Rational antibiotic prescribing for children with respiratory tract infections

Anne R.J. Dekker

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Rational antibiotic prescribing for children with respiratory tract infections

Rationeel antibioticabeleid voor kinderen met luchtweginfecties

(met een samenvatting in het Nederlands)

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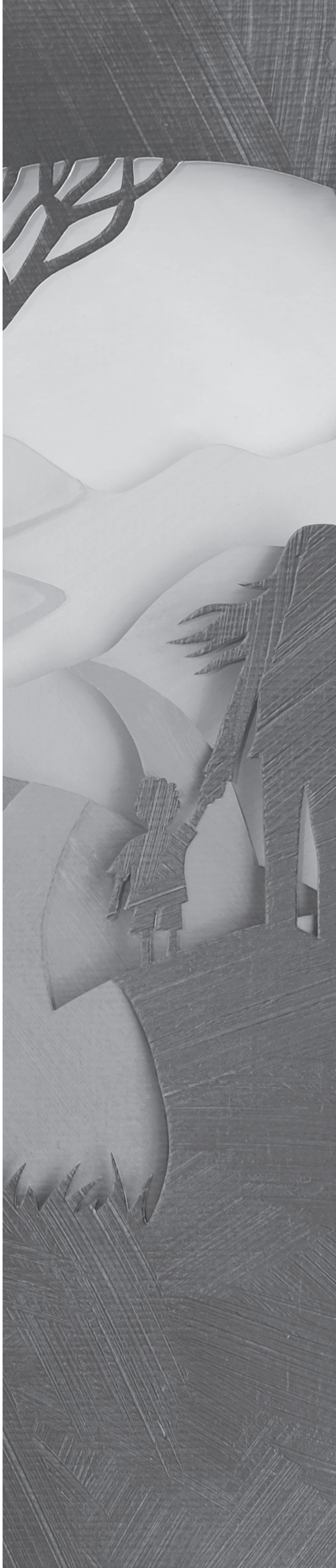
CHAPTER 1

General introduction



Respiratory tract infections in primary care

Patients almost daily present with symptoms of a respiratory tract infection (RTI) at the general practice, especially in the winter months. Upper RTI and cough are reported as the fourth and fifth most frequent health problems presented to the general practitioner (GP).[1] The annual incidence of RTI and ear infections is around 650 per 1000 patients over all ages.[2] Irrespective of the viral or bacterial cause, most RTIs have a mild course, and are self-limiting.[3] However, for some patients RTIs can have a longer duration, a complicated course, or could even be life-threating, especially in very young children, the elderly, and patients with relevant comorbidity.[3] Antibiotics are indicated for selected groups of patients for whom the benefits outweigh the harms of antibiotics for themselves and the community, like side-effects and bacterial resistance. For these patients, antibiotic treatment is of high relevance to reduce symptoms, to prevent severe disease, or complications, and could thereby be a matter of life and death. In the Netherlands, these groups of patients are specified in the clinical guidelines of the Dutch College of GPs, which are based on the latest evidence.[3] It is the GP's task to select patients at risk for a complicated course and in need for treatment, or further investigation. Another important aspect is to make clear what drives the patients to consult, what they expect and what their main question for help is.[4] Patients might suffer from symptoms, feel restricted in their daily activities, be worried about the underlying cause, want to know how long symptoms will last, and/or need advice or medicine to support their recovery or control their symptoms.

Over-prescription of antibiotics

Around 80% of antibiotics used in health care are prescribed by GPs.[5] Most antibiotics are prescribed for RTIs and ear infections.[2] Many randomized controlled trials showed no relevant clinical effectiveness of antibiotic treatment of upper RTI, sinusitis, bronchitis, and sore throats.[6-10] Despite the evidence of randomized controlled trials and clinical guidelines, there is a clear misuse of antibiotics, which is furthermore illustrated by large variation in antibiotic prescribing between GPs, practices and countries. In addition to prescribing antibiotics for inappropriate indications, GPs are also prescribing antibiotics which are not recommended to treat common infections.[11] Even in a low prescribing country as the Netherlands, antibiotics are overprescribed.[12] Over-prescription of antibiotics is caused by several factors such as GPs' unfamiliarity with recent guidelines, diagnostic uncertainty to identify a serious bacterial infection, time constraints to explain the cause of the illness and the reasons why an antibiotic is not indicated, unawareness of problems related to antibiotic prescription and fear that patients will not accept a non-prescribing decision.

There is compelling evidence that patients who have used an antibiotic carry resistant bacteria and spread these in the population.[13] Although antibiotics are amongst the most important drugs of our time, bacterial resistance is an increasingly serious threat to global public health.[14] Patients with infections caused by drug-resistant bacteria are at increased risk of worse clinical outcomes and death, and need more health-care resources than patients infected with non-resistant strains due to longer illness duration, additional tests, use of more expensive drugs and hospitalization.[14] Without effective antibiotics for prevention and treatment of infections, medical procedures for serious conditions such as organ transplantation, cancer chemotherapy, diabetes management and major surgery become high-risk procedures. Furthermore, overprescribing of antibiotics results in medicalization, where patients belief they need to consult and use medication when similar symptoms recur, creating a "vicious cycle" of unnecessary consulting and medications use.[15] Finally, overuse unnecessarily exposes patients to adverse effects, like rash, diarrhea, and allergic reactions.[16]

Improving antibiotic use

Increasing awareness of antibiotic-related problems has initiated numerous interventions aiming to improve antibiotic prescribing practice.[17-22] These interventions included educational materials, educational meetings, educational outreach visits, audit and feedback, reminders, introducing point-of-care tests, and improving communication strategies. The multi-factorial causes of over-prescription, different patient populations, cultural contexts and prescribing practices between countries may warrant a variety of interventions to improve antibiotic use in different settings.[17] Multifaceted interventions, mostly focusing on adult patients, showed to be effective, however, broad implementation of these often complex interventions is rare, because of logistical complexity and costs.[17,18,21-25] Little *et al*. showed that an online educational program for GPs, which is less intensive and complex, was effective as well in improving antibiotic management of adults with lower RTI.[19] In the Netherlands, previous interventions including educational outreach, audit and feedback, point of care testing and training in communication skills, were effective in reducing antibiotic use in adult patients.[20,21,26,27]

Antibiotics for children

Children mainly visit their GP with infectious diseases, and RTI and ear infections are responsible for most antibiotic prescriptions, despite their marginal benefit in these infections.[28-30] Since the late 1990s, initially an overall decrease in antibiotic prescription rates for children has been reported in the USA and UK till 2000.[31,32] Between 2000 and 2005 antibiotic prescribing significantly increased for children in the Netherlands, as well as in the UK,[32] however, a slight, but significant decrease was observed in the Netherlands from 2006 to 2010. As clinical guidelines had not changed in this period, this decrease could be attributed to the initiation of the Dutch nationwide pneumococcal vaccination campaign in 2006, and/or to an increased awareness for prudent antibiotic use.[30] Overall antibiotic use by children has rarely been described in relation to the specific diagnoses for which they were used.[30,33-35] This information is needed to obtain a complete picture of antibiotic management of children by GPs, including consultation incidences and the proportion of episodes with an antibiotic prescription. In contrast to the evidence of effective interventions to reduce prescribing for adults, there is a paucity of interventions aiming to improve antibiotic prescribing specifically for children in primary care.[36-38] A child-specific intervention might be needed, since indications for antibiotic prescribing and risk-factors for a complicated course are different for children than for adults.[3] Especially in children, GPs tend to prescribe an antibiotic, as the safer course of action, because they feel uncertain about indicating seriously ill children.[39-42] Besides, parental fears, their beliefs and expectations can play an important role in the GP's decision to prescribe an antibiotic.[43] Parents' expression of concern or request for additional information can sometimes result in a misunderstanding, and contribute to unnecessary and unwanted prescription of antibiotics.[41,42] Therefore, an intervention directed at both GPs and parents would be needed to improve antibiotic prescribing for children with RTI, and adequately informing parents seems to be essential. There has been one study in the United Kingdom on informing parents during the consultation to improve antibiotic use.[44] Francis *et al.* showed a decrease in antibiotic prescribing for children with RTIs by using an interactive booklet during the consultation.[44] An online educational program for GPs as studied previously for adult patients with lower RTI has not been studied to improve antibiotic prescribing for children.[19]

Aims and outline of this thesis

The first part of this thesis aims to give insight in the presentation and antibiotic management of children with infectious diseases and to assess the appropriateness of antibiotic prescribing for patients of all ages with RTI.

In chapter 2 we present consultation and antibiotic management for infectious diseases of children in Dutch primary care, related to clinical diagnoses. This overview enables defining focus and targets for improvement and is needed to reliably compare antibiotic prescribing quality between GPs and/or countries. In chapter 3 we benchmarked all relevant patient and illness characteristics to the guidelines of the Dutch College of GPs to quantify and qualify inappropriate antibiotic prescribing for RTIs.

The second part of this thesis describes the RAAK intervention, aiming to reduce antibiotic prescribing for children with RTI in primary care.

In chapter 4 we studied the effectiveness of the RAAK intervention, consisting of GP online training and information booklets for parents, on antibiotic prescribing for children with RTI in a cluster randomised controlled trial.

The third part of this thesis aims to evaluate the RAAK intervention.

Chapter 5 provides a trial-based cost-effectiveness analysis of the RAAK intervention and gives insight in the societal impact of RTI in children. In chapter 6 we explored the attitude and views of parents towards antibiotic management of childhood RTI, and the influence they perceived of the information booklet. Chapter 7 describes the experiences of GPs, focusing on the process of informal (workplace) learning after the online training, and the influence they perceived from this on their antibiotic prescribing practice.

Chapter 8 discusses the main results of this thesis and future perspectives.

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PART ONE

Antibiotic management in primary care

CHAPTER 2

Antibiotic management of children with infectious diseases in Dutch primary care

Anne R.J. Dekker

Theo J.M. Verheij

Alike W. van der Velden

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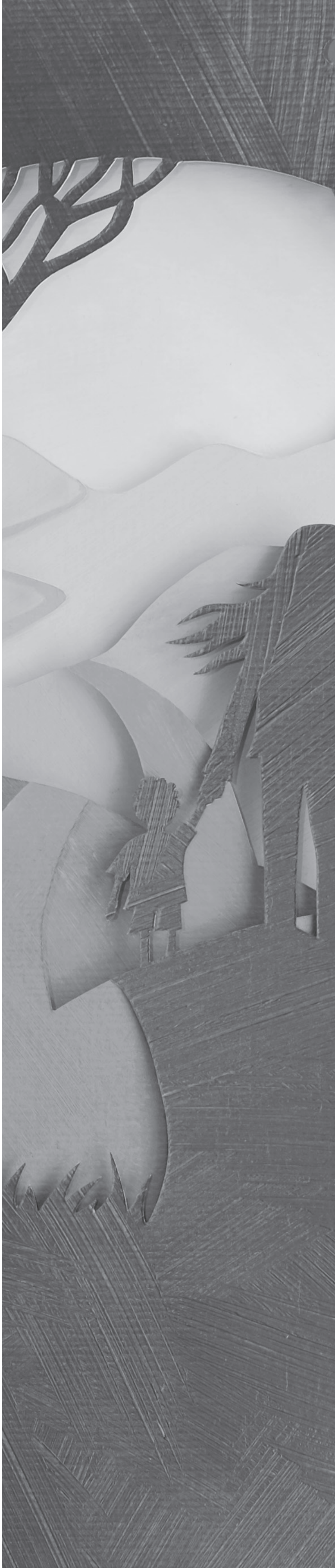

ABSTRACT

Background: Childhood infections are common in general practice. Although clinical guidelines recommend restrictive antibiotic use for children, antibiotics are too often prescribed.

Objective: The aim of this study was to obtain insight in antibiotic prescribing for children, related to clinical diagnoses. This is pivotal to define improvement strategies in the antibiotic management.

Methods: In this observational study, we used consultation data collected from 45 general practices in the Netherlands in 2012. Infectious disease episode incidences, the number of antibiotic prescriptions per 1000 person-years, the proportion of episodes with an antibiotic prescription, and the choice of antibiotic subclass were analysed for the most relevant diagnoses, over different ages.

Results: A total of 262 antibiotic courses were prescribed per 1000 person-years on average, with the highest number among children of 1 year (714/1000 person-years). Antibiotics were prescribed in 24% of infectious disease episodes. Acute upper respiratory tract infection (RTI) was the most common reason to visit the general practitioner (173/1000 person-years), and the second most frequent indication to prescribe antibiotics. Antibiotics were most often prescribed for acute otitis media (58/1000 person-years). Amoxicillin dominated prescribing (55%), followed by macrolides (14%) and amoxicillin/clavulanate (10%), prescribing of narrow-spectrum antibiotics was low (10%).

Conclusions: This detailed insight in antibiotic management of childhood infections shows targets for Dutch improvement strategies: (i) prevent antibiotic prescribing for acute upper RTI and bronchitis; (ii) stimulate the use of narrow-spectrum antibiotics; and (iii) reduce the use of macrolides and amoxicillin/clavulanate. Furthermore, this information is helpful to compare antibiotic policy between countries.

BACKGROUND

Children mostly visit their general practitioner (GP) with infectious diseases, including respiratory tract, ear, urinary tract, and skin infections.[1] Respiratory tract and ear infections are often viral and self-limiting. Antibiotic treatment is therefore only recommended for specific indications and/or severity of disease and for vulnerable children, with a preference for narrow-spectrum antibiotics.[2-6] Meanwhile, inappropriate use of antibiotics is a worldwide concern, because antibiotic consumption is directly related to the development of bacterial resistance.[7] Furthermore, overprescribing results in medicalization and unnecessarily exposes children to adverse effects, all of which increase health care costs. Overprescribing of antibiotics has repeatedly been shown, even in a low-prescribing country like the Netherlands.[8-10]

Antibiotic management varies across countries in Europe due to differences in incidence and severity of patient presenting with infectious diseases, GPs' treatment decisions and types of prescribed antibiotics. Overall trends of antibiotic use by children have often been described, but rarely in relation to the specific diagnoses for which they were used.[11-14] To obtain a complete picture of antibiotic management of children by GPs, all successive steps, consultation incidences, the proportion of episodes with an antibiotic prescription and the choice of antibiotic, should be described per individual diagnoses. The aim of this study is therefore to provide this detailed description of infectious disease management of children of various ages. This is expected to be helpful to define focus and targets for improvement strategies.

METHODS

Data source

The primary care network and data collection have been described previously.[8] In short, anonymous routine primary healthcare data from 2012 were retrieved from the digital patient records from Julius General Practitioners Network practices. This network consists of 45 general practices in Utrecht and its vicinity with 160 GPs, full time and part time. Participating practices are located in the city of Utrecht and in the surrounding villages. We regard this group of GPs with their population as a representative sample of the Dutch population. The database contains information on all office-hours contacts during week days, including diagnoses and prescription data. Consultations are coded with a diagnosis or main symptom using the International Classification of Primary Care (ICPC), and all antibiotic prescriptions are registered according to the WHO guidelines for Anatomical Therapeutic Chemical classification.[15,16] For this study we used all infectious disease contacts of children under 18 years of age. Our analysis was based on constructed disease episodes that included individual consultations with the same ICPC code within a pre-defined timeframe. This timeframe was different for all ICPC codes, and based on expert opinion, timeframes were described in the supplementary data of the study of van den Broek d'Obrenan *et al.*[8]

Study outcomes and analyses

We calculated the following outcomes in order to present the complete picture of infectious disease management in children:

1. The number of infectious disease episodes per 1000 person-years. Person-years refer to the number of registered children in the participating practices in 2012, adjusted for the time that they were registered (birth/death and entering/leaving the practice were taken into account). Infectious disease episodes were shown for all ages and per specific diagnosis for the following age categories: 0–2 years, 3–5 years, 6–11 years and 12–17 years of age.
2. The number of antibiotic prescriptions per 1000 person-years, presented for all ages and per age category, distributed over the following antibiotic subclasses: tetracyclines (J01A), amoxicillin (J01CA), pheneticillin (J01CE), flucloxacillin (J01CF), amoxicillin/clavulanate (J01CR), sulphonamides and trimethoprim (J01E), macrolides (J01FA), fluoroquinolones (J01MA), and nitrofuran derivatives (J01XE).
3. The proportion of the disease episodes in which at least one antibiotic was prescribed. This proportion was calculated per age and within the age categories per specific diagnosis, for the most frequent indications for antibiotic prescribing.
4. The choice of antibiotic subclass for the specific diagnoses.

All analyses were performed with SPSS version 21.0 and Excel.

RESULTS

Incidences of episodes and antibiotic prescriptions

The study population consisted of 55,794 children, which resulted in 52,022 person-years. This difference was mainly due to newborns during the year. In total, 53,517 infectious disease episodes were identified and 13,616 antibiotic courses were prescribed, resulting in 1029 disease episodes and 262 antibiotic courses per 1000 person-years on average. For all ages, the number of disease episodes, together with the number of prescribed antibiotics per 1000 person-years are shown in Figure 2.1. As expected, these outcomes coincided well, with the highest number

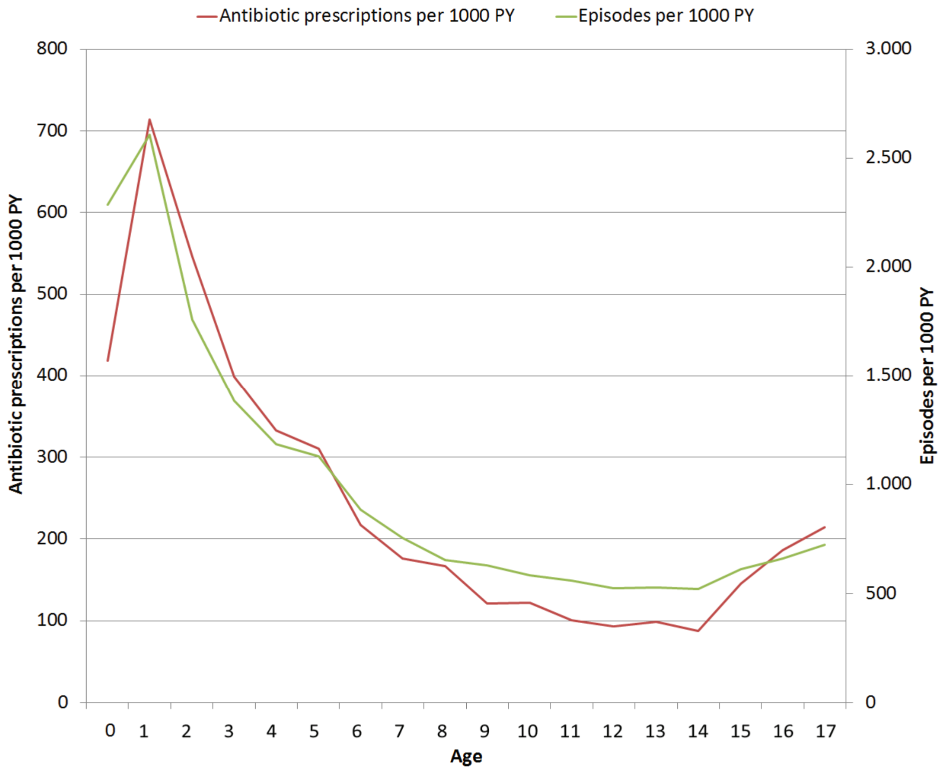

Figure 2.1 Infectious disease incidences and antibiotic prescriptions by age.
Numbers on the left-hand Y-axis refer to the number of prescriptions per 1000 person-years. Numbers on the right-hand Y-axis refer to the numbers of episodes per 1000 person-years.

of disease episodes and the highest number of prescribed antibiotics among children aged 1 year (respectively, 2606/1000 person-years and 714/1000 person-years) and the lowest among children aged 14 years (520/1000 person-years and 88/1000 person-years, respectively). The proportion of disease episodes with at least one antibiotic prescription is shown in Figure 2.2 for all ages. The mean proportion was 24%, but varied with age. The highest proportion antibiotic prescriptions was observed for children aged 2 years (29%) and the lowest for children aged 14 years (16%), with a steadily increase from 14 to 17 years of age.

Most relevant diagnoses for consulting the GP and prescribing antibiotics

Figure 2.3 shows the 10 most frequent diagnoses for antibiotic prescribing and the proportion of antibiotic prescriptions per age. Per indication prescribing proportions were about similar for the

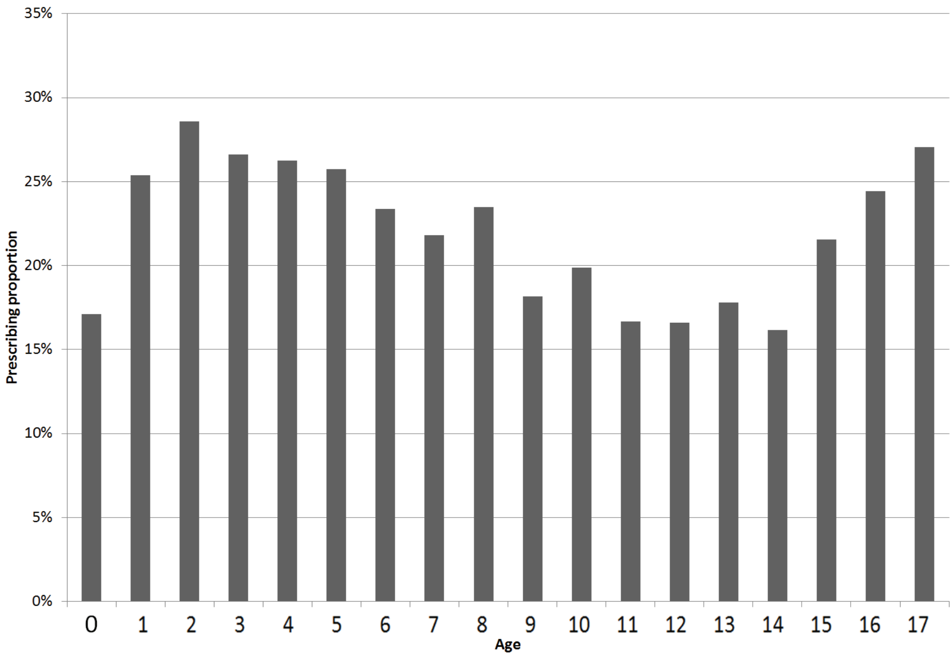

Figure 2.2 Proportion of infectious disease episodes treated with antibiotics by age.
The proportion of episodes with at least on antibiotic prescription was calculated for all ages.

age categories. However, for acute otitis media and asthma, the proportion of episodes treated with antibiotics decreased with age, and for cystitis these episodes relatively increased with age. For children aged 0–2 years, the episode incidence was highest in acute upper respiratory tract infections (RTIs). Most antibiotics were prescribed for acute otitis media (193/1000 person-years). In 55% of the episodes with acute otitis media an antibiotic was prescribed, followed by 14% of the episodes with acute upper RTI, resulting in 77 antibiotic courses per 1000 person-years, which was therefore the second most frequent indication to prescribe antibiotics. Children of 3–5 and 6–11 years consulted again most for acute otitis media, acute upper RTI and cough. Antibiotic prescribing was most frequent in the following diagnoses: acute otitis media (79/1000 person-years and 20/1000 person-years, respectively), and acute upper RTI, followed by acute tonsillitis and cystitis. Among the oldest children (12–17 years of age), the most frequent indication to consult the GP was asthma, the most common indication for antibiotic prescribing was cystitis. Moreover, acne appeared in this age group for which in 16% of the episodes an antibiotic was prescribed, resulting in 7 prescriptions per 1000 person-years.

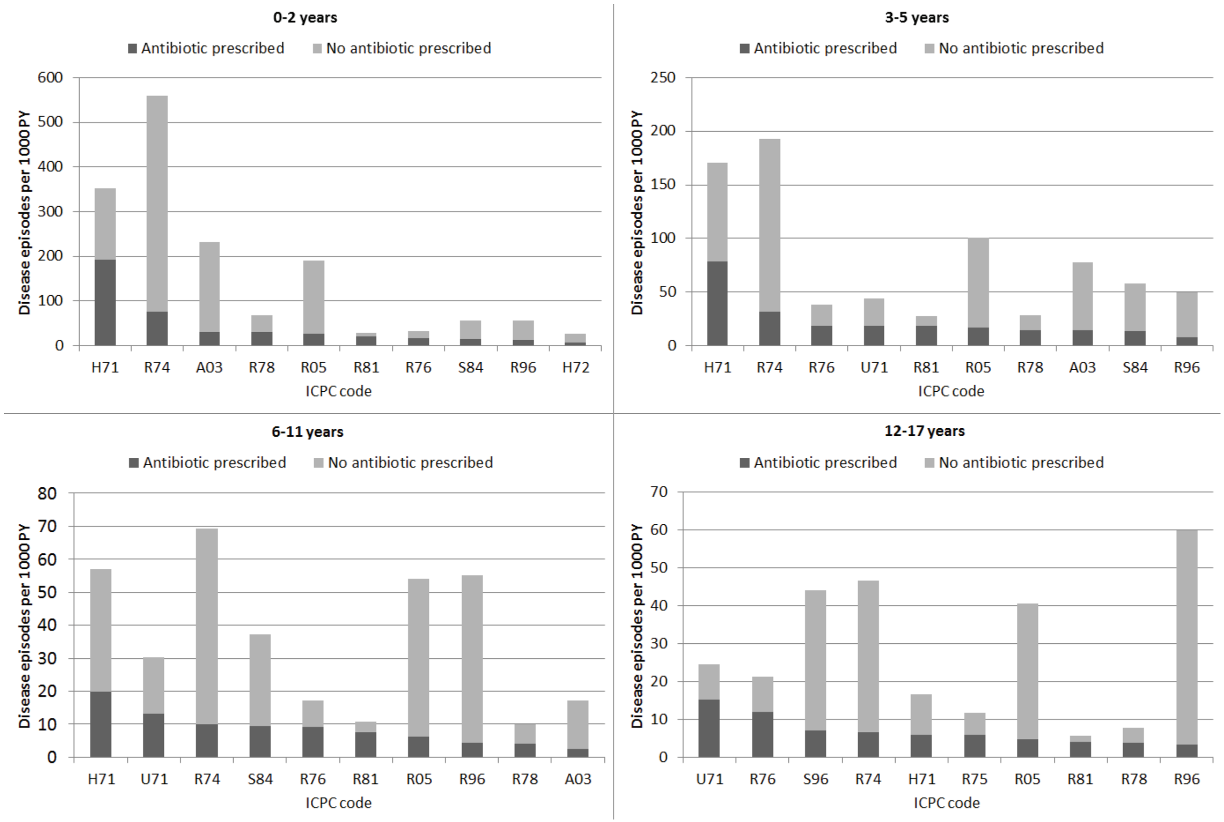

Figure 2.3 Most relevant diagnoses for consulting the GP and antibiotic prescribing.
The numbers of disease episodes/1000 person-years with and without antibiotic prescription are shown for the 10 most often used indications for antibiotic prescribing per age category. Note the different scales on the Y-axes.
H71: acute otitis media; U71: cystitis; R74: acute upper RTI; S84: impetigo; R76: acute tonsillitis; R81: pneumonia; R05: acute cough; R96: asthma; R78: acute bronchitis/ bronchiolitis; A03: fever; R75: sinusitis acute/chronic; H72 serous otitis media; S96: acne.

