusitis and tonsillitis), percentages of episodes treated with antibiotics may vary according to patient case mix (bacterial or viral etiology, severity of symptoms, risk of complications), so the ideal indicator values could not be specified. The second set of indicators evaluated what antibiotics were prescribed for each of the five ICPCs that would require antibiotics according to the guidelines (H71, R72, R75, R76 and R81). Higher indicator values mean that more first-choice antibiotics were prescribed and thus represent better adherence to guidelines.

## Analysis

At the start, we identified the age-specific advices for antibiotic prescribing in children in the selected NHG guidelines, as presented in Table S1. Next, the incidence rates for each ICPC were calculated per 1,000 person-years by dividing the number of episodes by the total number of person-years in a specific age group. The incidence rates were required to quantify the extent of health problems by age categories and obtain numerators for the indicators.

The first sets of indicators for each age group were calculated by dividing the number of ICPC episodes with an antibiotic prescription by the total number of episodes for that ICPC. The second sets of indicators for each age group were calculated by dividing the number of ICPC episodes prescribed an antibiotic with a specific ATC code by the total number of the ICPC episodes prescribed an antibiotic.

$\chi^2$  Tests were used to compare differences in the degree of prescribing per diagnosis and first-choice antibiotics between age subgroups. Results with probability level of  $P < 0.05$  were considered as statistically significant. Data were analyzed with SPSS version 20.0 (SPSS Inc., Chicago, IL).

## RESULTS

During 2012, the total number of pediatric episodes with fever, ear or RTIs was 13,755. Across all ages, the most frequently reported episodes were related to AOM, fever, acute bronchitis/bronchiolitis and tonsillitis, while pneumonia, sinusitis and strep throat episodes were registered less frequently (Table 1). Table 1 also shows that children in the 0–4 years age group had the highest incidence rates for all studied ICPCs, except for sinusitis. Their most common reasons for GP consultations were AOM, fever and bronchitis/bronchiolitis (199, 135 and 61 episodes per 1,000 person-years, respectively). The 5–11 years age group most frequently reported AOM, tonsillitis and bronchitis (56, 17 and 16 episodes per 1,000 person-years, respectively). Adolescents had the lowest incidence rates for all ICPCs, except for sinusitis. They mostly suffered from tonsillitis, sinusitis and AOM (19, 15 and 14 episodes per 1,000 person-years, respectively).