Types of antibiotics prescribed

Amoxicillin was the most frequently prescribed antibiotic in all age categories (143/1000 person-years), followed by macrolides (36/1000 person-years) and amoxicillin/clavulanate (27/1000 person-years), as shown in Table 2.1. Amoxicillin comprised 72% of all antibiotic prescriptions for children aged 0–2 years. The absolute number of prescribed macrolides was highest in the youngest children (75/1000 person-years) and declined with age, as was seen for amoxicillin/clavulanate. Fluoroquinolones and tetracyclines were rarely prescribed for young children. As age progresses, relatively less amoxicillin was prescribed, which was replaced by tetracyclines, narrow-spectrum penicillins (pheneticillin and flucloxacillin), fluoroquinolones and nitrofuran derivatives. Nitrofuran derivatives were mostly prescribed to children of 12–17 years (23/1000 person-years).

Table 2.1 Numbers of prescribed antibiotic subclasses per age category

		Age group				
ATC code	Name	0–2 years [n (%)]	3–5 years [n (%)]	6–11 years [n (%)]	12–17 years [n (%)]	Total [n (%)]
J01A	Tetracyclines	0 (0)	0 (0)	1 (1)	18 (13)	5 (2)
J01CA	Amoxicillin	421 (72)	193 (55)	67 (44)	30 (23)	143 (55)
J01CE	Pheneticillin	14 (2)	22 (6)	11 (7)	16 (13)	15 (6)
J01CF	Flucloxacillin	11 (2)	14 (4)	12 (8)	10 (7)	12 (4)
J01CR	Amoxicillin/ clavulanate	48 (8)	42 (12)	18 (12)	13 (10)	27 (10)
J01E	Sulphonamides and trimethoprim	18 (3)	13 (4)	6 (4)	4 (3)	9 (3)
J01FA	Macrolides	75 (13)	55 (16)	20 (13)	19 (14)	36 (14)
J01MA	Fluoroquinolones	0 (0)	1 (0)	2 (1)	2 (1)	1 (1)
J01XE	Nitrofuran derivatives	1 (0)	8 (2)	14 (9)	23 (17)	13 (5)
	Total	588 (100)	349 (100)	151 (100)	134 (100)	262 (100)

Numbers of prescribed antibiotic courses per 1000 person-years (n), for each subclass and per age category. Percentage of total prescribed antibiotics is given (%).

Distribution of antibiotic subclasses per diagnosis

Figure 2.4 presents the subclasses of prescribed antibiotics for the 10 most relevant diagnoses for antibiotic prescribing. For acute otitis media 86% of the prescribed antibiotics comprised amoxicillin. For the RTIs the most often prescribed antibiotic was also amoxicillin, however, second choice antibiotics, like macrolides and amoxicillin/clavulanate were also prescribed for cough,

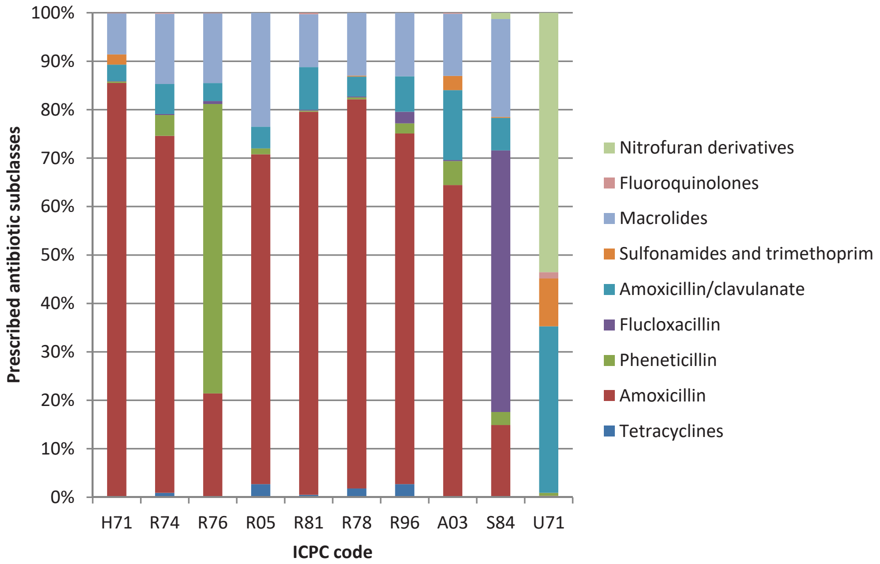

Figure 2.4 Distribution of prescribed antibiotic subclasses per diagnosis.
For the most frequent used diagnoses for antibiotic prescribing, the relative distribution of prescribed antibiotics is shown. When more than one antibiotic course was prescribed within one episode, only the first prescribed antibiotic was included. H71: acute otitis media; R74: acute upper RTI; R76: acute tonsillitis; R81: pneumonia; R05: acute cough; R78: acute bronchitis/bronchiolitis; R96: asthma; A03: fever; R75: sinusitis acute/chronic; S84: impetigo; U71: cystitis.

upper RTIs, bronchitis, pneumonia and asthma. For cystitis, amoxicillin/clavulanate was mainly prescribed for the youngest children (91%), with a shift to nitrofuran derivatives (87%) and sulphonamides and trimethoprim (9%) for the oldest children as shown in the supplementary data. For acute tonsillitis, the first choice antibiotic, pheneticillin, was prescribed in 60%, whereas broad-spectrum antibiotics like macrolides and amoxicillin were mainly prescribed in the youngest age category (respectively 20% and 44%, see supplementary data). Also for impetigo, relatively more broad-spectrum antibiotics, were prescribed for younger children.

CONCLUSION

Main findings

Our study showed that for children a total of 262 antibiotic courses were prescribed per 1000 person-years, with the highest number for children of 1 year of age (714/1000 person-years). Overall, in 24% of the presented infectious disease episodes an antibiotic course was prescribed.

Our data fully captured the diagnoses for which the antibiotics were prescribed, and acute upper RTI was the second most frequent indication for antibiotic prescription, and the most common reason to visit the GP. Amoxicillin dominated prescribing (55%), followed by the second choice antibiotics, macrolides (14%) and amoxicillin/clavulanate (10%). The overall proportion of narrow-spectrum antibiotics, pheneticillin (6%) and flucloxacillin (4%), was low.

Strengths and limitations

Our study provided detailed insight into consultation of and antibiotic prescribing for infectious diseases in a population of over 55,000 children. Moreover, as antibiotics are not available over-the-counter in the Netherlands, and patients always visit their own practice, these data are highly representative of antibiotic management in the community. The main strength of this study is that consultation and antibiotic prescribing are linked to clinical diagnoses, providing a detailed insight into both consultation behaviour and antibiotic prescribing for each individual diagnosis. This is highly relevant for two reasons. First, to enable defining focus and targets for improvement strategies, and second, to compare antibiotic prescribing quality between countries. By simply comparing antibiotic prescribing proportions, misinterpretation can occur when consultation incidences differ. Even with a lower proportion of episodes treated with antibiotics, the absolute number of prescriptions can be higher when patients present more often, this can obscure data interpretation in countries where many patients present with mild illness. Data from different countries are better interpretable when a complete description of patient consultation and GP prescribing practice per diagnosis is provided. A possible limitation of this study can be diagnostic labeling to justify an antibiotic prescription. For example, when a cough without alarm symptoms is labeled as pneumonia to "allow" antibiotic prescribing. However, in routine care data the possibility of intentional misclassification is lower as compared to audit-based data. Furthermore, intentional misclassification seemed less likely in these data as there was substantial antibiotic prescribing for indications for which antibiotics are not indicated. Second, we analysed prescribing data, and it is not clear whether patients indeed collected and took their prescribed medication. A previous study showed non-adherence to antibiotics for acute cough or lower RTI.[17] Our study therefore might have overestimated antibiotic usage. However, these data do provide reliable information on patient consultation and GPs' prescribing practice, which was the goal of this study. Finally, according to the guidelines of the Dutch College of GPs, antibiotic treatment is always indicated for pneumonia and for children, under 12 years, with cystitis.[2,18] We haven't found this adherence in the data, but don't expect underprescribing either. GPs could have chosen for additional investigation and/or referral to secondary care for these patients. A third limitation is that our database didn't capture information on these management strategies.

Comparison with existing literature

Antibiotic prescribing was studied for the whole population with data from 2010, collected from the same network.[8] This previous study showed a total number of 1065 infectious disease episodes with 299 antibiotic prescriptions per 1000 person-years compared with 1029 episodes with 262 antibiotic prescriptions per 1000 person-years in our child specific study. This comparison shows prudent antibiotic use for children, which fits the reticent attitude of Dutch parents and the trust they have in the reassurance and decision of their GP. For the whole population, most antibiotics were prescribed for cystitis, acute upper RTI and acute otitis media. Their analyses also included children, and as it is known that otitis media is mainly child-specific, for adults most antibiotics were prescribed for cystitis, acute upper RTI, acute sinusitis and bronchitis. Compared to other European countries, antibiotic prescribing in the Netherlands is low for children as well as for adults.[13,14,19] A recent study from Denmark, also known for low prescribing, showed a slightly higher number of antibiotic prescriptions redeemed in 2012, with 961/1000 person-years for children under 2 years, 607/1000 for children aged 2–4 years and 282/1000 for 5–11 year-olds.[13] Otters *et al.* described antibiotic prescribing for children in the Netherlands in 2001.[20] Our data of a decade later add relevant information, the antibiotic subclasses, prescribing per age category and most importantly the diagnostic indication for prescribing. The comparison between the number of prescribed antibiotics in 2001 (232/1000 person-years) and 2012 (262/1000 person-years) does not imply a simple increase in antibiotic prescriptions for children. It was shown that overall prescription of oral antibiotics increased from 2000 to 2005 and decreased afterwards.[12] Broad-spectrum antibiotic prescribing remained high in the Netherlands since 2001. Amoxicillin and amoxicillin/clavulanate were prescribed for 65% in 2012, compared with 58% in 2001. A higher use of real narrow-spectrum penicillins is apparent in other European countries. In the Netherlands, only for throat infections, pheneticillin is the first choice antibiotic, but in Scandinavia it is often prescribed for acute upper RTIs and acute otitis media as well. For example, in Denmark, 33% of the prescribed antibiotics for children of 0–2 years are beta-lactam sensitive penicillins (J01CE) versus 2% in the Netherlands.[13] Guideline recommendations in Denmark explicitly discourage the use of broad-spectrum antibiotics as first line treatment.[13] Macrolide prescribing has decreased slightly since 2001, from 16% to 14%. The use of macrolides might be explained by convenience (a short, once-daily regimen) and by childhood taste preferences.

Recommendations to improve antibiotic prescribing in Dutch primary care

Our data comprehend implications for clinical action. First, awareness and focused attention is needed to prevent unnecessary antibiotic prescribing for viral and/or self-limiting disease.

Although the number of prescribed antibiotics is comparatively low in the Netherlands, there is clear evidence from this and previous studies for overprescription for respiratory disease.[9,10] We showed that among children many antibiotics were prescribed for diagnoses, for which antibiotics are generally considered inappropriate: acute upper RTI, acute cough, bronchitis and for asthma, which is not considered as a risk factor for a complicated course of cough.[2] Better recommendations for a non-antibiotic, symptomatic relief treatment and a better explanation to parents about this are needed to prevent unnecessary prescribing. This might furthermore reduce the number of (re)consultations for these high-incidence diagnoses and improve knowledge. Second, the widespread use of amoxicillin in the Netherlands for children needs attention, by propagating prescribing of the narrow-spectrum antibiotic pheneticillin, especially in throat infections.[5] Guideline developers should incorporate resistance profiles for small-spectrum penicillins in recommendations for acute otitis media and other RTIs. Third, reducing prescribing of macrolides and amoxicillin/clavulanate should be a target for intervention, as these are only indicated for children with penicillin allergy, or for specific diseases like whooping cough.[2,5]

International implications

Improving GPs' antibiotic prescribing practice requires detailed insight in current infectious disease management. Therefore, we encourage other countries to relate their antibiotic prescriptions to clinical diagnoses as well. This better allows for benchmarking between countries, which provides tools for national improvement strategies and stimulates quality improvement.

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SUPPLEMENTARY DATA

Table S2.1 Recommendations for antibiotic prescribing according to the guidelines of the Dutch College of GPs in 2012

Guideline	AB	Definition of patient- and disease characteristics	First choice AB
Acute otitis media	Indicated	• Age <6 months • Severe or increasing illness • Risk for complicated course: anatomy abnormalities, compromised immune system	Amoxicillin
	May be considered	• Age <2 years with bilateral AOM • Otorrhea at first presentation • No improvement after 3 days	
Acute sore throat	Indicated	• Severe illness (severely inflamed pharynx, with problems of swallowing/opening the mouth) and fever ≥38°C • Peritonsillar infiltrate or abscess • Heavily swollen lymph nodes • Risk for complicated course: history of acute rheumatic fever, compromised immune system	Pheneticillin
Rhinosinusitis	May be considered	• Severe illness • Fever >5 days or relapse of fever within the same episode • Compromised immune system	Amoxicillin
Acute cough	Indicated	Signs and symptoms indicative for pneumonia: • Severe illness with localised auscultation abnormalities or tachypnea • Duration of symptoms ≥7 days, with fever (≥38°C) ≥7 days Risk for complicated course, dependent on the clinical assessment • Age <3 months with fever (≥38°C) • Relevant comorbidity: congenital heart- or lung disease (except asthma)	Amoxicillin
Bacterial skin infections	Indicated	• General illness • Fever • Insufficient improvement by local treatment	Flucloxacillin
Urinary tract infections	Indicated	• Positive nitrite test, dipslide or urinary sediment • Typical symptoms and signs for urinary tract infections	Uncomplicated, or without tissue invasion: nitrofurantoin Complicated with tissue invasion: amoxicillin/ clavulanate

A non-antibiotic management, with reassurance and, if possible, a symptomatic treatment advice, is advised for all other patients.

Table S2.2 Distribution of prescribed antibiotics per diagnosis for the different age categories

	0–2 years		3–5 years		6–11 years		12–17 years	
Diagnosis	Antibiotic	%	Antibiotic	%	Antibiotic	%	Antibiotic	%
Acute otitis media	J01CA	86	J01CA	87	J01CA	84	J01CA	78
	J01FA	8	J01FA	8	J01FA	10	J01FA	10
	J01CR	3	J01E	2	J01CR	4	J01CR	9
	J01E	2	J01CR	2	J01E	1	J01E	1
Acute upper RTI	J01CA	82	J01CA	67	J01CA	71	J01CA	43
	J01FA	11	J01FA	19	J01FA	20	J01CE	19
	J01CR	5	J01CR	10	J01CE	6	J01FA	17
	J01CE	2	J01CE	5	J01CR	3	J01CR	8
Asthma	J01CA	81	J01CA	74	J01CA	70	J01CA	56
	J01FA	10	J01FA	15	J01FA	17	J01A	18
	J01CR	7	J01CR	7	J01CR	9	J01CE	6
	J01CF	2	J01CF	2	J01CF	4	J01CR	6
Acute tonsillitis	J01CA	44	J01CE	59	J01CE	69	J01CE	78
	J01CE	33	J01CA	20	J01CA	19	J01CR	9
	J01FA	20	J01FA	19	J01FA	12	J01FA	6
	J01CR	3	J01CR	2	J01CR	1	J01CA	4
Acute cough	J01CA	78	J01CA	70	J01CA	62	J01CA	39
	J01FA	17	J01FA	27	J01FA	25	J01FA	37
	J01CR	4	J01CR	3	J01CR	9	J01A	21
	J01CE	1	J01CE	1	J01CE	3	J01CE	2

Table S2.2 continues on next page

Table S2.2 ***Continued***

	0–2 years		3–5 years		6–11 years		12–17 years	
Diagnosis	Antibiotic	%	Antibiotic	%	Antibiotic	%	Antibiotic	%
Pneumonia	J01CA	84	J01CA	80	J01CA	77	J01CA	67
	J01CR	8	J01FA	12	J01FA	12	J01FA	16
	J01FA	8	J01CR	9	J01CR	8	J01CR	12
	-		-		J01MA	2	J01A	4
Acute bronchitis	J01CA	84	J01CA	80	J01CA	82	J01CA	60
	J01FA	10	J01FA	15	J01FA	12	J01FA	22
	J01CR	5	J01CR	3	J01CR	4	J01A	17
	J01CF	0.4	J01CE	1	J01A	1	J01CR	2
Cystitis	J01CR	91	J01CR	62	J01XE	60	J01XE	87
	J01CA	3	J01XE	22	J01CR	26	J01E	9
	J01E	3	J01E	11	J01E	12	J01CR	4
	J01XE	3	J01CE	2	J01MA	2	-	
	J01CE	3	J01CE	5	J01CR	15	J01CR	20
Impetigo	J01CF	37	J01CF	54	J01CF	64	J01CF	66
	J01CA	26	J01FA	25	J01FA	15	J01FA	20
	J01FA	22	J01CA	12	J01CA	10	J01CA	11
	J01CR	10	J01CR	4	J01CR	7	J01CR	3

Per age category, the distribution of antibiotics prescribed for the most relevant indications is shown. When more than one antibiotic course was prescribed within one episode, only the first prescribed one was included.
J01A: tetracyclines, J01CA: amoxicillin, J01CE: pheneticillin, J01CF: flucloxacillin, J01CR: amoxicillin/clavulanate, J01E: sulfonamides and trimethoprim, J01FA: macrolides, J01MA: fluoroquinolones, J01XE: nitrofuran derivatives.

CHAPTER 3

Inappropriate antibiotic prescription for respiratory tract indications

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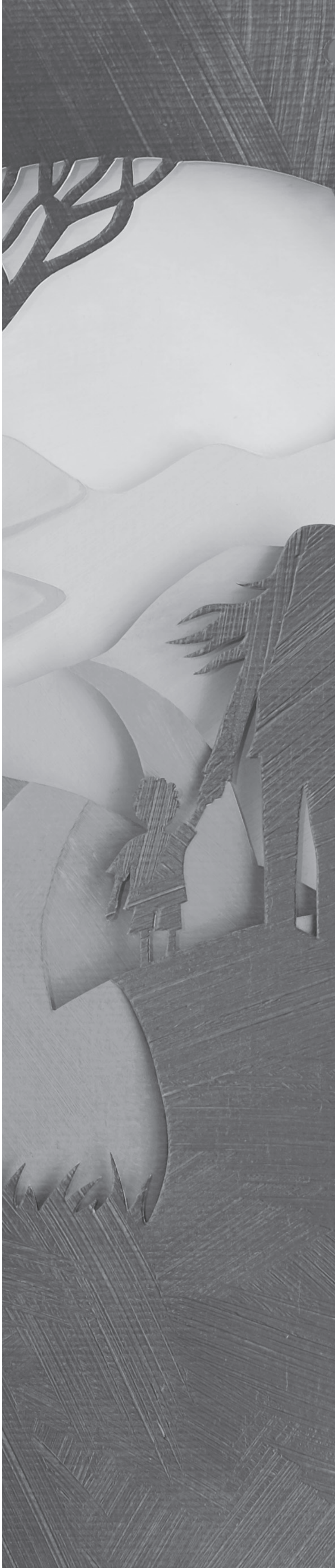

ABSTRACT

Background: Numerous studies suggest overprescribing of antibiotics for respiratory tract indications (RTIs), without really authenticating inappropriate prescription; the strict criteria of guideline recommendations were not taken into account as information on specific diagnoses, patient characteristics and disease severity was not available.

Objective: The aim of this study is to quantify and qualify inappropriate antibiotic prescribing for RTIs.

Methods: This is an observational study of the (antibiotic) management of patients with RTIs, using a detailed registration of RTI consultations by general practitioners (GPs). Consultations of which all necessary information was available were benchmarked to the prescribing guidelines for acute otitis media, acute sore throat, rhinosinusitis or acute cough. Levels of overprescribing for these indications and factors associated with overprescribing were determined.

Results: The overall antibiotic prescribing rate was 38%. Of these prescriptions 46% were not indicated by the guidelines. Relative overprescribing was highest for throat (including tonsillitis) and lowest for ear consultations (including acute otitis media). Absolute overprescribing was highest for lower RTIs (including bronchitis). Overprescribing was highest for patients between 18–65 years of age, when GPs felt patients' pressure for an antibiotic treatment, for patients presenting with fever and with complaints longer than one week. Underprescribing was observed in less than 4% of the consultations without a prescription.

Conclusion: Awareness of indications and patient groups provoking antibiotic overprescribing can help in the development of targeted strategies to improve GPs' prescribing routines for RTIs.

BACKGROUND

The vast majority of antibiotics are prescribed in primary care and respiratory tract indications (RTIs) are the most common reason for antibiotic treatment.[1] There is clear evidence that antibiotics are heavily overprescribed for respiratory disease.[2-4] Primary care guidelines recommend restrictive antibiotic use for upper and lower RTIs because of their limited treatment effectiveness in the majority of these indications; most RTIs are of viral origin and self-limiting. In addition, the use of antibiotics results in development of resistant micro-organisms, which affects both the individual and the population.[5,6] Inappropriate antibiotic use furthermore encourages medicalization and unnecessarily exposes patients to side effects; this all results in unnecessary costs.[7,8]

Despite widespread implementation and use of guidelines, numerous studies revealed inappropriately high levels of antibiotic prescribing for RTIs,[1-4, 9-11] as well as higher prescribing rates for adults and an increase in prescribing for the elderly.[12-13] These studies, however, were unable to quantify the level and define the detailed backgrounds of inappropriate prescribing, as no information on specific diagnoses, patients' characteristics, comorbidity, disease severity, and specific signs and symptoms was available. Guidelines define strict combinations of these aspects in their prescribing advice. The only detailed analyses on over- and underprescribing for RTIs were done by Akkerman *et al.* in 2001, showing that even in a low-prescribing country as the Netherlands,[6] 50% of prescriptions for bronchitis, tonsillitis and sinusitis were not in accordance to the guidelines.[4]

Instead of focussing on a few indications, our study provides an up-to-date and detailed analysis of antibiotic overprescribing for the whole repertoire of respiratory disease in primary care. Using consultations of which all information was available to allow comparison to the prescribing guidelines, we aimed to obtain detailed insight in specific indications and patient-related factors provoking inappropriate prescribing. This overview nails the problems in antibiotic prescribing for respiratory disease and could therefore aid in developing strategies to improve general practitioners' antibiotic prescribing routines.

METHODS

Data

Data for this study were obtained from a detailed registration of 2739 RTI consultations by general practitioners (GPs) from 48 Dutch primary care practices in the winter seasons of 2008 until 2010. GPs were asked to register all patients with an acute RTI, and filled in the registration form during the consultation. The registration forms were specifically designed for this study, and were easy to use to facilitate data collection. They contained all relevant aspects mentioned in the guidelines of the Dutch College of GPs for acute otitis media (AOM), rhinosinusitis, acute sore throat and acute cough (Box 3.1).[14-17] These evidence-based guidelines are updated regularly to include recent literature, and are in line with the NICE guideline "Respiratory tract infections-antibiotic prescribing".[18] The Dutch prescribing recommendations are not based on specific diagnoses (except for pneumonia), but rather on combinations of signs and symptoms, patient characteristics and disease severity. GPs therefore registered: 1) patient characteristics: age, gender, general health state (on a 5-point scale: 1=good general health state to 5=bad general health state), and comorbidity (specifically, the comorbidities mentioned in the guidelines: Box 3.1); 2) medical history: duration of symptoms, fever, number of similar episodes in the past year, illness severity (1=minimally ill to 5=severely ill), first or subsequent consultation for this episode, (non) increasing severity compared to a previous consultation; 3) patient's specific signs and symptoms: location of pain, sputum purulence, dyspnoea, tachypnea; 4) findings of physical examination: inspection of tympanic membranes, throat, tonsils, and auscultation. GPs also registered whether they thought the patient or patient's parent expected antibiotic treatment (1=not expecting to 5=definitely expecting an antibiotic). The diagnostic evaluation was classified according to the International Classification of Primary Care (ICPC).[19] If an antibiotic was prescribed it was recorded with its Anatomical Therapeutical Chemical code (ATC). Finally, additional management -reassurance and/or advice, referral to secondary care, or additional testing- was registered. Consultations with missing data were excluded (n=15).

Study outcomes

Baseline characteristics of 2724 consultations were determined by calculating percentages, means and standard deviations.

To be able to classify the GPs' prescribing decision as correct or incorrect, the recommendations from national guidelines were used as benchmark (Box 3.1).[14-17] Guidelines for AOM and rhinosinusitis also define categories of patients for whom the GP can consider prescribing an antibiotic. By comparing GPs' registrations to the recommendations from the guidelines, we could identify: 1) prescribing when indicated by the guideline (correct); 2) non-prescribing when not indicated (correct); 3) prescribing when not indicated by the guideline (over-prescription); 4) non-prescribing when treatment was actually indicated (under-prescription). The prescribing rates (% of consultations with antibiotic prescription) and overprescribing rates (% of non-indicated prescriptions) were calculated overall and 1) per age category: children (<18 years); adults (18–65 years); and elderly (≥65 years), 2) per general indication: ear; throat; nose/sinuses; and lower respiratory tract, and 3) per individual ICPC code.

Box 3.1 Recommendations for antibiotic prescribing according to the guidelines of the Dutch College of GPs (NHG)

Guideline	Antibiotic treatment	Definition of patient- and disease characteristics	First choice antibiotic
Acute otitis media NHG 2006	Indicated	• Age <6 months • Severe or increasing illness* • Patients at risk for complicated course: anatomy abnormalities, compromised immune system	Amoxicillin
	May be considered	• Age <2 years with bilateral AOM • Otorrhea at first presentation • No improvement after 3 days	
Acute sore throat NHG 2007	Indicated	• Severe illness* with severely inflamed pharynx and fever ≥38.5°C • Peritonsillar infiltrate or abscess • Heavily swollen lymph nodes • Patients at risk for complicated course: history of acute rheumatic fever, compromised immune system	Pheneticillin or phenoxymethyl-penicillin
Rhino sinusitis NHG 2005	May be considered	• Severe illness* • Duration of symptoms >14 days • ≥3 similar episodes in past 12 months • Compromised immune system	Adults: doxycycline or amoxicillin Children: amoxicillin
Acute cough NHG 2003	Indicated	Signs and symptoms indicative for pneumonia: • Severe illness* with localized auscultation abnormalities or tachypnea • Duration of symptoms ≥7 days with fever (≥38°C) ≥7 days Patients at risk for complicated course: • Age <6 months, or >75 years with fever (≥38°C) • Relevant comorbidity: - congenital heart- or lung disease in children - heart failure, severe neurological disease in adults - COPD in combination with fever ≥38°C and disease severity ≥3 and age >50 years	Adults: doxycycline Children: amoxicillin

Antibiotic treatment is not indicated for all other patients.
* Severe illness was defined as 4 or 5 on the item: GP's judgement of illness severity.

Analysis of factors associated with over-prescription

The factors associated with over-prescription were investigated using multivariable logistic regression analysis (backward-stepwise), using determinants with a p-value <0.2 (X^2 test), with a cut-off value of 0.05 for expulsion from the model. In this analysis the over-prescription cases were compared to the correct non-prescriptions. For this analysis, the following characteristics were used: age >18 years, female gender, reduced general health state (3–5), presence of any comorbidity, fever, symptoms duration ≥7 days, more severely ill (3–5), and high patient/parent expectation for an antibiotic (4–5). Age and RTI type stratified regression analyses were performed to determine whether associated factors were similar across these strata. The unadjusted and adjusted odds ratios (OR), with corresponding 95% confidence intervals (CI) and p-values were determined. All statistical analyses were performed with SPSS version 20.0.

RESULTS

Study population: characteristics, antibiotic- and additional management

Characteristics of the 2724 RTI consultations are presented in Table 3.1. Slightly more women consulted the GP and any comorbidity was registered for 26% of all patients. The mean number of symptomatic days prior to the first consultation was eight, and 11 days before a subsequent consultation. The time between onset of symptoms and GP consultation was the longest in adults (8.6 days) and shortest in children (6.5 days). Fever was reported in 31% of all consultations, with the highest incidence in children. Although GPs judged the severity of the RTI as relatively mild, illness severity was rated higher in the elderly. GPs' perception of patients' expectation for an antibiotic was highest in adults. The overall antibiotic prescribing rate was 38% and increased with age. Amoxicillin was most often prescribed for children and doxycycline for adults and the elderly. Macrolides and amoxicillin/clavulanate were prescribed in respectively 12% and 8% of all consultations. Fluoroquinolones were more often prescribed for elderly. Reassurance and/or advice were offered in nearly 80% of all consultations, especially in children. Patients were referred to secondary care in 2.5% of all consultations and underwent additional testing (most often blood tests or X-ray) in 7.9% of all consultations.

Appropriateness of antibiotic prescribing for RTIs

The appropriateness of (non-)antibiotic prescribing is shown in Figure 3.1. Of all consultations in which antibiotics were prescribed, in 36% the antibiotic prescription was indeed indicated, antibiotic prescription could be considered in 18%, and in 46% the antibiotic was not indicated by the guidelines (over-prescription). Of all consultations without antibiotic prescription, 85% indeed did not meet the criteria for prescribing according to the guidelines, 11% included patients for whom the GP could consider an antibiotic, and in 4% a prescription was actually

Table 3.1 Characteristics of the RTI consultations, GPs' antibiotic prescribing and additional management (n=2724)

	Total n=2724	<18 years n=900 (33%)	18–65 years n=1471 (54%)	≥65 years n=353 (13%)
Age, mean (SD)	34.4 (24.9)	5.7 (5.1)	42.3 (12.9)	74.7 (6.7)
Gender male, %	42	49	37	47
Presence of any comorbidity (%)	26.2	11.9	27.4	58
Days prior to consultation				
First consultation, mean (SD)	8 (6)	6.5 (5.6)	8.8 (6.2)	8.6 (5.7)
Subsequent consultation, mean (SD)	11.1 (6.6)	9 (6.2)	12.7 (6.2)	12.2 (7.1)
Presence of fever (%)	31	43	25	23
GPs' judgement of illness severity, %				
1	44	49	44	32
2	34	31	35	38
3	17	15	17	20
4	5	5	4	8
5	0	0	0	2
GPs' perception of patients' expectation for antibiotic, %				
1	10	11	9	10
2	24	27	22	23
3	36	39	35	34
4	19	17	21	20
5	11	6	13	13
ICPC codes, %				
Upper respiratory tract infection	21	23	20	22
Acute cough	17	17	16	20
Acute/chronic sinusitis	12	2	18	9
Acute bronchitis	11	8	11	20
Acute otitis media	8	22	2	0.3
Throat, tonsil symptoms/complaints	7	7	8	4
Pneumonia	5	3	4	10
Acute tonsillitis	4	4	4	1
Asthma	3	4	3	1
COPD (exacerbation)	3	0	3	10
Prescription, %	38	32	39	48
Antibiotic choice, %				
Doxycycline	39	4	52	55
Amoxicillin	30	70	15	15
Pheneticillin/phenoxymethylpenicillin	9	6	12	3
Amoxicillin+clavulanate	8	9	6	11
Macrolides	12	11	13	9
Fluoroquinolones	1	0	1	4
Trimethoprim/sulfamethoxazole	1	0	1	3
Additional management, %				
Reassurance/advice	79	86	78	69
Referral	2.5	3.7	1.7	2.9
Investigation	7.9	4.1	9.6	11

Chapter 3

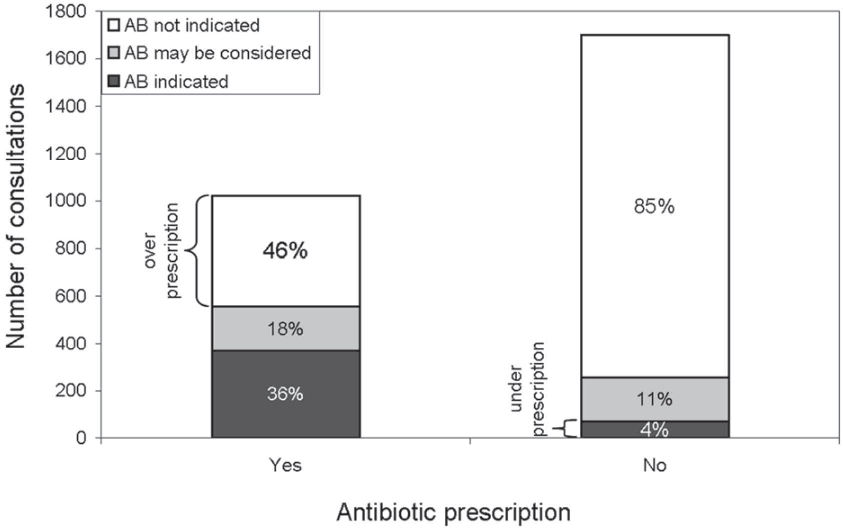

Figure 3.1 Appropriateness of (non-) antibiotic prescribing for RTIs.
GPs' prescribing decision (yes/no) was set against the prescribing recommendations: antibiotic indicated, may be considered, not indicated. Percentages of consultations within the groups are given.

indicated (under-prescription). About half of the patients with AOM and sinusitis for whom the GP could consider prescribing indeed received antibiotics.

Closer examination of the 71 under-prescription cases revealed that 18 patients already received antibiotic treatment in a previous consultation and most of them were now referred to secondary care. Another six patients received additional investigation and two were also referred to secondary care. COPD or heart failure indicated antibiotic treatment for respectively 14 and four patients, but the symptoms were apparently not judged severe enough by the GP to prescribe antibiotics. Finally, 13 patients with sore throat and severely swollen lymph nodes were not prescribed antibiotics.

Prescribing behaviour was analysed separately for ear, throat, nose/sinus and lower respiratory tract indications. Figure 3.2 shows that relative over-prescription was highest in consultations for throat indications – including tonsillitis – (58%), and lowest for ear indications – including AOM – (4%). Absolute over-prescription was highest for lower respiratory tract indications – including bronchitis –, due to a higher number of patients in this group.

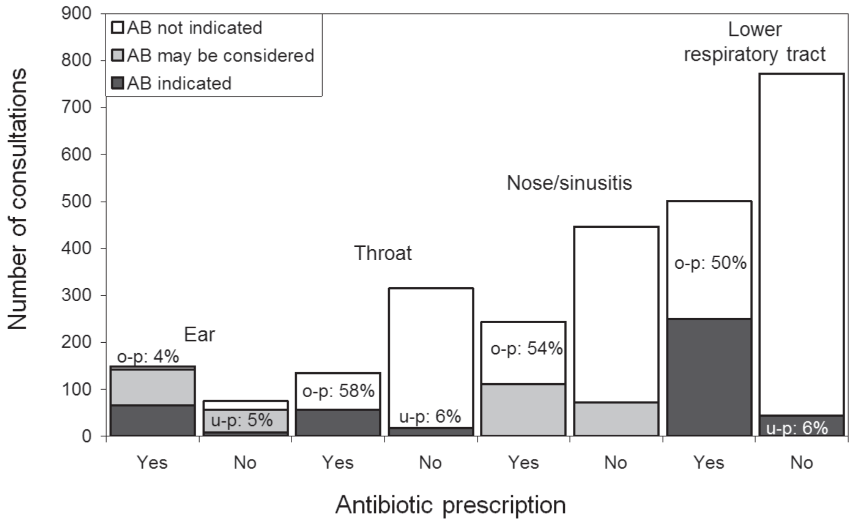

Figure 3.2 Appropriateness of (non-) antibiotic prescribing per RTI group.
GPs' prescribing decision (yes/no) against the guideline recommendations (antibiotic indicated, may be considered, not indicated) was analysed for ear, throat, nose/sinus and lower respiratory tract indications. Percentages of over-prescription (o-p) and under-prescription (u-p) are given. No percentage of under-prescription of nose/sinus infections is given, because the guideline rhinosinusitis does not define a category where an antibiotic is indicated, only for whom the GP can consider prescribing an antibiotic.

Factors associated with antibiotic overprescribing

To obtain insight in factors related to overprescribing, consultations with over-prescription were compared to consultations in which appropriately no antibiotics were prescribed. Patients of whom the GP perceived more pressure to prescribe antibiotics, with more severe illness, fever, >18 years of age, and with a symptom duration ≥7 days were more likely to inappropriately receive antibiotic treatment (Table 3.2).

Because of the association of age with prescribing rates (Table 3.1) and with overprescribing (Table 3.2), GPs' prescribing behaviour was broken down by age, as well as analysed per specific indication. Table 3.3 shows that overprescribing was highest for adults (54%) and lowest for children (32%). Overall, children received 90 inappropriate prescriptions, elderly 73, and adults 304. For throat indications, especially for tonsillitis, both the prescribing rate and overprescribing were highest in the adult population. For lower RTIs, prescribing rates increased with age (due to more comorbidity and pneumonia in the elderly), but over-prescription was again highest for adults (57%), with a percentage of 79% specifically for bronchitis. For the diagnosis COPD (exacerbation) (R95), 58% of the elderly received antibiotic treatment, of which 24% was

Table 3.2 Consultation and patient characteristics associated with antibiotic overprescribing (n=1914)

Characteristic	n	OR	95% CI	p-value	aOR	95% CI	p-value
GPs' perception of high patient expectation for antibiotic	496	5.8	4.6–7.3	<0.001	4.9	3.8–6.3	<0.001
Presence of fever	477	3.0	2.4–3.8	<0.001	3.4	2.5–4.5	<0.001
GPs' judgement of more severe illness	243	4.8	3.6–6.3	<0.001	3.2	2.3–4.5	<0.001
Age >18 years	1317	2.3	1.8–2.9	<0.001	2.3	1.7–3.2	<0.001
Duration of symptoms ≥7 days	1137	1.6	1.3–2.0	<0.001	2.0	1.5–2.6	<0.001
Presence of comorbidity	460	1.7	1.3–2.1	<0.001			
Reduced general health state	142	1.3	0.9–1.9	0.182			
Female gender	1084	1.2	1.0–1.5	0.043			

Characteristics tested for association with antibiotic overprescribing, by univariate (OR) and multivariate logistic regression analysis (adjusted OR), are shown. Numbers of consultations with the specific characteristics included in this analysis are given. Definitions of characteristics are provided in the methods section.

Table 3.3 Prescribing rates and over-prscription per age category, per main and individual indication

		Total	<18 years	18–65 years	≥65 years
All consultations	n	2724	900	1471	353
	Prescription, n (%)	1023 (38%)	286 (32%)	568 (39%)	169 (48%)
	Overprescription, n (%)	467 (46%)	90 (32%)	304 (54%)	73 (43%)
Acute upper RTI*	n	575	209	290	76
	Prescription (%)	12%	9%	13%	18%
	Overprescription (%)	61%	78%	58%	50%
Ear	n	310	251	57	2
	Prescription (%)	46%	49%	37%	100%
	Overprescription (%)	4%	4%	5%	50%
AOM	n	228	196	32	-
	Prescription (%)	59%	59%	59%	-
	Overprescription (%)	4%	4%	5%	-
Nose, sinus	n	691	152	465	74
	Prescription (%)	35%	13%	42%	39%
	Overprescription (%)	54%	74%	52%	59%
Acute, chronic sinusitis	n	319	18	268	33
	Prescription (%)	60%	39%	60%	67%
	Overprescription (%)	50%	57%	49%	55%
Throat	n	450	135	284	31
	Prescription (%)	30%	23%	34%	26%
	Overprescription (%)	58%	52%	60%	50%

Table 3.3 continues on next page

Table 3.3 ***Continued***

		Total	<18 years	18–65 years	≥65 years
Throat, tonsil symptom/ complaint	n	196	66	117	13
	Prescription (%)	11%	5%	13%	23%
	Overprescription (%)	81%	67%	87%	67%
Acute tonsillitis	n	103	35	64	4
	Prescription (%)	78%	69%	83%	75%
	Overprescription (%)	53%	54%	51%	67%
Lower respiratory tract	n	1273	362	665	246
	Prescription (%)	39%	32%	38%	54%
	Overprescription (%)	50%	48%	57%	39%
Acute cough	n	454	149	238	67
	Prescription (%)	14%	15%	11%	21%
	Overprescription (%)	70%	61%	77%	71%
Acute bronchitis	n	302	75	160	67
	Prescription (%)	77%	69%	76%	87%
	Overprescription (%)	69%	62%	79%	57%
Asthma	n	86	34	48	4
	Prescription (%)	20%	12%	27%	0%
	Overprescription (%)	94%	75%	100%	0%
COPD	n	76	-	40	36
	Prescription (%)	50%	-	43%	58%
	Overprescription (%)	21%	-	18%	24%

For all consultations, consultations specific for ear-, nose/sinus-, throat-, lower respiratory tract indications, and for the individual ICPC codes R74, H71, R75, R21/22, R76, R05, R78, R96 and R95 prescribing rates (% of consultations with antibiotic prescription) and over-prescription % (% of non-indicated prescriptions) were determined in total and per age category.
* Consultations for upper RTIs were mirrored to the guideline belonging to the described complaints, most often the rhinosinusitis one, but also to the sore throat, acute cough and AOM guidelines.

inappropriate. Nearly half of the consultations for nose/sinus indications were for sinusitis, predominantly in adult patients, with high prescribing and overprescribing rates. Overall, lower prescribing rates were found for children, e.g. in acute upper respiratory tract infection and throat indications. 59% of children received antibiotics for AOM, with hardly any over-prescription.

Across the four RTI types the same factors were generally associated with over-prescription and with similar strengths. The presence of comorbidity and female gender, however, were also associated with overprescribing for nose/sinus indications (OR: 2; 95% CI: 1.2–3.5, p=0.01 and OR: 1.9; 95% CI: 1.1–3.1, p=0.01, respectively). For lower RTIs, GPs' perception of high patient expectation for an antibiotic seemed even more important in overprescribing (OR: 6.7; 95% CI: 4.7–9.5, p<0.001). Furthermore, across age groups, the same factors associated with overprescribing were found, with some variation in the strength of the association. In children, the presence of fever seemed more strongly associated with overprescribing than the GPs' perception of the parents' expectation for an antibiotic (OR: 4.3; 95% CI: 2.4–7.8, $p<0.001$ and OR: 3.1; 95% CI: 1.8–5.7, $p<0.001$, respectively).

DISCUSSION

Summary

Nearly half of the antibiotic prescriptions for RTIs were not in accordance with guideline recommendations in Dutch primary healthcare. Overprescribing was highest for adults between 18–65 years of age and lowest for children. Relative overprescribing was highest for throat indications and absolute overprescribing was highest for lower RTIs. Furthermore, patients of whom the GP perceived more pressure for an antibiotic treatment, with more severe illness, fever, and with a symptom duration ≥7 days were more likely to receive inappropriate antibiotic treatment. Our results showed that underprescribing was low in Dutch primary care.

Strengths and limitations

The strength of our study is the large sample size of detailed documented consultations, covering the complete range of RTIs. Dutch GPs provide first line care for patients of all ages, and as antibiotics can only be purchased with a prescription, our data provide detailed insight in the quality of community antibiotic use for RTIs. The detailed information enabled us to specifically compare the cases to the guideline recommendations. The forms were designed so they could be easily completed during the consultation, enabling GPs to work according to their everyday routine. We thereby facilitated that the registrations reflect normal RTI management as much as possible.

The audit-based design of this study is a possible limitation, as there was no verification on how GPs filled in their forms. First, we did not provide GPs with additional tools to rate illness severity, but allowed them to base it on their own clinical interpretation of signs, symptoms and patients' appearance. Therefore, this item was a subjective measure depending on personal judgement. Second, it has been described that GPs adjust their diagnostic labelling according to their intention to prescribe antibiotics.[20] If in our study, GPs overestimated disease severity, or labelled bronchitis as pneumonia in order to legitimate their prescription, the results of our study would even underestimate the actual overprescribing. Finally, the form left no room for reporting additional considerations of GPs to validate their decision to prescribe antibiotics or not. GPs' gut feeling, experience, and additional non-registered patient information could have provided valid reasons to deviate from guidelines.

Comparison with existing literature

There are numerous studies reporting that antibiotics are often prescribed for acute infections for which antibiotics are rarely indicated, like laryngitis, bronchitis, tonsillitis, sore throat and sinusitis, and also for other respiratory illness like asthma.[3,4,21] Recent Dutch and Irish studies on antibiotics for RTIs show higher contact-based prescribing for adults and increased prescribing for the elderly.[9,12] However, these studies did not take patient or disease characteristics into account, and therefore could not substantiate the inappropriateness of the observed antibiotic use.

To our knowledge this is the first study quantifying inappropriate prescribing, and authenticating more irrational prescribing for adults with RTIs. This is of particular importance since this age group represents the majority of patients, with higher initial prescribing rates, thereby reinforcing the number of inappropriate prescriptions. As said before, a Dutch study from 2001 showed over-prescription for sinusitis, bronchitis and tonsillitis of 22%, 63% and 71% respectively.[4] A decade later, with a larger focus on guideline implementation and an increased awareness of antibiotic-related problems, we found similar over-prescription for bronchitis, an increased over-prescription for sinusitis, and a decreased over-prescription for tonsillitis. These differences might partly be due to changes in the guidelines, but the overall problem of antibiotic overprescribing is persistent and apparent across the whole range of respiratory disease. For AOM a prescribing rate of 46% was found, with only 4% over-prescription. In 2001, a prescribing rate of 56% was found, with 32% over-prescription.[11] In 2006, the Dutch AOM guideline has been modified by including patient groups for whom the GP can consider prescribing an antibiotic; 41% of patients within this category were treated with antibiotics (Figure 3.2). The overall levels of underprescribing did not change in the last decade. The only exception was the ablated underprescribing for sinusitis in our study, as in the current guideline there is no hard indication for antibiotic treatment anymore.

Over-prescription of antibiotics for RTIs

The association between adult age and the risk to receive inappropriate antibiotic treatment cannot be explained from a medical perspective. We can however speculate about other reasons for more irrational prescribing in adults. This group contains working people, with the longest duration of symptoms prior to their consultation. It can therefore be expected that they do not want to spend more time to wait-and-see, or come in for a second consultation, but immediately expect a solution for their bothersome symptoms. Parents, on the other hand, might be more willing to come back to the GP with their child, in case of increasing worry or prolonged illness and might be more concerned about side-effects of antibiotic treatment. As in many other studies we found that GPs' prescribing behaviour was influenced by their perception of the patient's expectation for antibiotics. Physicians however seem to overestimate the patients' wish for antibiotics, since there is a striking difference between GPs' perception of the patient expectation for antibiotic treatment and the actual patients' wish.[22] Furthermore, it was shown that patients' satisfaction was not primarily related to receiving an antibiotic, but more to reassurance, adequate explanation and physical examination.[22]

Implications for clinical practice

We emphasize that we do not regard all over-prescription cases as wrong treatment decisions, as guidelines are not laws and GPs are not computers. However, we feel that our data advocate that improvements in prescribing behaviour are urgently needed.

We analysed Dutch antibiotic management according to the Dutch guidelines, which are very similar to the NICE guidelines, used in the United Kingdom.[18] These guidelines recommend a non-antibiotic or delayed prescribing strategy for mild, uncomplicated RTIs. Other countries may have slightly different guidelines, for example focusing more on diagnoses, providing a more 'liberal' prescribing advice, or recommending other antibiotics. The general opinion and tendency however is to promote prudent antibiotic use for self-limiting RTIs, stressing the importance of evidence-based, restrictive guidelines. With this in mind, it is quite clear that over-prescription is probably higher than 50% in countries where significantly more antibiotics are used than in the Netherlands.[6] It is important to recognize and tackle this problem worldwide.

Therefore, awareness of GPs as to which patient groups, indications and own interpretations drive overprescribing might help rationalizing antibiotic use for RTIs. It is apparently difficult to change ingrained personal and cultural prescribing habits, against a background of satisfying the patient. It was shown that training in communication skills and selective use of C-reactive protein point-of-care testing might help GPs to change their decision making and management of patients with RTIs.[23] Future improvement programs should focus on skills to efficiently explore patients' concerns and expectations, to reassure patients, and to provide understandable arguments to explain non-prescribing, with specific attention for adult patients.

Acknowledgements

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PART TWO

Intervention to reduce antibiotic prescribing for children

CHAPTER 4

Effectiveness of general practitioners online training and an information booklet for parents on antibiotic prescribing for children with respiratory tract infections in primary care: a cluster randomized controlled trial

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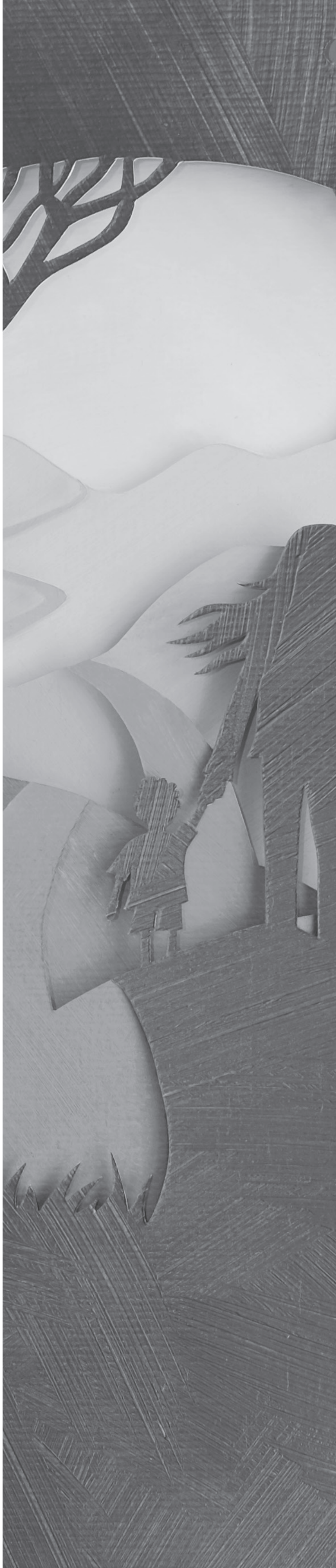

ABSTRACT

Objectives: Antibiotics are too often prescribed in childhood respiratory tract infection (RTI), despite limited effectiveness, potential side-effects, and bacterial resistance. We aimed to reduce antibiotic prescribing for children with RTI by online training for general practitioners (GP) and information for parents.

Methods: A pragmatic cluster randomized, controlled trial in primary care. The intervention consisted of an online training for GPs and an information booklet for parents. The primary outcome was the antibiotic prescription rate for children presenting with RTI symptoms, as registered by GPs. Secondary outcomes were number of reconsultations within the same disease episode, consultations for new episodes, hospital referrals and pharmacy dispensed antibiotic courses for children.

Results: After randomization, GPs of in total 32 general practices registered 1009 consultations. An antibiotic was prescribed in 21% of consultations in the intervention group, compared to 33% in the usual care group, adjusted for baseline prescribing (RR 0.65, 95% CI 0.46–0.91). The probability of reconsulting during the same RTI episode did not differ significantly between the intervention and control groups, nor did the numbers of consultations for new episodes and hospital referrals. In the intervention group antibiotic dispensing was 32 courses per 1000 children/year lower than the control group, adjusted for baseline prescribing (RR 0.78, 95% CI 0.66–0.92). The numbers and proportion of second choice antibiotics did not differ significantly.

Conclusions: Concise, feasible, online GP training, with an information booklet for parents showed a relevant reduction in antibiotic prescribing for children with RTI.

Trial registration: This trial was registered at the Dutch Trial Register (NTR), registration number: NTR4240.