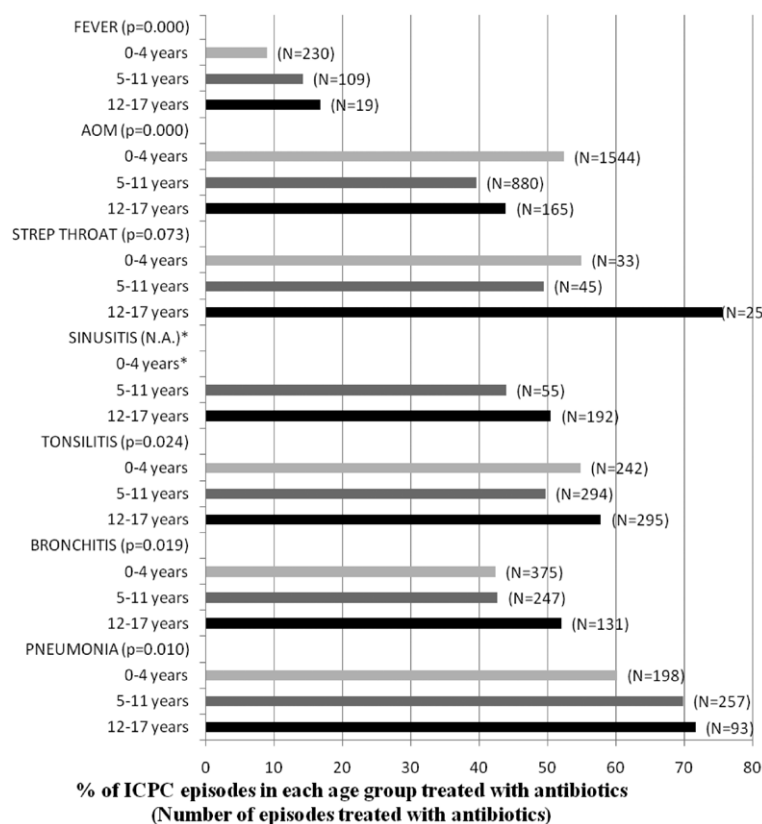
Figure 1 presents GPs' adherence to recommendations on whether or not antibiotics were prescribed, stratified by ICPC and age. Overall, an antibiotic prescription was registered in 39.5% of all pediatric episodes, ranging from 36.4% in the 0–4 years age group to 51.3% in the adolescent group. For the majority of clinical conditions that require antibiotics, adolescent episodes were more frequently treated with antibiotics than episodes in the age groups 0–4 years and 5–11 years (strep throat: 76.5% versus 55.0% and 49.5%, pneumonia: 71.6% versus 60.2% and 69.8% and tonsillitis: 57.8% versus 54.8% and 49.7%). Only for AOM, more episodes in the 0–4 years age group were treated with antibiotics (52.4%) than in the 5–11 years age group (39.6%) and adolescents (43.9%). Since antibiotics are recommended for all children younger than 2 years with bilateral AOM, a subgroup analysis was done in this age group. It showed that 1,008 of 1,831 AOM episodes (55.1%) in children 0–2 years of age were treated with antibiotics, compared with 536 of 1,118 AOM episodes (47.9%) in children 2–4 years of age, respectively. Concerning sinusitis, the small number of episodes in the 0–4 years age group ruled out any meaningful comparison on antibiotic treatment across age.

For those diagnoses where antibiotics are generally not recommended, more episodes in adolescents were treated with antibiotics as compared with the age groups 0–4 years and 5–11 years (bronchitis: 52.0% versus 42.4% and 42.7%, and fever: 16.8% versus 9.0% and 14.2%).

Table 2 shows GP adherence to first-choice antibiotics for diagnoses that require antibiotics, stratified by ICPC and age. AOM episodes in the 0–4 years age group were more frequently treated with first-choice amoxicillin (88.0%) compared with episodes in the 5–11 years age group (83.2%) and adolescents (81.8%). Similarly, 74.7% of pneumonia episodes in the 0–4 years age group was treated with first-choice amoxicillin, while the corresponding figures in the 5–11 years age group and adolescents were 57.2% and 53.8%, respectively. Conversely, more episodes in adolescents were prescribed first-choice narrow-spectrum penicillins than in the age groups 0–4 years and

**TABLE 1.** Fever, Ear and RTIs Episodes and Incidence Rates (Episodes/1000 Person-years) by Age Groups

Clinical Condition (ICPC)	Age Category (yr)	Number of Episodes (% of Total Episodes in Each Age Group)	Incidence Rates as Episodes per 1000 Person-Years
Fever (A03)	0–4	2544 (35.3)	135.1
	5–11	768 (16.2)	17.0
	12–17	113 (6.3)	4.0
AOM (H71)	0–17	3425	41.9
	0–4	2949 (40.9)	198.7
	5–11	2222 (46.8)	55.7
Strep throat (R72)	12–17	376 (21.0)	13.9
	0–17	5547	76.8
	0–4	60 (0.8)	6.6
Sinusitis (R75)	5–11	93 (2.0)	2.8
	12–17	34 (1.9)	1.7
	0–17	187	3.4
Tonsillitis (R76)	0–4	5 (0.1)	0.8
	5–11	125 (2.5)	4.2
	12–17	380 (21.2)	15.1
Bronchitis (R78)	0–17	510	7.10
	0–4	442 (6.0)	34.8
	5–11	591 (12.5)	16.6
Pneumonia (R81)	12–17	510 (28.4)	19.2
	0–17	1543	22.1
	0–4	885 (12.3)	60.5
	5–11	579 (12.2)	15.9
	12–17	252 (14)	9.9
	0–17	1716	24.9
	0–4	329 (4.6)	24.5
	5–11	368 (7.8)	9.9
	12–17	130 (7.2)	4.7
	0–17	827	11.7



**FIGURE 1.** Percentages of episodes of fever, ear and respiratory infections treated with antibiotics according to age groups. \*Total number of sinusitis episodes in the 0–4 years age group is 5.

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**TABLE 2.** AB Choice (%) for Disease Episodes According to Age Groups

ICPC Diagnosis	AB Treatment	Number of Episodes (% of Total Episodes in Each Age Group)			P Value for Differences Between Age Groups (Chi-Square Test)
		0-4 years	5-11 years	12-17 years	
H71 (AOM), N = 5547	In line with 1st choice	1359 (88.0)	732 (83.2)	135 (81.8)	0.001
	In line with 2nd choice	85 (5.5)	59 (6.7)	8 (4.8)	0.408
	In line with 1st or 2nd choice	1444 (93.5)	791 (89.9)	143 (86.7)	0.000
	Amoxi-clavulanate (J01CR02)	67 (4.3)	53 (6.0)	11 (6.7)	0.119
	Clarithromycin (J01FA09)	26 (1.7)	21 (2.4)	5 (3.0)	0.310
R72 (strep throat), N = 187	In line with 1st choice	21 (63.6)	28 (60.9)	18 (72.0)	0.641
	In line with 2nd choice	1 (3.0)	5 (10.9)	2 (8.0)	0.434 (small numbers)
	In line with 3rd choice	2 (6.0)	3 (6.5)	1 (4.0)	0.906 (small numbers)
	In line with 1st or 2nd or 3rd choice	24 (72.7)	36 (78.3)	21 (84.0)	0.590
	Amoxicillin (J01CA04)	5 (15.2)	9 (19.6)	3 (12.0)	0.695
R75 (sinusitis), N = 510	In line with 1st choice	/*	43 (78.2)	142 (74.0)	0.774 (small numbers)
	In line with 2nd choice	/*	7 (12.7)	25 (13.0)	0.799 (small numbers)
	In line with 1st or 2nd choice	/*	50 (90.9)	167 (87.0)	0.400 (small numbers)
	Clarithromycin (J01FA09)	/*	1 (1.8)	9 (4.7)	0.594 (small numbers)
	Amoxi-clavulanate (J01CR02)	/*	4 (7.3)	13 (6.8)	0.888 (small numbers)
R76 (tonsillitis), N = 1543	In line with 1st choice	80 (33.1)	135 (45.9)	200 (67.8)	0.000
	In line with 2nd choice	25 (10.3)	19 (6.5)	16 (5.4)	0.075
	In line with 3rd choice	12 (5.0)	21 (7.1)	23 (7.8)	0.402
	In line with 1st or 2nd or 3rd choice	117 (48.3)	175 (59.5)	239 (81.0)	0.000
	Amoxicillin (J01CA04)	112 (46.3)	110 (37.4)	39 (13.2)	0.000
R81 (pneumonia), N = 827	In line with 1st choice	148 (74.7)	147 (57.2)	50 (53.8)	0.000
	In line with 2nd choice	18 (9.1)	44 (17.1)	11 (11.8)	0.040
	In line with 1st or 2nd choice	166 (83.8)	191 (74.3)	61 (65.3)	0.002
	Amoxi-clavulanate (J01CR02)	15 (7.6)	35 (13.6)	16 (17.2)	0.036
	Clarithromycin (J01FA09)	11 (5.6)	21 (8.2)	8 (8.6)	0.036

\*Total number of sinusitis episodes in the 0-4 years age group is 5.