INTRODUCTION

Respiratory tract infections (RTI), including ear-infections, are the most common indication for consulting a general practitioner (GP) during childhood and for prescribing antibiotics.[1,2] Most RTIs are viral and self-limiting, and many high-income countries have guidelines aiming to restrict the use of antibiotics.[3-5] However, even in a low-prescribing country like the Netherlands, one third of antibiotic prescriptions for children are not congruent with guideline recommendations.[6] The main drivers of over-prescription are GPs' interpretation of patient or parent expectations, time pressure, diagnostic and prognostic uncertainty and unfamiliarity with recent guidelines.[7-9] General practice has a major contribution and responsibility towards antibiotic stewardship, since primary care is a driver of antibiotic resistance.[10-12] Efforts to reduce antibiotic prescribing in primary care have been ongoing for decades, most often focusing on antibiotic use in adults, and consisting of a wide range of strategies.[13-16] A different approach might be needed for childhood RTI, because of child-specific indications and risk factors, and communication with parents instead of patients themselves.[17] Multifaceted approaches have been shown to be most effective, however, broad implementation of these interventions is rare because of time and costs.[13,18-20] Online educational programs could be a feasible and cost-effective intervention that could be broadly implemented, updated easily, and ensure more endurable antibiotic stewardship. Little *et al.* showed that such an intervention was effective in improving antibiotic management of adults with lower RTI.[16] In children, only online instruction on the use of information material was studied in the UK, which was effective.[21] In our study we aimed to assess the effects of an online training for GPs and an information booklet for parents on antibiotic prescribing for children with RTI in general practice.

METHODS

Trial design

The RAAK (Rational Antibiotic use Kids) study was a pragmatic, cluster randomized, two-arms, controlled trial with measurements before and after the intervention, to allow for adjustment for baseline antibiotic prescribing (baseline audit). GPs within a general practice influence each other and patients within a practice are often managed by different GPs, therefore, the general practice was the unit of randomization and the unit of analysis to minimize contamination and dilution of the intervention effect. GPs in the control group practised care as usual. We followed the Consolidated Standards of Reporting Trials guidelines, extended for cluster randomized trials.[22]

Ethics approval

This trial was exempted by the Ethics Committee of the University Medical Center Utrecht from obtaining parents' or patients' consent (reference number METC 13-237/C). The trial assigned GPs with the aim to improve their prescribing behaviour according to the national practice guidelines. Children were not the subject of the intervention and were treated according to the guidelines.

General practices and participants

For the baseline audit, GPs were asked to register 40 consecutive consultations of children younger than 18 years with signs and symptoms of RTI (nose, ear, throat and/or lower RTI symptoms), presenting at their general practice during the winter season 2013–2014. GPs registered the following anonymous information on consultation report forms: age, duration of symptoms, fever, most prominent symptoms, findings of physical examination, overall illness severity (1=minimally ill, 5=severely ill), the International Classification of Primary Care code for diagnosis, and whether an antibiotic was prescribed, including which one. General practices were excluded if GPs registered less than 10 patients in total per general practice, since low numbers could result in poor estimations of the baseline antibiotic prescription rates. After randomization and implementation of the intervention, this registration of consultations was repeated in the follow-up audit, during the winter season 2014–2015. In addition, parents were invited to fill in a diary for up to 2 weeks following the index consultation, and give permission to review the child's medical records after 6 months to collect secondary outcomes.

Intervention

The intervention consisted of online training for GPs and a written information booklet for parents. These were adapted from an intervention for adults that was: a) theory-based: the educational content was designed to promote positive expectations and self-confidence in GPs and patients to manage the infection without antibiotics, b) person-based: the content was developed with extensive feedback from GPs and patients to ensure that it addressed their concerns and was persuasive.[23-25] The online training consisted of three parts. The first part was a general background about the relevance of prudent antibiotic use and information about antibiotic-related problems. We presented over-prescription by percentages of prescribed antibiotics, not congruent with guideline recommendations, from a recent Dutch study, to make GPs aware of their responsibility in prudent antibiotic use.[6] The second part informed about the child-specific parts of the four national RTI guidelines of the Dutch College of

GPs,[5] including assessment of disease severity, risk factors, signs and symptoms, when to prescribe antibiotics, and the advised first and second choice antibiotic treatment. This part was summarized in a printable document, which is available as supplementary data at JAC online. The third part focused on training in enhanced communication skills, supported by videos of consultation techniques. The communication skills training was based on the elicit-provide-elicit framework, used in prior antibiotic interventions, adapted to communication with parents.[7,15,26] In summary, the GP first elicits what the parent's main worries and expectations are. Crucially, the GP actively asks how the parent feels about and what he/she expects from antibiotics. Secondly, the GP provides information relevant to the parents' individual understanding and interest, including findings from the medical history and physical examination of the child. Then, the GP elicits the parents' interpretation about what has been said and done, to reach mutual agreement and concludes with concrete safety netting, explaining which specific signs and symptoms require reconsultations.

GPs were invited by email to commence the training. If the training was not started or completed, a weekly reminder email was automatically sent with the request to complete the online training.

The booklet contained the following information in text and pictograms: epidemiology of RTI, their predominant viral cause, self-limiting prognosis, rationale to withhold antibiotics, and antibiotic related problems, including bacterial resistance. Additionally, self-management strategies for their child and signs and symptoms when to consult the GP were explained.

Outcomes, sample size, and randomization

The primary outcome was the antibiotic prescription rate per general practice in the follow-up audit, as documented on the consultation report forms filled in by the GPs.[16] The following secondary outcomes were assessed from the patients' medical records: number of reconsultations during the same disease episode, number of consultations for new RTI episodes and the number of hospital referrals during a follow-up of six months. Total and types of dispensed antibiotic courses for all children under 18 years were collected via the Dutch Foundation for Pharmaceutical Statistics.[27] Affiliated pharmacies of the participating general practices (n=68) were asked for permission to collect all dispensed antibiotics that resulted from prescribing by the participating GPs of that practice. Numbers of dispensed systemic antibiotics (ATC-code J01) were collected via an online module for the complete years prior to and after introducing the online training. Total numbers of antibiotics mainly used for RTIs were: tetracyclines (J01AA), amoxicillin (J01CA), pheneticillin (J01CE), amoxicillin/clavulanate (J01CR) and macrolides (J01FA). Amoxicillin (J01CA) and pheneticillin (J01CE) were considered as first choice antibiotics, the others as second choice. The numbers of registered children in the practice for the corresponding year were collected. The median duration of the time being logged-in and the short online evaluation of the GP training were assessed.

We calculated that we would need a minimum of 157 consultations per arm, to be able to detect an absolute difference of 15% in prescribing rate (42% and 27%), with 80% power and a 5% significance level. To adjust for clustering of the effect within general practices, we assumed an intra-cluster coefficient of 0.07 and a cluster size of 40, requiring a total of 1171 consultations in both arms.[28] In order to achieve this we set out to ask 30 practices to register 40 consultations each. Simple random allocation was performed by a computer generated list on general practice level.

Data analysis

The primary analysis was according to the principle of intention-to-treat and assessed the intervention effect on antibiotic prescribing to children as registered by the GPs in the follow-up audit. We aggregated the data to the cluster level and used a generalized linear model for Poisson distributed count outcomes, controlled for overdispersion.[29] We calculated Rate Ratios (RR) with corresponding 95% Confidence Intervals (CI) and adjusted for baseline prescription rates per general practice, as assessed in the year before the intervention. We chose not to adjust for signs/symptoms, or diagnosis, because the interpretation, judgment and use of these variables were part of the educational aspect of the online training.[30] The secondary outcomes were also aggregated to the cluster level and analysed similarly as the primary outcome. Pharmacy antibiotic dispensing data were retrieved per practice. The numbers of total dispensed antibiotics were analysed using a generalized linear model and controlled for the numbers of dispensed antibiotics in the year preceding the intervention, and the numbers of children in the practice. Prescription of second choice antibiotics was analysed related to the total number of children and to the total number of dispensed antibiotics and was controlled for baseline prescribing. Analyses were done in SPSS version 21.

RESULTS

Practice flow

Before randomization, 38 practices agreed to participate (Figure 4.1). Preceding the intervention, three practices were excluded, as they did not register any consultation during the baseline

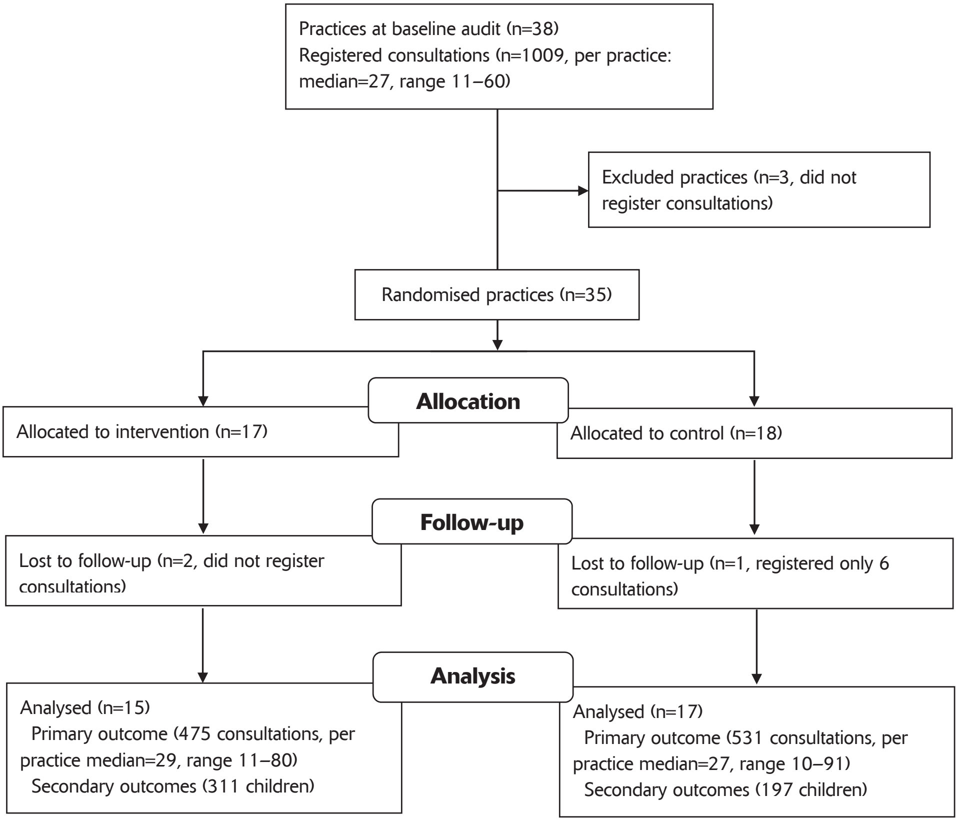

Figure 4.1 Trial profile, practice flow.

audit. Finally, 35 practices were randomized to the control or intervention arm. Three out of 35 randomized practices were excluded during the follow-up audit. They had not registered enough consultations, because of sick leave of participating GPs. Therefore, pharmacy data of these practices could not be obtained reliably. One single-handed GP was excluded for the pharmacy data, since his practice moved during the study period to another part of the city. Practices of the intervention and control group were comparable with respect to their total list size and numbers of listed children (Table 4.1).

Registration of consultations

During the baseline audit 1009 consultations of children with symptoms of RTI were registered by 75 GPs from 35 general practices (Figure 4.1). The mean antibiotic prescription rate from

Table 4.1 Characteristics of general practices allocated to the intervention and control group

	Intervention (n=15)	Control (n=17)
Median list size total (IQR)	2980 (2491–4850)	3275 (2589–3589)
Median list size children <18 years (IQR)	604 (518–999)	664 (421–810)
Participating GPs	40	35
Male/female GPs	46%/54%	43%/57%
Mean age GP (SD)	46 (11)	45.3 (9.5)

IQR, interquartile range.

this baseline audit was 29.6% (35.7%, SD 4.8 in the control group versus 24.2%, SD 4.3 in the intervention group). The follow-up audit included 1009 consultations in total, 532 from control and 477 from intervention practices. Consultations were comparable between the intervention and control group with respect to childrens' age, duration of illness before consultation, illness severity and presentation with fever (Table 4.2). Numbers of registered symptoms appeared to be higher in the intervention group as compared to the control group, especially for earache (37.1% versus 29.3%).

Intervention

The training was completed by all 40 GPs of the intervention group. Their median time logged-in was one hour and 18 minutes. Based on GPs' evaluation, the first and second part of the training,

Table 4.2 Characteristics of consultations of the follow-up audit after allocation to the intervention or control group

	Intervention (n=477)	Control (n=532)
Mean age, years (SD)	4.7 (4.4)	4.4 (4.1)
Median duration of illness before consultation, days (IQR)	5 (3–14)	5 (3–10)
Mean GPs' perception of illness severity, 1=not ill, 5=severely ill (SD)	1.6 (0.8)	1.9 (1.0)
Fever (%)	257 (53.9)	278 (52.3)
Earache (%)	177 (37.1)	156 (29.3)
Runny nose (%)	387 (81.1)	375 (70.5)
Sore throat (%)	128 (26.8)	121 (22.7)
Cough (%)	358 (75.1)	381 (71.6)

IQR, interquartile range.

with the general background and information of the four guidelines, were valued highest, with a mean score of 4.5 (1=low value, 5=high value); the third part about communication skills scored a mean of 4.2.

Numbers analysed

Analysis of the primary outcome was performed on 475 consultations in the 15 practices allocated to the intervention, and 531 consultations in 17 practices allocated to usual care. Three consultations lacked the primary outcome and were excluded from analyses. In 535 (53%) consultations of children, the parent gave permission to anonymously collect secondary outcomes after six months from the child's medical record and was willing to fill in a diary. These consultations showed no relevant differences compared to consultations in which parents were not willing to participate in the study (data not shown). Secondary outcomes of 508 children were available for analyses, 27 cases were lost to follow-up.

Outcomes

In 21.4% of consultations an antibiotic was prescribed in intervention practices, compared to 33.2% in the control group. The rate ratio after adjustment for baseline prescription was 0.65 (95% CI 0.46–0.91, Table 4.3). The intra-cluster coefficient was 0.09. The mean number of reconsultations per 100 children within the same disease episode was lower in the intervention group (42), as compared to the control group (64), but did not differ significantly (RR 0.66, Table 4.4). The probability of consultation for new RTI within six months did not differ significantly (RR 1.06), nor of hospital referrals (RR 0.66). In general practices exposed to the intervention antibiotic dispensing was 32 courses per 1000 children/year lower than the control group, based on the full year's pharmacy data (RR 0.78, 95% CI 0.66–0.92, Table 4.5). Adjusted for the year preceding the intervention, the number of dispensed antibiotics was 114 per 1000 children in the intervention group and 146 per 1000 children in the control group. The

Table 4.3 Effectiveness of the intervention on antibiotic prescription rates

	Intervention (n=475)	Control (n=532)	RR (95% CI)
Crude antibiotic prescription rate (95% CI)	20% (15.4–26)	36.9% (30.8–44.3)	0.54 (0.4–0.74)*
Adjusted antibiotic prescription rate** (95% CI)	21.4% (16.6–27.6)	33.2% (27–40.8)	0.65 (0.46–0.91)*

Data were retrieved from GP-registered consultations. * P<0.05. ** Adjusted for baseline prescription.

number of dispensed second choice antibiotics in the intervention group was lower (39.9/1000 children) as compared to the control group (49.2/1000 children), however, this difference was not significant. The percentage of second choice antibiotics neither differed between the control and intervention group (34.1%, versus 34.4%), relative to total antibiotics.

Table 4.4 Effectiveness of the intervention on reconsultation, consultations for new RTI episodes and hospital referrals

	Intervention (n=311)	Control (n=197)	RR (95% CI)
Reconsultations			
Absolute number	132	126	
Mean number/100 children (95% CI)	42 (29–63)	64 (43–96)	0.66 (0.38–1.16)
New RTI consultations			
Absolute number	252	150	
Mean number/100 children (95% CI)	81 (64–103)	76 (56–104)	1.06 (0.72–1.58)
Hospital referrals			
Absolute number	24	23	
Mean number/100 children (95% CI)	8 (5–13)	12 (7–20)	0.66 (0.31–1.40)

Data were retrieved from the child's medical registries.

Table 4.5 Effectiveness of the intervention on total and second choice yearly dispensed antibiotics

		Intervention	Control	RR (95% CI)
Total antibiotics/1000 children/year (95% CI)	Crude	110 (89.1–136)	161 (137–189)	0.68 (0.52–0.89)*
	Adjusted**	114 (100–129)	146 (132–162)	0.78 (0.66–0.92)*
Number of second choice antibiotics/1000 children/year (95% CI)	Crude	39.3 (29.1–53.1)	54.8 (43.3–69.4)	0.72 (0.49–1.05)
	Adjusted**	39.9 (32.6–48.7)	49.2 (41.7–58.1)	0.81 (0.63–1.05)
Percentage of second choice antibiotics/total antibiotics (95% CI)	Crude	35.7% (29–44)	34% (28.9–40)	1.05 (0.81–1.37)
	Adjusted**	34.1% (29.6–39.3)	34.4% (30.8–38.3)	0.99 (0.83–1.19)

Data were retrieved from a full year's pharmacy dispensing data. * P<0.05. ** Adjusted for baseline prescription.

DISCUSSION

Online training of GPs and information booklets for parents resulted in fewer antibiotic prescriptions, measured by GPs' registrations of consultations, as well as by data of total yearly antibiotic dispensing to children with RTIs. The intervention did not result in a significant reduction in second choice antibiotics, reconsultations in the same disease episode, consultations for new RTI episodes, or hospital referrals.

Outcomes of previous studies vary depending on setting, study population, and type of intervention.[13,18-20,31,32] Relatively intensive interventions targeting both parents and clinicians are considered to be most effective, and decrease antibiotic prescribing rates by 6–21%.[19] Focusing on GP-parent communication, supported by written information, also showed to be important.[14,18,19,31-33] In our study, the prescription rates adjusted for baseline prescription differed 11.8%. This effect was striking, particularly as our baseline prescription rates was already low in comparison with other countries. Previous studies often used complex and time consuming interventions, whereas our online training was feasible, concise and without personal (academic) involvement and showed a long-term effect on antibiotic prescribing. Online GP training to reduce antibiotic prescribing for children has not been used yet in primary care, except for one study in the UK.[21] This study primarily focused on consulting behaviour, using an information booklet endorsed by the GP; the online training was about how to use the booklet and did not include guideline education and background of antibiotic-related problems.[21]

Strengths and limitations

This cluster randomized controlled trial showed a convincing effect on antibiotic prescribing using GPs' registrations and pharmacy dispensing data during a full year after the intervention. In the context of continuously improving RTI treatment in children, our study aimed to make a simple, concise and feasible intervention, which was valued by GPs and parents.[34] The pragmatic study design did not interfere with daily practice and did not require large time investments or organizational adaptations. Our focus on the total childhood population with broad eligibility criteria, and without selection of subgroups, or controlling for patient characteristics, makes our results reliable and generalizable. By measuring both antibiotic prescribing outcomes in the year preceding the intervention, we were able to control for baseline prescribing, making our results more robust, since the number of clusters was not large.[35,36] Our study also has potential limitations. First, the pharmacy data could include GPs in the intervention group who did not receive the online training, since some GPs who were not involved in the trial, for example temporary locums or GPs in training, prescribed antibiotics on behalf of participating

GPs. This may have diluted the real, potentially higher, intervention effect. This change of employees in the participating practices was increasing over time, and prevented us from reliably measuring the intervention effect in the second year. Secondly, our study was not powered to study whether severe complications could occur more frequently due to reduced antibiotic prescriptions, nevertheless there was no evidence suggesting an adverse effect of the intervention. Our intervention taught GPs according to the evidence-based guidelines.[5] We therefore expect no risk of inducing under-prescription. Another Dutch intervention, aiming to reduce antibiotic prescribing showed that both over- and underprescribing improved.[27] And, a substantial reduction in antibiotic prescriptions was shown to be safe in a recent population-based study.[37] Finally, there is a non-significant difference in reconsultation in the intervention and control group, with large within group variation. Many parents of registered children were not invited to participate due to time constraints during the consultation and only half of the invited parents were willing to keep a diary and gave permission to assess the medical records of their child.

Conclusion

The intervention was effective in reducing antibiotic prescribing, and was feasible and acceptable.[34] Given the minimal training time and the clear impact on antibiotic prescriptions it is likely to be cost-effective. To implement this intervention at a national level some aspects could be further developed, e.g. considering presenting the information booklet electronically, stimulating informal learning activities including self-reflection, and potential linkage to a structural antibiotic stewardship program.[34,38]

Acknowledgements

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PART THREE

Evaluation of the intervention

CHAPTER 5

Cost-effectiveness analysis of a general practitioner- and parent-directed intervention to reduce antibiotic prescribing for children with respiratory tract infections in primary care

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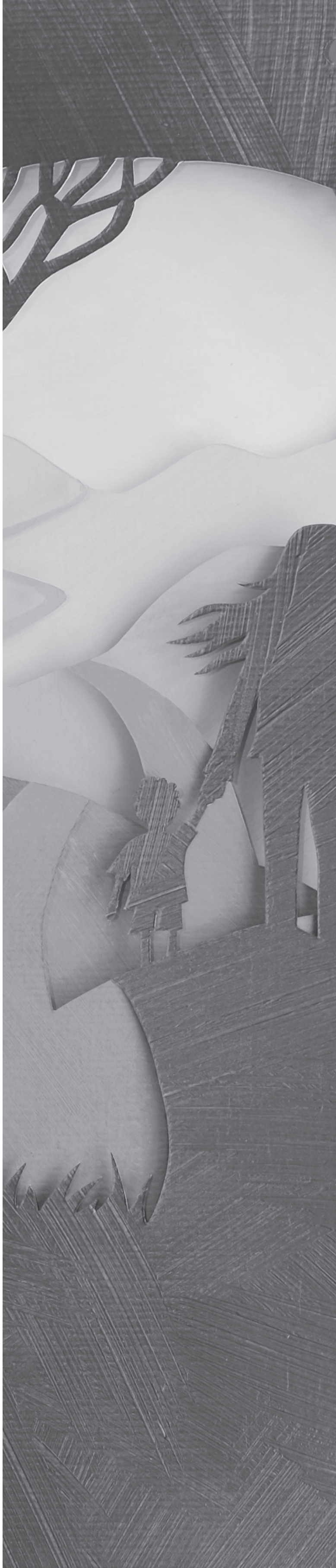

ABSTRACT

Objectives: We evaluated costs and effects of the RAAK intervention, GP online training and information booklets for parents, aiming to reduce antibiotic prescribing for children with respiratory tract infection (RTI).

Methods: A trial-based cost-effectiveness analysis from a societal perspective was conducted. We included children consulting the GP with RTI symptoms of whom parents kept a two-week (cost) diary. The cost difference between the intervention and usual care group per percentage decrease in antibiotic prescribing was calculated, resulting in an incremental cost-effectiveness ratio (ICER). Bootstrapping was used to assess the uncertainty surrounding the outcomes. A scenario analysis was performed analyzing costs from a healthcare perspective.

Results: Costs and effects of 153 children in the intervention and 107 in the usual care group were available for analysis. Antibiotic prescribing in the intervention group was 12% lower than in the usual care group and the difference in costs was €10.27 per child. This resulted in an ICER of €0.85 per percentage decrease in antibiotic prescribing. The bootstrap analysis showed that the probability that the intervention was effective but more expensive was 53% and that the intervention was effective, but cost-saving was 41%. The analysis from a healthcare perspective resulted in a decrease of the antibiotic prescribing rate of 12%, with mean cost-savings of €-8.98, implying that the intervention was more effective, against lower costs.

Conclusion: This online training for GPs and information booklet for parents resulted in a decrease in antibiotic prescribing in children with RTI at very low costs and should therefore be considered for implementation in primary care.

INTRODUCTION

Childhood infectious diseases result in over 1000 GP consultations and 262 antibiotic prescriptions per 1000 children annually in the Netherlands.[1] Most of these contacts concern respiratory tract infections (RTI). RTIs are often viral and self-limiting, and the limited effectiveness of antibiotics needs to be weighed against side effects and bacterial resistance.[2-4] Nevertheless, antibiotics are often prescribed when they are generally considered inappropriate, for diagnoses like upper RTI and bronchitis.[1,5]

General practice has a major responsibility towards prudent antibiotic use, and efforts to reduce antibiotic prescribing have been ongoing.[2,6,7] Multi-faceted interventions targeting GPs and patients, using combinations of education, audit-feedback, and communication skills training, with involvement of experts, or point-of-care testing are considered to be most effective.[8-12] Broad implementation of such interventions is, however, rare because of complexity, time investments and costs. In this respect, online training has interesting potential because of lower costs and easy implementation. Recently, we have assessed the effectiveness of GP online training in combination with information booklets for parents in the RAAK cluster randomised controlled trial (RCT), aiming to reduce antibiotic prescribing for children with RTI.[13] The simple, concise and feasible intervention was valued by GPs and parents and showed a significant reduction in antibiotic prescribing.[13-15]

Evaluation of costs of proven effective interventions to reduce antibiotic prescribing are limited, and not yet performed for children.[16-18] There is a need for cost-effectiveness analysis to identify the most cost-effective strategies to reduce antibiotic use. We therefore performed a trial-based cost-effectiveness analysis to evaluate the effect, GP antibiotic prescribing, and costs of the RAAK intervention. This evaluation furthermore includes the broad and yet largely unknown impact of RTI in children on healthcare- and society-related costs, such as over the counter (OTC) medication and productivity loss of parents.

METHODS

Study design

This trial-based cost-effectiveness analysis was conducted alongside the cluster two-arms RCT, with a measurement before and after the intervention to allow for adjustment for antibiotic prescribing at baseline. Full details on this RCT are described elsewhere.[13] In brief, general practices were allocated to usual care or the intervention group. The intervention consisted of an online training for GPs and a written information booklet for parents. For the assessment of baseline antibiotic prescribing, GPs registered the management of consultations of children younger than 18 years with signs and symptoms of a RTI (nose, ear, throat and/or lower RTI symptoms), presenting at their practice during the winter season 2013–2014, which was repeated after the intervention during the winter season of 2014–2015. In addition, parents were invited to keep a diary including healthcare use and other related costs, such as for OTC medication, additional childcare and their loss of work productivity, for up to two weeks following the index consultation, or until symptoms resolved.

Intervention

The online training for GPs consisted of three parts: 1) general background about the relevance of prudent antibiotic use and information about antibiotic-related problems, 2) child-specific information from the four national respiratory tract guidelines of the Dutch College of GPs[19], including assessment of disease severity, risk factors, signs and symptoms and the first and second choice antibiotic treatment advised, and 3) training in enhanced communication skills supported by videos of consultation techniques. The information booklet for parents contained the following information using text and pictograms: epidemiology of RTIs, their predominantly viral cause, self-limiting prognosis, rationale to withhold antibiotics, and antibiotic-related problems, including bacterial resistance. Additionally, the booklet explained about self-management strategies for their child, and signs and symptoms when to consult the GP.