5-11 years (strep throat: 72.0% versus 63.6%, and 60.9% and tonsillitis: 67.9% versus 33.1 and 45.9%). Once again, the small number of sinusitis episodes in the age group 0-4 years hampered any meaningful comparison on first-choice antibiotic treatment across age groups. First-choice doxycycline for pneumonia and sinusitis (with an age restriction) was not prescribed in any of the children.

**DISCUSSION**

Our study showed variation in GP adherence to antibiotic prescribing for fever, ear and respiratory infections in different pediatric age groups. Despite lower consultation frequency, adolescents received antibiotics more commonly, both for episodes when antibiotics are recommended (pneumonia, strep throat and tonsillitis), or not recommended (bronchitis, fever).

The differences in antibiotic treatment rates across ages may reflect the varying role of bacterial and viral infections between specific clinical entities and age groups. The most common causes of pneumonia in infants and preschool children are viruses (respiratory syncytial virus, influenza, parainfluenza virus and human metapneumovirus). In older children, viruses as a sole cause of pneumonia are less common, with the exception of influenza.<sup>26</sup> These findings may explain the difference in the proportion of pneumonia episodes treated with antibiotics in the oldest (71.6%) and youngest age groups (60.2%). Also, more frequent referrals of younger children to hospital could lead to an underestimation of antibiotic use in general practice in pneumonia for the 0-4 age group. The NHG guidelines consider a lower threshold for hospital admission of infants below 3 or 6 months of age because they need more supportive care and monitoring, and it is difficult to recognize their subtle, sudden deterioration clinically.<sup>23,27</sup> When a bacterial cause of pneumonia is found, it is predominantly *Streptococcus pneumoniae* in younger children, and *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in older school children and adolescents.<sup>26,28,29</sup> Such age-specific

etiology corresponds to our results on antibiotic selection for pneumonia by age groups. GP adherence to first-choice amoxicillin for *S. pneumoniae* was highest in children below 5 years (75%). But, over 40% in the other two age groups were treated with amoxicillin-clavulanate or macrolides (azithromycin, clarithromycin) instead, possibly targeting the atypical pathogens. Nonetheless, we could not determine to what extent the choice of antibiotics was consistent with the etiologic agents present in the studied age subpopulations.

These patterns may reflect adolescents' higher threshold of contacting GPs, and that they only went to visit their GPs when the symptoms were relatively severe and/or if there were risk factors for serious disease. We did not assess the presence of comorbidities in different age groups, which may have had an impact on their antibiotic prescribing. Further studies that include data on comorbidities are therefore needed to potentially interpret (higher) prescribing rates in adolescents. Such analysis could indicate whether guidelines need to address the management of common infections in the subgroup of pediatric patients with chronic diseases.

Only in AOM episodes, children 0-4 years of age were prescribed antibiotics more commonly than other age groups. This is consistent with previous Dutch study from 1998, when half of the AOM episodes in children below 5 years were prescribed antibiotics.<sup>30</sup> This corresponds to NHG guidelines that recommend antibiotics in all children under 2 years with bilateral AOM, who have higher risk for bacterial infection.<sup>31</sup> GP adherence to first-choice amoxicillin was over 80% for AOM episodes in all age groups, ensuring a good coverage for its main etiologic agent - *S. pneumoniae*.

In the light of current acute cough guidelines, prescribing antibiotics in over 40% of bronchitis episodes in all children, and more than 50% in adolescents is unexpectedly high. It is difficult to understand the reasons for such practices, except for (adolescents) higher threshold of contacting GPs, resulting in high-risk samples of patients, where pneumonia or secondary bacterial infections

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cannot be easily excluded. Also, antibiotics may be requested for the persistent cough that usually accompanies bronchitis, even if that is of no benefit for most cases. Our results may be reflected on in the guidelines by promoting near-patients tests to tackle diagnostic uncertainties for lower RTIs where appropriate, and address patients' concerns and pressure for antibiotics.<sup>32</sup>

Furthermore, this study provides an age-specific insight into the concerning issue of underuse of first-choice narrow-spectrum penicillins (pheneticillin and phenoxymethylpenicillin) for sore throat and tonsillitis. GP adherence to prescribing these antibiotics for tonsillitis episodes was twice as low in children 0–4 years of age compared with the adolescents (33% versus 67%). Instead, over half of tonsillitis episodes in the 0–4 years age group were treated with amoxicillin or macrolides. The palatable taste of these mixtures (compared with bitter testing penicillin liquids) and their administration frequency convenience improve treatment compliance and are likely explanations for this practice.<sup>31,33</sup> Additionally, GPs might be inclined to a broader spectrum of bacteria than just *group A beta haemolytic streptococcus* in the youngest age group. On the contrary, higher percentage of tonsillitis episodes (67%) and RTIs episodes (70%) were treated with phenoxymethylpenicillin in the 0–6 years age group in Norway and Sweden, respectively.<sup>34,35</sup> Such differences can be explained by the introduction of the quality indicator “80% of antibiotics used to treat RTIs in children 0–6 years of age should be phenoxymethylpenicillin” in the Swedish annual benchmarking of medical treatments and procedures, which may also be considered in the Netherlands.<sup>35</sup>

The main strength of this study is that the data come from a nationwide database, which contains information on diagnoses and prescriptions from a relatively large group of children. Further, individual patient records allow the assessment of the role of child age on disease frequencies and antibiotic prescribing patterns. The age classification can be arbitrary and context-specific, so our age groups were chosen for better comparability with literature on RTIs.

Since RTIs are often acute, short-term diseases for which patients generally contact the GP only once, we used the first prescription for our analysis. In all age groups, GPs were contacted once in 73.5% of the episodes, and multiple times in the remaining 26.5% of the episodes (twice in 16.6% of the episodes, and three or more times in 9.8% of the episodes). The number of prescribed antibiotics during these multi-contact episodes was on average 0.7, as in 88.3% of these episodes 0 or 1 antibiotic was prescribed.<sup>13</sup> Hence, no considerable difference in prescribing patterns would be expected even if more than one prescription are included in the analysis.

Moreover, our prior analysis of the trend of antibiotic use and compliance to guidelines for all children (0–18 years) in 2010, 2011 and 2012 in The Netherlands has hardly shown any changes over this period.<sup>13</sup> Therefore, the latest year (2012) was chosen to do this subgroup analysis by age groups.

As described elsewhere, our study has several limitations that are inherent to the use of electronic patient records, such as quality and completeness of the GP records, as well as historic differences in antibiotic prescribing between NIVEL - PCD participating and nonparticipating GPs.<sup>13,36,37</sup> It is, however, expected that recent policy measures have improved and expanded routine data registration practices at national level.<sup>38</sup> Our results can be assumed to represent regular GP consultation behavior in the Netherlands as much as possible.

In the present study, we did not control for clustering at practice level because of low patient numbers per age group and per diagnosis. But, our previous research on antibiotic prescribing in all children revealed that levels of adherence to guidelines varied largely between practices, especially for first-choice antibiotics.<sup>13</sup>

Nonetheless, we cannot regard the antibiotic under- and over-use, or choice of antibiotics as wrong treatment decisions in

the absence of clinical golden standards. In some patients, due to clinical characteristics, GPs may have to deviate from the recommendations. However, our results may point out at the following diagnoses and age groups where improvements in prescribing behavior are likely needed. The low adherence to guidelines is worrisome for all children diagnosed with acute bronchitis, and particularly in adolescents, such antibiotic prescribing patterns need more in-depth analysis. Another area to focus future efforts on is the underuse of first-choice narrow-spectrum penicillins in the 0–4 years age group.

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