Population

The patient population consisted of children younger than 18 years from 32 general practices in different regions in the Netherlands, who consulted their GP with symptoms of a RTI and of whom parents were willing to keep a diary. Parents kept a diary till symptoms resolved, with a maximum of 14 days to minimize the burden of trial participation, and as a review showed that in 90% of the children RTI symptoms resolve within 14 days, except for cough.[20] Children with returned diaries were included in the cost-effectiveness analysis.

Clinical outcome

The clinical outcome in this cost-effectiveness analysis was the antibiotic prescribing rate: prescribing at the index consultation and during the two-weeks follow-up. Prescribing rates of the intervention and usual groups were adjusted for baseline prescribing using the prescribing rate of the year before the intervention for both arms.

Resource use and costs

The costs for intervention development and GPs' time investment to follow the online training were upraised to patient level and distributed over the number of children who potentially could have consulted with RTI symptoms during one year, and therefore could have been targeted by the intervention. Based on routine care data, 500 RTI consultations take place per 1000 children per year.[1] Printing costs of the information booklets were calculated per patient. The costs for development of the online training were distributed over five years, since such an intervention is expected to be revised once every five years, first, to refresh knowledge, and second, as Dutch guidelines are generally revised about every 5–10 years.[19]

Costs related to the RTI were calculated from a societal perspective. Therefore, in the cost diary parents were asked to register all healthcare resources used from the healthcare system (general practice, out-of-hours care, emergency department and pharmacy), as well as healthcare resources from outside the healthcare system (OTC medication), and indirectly related costs (productivity losses of parents and additional childcare, transportation costs to healthcare facilities). We calculated costs of contacts with healthcare providers, including telephone contacts, consultations and/or home-visits of the GP, out-of-hours service, or emergency department, and prescribed medication using unit resource prices.[21,22] The costs of the index consultation were not considered as these concerned all patients in both groups. Doses of prescribed and OTC medication were calculated using mean weights of children based on their age.[23] Costs of medication were calculated using these doses and the pharmacy dispensing fee was added for prescribed medication.[21,24]

Costs for transportation to healthcare facilities, and additional childcare related to the RTI episode were directly registered in the diaries. Productivity losses were obtained from the parents' registered hours of work lost due to absence, and/or non-productivity due to decreased concentration, and corresponding costs were calculated using productivity costs of the Dutch guideline for health economic research.[21]

If parents stopped filling out the diary before the end of the two-weeks follow-up it was assumed that illness had resolved and consequently, that (OTC)-medication was no longer given, healthcare use and parents' absence from work stopped. Non-completed values for these variables were considered as not applicable. After two weeks the RTI episode was assumed to be over and no further health effects or costs related to the intervention were incorporated.

Analysis

In order to assess selection bias by incomplete follow-up, we first compared the index consultation of the included group of children with returned diaries to those of whom no diary was available from the complete RCT data with respect to mean age, illness severity, fever and antibiotic prescription, based on GPs' registration.

We performed a trial-based cost-effectiveness analysis from a societal perspective with a time horizon of two weeks after the index consultation. Mean prescribing rates, and costs, including 2.5–97.5% percentiles were used to compare the usual care and intervention groups. We calculated an incremental cost-effectiveness ratio (ICER), presenting the costs per percentage decrease in antibiotic prescribing. To assess the uncertainty surrounding the prescribing rate and costs, bootstrapping was performed with 5,000 replications using Excel. An incremental cost-effectiveness plane visualized the effects and costs and their surrounding uncertainty.

We additionally performed a scenario analysis from a strict healthcare perspective, hence omitting productivity losses, OTC medication, transportation costs and childcare. This allows for comparison with other studies in which a societal perspective was often not included.

RESULTS

Patients

In 535 consultations of children presenting with RTI parents agreed to fill out the diary. In total 263 (49%) diaries were returned. Children of whom diaries were available were significantly younger (mean age of 3.6) compared to GP-registered consultations of which no diary was available (4.9; $p<0.05$) and had more often fever (64% vs 49%, $p<0.05$), but did not significantly differ with respect to illness severity and antibiotic prescribing rate. Three cases lacked the prescription outcome and were excluded from analyses. This resulted in 153 children from 15 practices in the intervention group, and 107 from 15 practices in the usual care group available for analyses. Characteristics of children in the intervention and usual care groups are described in Table 5.1. The mean age in the intervention group was 3.5 versus 3.9 in the usual care group. The median duration of symptoms before consulting the GP was 5 days in both groups. The numbers of children with symptoms of cough, fever, and the mean illness severity registered by the GP were comparable (Table 5.1).

Table 5.1 Child characteristics per trial arm

	Intervention (n=153)	Usual care (n=107)
Mean age, years (SD)	3.5 (3.1)	3.9 (4)
Median pre-consultation illness duration, days (IQR)	5 (3–8)	5 (3–7)
Number of patients with symptoms of cough (%)	120 (78.4)	86 (80.3)
Number of patients with presence of fever (%)	97 (63)	70 (64.8)
Illness severity (1=not ill–5=severely ill), mean (SD)	1.7 (0.8)	1.8 (0.8)

Consultation characteristics registered by the GPs. SD=standard deviation, IQR=interquartile range.

Clinical outcome

After the intervention antibiotics were prescribed to 20% of the children in the intervention group and to 40% in the usual care group at the index consultation. Taking prescriptions during the two weeks follow-up into account, respectively 25% and 50% of the children received an antibiotic (Table 5.2). The mean antibiotic prescribing rate from these practices in the year preceding the intervention was 29% (25% in the intervention group and 35% in the usual care group). Adjusted for baseline prescribing, the antibiotic prescribing rate was 29% in the intervention group and 42% in the usual care group.

Resource use and costs

Resource use is shown in Table 5.2 and costs for these resources in Table 5.3. The mean number of GP reconsultation was lower in the intervention group (0.59) compared to the usual care group (0.7), including telephone consultations and home-visits. GP contact at the out-of-hours care was 0.03 in the intervention group and 0.19 in the usual care usual care group. The number of contacts at the emergency department was low in both groups (0.02 in the intervention and 0.03 in the usual care group). Parents indicated to have lost work hours due to absence and non-productivity while being at work, with on average 5 hours in the usual care and 4.6 hours in the intervention group. OTC medication (paracetamol, NSAID, cough syrup, nasal spray, eardrops, cough drops) was frequently given in the first week, to 73% of the children in the intervention and 67% of the children in the usual care group. Most common was the use of paracetamol, which was used by half of the children in both groups. Use of any OTC medication in the second week was more frequent in children in the intervention group (30%) as compared to the usual care group (12%). The average total costs per child were €217.95 in the intervention and €207.68 in the usual care group (Table

Table 5.2 Average resource use per patient in the intervention and usual care group

		Intervention	Usual care
Healthcare contacts	GPs assistant*	0.48	0.49
	GP reconsultation*	0.59	0.7
	Out-of-hours care*	0.03	0.19
	Emergency department~	0.02	0.03
	Total	1.12	1.41
Antibiotic prescribing**	Prescription at index consultation	0.2	0.4
	Prescription week 1	0.04	0.09
	Prescription week 2	0.02	0
	Total	0.25	0.50
Societal	Work absence parents (hours)	4.5	3.1
	Non-productivity (hours)	0.5	1.5
	Total	5	4.6
OTC medication***	Use of OTC medication (total) week 1	0.73	0.67
	Use of paracetamol	0.5	0.52
	Use of OTC medication (total) week 2	0.3	0.12
	Use of paracetamol	0.16	0.08

Mean number per patient. * Including telephone consultations and home visits. ~ Including telephone consultations and hospital admission. ** Not adjusted for baseline prescribing. *** Proportion of children receiving any OTC medication.

5.3). Of notice is that productivity loss of parents accounted for the highest costs, €172.04 in the intervention and €156.48 in the usual care group, followed by costs for general practice care. Based on the median duration of being logged-in, the GP's time investment to follow the online training was 1h18min. Taking into account the GP's hourly wages, the total costs of the intervention were €2.90 per child.

Cost-effectiveness

Following from the bootstrap analysis, antibiotic prescribing in the intervention group was on average 12% lower as compared to the usual care group, and the difference in total costs per child was on average €10.27. This resulted in an ICER of €0.85 per percentage decrease in antibiotic prescribing, as shown in Table 5.4. The incremental cost-effectiveness plane, showing the difference in costs and antibiotic prescribing rate between the intervention and usual care group resulting from the bootstrap analysis is shown in Figure 5.1. The probability that the intervention was effective but more expensive was 53.3% (north east quadrant) and that the intervention was more effective and less expensive was 41.4% (south east quadrant). The probability that the intervention was less effective (west) had a probability of 5.3%.

Table 5.3 Mean costs per patient in the intervention and control group

		Intervention	Usual care
Healthcare contacts (€)	General practice	20.98	23.95
	Out-of-hours care	1.2	6.46
	Emergency department	7.55	7.32
Medication (€)	Prescribed	4.77	8.81
	Over the counter	5.42	3.84
Non-medical costs (€)	Work absence and productivity loss	172.04	156.48
	Additional child care	1.63	0.48
	Transportation	0.45	0.6
Intervention (€)	Development online training	0.36	-
	Time investment GPs	0.75	
	Printing information booklet	1.79	-
	Subtotal intervention	2.9	-
Total (€)		217.95	207.68

Table 5.4 Incremental cost, effects and cost-effectiveness, after bootstrapping

		Intervention	Usual care
Effects	Mean antibiotic prescribing, adjusted for baseline prescribing (2.5–97.5 percentile)	0.30 (0.20–0.39)	0.42 (0.31–0.52)
	Decrease in antibiotic prescribing compared to usual care (2.5–97.5 percentile)	0.12 (-0.03–0.26)	
Costs	Mean costs (2.5–97.5 percentile))	€217.95 (150–301)	€207.68 (140–284)
	Difference in total costs compared to usual care (2.5–97.5 percentile)	€10.27 (-90.56–113.37)	
Cost-effectiveness	ICER; costs per % decrease in antibiotic prescribing compared to usual care	0.85	

In the scenario analysis, including only costs from a healthcare perspective, the mean costs in the intervention group were €37 and €47 in the usual care group, resulting in a decrease of the antibiotic prescribing rate of 12% at lower costs of €-8.98. The bootstrap analysis showed a probability of 76.7% that the intervention was more effective and less expensive (south east quadrant), and a probability of 18.4% that the intervention was more effective and more expensive (north east quadrant). The probability that the intervention was less effective (west) had a probability of 5% (slight difference with the 5.3% incremental effect because of bootstrap sampling).

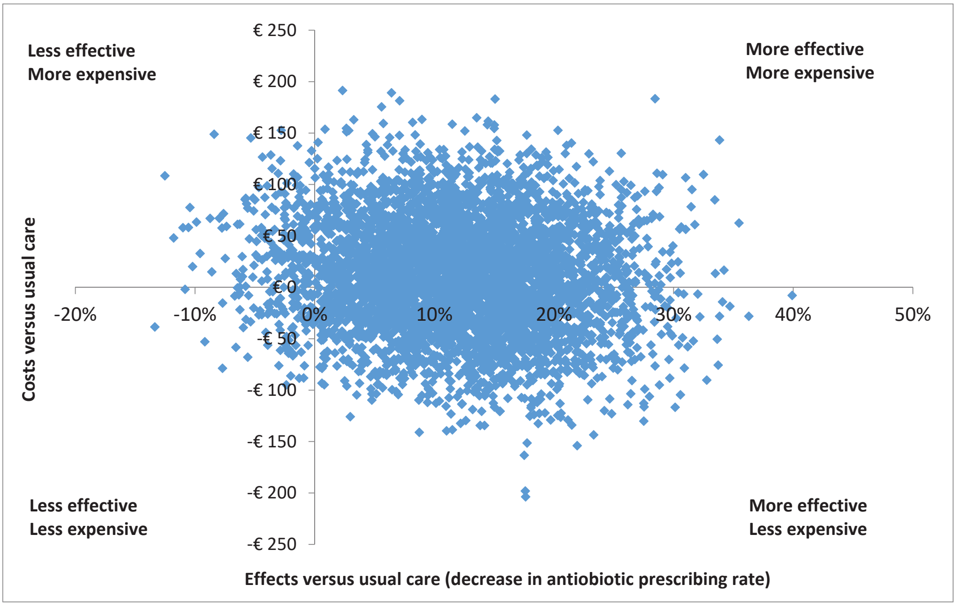

Figure 5.1 Incremental cost-effectiveness plane of RAAK intervention versus usual care.

DISCUSSION

This analysis showed that the RAAK intervention, online training for GPs in combination with information booklets for parents, is effective at very low costs in reducing antibiotic prescribing for children with RTI in primary care. From a societal perspective, incremental costs were €10.27 euro (€217.95 versus €207.68), with incremental effects of 12% (30% versus 42%) resulting in an ICER of €0.85 per percentage decrease in antibiotic prescribing. The intervention was dominant (more effective and less expensive) compared to usual care when analyzed from a healthcare perspective.

Numerous trials have described clinical effects of interventions aiming to improve antibiotic use, health economic evaluations are however very limited, especially in primary care, and were not yet performed for children.[17,25] Cals *et al.* evaluated the cost effectiveness of C-reactive protein point-of-care testing and communication skills training in adults with lower RTI from a healthcare perspective.[26] The different strategies showed a decrease in antibiotic prescribing ranging from 28% to 44%.[26] Using only healthcare-related costs, the differences in costs of the interventions in this study ranged from -€10.35 for the communication training to €1.82 for the C-reactive protein test. In our scenario analysis, only using a healthcare perspective, the cost saving was -€8.98. As ICERs from the RAAK intervention and the communication skills training of the IMPAC3T trial were dominant, these strategies are cost-effective. The cost difference between our analyses using the societal and healthcare perspectives mainly results from omitting productivity loss of parents.

The heterogeneity in setting, intervention and outcome of studies aiming to improve antibiotic prescribing is complicating the comparison of studies.[17] Quality adjusted life years are often used in health economic evaluations to measure different health effects, but are meaningless for the typically acute, short and mild course of RTIs and not in relation to our objective, which is to reduce antibiotic prescribing instead of a gain in individual health.[25] Therefore, we expressed our outcome as costs per percentage decrease in antibiotic prescribing, which might be difficult to interpret. We can provide an estimation of the costs per prevented antibiotic course by extrapolating the incremental costs from this cost-effectiveness analysis and using the decrease in antibiotic dispensing by pharmacies per 1000 children/year as incremental effects, which was a secondary outcome of the trial.[13] The intervention reduced antibiotic dispensing by 32 courses/1000 children/year,[13] which with the costs difference of €10.27 would result in approximately €0.32 per prevented antibiotic course.

A reduction in antibiotic use is of high relevance to tackle bacterial resistance and prevents costs related to this.[2] In our health cost-effectiveness analysis we did not incorporate the financial or patient-related benefits of reducing antimicrobial resistance, due to uncertainty of available data.[27] However, by ignoring the expected benefits of reducing bacterial resistance our results could underestimate the possible cost savings of reducing antibiotic use and therefore we might have presented a conservative ICER.[28]

A main strength is the extensiveness of our cost-effectiveness analysis including data from a societal perspective from RCT data.[29] It considered all relevant medical and non-medical cost data collected by prospectively collected diaries, which limited the chance of recall bias.[30] A limitation of our study is that the effect could only be measured during one winter season. The effect of the intervention may dilute over time; training needs repetition to ensure ongoing effectiveness. However, complete development costs and effect of the online training were spread over five years, which is conservative, since costs for revision or repetition of the training will be lower than the complete development.

Primary care is a driver of bacterial resistance development and thereby has the responsibility to improve antibiotic prescribing practice.[6] A proper cost-effectiveness analysis provides insight in both the effectiveness and cost outcomes for society and policy makers to decide whether or not, or how to invest in appropriate and cost-effective strategies.[7,27] Whether this intervention should be implemented depends on the willingness-to-pay threshold of society for a percentage decrease in antibiotic prescribing. The online training for GPs and information booklet for parents resulted in a decrease in antibiotic prescribing for children with RTI at very low costs, and would therefore be suitable for implementation in quality assurance programs primary care.

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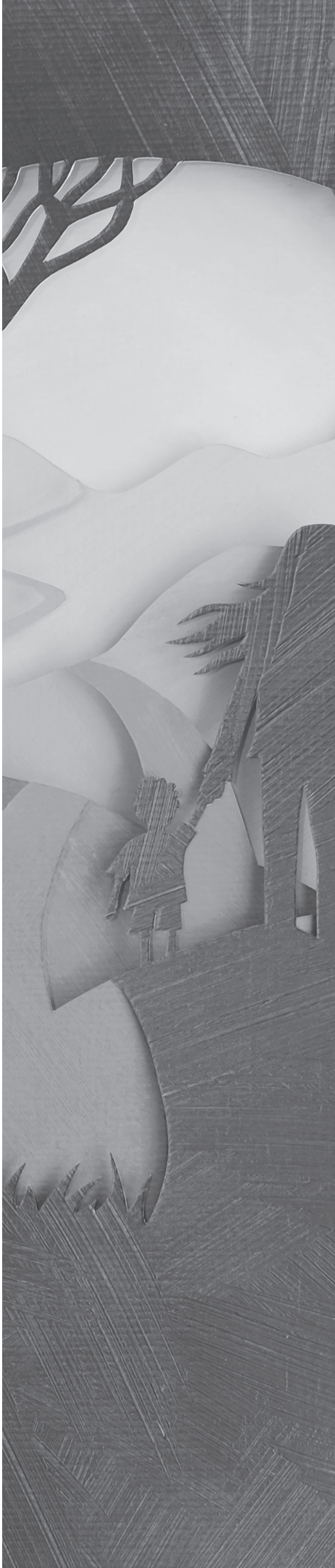

CHAPTER 6

Parents' attitudes and views regarding antibiotics in the management of respiratory tract infections in children: a qualitative study of the influence of an information booklet

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ABSTRACT

Background: Respiratory tract infection (RTI) is the most common reason to consult a general practitioner (GP) during childhood, and often results in unnecessary prescribing of antibiotics. Using an information booklet during the consultation has been shown to be a promising tool to reduce antibiotic prescribing. The influence of such information on parents' views, knowledge and expectations has not been investigated yet.

Aim: To explore the reported attitude and knowledge of parents towards antibiotics and management of childhood RTI, as well as the added influence of an information booklet, as perceived by parents.

Design and setting: Qualitative interviews were conducted with Dutch parents who consulted the GP with their child for RTI symptoms and received an information booklet.

Method: Semi-structured interviews were audio-recorded, transcribed, coded, and analysed using framework analysis by open-axial coding and describing themes.

Results: Eighteen parents were interviewed. Four themes were identified: prior reticence towards antibiotics; expectations of the consultation and trust in the GPs' treatment decision; confirmation and reassurance by the booklet; self-management and future consultation intentions. Dutch parents felt reassured and more confident about their pre-existing reticent attitude towards antibiotic treatment; therefore, they thought their opinion and attitude had not really changed by the booklet.

Conclusions: In a low-prescribing country like the Netherlands, information should focus on enhancing self-efficacy and providing concrete safety netting advice. For other countries with less reticence towards antibiotics, it is recommended that the knowledge, attitude and perceptions of the population is studied, in order to be able to tailor interventions.

How this fits in: Over-prescription of antibiotics is common in children, and information booklets are expected to reduce prescribing. However, their influence on parents' views and attitude towards antibiotics is unknown. In this qualitative study, Dutch parents reported reticence towards antibiotic use when their children were diagnosed with RTI; they felt the booklet confirmed these pre-existing views, and made them more confident to 'wait and see'. Parents mainly expected reassurance from their GP, trusted their treatment decision, and appreciated the safety-netting advice in the booklet, but the concept of antimicrobial resistance seemed difficult to comprehend. Therefore, information supply should first be piloted against pre-existing views and knowledge in the population.

INTRODUCTION

Respiratory tract infection (RTI) is the most common reason why children consult a general practitioner (GP).[1] RTIs are predominantly viral and self-limiting, therefore, antibiotic treatment is often not recommended.[2-5] However, over-prescription of antibiotics has repeatedly been shown.[6] Even in a low-prescribing country as the Netherlands about one third of antibiotic prescriptions for children with RTI are not in accordance with guidelines.[7,8] Over-prescription of antibiotics is a worldwide problem. Antibiotic consumption is directly related to bacterial resistance, unnecessary side effects and medicalization, all of which results in higher healthcare costs.[9-11]

Previous studies have shown that GPs' antibiotic prescribing behaviour is influenced by several mechanisms, including uncertain feelings about the clinical outcome, problematic communication, feeling pressured by parents, and fearing that parents will not accept non-prescribing.[12-15] RTI consultations are challenging for GPs as they need to make a rational treatment decision, provide reassurance, and offer evidence-based information. Recent reviews showed that the use of patient information booklets during the consultation is a promising tool to reduce antibiotic prescribing and patients' intention to re-consult.[16,17] Use of an interactive booklet about childhood RTI was evaluated in the UK.[18] A relevant issue is how such information influences parental perception, knowledge and attitudes, which could also be dependent on contextual factors, like the level of antibiotic use in a country.

A qualitative interview study was conducted with Dutch parents who visited the GP with their child with RTI and received an information booklet within the Rational Antibioic Use Kids (RAAK) trial.[19] The reported attitude and knowledge of parents towards (antibiotic) management of childhood RTI was explored, as well as the influence and added value they perceived of the booklet.

METHODS

Setting

This qualitative study was performed as part of the RAAK cluster randomised controlled trial, the first Dutch trial aiming to reduce antibiotic prescribing for children with RTIs in primary care.[19] The intervention consisted of a concise internet-based training for GPs and the provision of GPs with an information booklets for parents, without specific instructions how to use it during the consultation. The booklet contained the following information in simple text and pictograms: epidemiology of RTIs, their predominant viral cause, the self-limiting prognosis, rationale to withhold antibiotics, and antibiotic-related problems, including bacterial resistance. Additionally, child-specific self-management strategies and signs and symptoms when to consult the GP were explained. The information booklet is available from the authors on request.

Participants

Parents of children included in the intervention arm of the trial were consecutively approached by telephone within 3 weeks after their index consultation, and were asked to take part in a telephone interview. All participants provided verbal informed consent. All interviews were transcribed verbatim and anonymised.

Data collection

An interview guide was developed during an expert discussion. The questions were structured into five topics:

1. parents' attitude and views on antibiotics before having read the information booklet and what might have contributed to these;
2. parents' general impression of the information booklet;
3. what parents learned from the information booklet and what information they regarded most useful;
4. parents' perceived changes in attitude and/or views after having read the information booklet and what was considered to have contributed to this change; and
5. how the information booklet might affect their expectations of antibiotics and their consultation intentions in the future.

Finally, parents were asked whether or not they received an antibiotic prescription for their child. Semi-structured interviews were conducted from March 2015 to May 2015. Data collection and analyses were conducted in parallel and interviews continued until no new themes emerged. Interviews were carried out by a researcher with Skype (version 7.5); were audio-recorded with Pamela (version 4.9), or MP3 Skype recorder (version 4.11); and were transcribed verbatim.

Analysis

The first four interviews were coded independently by three researchers, and discussed to minimise inconsistencies in coding and to adapt the interview guide when necessary. The coding scheme based on these interviews was discussed with a fourth researcher, and was adjusted several times until the final coding scheme was unanimously accepted. Framework analysis was used; open-axial coding was applied to relate codes to each other. Related codes were grouped and discussed with all researchers, and four themes were developed based on consensus.[20,21] Different perspectives on the concepts in our study were sought by analysing the data with a group of researchers from different backgrounds: qualitative research, learning sciences, primary care research and work in general practice.[22] Nvivo software (version 10.0) was used for analysis.

RESULTS

Eighteen parents who received the booklet were interviewed, 16 mothers and two fathers, with a mean age of 34 years (range 29–38 years). The mean age of their child was three years (range 5 months–6 years). The mean number of siblings was 1.1 (range 0–4). Of these parents, two received an antibiotic prescription for their child during the consultation.

Overall, parents were very enthusiastic about the information booklet. They regarded the booklet as complete, attractive, concise, easy to read and clear. Some stated they would absolutely keep the booklet as a reference, or share it with others:

> '*[…] Later when I read everything at home I began to think, "hey this is useful!" I even texted some information to a friend of mine. I quickly took a picture of one of the pages.*' (P06)

From the interviews four main themes emerged: (i) Prior reticence towards antibiotics; (ii) Trust in the GP, and parental expectations of the consultation; (iii) Confirmation and reassurance by the booklet; (iv) Self-management and future consultation intention. These themes will be elaborated on in further detail.

Prior reticence towards antibiotics

Almost all parents mentioned that they were reticent towards antibiotic treatment for their child before having read the information booklet. A few thought antibiotics were useful for all infections to help their child recover more quickly. In general, parents believed antibiotics should be avoided for their child if possible:

> '*I was not just going to administer antibiotics to my son without reason, only if it is really necessary. I was already sure of that, and with that attitude I went to see the GP.*' (P06)

Concomitantly, parents also showed a hesitation towards using any medicine, for example, paracetamol. They preferred to consider medication when the body itself seemed unable to fight the illness properly:

> '*To be honest, I always had this view of using as little medication as possible or even avoiding them at all, unless it is necessary. […] Well, I do believe in the self-healing abilities of the body. So I consider it as administering extra junk when it's not necessary. If it really helps, I mean, if the body really needs it to get better, or at least get better faster, then it's fine. But if it's not really necessary, then I don't want it.*' (P01)

Parents explained their reticence towards antibiotics with reference to antibiotic resistance. Most parents did seem to know something about resistance before having read the information booklet:

> '*I know you should be cautious using antibiotics, and that is of course also because bacteria can form a resistance against it.*' (P02)

Half of the parents had understood resistance as a 'resistant human body' despite the information explaining development of 'resistant bacteria'. They mainly believed that using antibiotics can make the body resistant to any antibiotic. They thought that when they would really need antibiotics, treatment would have limited effect on them. These parents were often also unaware of the fact that antibiotics are ineffective against viral infection and concomitantly, that most of their child's RTIs are viral:

> '*I always thought you yourself could become resistant to antibiotics. […] I mean the body itself, because the bacteria are in the body, right? […] So, if you use a lot of antibiotics you will slowly become resistant to them.*' (P03)

Sometimes parents considered the resistance of the body as a general problem with medicine, for example, also with painkillers:

> '*For something simple such as paracetamol, I do not prefer to take all that too much, because, I do not know, maybe your body gets used to it and then they do not have the effect that they could have.*' (P13)

A minority knew nothing about bacterial resistance, but also had a clear attitude towards antibiotic use:

'*I think they (GPs) prescribe it a little too quickly, maybe waiting to see what happens might be better. [...] I don't really know why I think this way, I just believe that antibiotics are prescribed too quickly in general. [...] I didn't know anything about resistance before I read the information booklet.*' (P12)

Most parents were unable to point to what their initial views and opinions were based on. They mentioned education, their GP, family and friends, and/or the media:

'*Well, it is mainly based on information from other mothers, who say uh, well that you shouldn't use antibiotics on children, if for instance they only have a simple ear, or respiratory tract infection, or an inflammation of the throat. This, because it will resolve naturally most of the time.*' (P16)

'*Well what you read in the papers, people can become really ill of some kind of resistant hospital bacterium.*' (P18)

Trust in GP and parental expectations of the consultation

Parents showed a high degree of trust in their GP; when the GP did not prescribe antibiotics, they concluded this was not necessary. When antibiotics were prescribed, then this was deemed necessary, or, at least it would be unwise not to use antibiotics in this particular situation:

'*[...] I have a really good relationship with my GP and the GP knows how I think about antibiotics. The GP will only prescribe if it is really necessary, you know. In cases where it wouldn't work with just good care and no antibiotics.*' (P6)

Parents noticed that GPs are nowadays quite reticent to prescribe antibiotics:

'*I know that they [GPs] are not very keen on giving antibiotics to children.*' (P16)

Parents felt that their GP's attitude towards antibiotics is in line with their own. Trust made them accept the GPs' decision whether or not to prescribe antibiotics:

'*If the GP prescribes antibiotics, then, I will trust him. I still might ask him a second time whether it is really necessary or whether we can wait and see for a few more days. Yes, I always ask just to be sure, and my GP always explains it clearly.*' (P12)

As a consequence, most parents did not expect an antibiotic prescription, however, they do expect reassurance and advice about symptoms from their GP when they are in doubt how to manage the child's illness:

> '*I did not go to the GP to get antibiotics, I just wanted the GP to listen to his lungs, that kind of examination.*' (P4)

The booklet seemed to bring some understanding for those who did not fully understand the GP's choice to prescribe or not prescribe antibiotics. This was mainly due to the information about the ineffectiveness of antibiotics against viral infection and the disadvantages of antibiotic use:

> '*I think that the booklet throws some light on it for many people: that it is not unwillingness of my GP, but that the antibiotic really is ineffective for this illness.*' (P07)

Most GPs provided the booklet at the end of the consultation and briefly mentioned the content; they advised reading it at home. Parents were satisfied with not discussing the booklet during the consultation because of the clear information:

> '*… No, I can do without, the booklet was clear enough to read it on my own at home.*' (P18)

Only one parent wished the information booklet was explained more by the GP during the consultation; for this parent the booklet contained a lot of new information.

Confirmation and reassurance by the information booklet

When asked what new knowledge parents gained from the booklet, half of them said the information was not new but was useful to read. The information was a confirmation and better explanation of what they already knew or thought. It brushed up their knowledge, reinforced symptomatic management of their children and provided confidence in the self-limiting character of RTIs:

> '*Actually, it was mostly a confirmation of what I already knew. But it's always good to read it again.*' (P01)

> '*If someone asks me, "why don't you ask for antibiotics?" Yes, then I can say: "I don't do that, because it is not the right solution"… I feel more confident, more convinced.*' (P15)

Some parents did learn new information from the booklet. They mostly stated to have learned that antibiotics do not work for all infections, only for bacterial and not for viral ones, and/or when to call the GP with alarming symptoms. Other new insights included the disadvantages of antibiotic use, such as resistance and side effects. To a lesser extend information about symptom duration, fever, and self-management advice were considered new:

> '*Yes, it provided some (new information); […] all those viruses that go round now, for which it is useless to give antibiotics, and that is what I did not know.*' (P14)

Most of the parents did not feel their opinion about antibiotics, or knowledge of RTIs had changed by the booklet. They already were quite reticent and this view was confirmed by the information of the booklet. However, they felt they could better explain their opinion:

> '*The booklet confirmed that I indeed have to be careful with antibiotics. But, that is what I already knew before. I just did not exactly know why. Now, I really understand why.*' (P6)

Despite the fact that parents often said that the booklet was easy to read and contained clear pictograms, it nevertheless appeared that they often misreported the information in the booklet. Viruses and bacteria were often mixed up in their explanation why antibiotics do not work; they, for example, said antibiotics only work for specific viruses. As earlier mentioned, the concept of bacterial resistance was often still not fully understood after reading the booklet:

> '*Well the information that antibiotics have advantages and disadvantages was most useful to me… The advantage is that antibiotics, mmm, kill those viruses that make you ill, but, that those viruses can adapt themselves, which you actually need for your own resistance I think.*' (P06)

Self-management and future consultation intention

The information about 'when to contact your GP' was regarded as most useful. Some parents thought that the booklet would change their consultation behaviour as a result. Some parents did not think the booklet would have that effect, as they were already reticent about consulting their GP:

> '*Especially the last page, about when you should call the GP, was the most important for me. I mean, knowing when something is considered minor, and when it is actually necessary to call the GP.*' (P13)

> '*Well, it did change something. I will probably not call the GP as quickly as before, because of the guidance when to call the GP from the booklet. Of course, I take these things into consideration, I mean, does my child have a fever, or not, is the fever persisting for three days now. I've always considered these things, but now I know that when my child starts coughing, I will wait a week and see how it turns out.*' (P16)

Although parents were quite reticent towards antibiotics and consulting the GP soon after the onset of symptoms, most parents do acknowledge that once symptoms persist, they start to worry. Such a consultation is not necessarily for antibiotics, but for reassurance that the illness is not severe, or for self-management options for symptom relief:

> '*Well, the problem was that he wasn't getting enough sleep and was also keeping us awake all night. So, consulting the GP is a way of seeking a solution, but it depends on the symptoms. […] No, no, I didn't consult to get antibiotics. I just wanted to know if it was just a common cold, or something with his ears, and whether there was something I could do about it.*' (P17)

DISCUSSION

Summary

The information booklet confirmed parents' pre-existing views towards antibiotics. Therefore, parents reported that it did not really change their attitude, but it did make them feel more confident to 'wait and see' first. They valued that the booklet substantiated their prior reticence towards antibiotics, and provided a better understanding of the GPs' treatment decision. Most parents trusted the GPs' professionalism and valued their judgement about the severity and treatment of the illness, and they expected reassurance during the consultation. For some parents the information that antibiotics are not effective for most RTIs and the concept of bacterial resistance were new, but they neither expected that to change their attitude towards antibiotics. The antibiotic-related information, especially about bacterial resistance, seemed difficult to understand. Information about when to consult the GP was regarded as most relevant.

Strengths and limitations

A previous qualitative study performed in the UK explored parents' and clinicians' views on the development, process evaluation and implementation of an interactive information booklet for parents.[18,23] The present study focused on gaining insight into parental reporting on how and why the information booklet influenced their views and attitudes. This information might be relevant to understand the intervention's effect, to know which elements were most relevant and to further optimise the intervention. A limitation was that parents' views and attitudes were not obtained before they had read the information booklet; after having read the booklet this might have been difficult to recall and explain. A second limitation was that parents could interpret, favour and recall information from the booklet in a way that confirmed their pre-existing beliefs. In addition, the parents visited GPs who had followed an online training in prudent antibiotic prescribing for RTIs and communication skills, which could have influenced the consultation and thereby the parents' views. Finally, parents knew about the aim of the trial, and could have provided socially acceptable answers.

Comparison with existing literature

It has been shown that GPs can interpret parental concerns as an implicit demand for antibiotics, which is thought to contribute to over-prescription of antibiotics.[7,14,24] In the present study, parents reported their prior reticence towards antibiotics and high trust in the GP, which resulted in a limited influence of the information booklet on their views. This finding should be understood in the Dutch context, with its sober attitude concerning treatment (for example, the use 'watchful waiting') which might explain the low antibiotic use in comparison with other countries.[25] Furthermore, the high continuity of care in Dutch primary care, where patients are registered at one practice and often linked to one GP, is probably the basis for patients' trust in the GP's non-prescribing decision. These elements are considered to be of high importance in promoting appropriate antibiotic use.[26]

This reticent attitude towards antibiotics could, apart from culture, also be caused by misunderstanding of the concept 'resistance'. The idea that 'the less often children take medicine, the better they work' was described in an earlier study about the opinions of parents about analgesics for their children.[27] Most parents were aware of 'antimicrobial resistance' before having read the information booklet, but it appeared that most parents did not fully understood the concept, despite efforts to explain this clearly in the booklet. Brookes-Howell *et al.* previously described that people in Europe are aware of the link between antibiotic use and resistance, with the misinterpretation of antibiotic resistance as a property of a 'resistant human body' rather than a property of bacteria. They suggested interventions, emphasising the transferability of resistance, and the societal contribution individuals can make through more appropriate antibiotic use to limit bacterial resistance.[28] In the present study, it seemed difficult for parents to exactly understand what antimicrobial resistance entails, and therefore completely understanding the concept appeared not important in a prudent attitude towards antibiotics. This study showed that the general knowledge that antibiotics have disadvantages, side-effects and cause 'resistance', was enough to result in a reticent attitude.

The parents mentioned that the booklet was often not discussed during the consultation, but they did not regard this interactive use as necessary. In the study of Francis *et al.*, the interactive use of their booklet did not appear to be consistently implemented, but was regarded as important, contrary to the present study's findings.[18] Not discussing the booklet during the consultation might save time, and allow the booklet to be distributed already in the waiting room, or via the internet. However, in situations without continuity of care, for example out-of-hours care were patients tend to ask for antibiotics more easily, it might be preferable to use the booklet interactively during the consultation.[16,26]

Implications for practice and research

Educating parents specifically on the effectiveness of antibiotics and antimicrobial resistance seemed less relevant than trust in the GP, reassurance and clear safety-netting. In countries with a comparable context of low antibiotic use, focus of information supply should be on enhancing self-efficacy and providing safety-netting advice. For other countries, the present authors recommend studying the population's pre-existing knowledge, attitude, and perception towards antibiotic management for RTI, in order to tailor information supply. In countries, where a reticence attitude regarding antibiotics might be less ingrained, an information booklet could, for example, help patients understand their GP's non-prescribing treatment decision.

ADDITIONAL INFORMATION

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Ethical approval

The Act on Medical Research involving human subjects did not apply to this study, and therefore an official approval of this study by the Medical Ethics Research Council of the University Medical Center Utrecht was not required (reference number: METC 15-107/C).

Competing interest

The authors have declared no competing interests.

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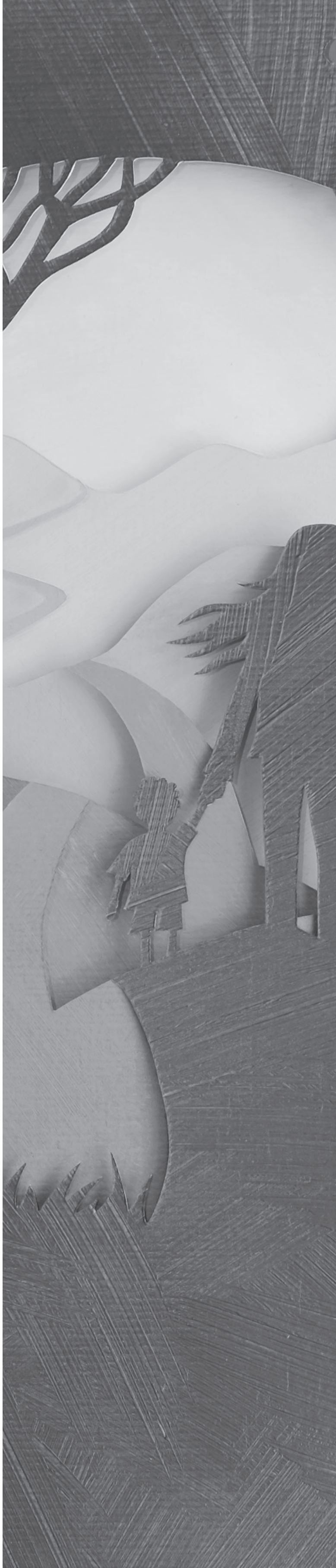

CHAPTER 7

Informal and formal learning of general practitioners

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ABSTRACT

Purpose: The purpose of this study is to understand the influence of formal learning from an online training and informal (workplace) learning afterwards on the behaviour of general practitioners (GPs) with respect to prescription of antibiotics.

Approach: To obtain insight in various learning processes, semi-structured interviews were conducted with 19 GPs. These interviews were transcribed and analysed with a theory-based template, that had been defined beforehand, but with an open mind for emerging themes.

Findings: The online training was perceived by GPs to change their prescription behaviour, mostly as a result of informal learning processes. Research participation and/or being a GP supervisor appeared to create more opportunities for informal learning.

Implications: The current research shows that informal learning activities, for example reflection and social interaction enhanced the effect of the formal training. It is recommended to stimulate GPs to reflect on their prescribing behaviour and seek social interaction besides participating in formal training.

Value: Our study adds to the existing literature by considering informal learning processes in an evaluation of the perceived effects of formal training. Our findings have implications for the design and evaluation of formal trainings with the purpose of behavioural change of doctors.

INTRODUCTION

Lifelong learning is important to keep track of developments in professional domains, as knowledge and insights develop fast, leading to a transition in professional's work routines.[1,2] Even though opinions differ about the boundaries of formal and informal learning,[3,4] learning that takes place while performing the job seems to be more efficient than formal training alone to learn job-related skills, because skills are often situation-specific and need practice at the workplace.[5] Formal learning is not sufficient for solid transfer of training and as a consequence, formal learning alone is probably not the most efficient way to accomplish behavioural changes.[6] Informal learning provides the learner with opportunities to practice the knowledge from the formal training in an everyday, workplace situation. Studies in informal learning have been done in many professional contexts,[7-9] but studies about informal learning of general practitioners (GPs) are scarce.[10,11]

Self-directed learning, based on experience, has been advocated to be at the centre of continuing professional development for general practice.[11] Continuing learning is needed, because guidelines frequently change, medical developments progress rapidly and social contexts change. As an example: GPs have to learn to be restrictive in antibiotic treatment of respiratory tract infections (RTIs), as is recommended in recent guidelines. Previous studies showed that antibiotics are often over-prescribed,[12] which leads to antibiotic resistance, patient medicalization and unnecessary side-effects and costs. An intervention with an online training could help to change the prescribing behaviour of GPs for RTIs in children.

The present study aims to help understanding prescribing behaviour of GPs and how this is influenced by formal learning, through an online training as part of a broader intervention, and by informal learning afterwards. In contrast to previous research,[13-15] this study uses a qualitative methodology to find out how formal and informal learning may strengthen each other. A better understanding of how GPs learn and gain new skills after the formal training, by performing informal learning activities, will be valuable for understanding and accomplishing behavioural change processes. This could be used in the design and evaluation of future formal GP-directed educational interventions.

Informal learning at work

Learning at work is different from learning at school in the way that learning at school is more formal and planned intentionally, while learning at work is of an informal nature.[2,5] According to Tynjälä *et al.*[2] workplace learning can take many different forms. It can be informal and incidental as a side-effect or consequence of work, intentional non-formal as activities related to work and formal as in training.[2,5] Marsick and Watkins described informal learning as experiences from outside formal training which can be planned.[16] Informal learning is implicit, unintended, opportunistic and not structured by a teacher.[5] Even when informal learning occurs mainly unintentional, still the willingness to learn is helpful for achieving learning outcomes.[17] The definition used in our study is: informal learning takes place by experience, is mostly unstructured, takes place after the formal training and is in the control of the learner.[5,16]

The implicit nature of informal learning makes it difficult to observe, or assess what has been learned, especially when evaluating unintentional informal learning.[18] Different activities or processes of workplace learning can be observed by researchers, such as: learning during the job, through cooperation and interaction with colleagues, through observing and listening to others, by dealing with novel and challenging tasks, through reflection and evaluation, through formal training, through extra-work contexts, and through working with patients.[2,5,19,20] Working with patients gives more context to learning, by specific and individual knowledge about the patient, their problems and the consultation. Relations at work are also important for the success of workplace learning, where informal relations appear to be more important than formal relations. Also much can be learned as a result of learning from mistakes, and asking about the experience of a colleague and short- and long-term feedback appear to be helpful. Thus, the concept of workplace learning implies social activity in which interaction, dialogue, challenging tasks and reflection of learning and planning of future learning are necessary.[2] The engagement in informal learning was, among other factors, shown to be dependent on access to computer technology, and less on physical proximity to colleagues.[18] This could be interesting in GP education, as they mainly work independently.

Learning could benefit from the combination of formal training with informal learning at the workplace.[21] This could be due to the more individual nature of formal learning in contrast to the more social nature of informal learning at the workplace. Formal training only supports individual knowledge transfer, but lacks the benefits of learning from social interaction. Therefore, this study takes informal learning into account to explore the combination of formal and informal learning in the behavioural change of general practitioners.

Formal and informal learning by general practitioners

To guarantee the professional development of GPs formal training is provided and often mandatory, but their work mostly consists of patient consultations and, therefore, these encounters with patients are an important source of learning.[11] However, consultations are generally done alone, without colleagues. Professional isolation might influence informal learning activities negatively,[22] although Berg and Chyung[18] found that physical proximity to colleagues was not most important for engagement in informal learning. Differences can be expected between informal learning activities by GPs working in a group practice, or working in a solo practice, because interaction was shown to be important in informal learning.[23] It is known that GPs value opportunities for informal learning during formal educational activities.[10] In addition, positive experiences with online learning of GPs have been described,[24,25] but whether GPs themselves combine a formal online training with self-directed informal learning is yet unknown.

Changing antibiotic prescribing behaviour

Antibiotics for respiratory tract infections (RTI) are often over-prescribed, also for children.[12] The RAAK study aims to improve the antibiotic prescribing behaviour of general practitioners for children with RTIs. An intervention, including an online training was developed as formal education. This online training consists of an introduction about antibiotic-related problems, the prescribing guidelines for RTIs and training in communication skills. The intervention further consisted of written information booklets for parents.[26] The anticipated outcomes of the intervention are an attitude change towards prescription of antibiotics, by better knowledge of the prescribing guidelines, more awareness of antibiotic-related problems and improved communication skills, measured by antibiotic prescribing rates. Although much research into interventions for behavioural change towards antibiotic prescribing exists,[27] none of those studies have looked into the learning processes involved, or self-initiated afterwards.

The current research aims to explore GPs opinions on how their prescribing behaviour was affected by the intervention (especially the online training), and by subsequent informal learning processes. It was expected that informal learning activities of general practitioners would also help them to change their prescribing behaviour, as the learned knowledge, skills and attitude are directly connected to activities performed at the workplace.[21] In addition, we explored which informal learning activities they had undertaken during and after the intervention. It was expected that GPs learn mostly during their consultations with patients, as this is the major part of their profession.[11]

METHODS

For this study we chose a qualitative design to obtain insight in learning processes that might have changed prescribing behaviour of GPs. What and how the GPs thought they had learned during and after the online training was investigated with an interview. The script of the interview was first tested during a pilot with one GP, to test whether the questions were understandable and made sense for GPs. A convenience sample was used.[28] During the process of interviewing the number of participants was determined.[29] After nineteen interviews it was decided that saturation was reached and no other GPs were interviewed. The Netherlands Association for Medical Education (NVMO) and the Ethical Review Board gave permission for this research design.

Data collection

All GPs who had followed the online training by participating in the RAAK trial were invited to participate in the current study. Besides this online training, the GPs received printed information booklets to discuss and give to the parents and the memory aid summarizing all the guidelines recommendations with respect to antibiotic prescribing for children, which was online available in the training as a printable document. As part of evaluating the RAAK intervention, the GPs had to register children presenting with a RTI on a form, with questions about signs and symptoms, whether they thought the parent had a request for antibiotics and whether they prescribed antibiotics.

When GPs were interested in participating, they were invited for an interview and an information letter and informed consent were sent to them a week before the interview. A handout of the online training was also included to bring the online training back into their memories. Nineteen GPs consented to participate in the interview study, of which eleven were female and eight male. The GPs all worked in different practices; two worked in a solo practice, ten in a group practice, and seven in an educational practice with a doctor in training (trainee). The interviewer visited the general practice of the interviewees. The interviews lasted about half an hour (maximum).

The instrument used in this study was a semi-structured interview. The script of the interview, based on our research questions, was the starting point for the interview. The first part questioned the ways GPs had learned from the intervention, through the different components of the formal intervention: *the problem description*, *the guidelines* and *the communication skills*. The second part, including the topic list was based on literature of the informal activities people undertake at work.[2,5] The topics were: *reflection*, *dialogue*, *collaboration*, *consultation*, *planned learning*, *observing*, *listening*, *challenging tasks or situations*, *giving feedback* and *receiving feedback*.

Data analysis

After the interviews, recordings were transcribed and imported in NVivo (10). Participants' names were coded. A template was developed using the literature of Tynjälä[2] and Eraut[5] containing codes about acquired knowledge, skills, changed attitudes and awareness, and on the formal and informal learning activities. Subsequently, the transcribed interviews were coded using the template, with an open mind for emerging themes.[30] Coding was an iterative process, where the template was revised during the analysis through reflecting on and discussion about the research with two other researchers (AD, EG). The mentioned informal learning activities were counted and organized in tables. If the GPs themselves mentioned having carried out an informal learning activity, or agreed having carried out an informal learning activity after asking them explicitly using the topic list, this was counted as an informal learning activity. When the GP mentioned having carried out an informal learning activity but not in relation to the intervention under study, or if they were not certain, this was not regarded as an informal learning activity.

RESULTS

During the analyses of the interviews themes were identified and those most relevant for the research questions were selected. Quotes illustrate the findings. The online training was thought to have influenced prescribing behaviour, also as a result of several informal learning activities. Additionally, being a research participant and/or a supervisor appeared as themes that influence prescribing and consultation behaviour. In the following sections these themes will be discussed.

Informal learning

All participants had performed informal learning activities after, or during the online formal training. Frequencies of total informal learning activities are shown in Table 7.1. The informal learning activity mentioned the most was *consultation*, followed by *transfer in other contexts*, *reflection* and *dialogue*. The informal learning activity *planned learning* wasn't mentioned by any of the GPs. This suggests that the GPs had not planned moments for future learning induced by the formal training, or after finding out what they still regarded difficult on this topic. All informal learning activities are briefly discussed below.

The online training provided the GPs with some useful tools, with which they experimented and learned informally during subsequent *consultations*. This learning was supported by the booklet

Table 7.1 Number of informal learning activities and perceived changed prescription behaviour of the GPs

Prescribing behaviour changed?	Total	No (n=10)	Yes (n=6)	Doubtful (n=3)
Consultation	16	9	6	1
Transfer in other context	13	5	6	2
Reflection	12	4	5	3
Dialogue	10	5	4	1
Giving feedback	8	4	3	1
Observing	7	2	3	2
Reading	5	0	4	1
Collaboration	3	2	1	0
Receiving feedback	3	2	1	0
Listening	2	1	1	0
Planned learning	0	0	0	0
Total	79	34	34	11
Mean	4.2	3.4	5.7	3.7

and the memory aid. They used the booklet to explain the information to the parents which could support their decision not prescribing antibiotics. The aid with the guidelines summarising the patient groups for which antibiotics are indicated was also used to show to parents, or to brush up their own memory. Asking explicitly about the aim of the parent for the consultation and/or expectation of antibiotics was also mentioned being done during the consultation, as part of informal learning. They were taught in doing this through the communication training which was part of the formal learning.

> (...) I notice that I'm more conscious about the reason of the appointment if parents are worried and then asking about it directly. So that has changed. (G)

Transfer in other contexts was often mentioned by the GPs. The formal training was about prescribing for children, but elements of the learning were also applicable to adults. They used for example the communication skills, like asking about the patients' expectations regarding antibiotics, in consultations with adults too. The knowledge about the specific indications for antibiotic use and the duration of complaints was also used in communication with adult patients. Furthermore, the GPs were also more critical about antibiotics and better aware of antibiotic-related problems when they had an adult with an RTI.

The GPs mentioned that they had *reflected* on their own prescribing behaviour during their trial participation, but also that they were not really aware that they attained specific new knowledge, apart from brushing up existing knowledge. They referred to being more aware of their own prescribing behaviour and communication with patients and, therefore, wondered whether this had indeed changed their prescribing behaviour. With respect to *dialogue*, the GPs referred to talking to people about the online training and their participation in the research project. Most of them talked to colleagues about the content of the training and discussed particular patient cases to learn how colleagues felt about treatment with antibiotics. These interactions were mostly during coffee breaks, or other casual moments during the day.

> So I think yes, it has regularly been discussed informally. We didn't make it structural, but it comes up regularly because it is a common problem. (E)

They also discussed the topic with others than colleagues, like friends. With them they talked more about their participation in the trial and the general topic of antibiotics, for example, increased antimicrobial resistance. Learning something really new from talking with others was not the most important to them, but becoming more aware about prescription of antibiotics was. The other informal learning activities were mentioned less. When *collaboration* was mentioned, this happened within groups of GPs together in a practice and during pharmaceutical therapeutic consultation meetings with the pharmacists. In these groups the GPs talked about antibiotics using the information and knowledge they had learned from the web-based training.

> (...) and in this meeting this was useful, that I had all the guidelines in my memory and I could share it very well and easily with others, such as when you prescribe which antibiotics and which definitely not. (B)

Feedback came up mostly in discussing the approach of the consultation and particular patient cases. Especially the GPs with a trainee in their practice provided feedback to each other, because in educational practices consultations are discussed between GPs and trainees. GPs without trainees didn't mention feedback, because of a lack of time or opportunities for this. These GPs referred to working mainly on their own, with their own patients.

> (…) not a lot of feedback within the practice, we all do our own thing and we have our own patients. It is not that we are having coffee to discuss each other's consultations each week. No, that doesn't happen. (C)

The GPs (n=6) who thought their prescribing behaviour had changed due to the intervention participated in more informal learning activities (M=5.7) than the GPs (n=10) who didn't think their prescribing changed (M=3.4), as is shown in Table 7.1.

Being a research participant

The intervention as a whole seemed to be important for the GPs. The booklet, the online training and participating in the trial were all mentioned separately as being useful to them. For example, while participating in the trial the GPs were asked to register children with RTIs, and whether they did, or did not prescribe antibiotics; this stimulated reflection.

> (...) you do that all the time. And the RAAK research stimulates that. Because every time you see someone with an RTI you have to fill in whether you prescribe antibiotics or not, and you think why? So that's a reflective moment for every patient. (J)

Particularly the question whether they thought the parents were expecting antibiotics for their child created awareness and led some GPs to change and reflect on their consultation behaviour.

> You have to fill in on this form whether you thought the parent wants antibiotics. That is a nice realization moment, because then you write down your expectation about it. It would be easier if you just directly ask the parents about it. And sometimes I do that now. (G)

One GP mentioned the feeling that someone, as part of the research team, was checking on him, whereas another referred to more interaction with colleagues because of their mutual participation in the project, as well as more looking into the guidelines because of being a research (trial) participant. Being reminded now and then to include patients also helped them to apply the training more.

> If you participate in a research project, you talk about it with each other. (R) Look, by participating in research like this you get stimulated to look up some things again. (O)

Being a supervisor

Some GPs were supervisor during the intervention and indicated that this also helped them to integrate the intervention better into their behaviour. Some consultations are being recorded for educating purposes and evaluated which stimulated the GPs to also reflect on their own behaviour and communication skills, besides that of their trainee. After being asked whether they learned something from it, they confirmed using knowledge of the intervention during supervision.

> (…) because you are looking consciously at how a consultation must be and things you could improve, but you also realise that you see "mistakes" that you make yourself as well. For that matter you apply the changes or give feedback you could also apply to yourself. (E)

GP supervisors also need to follow modules to supervise their GP trainee with a beneficial side-effect that they gain the awareness of applying this knowledge and skills in their own consultations. Also noticing the prescribing and consultation behaviour of a GP trainee was helpful and made them remember this knowledge.

> Yes, that is of course the case with a lot of knowledge (...) first knowledge is conscious and at a given moment knowledge becomes unconscious and you're naturally applying it. But, then in this routine you are developing blind spots, and when working with a GP trainee you have to explain and discuss why you are doing particular things. (O)

Particularly, the informal learning activities *dialogue*, *giving feedback* and *observing* are typical for a supervisor. Table 7.2 shows that supervisors undertook more informal learning activities (M=5.4) than GPs who work alone (M=4.5), or in a group practice (M=3.4). It therefore seems that being a supervisor provides more opportunities for informal learning.

Table 7.2 Number of informal learning activities and work setting of the GP

Work setting GP	Total	Single-handed practice (n=2)	Group practice (n=10)	Educational practice (n=7)
Consultation	16	2	8	6
Transfer in other context	13	2	5	6
Reflection	12	2	7	3
Dialogue	10	1	2	7
Giving feedback	8	0	2	6
Observing	7	0	2	5
Reading	5	0	4	1
Collaboration	3	1	1	1
Receiving feedback	3	0	1	2
Listening	2	1	0	1
Planned learning	0	0	0	0
Total	79	9	32	38
Mean	4.2	4.5	3.4	5.4

DISCUSSION

In our study we explored the ways GPs had learned from an online training, through formal and/or informal learning. The results indicate that GPs who undertook more informal learning activities expected that their prescription behaviour had changed more, and that GPs mostly learned from the content provided in the formal training, when they put it into practice during interaction with patients in routine consultations. This way of informal learning has been indicated already by Stanley *et al.*[11] These results support the notion that it is most efficient to combine formal training with informal learning activities.[21] Furthermore, it became clear that the complete intervention was important for a behavioural change of GPs, not only the formal web-based training, but also the information booklet for parents, being a research (trial) participant, and the informal learning activities afterwards. GPs supervising a GP trainee had more informal learning opportunities at their disposal as these GPs proved to be more used to reflection and open for discussions about prescribing decisions.

The current research shows that being a research participant, and/or being a supervisor enhances informal learning activities, for example by reflection, and as a result the participants expect the formal training to be more effective. Reflection is sometimes difficult for professionals because of a lack of time during routine consultations, but our results suggest that filling in a form registering the prescribing decision seems to induce this reflection when the GP has an encounter with a patient from the target group. Eraut *et al.* suggested that an open culture stimulates reflection and experiential learning, which may be the case for GPs in their role as supervisor.[31] Supervisors are encouraged to think consciously about behaviour, their own and of their trainee. To provide the trainee with feedback, and to explain one's own view an open culture of reflecting and expressing concerns is essential.[9] Whether formal and informal learning should be seen as two distinct categories, or more as inseparable is open for debate.[3,4] In our work, categorizing these two types of learning was helpful for exploring the learning activities the GPs have undertaken.

The results of the present study contribute to literature about learning conditions for different kinds of groups because of differences in opportunities for informal learning. Opportunities for reflection, as well as for communication and interaction are important learning conditions.[23] Being a supervisor and research participant are situations where reflection, communication and interaction are naturally enhanced, as became apparent from the interviews. Furthermore, most GPs mentioned the consultation and dialogues with patient as important learning activities. This makes sense, as part of the training was to teach enhanced communications skills. GPs indicated having practiced these during routine patient consultations and having evaluated the effects of these advices during many patient encounters. As such, this social interaction undertaken at the workplace after the formal learning seems to play an important supportive role in learning. Other professionals play an important role in informal learning and helping others with handling complex problems.[9]

Furthermore, this social interaction is evident for supervisors and can be explained by the theory of legitimate peripheral participation of Lave and Wenger.[32] In the work on communities of

Bjørk *et al.*,[7] it was evident that not only the newcomer learns to become a full participant in a sociocultural practice through learning about the community, but the already full member of the community does as well. In our study qualified GPs also learn from discussing with trainees and receiving feedback. Sharing knowledge is more important than ever, as knowledge isn't stable. The changing knowledge used for the profession of GP is asking for new responsibilities and new opportunities for engagement.[33]

Especially with a concise online training, the informal learning activities learners consciously or unconsciously undertake afterwards are important, since the training itself does not provide practice at the workplace. Informal learning combined with the formal training might help to turn tacit knowledge into explicit knowledge and combine academic knowledge with practical experience. The research participation might stimulated the GPs to reflect and think about their prescribing decision by for example the registration of patient consultations.

Implications for practice

A review of Arnold and Straus concluded that multi-faceted interventions are most effective in reducing inappropriate use of antibiotics for RTIs; single-intervention studies, such as guideline publication and distribution, didactic educational meetings and audit and feedback generally resulted in no or small changes in prescribing behaviour.[27] In our study as well, it appeared that the complete intervention, including registrations and informal learning afterwards, contributed to the effect the GPs expect regarding their antibiotic prescribing. For a better or longer effect of a formal learning intervention, it is therefore recommended to support and evoke informal learning, for example by inclusion of tasks stimulating GPs to undertake informal learning activities and to help them to regularly evaluate their prescribing behaviour. Furthermore, when evaluating a formal learning intervention, it is useful to not only consider outcome variables, but to investigate informal learning as well. This will give a better understanding what might have contributed to the learning outcomes and behavioural change in the longer run.

The findings illustrate how GPs learn at the workplace and which formal and informal activities they perform, consciously and unconsciously. As GPs mainly work alone with patients in a consultation, the main informal learning activity they perform are their consultations. Some GPs talked with others about the content of the training, but others didn't, even if they worked in a group practice. Because of the importance of social learning, online training needs to stimulate social interaction afterwards. This could be supported for example by providing the participants with access to an online learning community where they can discuss topics and share experiences. The latest insights, new research and guidance how to obtain prescribing data and personal feedback at online platforms of communities with healthcare professionals might support GPs' engagement.[18,34]

To support and evoke informal learning, more awareness about informal learning is needed for designers of future formal learning interventions for GPs. In primary care in the Netherlands, the Dutch College of General Practitioners (NHG) organises post-doctoral training and develops online learning for GPs. GPs are assisted and motivated by NHG quality consultants in oversight in prescribing data, and implementation and quality assurance processes. The NHG and consultants should be made aware of the importance to support and evoke informal learning activities within and after the formal training.

Limitations and further research

The interviews were held six months after the GPs had followed the web-based training, and some GPs didn't memorize the training clearly, even though they received a brief reminder in advance. It would have been interesting to know the opinions of GPs about the training sooner, to learn more about the aspects of the e-learning itself. On the other hand, the 'delayed' interview allowed for more information on the long-term process for more time for informal learning activities. Another limitation is that sample selection is possible; many of the self-selected GPs had the impression to be conscious already about antibiotics and related problems, which is perhaps not true for all GPs. Furthermore, the sample was relatively small but our study is merely claiming transferability, and not generalisability. This research analysed GPs opinions and beliefs, and did not intend to determine whether their behaviour indeed had changed.

Further research should focus on how to create optimal situations and possibilities for informal learning after having offered formal training, and on studying for example how to enhance reflection, not only during research participation, but for every busy GP during training and implementation processes. In addition, it is recommended to investigate how to effortlessly stimulate informal learning activities after formal training. Our research underlines the importance of informal learning activities, such as reflection and social interaction, after formal intervention aiming for a behavioural change of healthcare professionals.

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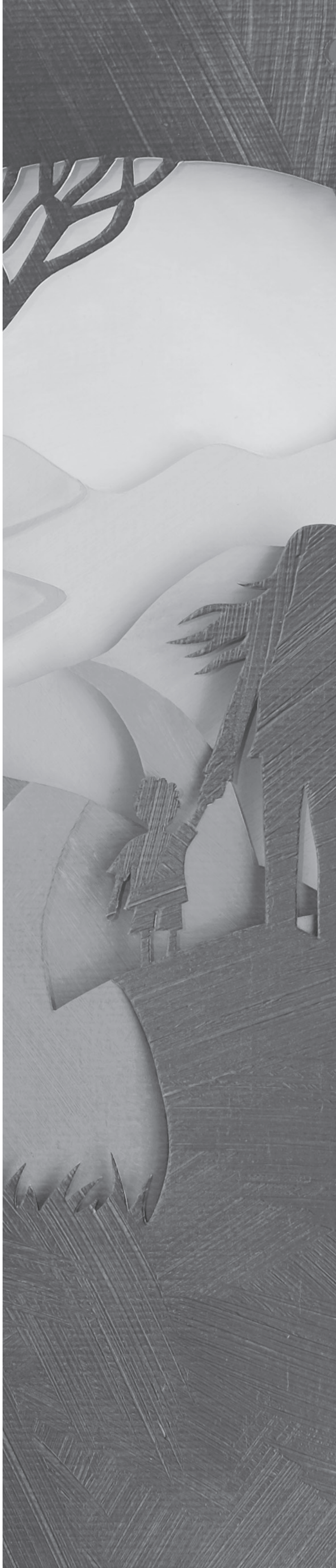
CHAPTER 8

General discussion



MAIN FINDINGS OF THIS THESIS

The first part of this thesis presented the antibiotic management of children with infectious disease in the Netherlands. Routine care data showed 1029 disease episodes with 262 antibiotic prescriptions per 1000 person-years. Acute upper RTI was the most common reason to visit the GP and the second most frequent indication for antibiotic prescription. Detailed clinical registration of RTI consultations of patients of all ages resulted in an antibiotic prescribing rate of 38%, and revealed that 46% of these prescriptions were not indicated according to the guidelines. Over-prescription in children was 32%, and although lower than for adults, a child-specific intervention for these patients and their parents is also needed, since risk-factors for a complicated course and indications for antibiotic treatment are different for children, and because the interaction between parent and GPs is supposed to play a role in over-prescription. In the second part of this thesis we assessed the effect of the RAAK intervention, an online training for GPs and information booklets for parents. Antibiotic prescribing was significantly reduced based on GPs' registrations of consultations (antibiotic prescription rate of 21% in the intervention group, versus 33% in the control group) and on pharmacy dispensing data (32 courses per 1000 children/year less in the intervention group). In the third part we evaluated various aspects of the RAAK intervention. First, its cost-effectiveness from a societal perspective: the simple and concise online intervention was effective in reducing antibiotic prescribing at very low costs, given an incremental cost effectiveness rate of €0.85 per percentage decrease in antibiotic prescribing. Second, from the perspectives of the intervention-targeted groups, the parents reported a prior reticence towards antibiotics for their children. Educating parents specifically on the (non-)effectiveness of antibiotics and antimicrobial resistance seemed less relevant than trust in the GP, reassurance, and clear safety netting. GPs expected that they had also learned as a result of informal learning processes consciously, or unconsciously initiated after the formal training when they applied the acquired knowledge in practice, for example by asking explicitly about the parents' aim of the consultation, or their expectations of antibiotics. GPs who undertook more informal learning activities such as reflection on their own prescribing routines, dialogue with colleagues about their experiences and giving feedback to GP trainees expected that their prescription behaviour had changed more.

STUDY OUTCOMES

The primary outcome of the RAAK intervention (chapter 4) was as in many primary care interventions the proportion of consultations in which an antibiotic was prescribed, the antibiotic prescription rate.[1,2] However, the effect size of this outcome is highly dependent of the setting and study population. The prescribing rate in our Dutch trial was already low as compared to other studies and, therefore, the decrease might be lower than in settings where (over)prescription is more frequent.[3] Some studies aim to determine the appropriateness of antibiotic prescribing, by measuring compliance with prescribing guidelines, especially in hospital settings, but also in primary care.[4,5] To this aim detailed registration of consultations is needed, which is complex, labour intensive and could thereby interfere with daily practice. Our second outcome was the total number of dispensed antibiotics per 1000 PY from pharmacy data. This outcome provides proper insight in the effect size of the intervention in comparison to other studies, since the denominator is equal. However, this outcome is less specific since the clinical diagnosis for prescribing is lacking from pharmacy data.

Bacterial resistance has been suggested to be included as an outcome in antibiotic stewardship interventions, since this is the major problem to be tackled by these programs.[1,2,6] Wide inter-country susceptibility variation is noted for Streptococcus pneumoniae, which is the most common bacterial cause for RTI infections. The percentages of isolates with penicillin non-susceptibility in Europe ranged in 2016 between 0.4% in Belgium (followed by 2.2% in the Netherlands) and 41% in Romania, and for macrolide non-susceptibility between 0% in Iceland (followed by 3.1% in the Netherlands) and 60% in Cyprus.[7] Reported resistance rates of bacterial respiratory pathogens from unselected hospital wards showed that S. pneumoniae is rarely non-susceptible in the Netherlands. However, this percentage was slowly increasing from <1% in 1998 to 2% in 2008, of which 50% had intermediate resistance.[8] Resistance for doxycycline of community isolates of S. pneumoniae increased to 11.5% in 2008, which resulted in a switch from doxycycline to amoxicillin as first choice treatment in primary care guidelines for RTIs.[8] The etiology of clinically diagnosed lower RTI in adults was studied in the Dutch community in 2004.[9] A bacterial cause was established in 30% of the cases, mainly including Streptococcus pneumoniae, Haemophilus influenza and Mycoplasma pneumoniae, and a viral cause in 39%, mainly influenza virus A; in many patients no causative pathogen could be identified.[9] Moreover, childhood community-acquired pneumonia is often caused by a virus.[10] Recent and routine care data on resistance patterns of respiratory pathogens in the community are missing in many countries, including the Netherlands. GPs hardly ever collect respiratory samples for bacteriological cultures and antibiotic susceptibility testing. Mainly urine samples from a selected patient population are collected in case of complicated urinary tract infection, or antimicrobial therapy failure. Concluding, as resistance rates are low in the Netherlands and a bacterial pathogen is often not identified in patients with RTI, a reduction in the incidence of antibiotic-resistant bacteria is currently not a relevant outcome for trials in the Dutch population. The high resistance to penicillin in other European countries should still be considered as an encouragement to pursue rational antibiotic prescribing in Dutch primary care to maintain our unique low resistance rates.

The antibiotic prescribing rate as study outcome provides relevant information for specific indications, and the number of dispensed antibiotics/1000 PY provides comparison of effect sizes between different studies with different study populations. For the future, it would be preferable when routine primary healthcare data could be retrieved directly from the digital patient records, including consultation and prescribing data linked to clinical diagnoses, as described in chapter 2 for practices participating in a specific research network. For other practices reliable collection of routine care data is still problematic because of technical problems linked to the various information systems, the varying ways GPs use their information system, missing data and inconsistencies. Algorithms for data collection from the information system should be developed and tested in the near future and could then be used for research purposes.

SAFETY OF REDUCING ANTIBIOTIC USE

Because of the results of chapter 2 and 3, we are convinced that even in a low prescribing country as the Netherlands there is room for improvement in antibiotic management. However, reducing antibiotic use should not increase the risk of potential harm, such as complications or hospital admissions. To accomplish reduction in a comprehensible and safe way the RAAK intervention focused on the clinical guidelines of the Dutch College of GPs. In chapter 4 we did not find a difference in hospital referral between both groups, and a previous intervention in the Netherlands showed that after guideline education, over- as well as under-prescription decreased, meaning that prescribing was better targeted.[5] This indicates the safety of interventions including guideline education. When we ask ourselves 'how low can you go?', we refer to the detailed registration of 900 RTI consultations for children in chapter 3 of this thesis. These consultations were mirrored against the guidelines to judge the appropriateness of antibiotic management. Antibiotic management was considered appropriate in 196 out of 900 consultations. Therefore, the prescription rate for children with RTI could be 22%, resulting in a possible absolute reduction of 10%. Since the RAAK intervention reduced antibiotic prescribing by 12% in a comparable population, we assume to have reached an appropriate antibiotic prescribing rate based on guideline recommendations.

Randomized controlled trials generally have insufficient power to examine the effects of antibiotic prescribing on rare complications and hospital admissions, since the risk of these are already low and large sample sizes are therefore needed. A Cochrane review focusing on the effect of antibiotics for children with acute otitis media used just over 3000 children and severe complications were rare in high income countries and did not differ between children treated with antibiotics and those treated with placebo.[11] To treat thousands of children to prevent one complication will be meaningless and will result in harm due to children experiencing more often adverse events, such as vomiting, diarrhea or rash; the number needed to treat for an additional harmful outcome was 14 for otitis media. A large primary care database study with over 3 million episodes analysed the risk of serious complications in treated and untreated patients with common infections in the month after diagnosis. Serious complications were rare in the community after upper RTI, sore throat, and otitis media and the number needed to treat to prevent one complication was over 4000.[12] Gulliford *et al*. studied the association between low antibiotic prescribing and the incidence of serious complications in the United Kingdom using routine care data of roughly 45 million patient years.[13] General practices in which GPs prescribed antibiotics less often for RTI had slightly higher rates of pneumonia and peritonsillar abscess, but not of other serious infections. The magnitude of this effect is put into perspective in the next calculation: if a general practice with 7000 patients reduces antibiotic prescribing by 10%, they might encounter one case of pneumonia more each year, and one case of acute peritonsillar abscess more each decade.[13] Extending this for an average Dutch practice with 2000 patients a 10% reduction will result in one additional pneumonia case every three to five years, and one extra peritonsillar abscess case every 30 to 40 years. Based on our own studies and these community studies we expect that the risk of potential harm of reducing antibiotic use by guideline education and information for parents is not in proportion to the benefits: demedicalization of self-limiting disease, reducing antibiotic-associated side-effects and reducing antibiotic resistance. However, when patients start accepting the self-limitedness of mild RTIs and experiencing the GPs' non-prescribing decision, this could result in lower consultation on a long term. Therefore, safety netting, including clear advice when a GP consultation is needed will become essential, and above all, primary care should remain easily accessible to limit the risk of complications.

CHANGING PRESCRIBING BEHAVIOUR

We showed a significant reduction in antibiotic prescribing by GPs in the intervention group (chapter 4). For further implementation purposes it is of upmost interest to know why and which elements of the intervention influenced antibiotic prescribing. Previous multifaceted interventions also showed a significant effect, as well as interventions including an information booklet.[2,14] The RAAK intervention targeted GPs as well as parents since the cause of over-prescription is multifactorial; it is influenced by both GPs' and parents'/patients' beliefs, expectations and knowledge. We anticipated that a simple, concise, online intervention would be a good opportunity to influence prescribing behavior, without too much time investment.

GPs valued the various parts of the online training, the guideline information and communication skills videos, as explored in chapter 7. No specific aspect from the intervention was indicated to be solely responsible for the effect. Despite the message that most information was not new to them, it did help them to brush up existing knowledge and it created more awareness of antibiotic overprescribing and for antibiotic-related problems; this motivated them to improve their prescribing routines. As described in chapter 6, parents were enthusiastic about the RAAK information booklet, as it confirmed their pre-existing views. Although interactive use of information material has been recommended in previous studies, the Dutch parents regarded this not necessary.[15,16] This might have been because the content was not contrary to their views and expectations. Furthermore, the booklet might provide or facilitate a dialogue about antibiotic management and safety netting during the index consultation and/or future consultations. Parents preferred to read the booklet in detail at home, and the information about self-management and safety-netting was regarded as most relevant and useful to them.

Although we showed that an intervention does not need to be very complex, a too simple intervention can be ineffective, or even have undesirable effects as was recently shown in an intervention for children in Belgium.[17] This intervention stimulated eliciting parental concerns by asking parents three questions at the start of the consultation: "Are you concerned?", "What exactly concerns you?" and "Why does this concern you?", supplemented with an information leaflet as safety netting advice. This way of eliciting parental concerns appeared to increase antibiotic prescribing.[17] Discussing parents' request for help and worries were also imbedded in the RAAK training, but supported by explanation and videos of communication techniques. GPs were also stimulated to directly elicit parents' expectations of antibiotics' effectiveness rather than general concerns only. More educational support seems to be needed in an intervention to be effective.

We can conclude that the multifaceted design and not specifically one aspect of the RAAK intervention was relevant for its effect. Stimulating awareness of both GPs and parents and facilitating their dialogue enhanced more rational antibiotic prescribing (chapter 6 and 7). We expect that stimulating self-reflection on GPs' prescribing routines, feedback to others, and dialogue with colleagues would support a permanently targeted prescribing practice after the online training (chapter 7).

FUTURE PERSPECTIVES

In addition to the registration period, we could measure the effect of the intervention over one complete year by using pharmacy data. The intervention effect may dilute over time and the content needs to be revised to maintain focus, and since medical science is evolving quickly, especially research in the field of general practice has undergone rapid development over the past thirty years.[18] Chapter 2 and 3 showed that GPs could need an incentive to warrant continuously working on prescribing routines. It is open for discussion how much control should be involved and what the consequences would be of inappropriate prescribing. For example, antibiotic prescribing could be regularly evaluated with affiliated pharmacists and become part of the practice accreditation of the Dutch college of GPs. Education, such as the RAAK intervention, could be provided if deemed necessary. However, many GPs in the Netherlands currently feel overloaded due to administrative obligations in healthcare.[19] Nevertheless, administrative obligations which improve direct patient care, appropriate use of care and transparency of care are regarded as relevant by these GPs.[19] How to easily collect and evaluate data from daily practice and select GPs for education should be further investigated.

Evidence of the effectiveness of antibiotics in children with RTI and specific diagnostic possibilities are lacking, which creates uncertainty for clinicians and thereby result in over-prescription. Future research might provide better insight in which groups of children do benefit from antibiotic treatment, and how to identify these children by new diagnostic opportunities. This will support to solve the problem of inappropriate antibiotic prescribing.

High attention is needed for the expected global increase in antibiotic consumption, since the daily defined doses between 2000 and 2015 increased by 65%.[20] While providing access to these lifesaving drugs in low- and middle-income countries, with higher burden of infectious diseases, there is a need for global surveillance of antibiotic consumption. Successful interventions such as the Dutch RAAK intervention need to be tailored and investigated in low- and middle-income countries, to reduce antibiotic consumption and resistance where it is highly needed.

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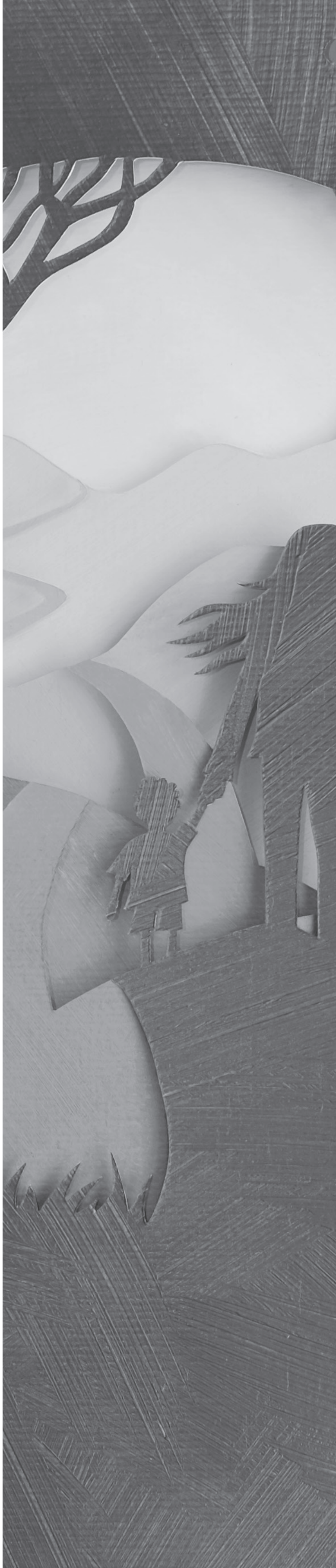
Summary



Around 80% of antibiotics used in health care are prescribed by general practitioners (GPs). Most antibiotics are prescribed for respiratory tract infections (RTIs) and ear infections. Irrespective of the viral or bacterial cause, most of these infections have a mild course, and are self-limiting. Antibiotics are only indicated for selected groups of patients for whom the benefits outweigh the harms of antibiotics for themselves and the community, as described in the guidelines of the Dutch College of GPs. However, there are clear signs of misuse of antibiotics in primary care, resulting in the development of bacterial resistance, which is an increasingly serious threat to global public health. Furthermore, overprescribing of antibiotics leads to medicalization and unnecessarily exposes patients to adverse effects. Increasing awareness of antibiotic-related problems has initiated numerous interventions aiming to improve antibiotic prescribing practice.

Children mainly visit their GP with infectious diseases, and RTI and ear infections are responsible for most antibiotic prescriptions, despite their marginal benefit in these infections. In contrast to the evidence of effective interventions to reduce prescribing for adults, there is a paucity of interventions aiming to improve antibiotic prescribing specifically for children in primary care. GPs tend to prescribe an antibiotic for children, as the safer course of action, because they feel uncertain about indicating seriously ill children. Besides, parental fears, their beliefs and expectations can play an important role in the GP's decision to prescribe an antibiotic. An online educational program for GPs as studied previously for adult patients with lower RTI has not been studied to improve antibiotic prescribing for children in primary care.

In part I of this thesis we provide insight in the presentation and antibiotic management of infectious diseases in primary care and assess the appropriateness of antibiotic prescribing for RTI. In part II we aim to reduce antibiotic prescribing for children with RTI in primary care by the RAAK intervention. In part III we evaluate the cost-effectiveness and the perceived influence by parents and GPs of the RAAK intervention.

PART I ANTIBIOTIC MANAGEMENT IN PRIMARY CARE

Overall antibiotic use by children has rarely been described in relation to the specific diagnoses for which they were used. This information is needed to obtain a complete picture of antibiotic management of children by GPs, including consultation incidences and the proportion of episodes with an antibiotic prescription. In **chapter 2** we used consultation data collected from 45 general practices in the Netherlands in 2012. These routine care data showed 1029 infectious disease episodes with 262 antibiotic prescriptions per 1000 person-years, with the highest number of prescriptions for children of 1 year of age (714/1000 person-years). Acute upper RTI was the most common reason to visit the GP and the second most frequent indication for antibiotic prescription. Use of broad spectrum antibiotics, including amoxicillin (55%), macrolides (14%) and amoxicillin/clavulanate (10%) was high and use of narrow spectrum antibiotics was low (10%). This detailed insight in antibiotic management of childhood infections showed targets for Dutch improvement strategies: (i) prevent antibiotic prescribing for acute upper RTI and bronchitis; (ii) stimulate the use of narrow-spectrum antibiotics; and (iii) reduce the use of macrolides and amoxicillin/clavulanate. Furthermore, this information is helpful to compare antibiotic policy between countries.

Numerous studies suggest overprescribing of antibiotics for RTIs, without really authenticating inappropriate prescription. In **chapter 3** we studied detailed registration of RTI consultations by GPs, including all relevant clinical information. These consultations were benchmarked to the prescribing guidelines for acute otitis media, acute sore throat, rhinosinusitis or acute cough. The overall antibiotic prescribing rate was 38%. Of these prescriptions 46% were not indicated by the guidelines. Relative overprescribing was highest for consultations of throat symptoms (including tonsillitis) and lowest for ear symptoms (including acute otitis media). Absolute overprescribing was highest for lower RTIs (including bronchitis). An antibiotic was prescribed in 32% of the consultations for children till 18 years, of which one third did not meet the guideline indications. Overprescribing was highest for patients between 18–65 years of age, when GPs felt patients' pressure for an antibiotic treatment, for patients presenting with fever and with complaints longer than one week. Underprescribing was observed in less than 4% of all consultations without a prescription.

PART II INTERVENTION TO REDUCE ANTIBIOTIC PRESCRIBING FOR CHILDREN

In **chapter 4** we aimed to reduce antibiotic prescribing for children with RTI by the RAAK intervention (Rational Antibiotic use Kids), an online training for GPs and information booklets for parents. We performed a pragmatic cluster randomized, controlled trial in primary care. After randomization, GPs of in total 32 general practices registered 1009 consultations. An antibiotic was prescribed in 21% of consultations in the intervention group, compared to 33% in the usual care group, adjusted for baseline prescribing (RR 0.65, 95% CI 0.46–0.91). The probability of reconsulting during the same RTI episode did not differ significantly between the intervention and control groups, nor did the numbers of consultations for new episodes and hospital referrals within 6 months. In the intervention group antibiotic dispensing was

32 courses per 1000 children/year lower than the control group, adjusted for antibiotic dispensing at baseline (RR 0.78, 95% CI 0.66–0.92). The numbers and proportion of second choice antibiotics did not differ significantly. With this trial we showed that a concise, feasible, online GP training, with an information booklet for parents resulted in a relevant reduction in antibiotic prescribing for children with RTI.

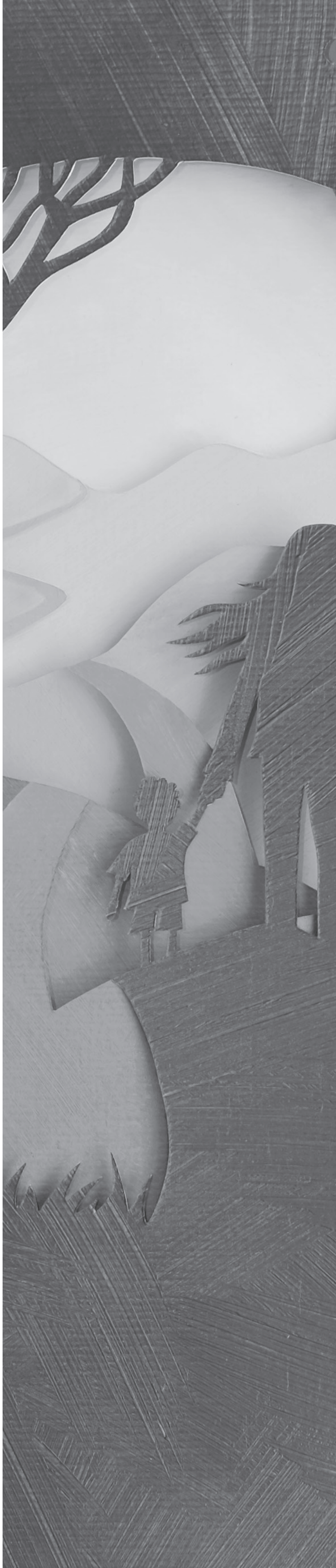
PART III EVALUATION OF THE INTERVENTION

Evaluation of costs of effective interventions to reduce antibiotic prescribing are limited, and not yet performed for children. There is a need for cost-effectiveness analysis to identify the most cost-effective strategies to reduce antibiotic use. In **chapter 5** we performed a trial-based cost-effectiveness analysis to evaluate the effect, GP antibiotic prescribing, and costs of the RAAK intervention from a societal perspective. We included children consulting the GP with RTI symptoms of whom parents kept a two-week (cost) diary. The cost difference between the intervention and usual care group per percentage decrease in antibiotic prescribing was calculated, resulting in an incremental cost-effectiveness ratio (ICER). Costs and effects of 153 children in the intervention and 107 in the usual care group were available for analysis. Antibiotic prescribing in the intervention group was 12% lower than in the usual care group and the difference in costs was €10.27 per child. This resulted in an ICER of €0.85 per percentage decrease in antibiotic prescribing. The bootstrap analysis showed that the probability that the intervention was effective but more expensive was 53% and that the intervention was effective, but cost-saving was 41%. The scenario analysis from a healthcare perspective resulted in a decrease of the antibiotic prescribing rate of 12%, with mean cost-savings of €-8.98, implying that the intervention was more effective, at lower costs. We conclude that the RAAK intervention resulted in a decrease in antibiotic prescribing for children with RTI at very low costs and should therefore be considered for implementation in primary care.

In **chapter 6** we conducted semi-structured qualitative interviews with 18 Dutch parents, who consulted the GP with their child for RTI symptoms and received the RAAK information booklet. We explored their reported attitude and knowledge towards antibiotics and management of childhood RTI, as well as the added influence of an information booklet, as perceived by parents. The information booklet confirmed parents' pre-existing views towards antibiotics. Therefore, parents reported that it did not really change their attitude, but it did make them feel more confident to 'wait and see' first. They valued that the booklet substantiated their prior reticence towards antibiotics, and provided a better understanding of the GPs' treatment decision. Most parents trusted the GPs' professionalism and valued their judgement about the severity and treatment of the illness, and they expected reassurance during the consultation. The antibiotic-related information, especially about bacterial resistance seemed difficult to understand. Information about when to consult the GP was regarded as most relevant. In countries with a comparable context of low antibiotic use, focus of information supply should be on enhancing self-efficacy and providing safety-netting advice. For other countries it is recommended that the knowledge, attitude and perception of the population is studied, in order to be able to tailor information supply.

In **chapter 7** we aimed to understand how prescribing behaviour of GPs is influenced by the online training and by informal learning afterwards. We conducted semi-structured interviews with 19 GPs, who followed the online training within the RAAK trial. GPs valued the various parts of the online training, the guideline information and communication skills videos. No specific aspect from the intervention was indicated to be solely responsible for the effect. Despite the message that most information from the training was not new to them, it did help them to brush up existing knowledge and it created more awareness of antibiotic overprescribing and for antibiotic-related problems; this motivated them to improve their prescribing routines. GPs expected that they had learned as a result of informal learning processes consciously or unconsciously initiated after the formal training when they applied the acquired knowledge in practice, for example by asking explicitly about the parents' aim of the consultation, or their expectations of antibiotics. GPs who undertook more informal learning activities, such as reflection on their own prescribing routines, dialogue with colleagues about their experiences and giving feedback expected that their prescription behaviour had changed more. GPs supervising a GP trainee had more opportunities for these informal learning activities.

Nederlandse samenvatting



Van alle antibiotica in de gezondheidszorg wordt ongeveer 80% voorgeschreven door huisartsen en voornamelijk voor luchtweginfecties en oorontstekingen. Deze infecties hebben meestal een mild beloop en gaan vaak vanzelf over, ongeacht of de ontsteking door een virus of een bacterie wordt veroorzaakt. Antibiotica zijn geïndiceerd voor een geselecteerde groep patiënten, waar de voordelen van behandeling met antibiotica opwegen tegen de nadelen voor henzelf en die van de bevolking. Desondanks zijn er signalen van onnodig gebruik van antibiotica in de eerste lijn. Dit resulteert in de ontwikkeling van bacteriële resistentie, een toenemende bedreiging voor de wereldwijde volksgezondheid. Over-prescriptie van antibiotica leidt daarnaast tot medicalisering en stelt patiënten onnodig bloot aan bijwerkingen. Door een toegenomen bewustwording van problemen gerelateerd aan antibioticagebruik zijn verschillende interventies geïnitieerd om het voorschrijven van antibiotica te verbeteren.

Kinderen bezoeken de huisarts voornamelijk voor infecties. Luchtweginfecties en oorontstekingen leiden tot de meeste antibioticavoorschriften, ondanks het beperkte effect op ziekteduur en symptomen. In tegenstelling tot het aantal onderzoeken met het doel antibioticavoorschriften voor volwassen te reduceren, zijn er nauwelijks onderzoeken om het voorschrijven van antibiotica voor kinderen in de eerste lijn te verbeteren. Huisartsen neigen antibiotica voor te schrijven voor kinderen als de veiligere keuze, doordat ze zich onzeker kunnen voelen over de ziekte-ernst van een kind. Daarnaast spelen de onzekerheden, overtuigingen en verwachtingen van ouders ook een belangrijke rol in de beslissing van de huisarts om antibiotica voor te schrijven. Een online scholingsprogramma voor huisartsen, zoals eerder onderzocht bij volwassenen met lage luchtweginfecties, is niet onderzocht om het voorschrijven van antibiotica voor kinderen in de huisartsenpraktijk te verbeteren.

In deel I van dit proefschrift geven wij inzicht in de presentatie van en het antibioticabeleid voor infecties in de huisartsenpraktijk en bepalen wij in hoeverre antibiotica terecht worden voorgeschreven voor luchtweginfecties. In deel II onderzoeken wij het effect van de RAAK interventie op het voorschrijven van antibiotica voor kinderen met luchtweginfecties in de huisartsenpraktijk. In deel III evalueren wij de kosteneffectiviteit van de RAAK interventie en de ervaringen van huisartsen en ouders met de online scholing en het informatieboekje.

DEEL I ANTIBIOTICABELEID IN DE HUISARTSENPRAKTIJK

Het voorschrijven van antibiotica voor kinderen in de eerste lijn is nog maar zelden beschreven in relatie tot de diagnose waarvoor ze worden gebruikt. Deze informatie is relevant om een compleet beeld te krijgen van het antibioticabeleid van huisartsen. In **hoofdstuk 2** gebruikten wij anonieme routinezorgdata van kinderen onder de 18 jaar met infecties, welke werden verzameld in 45 huisartspraktijken in Nederland in 2012. Deze toonden 1029 episoden per 1000 persoonsjaren waarin 262 antibioticakuren per 1000 persoonsjaren werden voorgeschreven. Het hoogste aantal voorschriften was voor kinderen van 1 jaar (714/1000 persoonsjaren). De meest voorkomende reden om de huisarts te bezoeken was voor acute bovenste luchtweginfecties en dit was de tweede meest frequente indicatie om antibiotica voor te schrijven (na oorontstekingen). Het gebruik van breedspectrum antibiotica, inclusief amoxicilline (55%), macroliden (14%) en amoxicilline/clavulaanzuur (10%) was hoog en het gebruik van smal-spectrum-antibiotica was laag (10%). Deze observationele studie gaf inzicht in het antibioticabeleid voor kinderen en toonde kernpunten voor verbetering: (i) voorkom onnodig antibioticagebruik voor bovenste luchtweginfecties en bronchitis; (ii) stimuleer het gebruik van smal-spectrum-antibiotica en (iii) verlaag het gebruik van macroliden en amoxicilline/clavulaanzuur. Tenslotte is deze inzage in het antibioticabeleid van kinderen in Nederland relevant om het antibioticabeleid eerlijk te kunnen vergelijken met andere landen.

Eerdere studies suggereerden dat antibiotica vaak onnodig worden voorgeschreven voor luchtweginfecties, zonder concreet vast te stellen wanneer het voorschrift niet geïndiceerd is. In **hoofdstuk 3** onderzochten we gedetailleerde huisartsenregistraties van consulten voor luchtweginfecties over alle leeftijden. Deze consulten werden gespiegeld aan de volgende richtlijnen van het Nederlands Huisartsen Genootschap: acuut hoesten, acute otitis media, acute keelpijn en acute rhinosinusitis. In 38% van de consulten werd een antibioticum voorgeschreven, hiervan was 46% niet geïndiceerd volgens de richtlijnen (over-prescriptie). Relatief was er het meeste sprake van over-prescriptie bij keelklachten (inclusief tonsillitis), en het minste bij oorklachten (inclusief otitis media acuta). Over-prescriptie kwam absoluut het meeste voor bij lage luchtweginfecties (inclusief bronchitis). In 32% van de consulten bij kinderen werd een antibioticum voorgeschreven, waarvan een derde niet voldeed aan de indicaties volgens de richtlijnen. Over-prescriptie kwam het meest voor bij patiënten tussen 18 en 65 jaar, wanneer huisartsen druk van patiënten ervaarden om een kuur voor te schrijven, bij patiënten met koorts en klachten die langer dan een week duurden. In minder dan 4% van de consulten werd geen kuur voorgeschreven, terwijl dit volgens de richtlijnen wel geïndiceerd was (onder-prescriptie).

DEEL II INTERVENTIE OM ANTIBIOTICA-VOORSCHRIFTEN TE REDUCEREN

In **hoofdstuk 4** onderzochten we het effect van de RAAK interventie (Rationeel Antibiotica-gebruik Kinderen), een online scholing voor huisartsen en informatieboekjes voor ouders, op het voorschrijven van antibiotica voor kinderen met luchtweginfecties. Wij voerden een pragmatische, cluster-gerandomiseerde studie uit. Na randomisatie van de interventie- en controlegroep registreerden huisartsen uit 32 praktijken 1009 consulten van kinderen met luchtweginfecties. In 21% van de consulten in de interventiegroep werd een antibioticum voorgeschreven vergeleken met 33% van de consulten in de controlegroep, gecorrigeerd voor het voorschrijven van antibiotica in het jaar voor de interventie (RR 0.65, 95% CI 0.46–0.91). De kans op herconsultatie van de huisarts binnen dezelfde ziekte episode verschilde niet significant tussen beide groepen, net als het aantal nieuwe episoden voor luchtweginfecties en het aantal ziekenhuisverwijzingen binnen zes maanden. Het aantal antibiotica-uitgiften door apotheken gerelateerd aan de interventiegroep was 32 kuren per 1000 kinderen per jaar lager dan in de controlegroep, gecorrigeerd voor het aantal uitgiften in het jaar voor de interventie (RR 0.78, 95% CI 0.66–0.92). Het aantal en het percentage tweedekeusantibiotica verschilden niet significant tussen beide groepen. Met deze gerandomiseerde studie toonden wij aan dat een beknopte, haalbare online scholing voor huisartsen in combinatie met informatieboekjes voor ouders resulteerde in een klinisch relevante reductie van antibioticavoorschriften voor kinderen met luchtweginfecties.

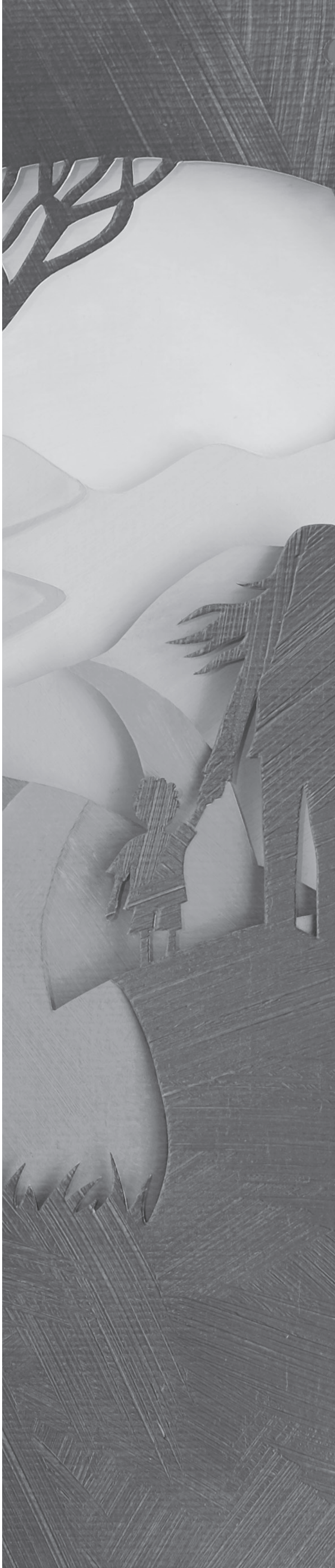
DEEL III EVALUATIE VAN DE INTERVENTIE

Er zijn weinig kosteneffectiviteitsevaluaties uitgevoerd van interventies om antibioticavoorschriften te reduceren, en niet eerder voor interventies gericht op kinderen. Kosteneffectiviteitsanalyses zijn relevant om de meest kosteneffectieve strategie voor het reduceren van antibioticagebruik te identificeren. In **hoofdstuk 5** voerden wij een kosteneffectiviteitsanalyse uit om de effecten op het voorschrijven van antibiotica door huisartsen en de kosten van de RAAK interventie te evalueren vanuit een maatschappelijk perspectief. We includeerden kinderen uit het RAAK onderzoek, waarvan de ouders een kostendagboek gedurende maximaal twee weken hadden bijgehouden. Het verschil in kosten tussen de interventie- en controlegroep werd berekend per percentage daling in antibioticaprescriptie. Kosten en effecten van 153 kinderen in de interventiegroep en 107 kinderen in de controlegroep waren beschikbaar voor de analyse. Het percentage antibioticaprescriptie was 12% lager in de interventiegroep vergeleken met de controlegroep. Het verschil in kosten was €10,27 per kind. Dit resulteerde in een kosteneffectiviteitsratio van €0,85 per percentage daling in antibioticaprescriptie. Uit de bootstrapanalyse bleek een kans van 53% dat de interventie effectief maar duurder was en 41% dat de interventie effectief was en kosten zou besparen. De scenario-analyse vanuit een gezondheidszorgperspectief resulteerde ook in een daling in antibioticaprescriptie van 12%, met een kostenbesparing van €-8,98. Hierbij was de interventie dus effectiever met lagere kosten vergeleken met gebruikelijke zorg. Wij concluderen dat de RAAK interventie resulteert in een daling van antibioticaprescriptie voor kinderen met luchtweginfecties voor zeer lage kosten. Verdere implementatie in de eerste lijn moet daarom overwogen worden.

In **hoofdstuk 6** interviewden wij 18 ouders die de huisarts bezochten met hun kind vanwege een luchtweginfectie en het RAAK informatieboekje ontvingen. We exploreerden hun opvattingen en kennis ten aanzien van antibioticagebruik voor luchtweginfecties bij kinderen, en de invloed van het RAAK informatieboekje. Ouders voelden zich na het lezen van de informatie bevestigd in hun bestaande opvattingen over antibiotica. Ze verwachtten daardoor niet dat het boekje hun visie had veranderd, wel voelden ze zich meer zelfverzekerd om een natuurlijk herstel van een luchtweginfectie af te wachten. Ze waardeerden dat het boekje hun terughoudendheid voor antibiotica bevestigde en een beter begrip gaf in de behandelbeslissing van de huisarts. De meeste ouders hadden veel vertrouwen in het oordeel van de huisarts over de ziekte-ernst. Zij verwachtten voornamelijk geruststelling van de huisarts. De informatie over de effectiviteit van antibiotica en bacteriële resistentie bleek voor veel ouders lastig om te begrijpen. Ouders vonden de informatie wanneer de huisarts opnieuw geconsulteerd moest worden het meest relevant. In landen met een vergelijkbare context van laag antibioticagebruik, zal de informatie voor ouders voornamelijk gericht moeten zijn op het geven van zelfzorgadviezen en het bespreken van alarmsignalen. Voor andere landen wordt het aangeraden om eerst de kennis, opvattingen en perceptie van de populatie te onderzoeken, om de informatievoorziening daarop af te kunnen stemmen.

In **hoofdstuk 7** onderzochten wij hoe het voorschrijfgedrag van huisartsen werd beïnvloed door de online scholing en informeel leren nadien. Er werden semi-gestructureerde interviews afgenomen met 19 huisartsen, die de online scholing binnen het RAAK onderzoek hadden gevolgd. Huisartsen waardeerden de verschillende onderdelen van de online scholing, zowel de informatie uit de richtlijnen als de video's met communicatieve vaardigheden. Er kwam niet specifiek een aspect naar voren wat uitsluitend verantwoordelijk was voor het effect op hun voorschrijfgedrag. Ondanks dat veel informatie uit de scholing niet nieuw was voor de huisartsen, werd bestaande kennis opgefrist. Dit leidde tot meer bewustzijn van over-prescriptie en problemen gerelateerd aan het voorschrijven van antibiotica en motiveerde de huisartsen hun voorschrijfgewoonten te verbeteren. Huisartsen verwachtten dat zij bewust en onbewust leerden als gevolg van informele leeractiviteiten na het volgen van de scholing door de verkregen kennis toe te passen in de praktijk: wanneer ze ouders actief vroegen naar hun hulpvraag of naar hun verwachtingen ten aanzien van antibiotica. Huisartsen die meer informele leeractiviteiten ondernamen zoals reflectie van eigen voorschrijfgedrag, het uitwisselen van ervaringen met andere collega's en het geven van feedback, verwachtten dat hun voorschrijfgedrag meer was veranderd. Huisartsen die een arts in opleiding tot huisarts begeleidden hadden meer mogelijkheden voor deze informele leeractiviteiten.

Dankwoord



Tijdens mijn coschappen was ik er al uit, ik wilde huisarts worden! Ik ben dankbaar dat ik de kans kreeg om na mijn afstuderen dit promotieonderzoek te combineren met de huisartsopleiding. Hieronder wil ik de mensen bedanken die mij hebben begeleid en geholpen dit mogelijk te maken. Promoveren doe je niet alleen.

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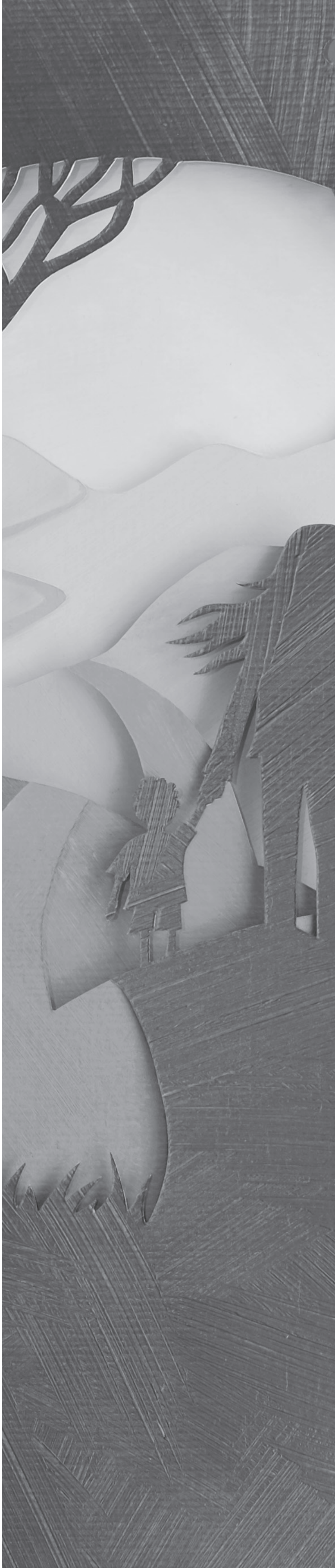
Curriculum vitae



Anne Dekker was born on August 13th 1989 in Leiden, the Netherlands. She attended the Stedelijk Gymnasium in Leiden and moved to Utrecht in 2007 to start her studies in Medicine at Utrecht University. In 2010 she travelled to Australia in her fourth year of medical school for an internship in Gynaecology at the Lyell McEwin Hospital in Adelaide under supervision of prof. dr. G.A. Dekker, followed by a three-month journey through Australia, Indonesia and Borneo. In 2011 she followed her Austrian roots and performed an internship in ophthalmology at the Salzburger Landeskliniken under supervision of prof. dr. G. Grabner. During her research internship at the Julius Center for Health Sciences and Primary Care of the Utrecht Medical Center (UMC) Utrecht, she became fascinated about how science could influence health for the population in contrary to individual care in practice. This internship formed the basis of her interest in research on antibiotic use for respiratory tract infections in primary care. She analysed over-prescription of antibiotics for respiratory tract infections, which resulted in her first publication. After graduating from medical school, her work could be continued as a PhD-student under supervision of prof. dr. Th.J.M. Verheij and dr. A.W. van der Velden. She continued the project as an AIOTHO, combining her work as a general practice trainee with her PhD project. After almost two years of research, she did her first year as a general practice trainee in Amersfoort under supervision of Karel Bos. Subsequently, she continued her research, alternated with her second year of general practice vocational training and completed the postgraduate Master in Clinical Epidemiology at Utrecht University. After her PhD defense, she will continue her training to become a general practitioner.