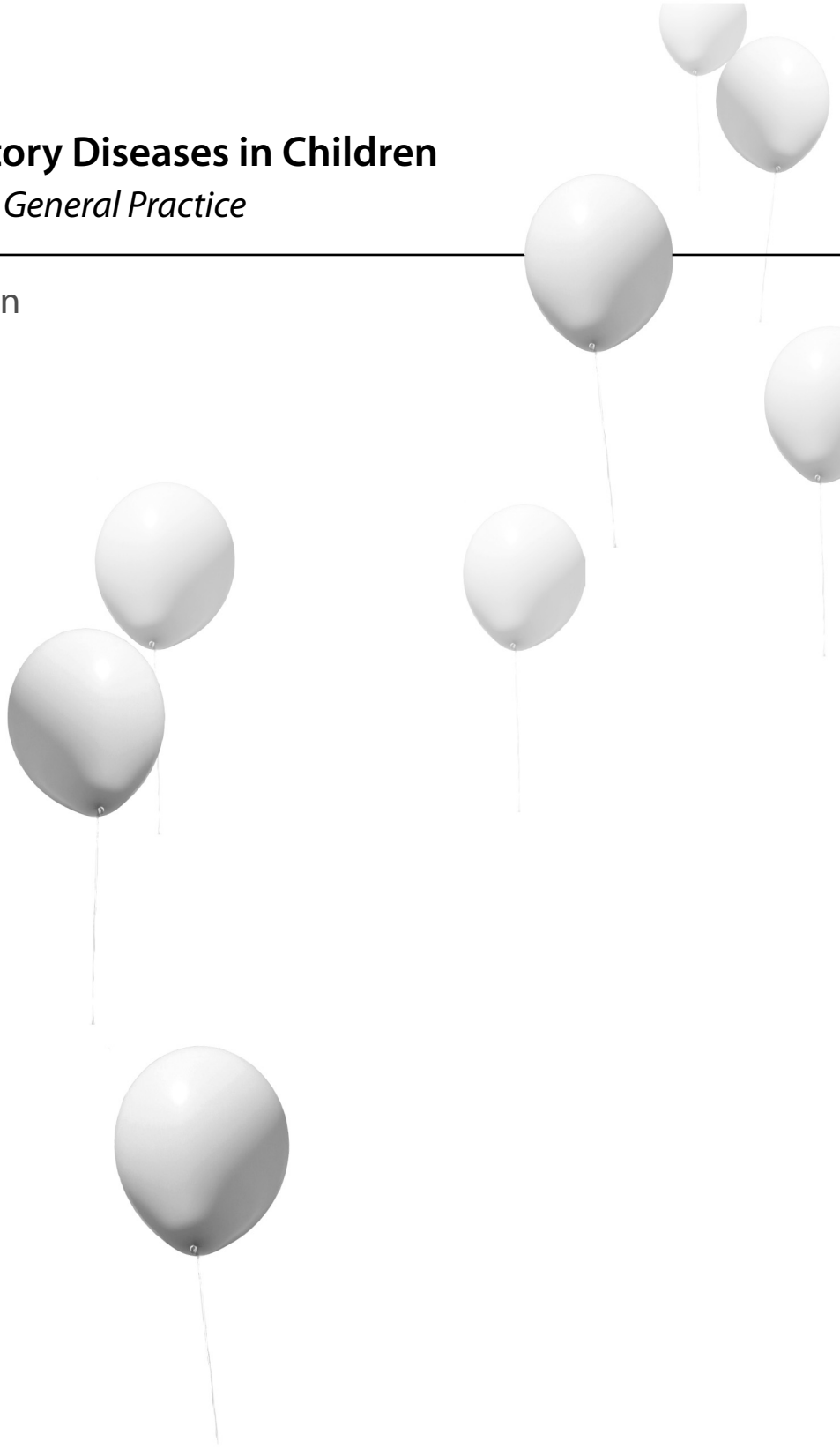
Respiratory Diseases in Children

Studies in General Practice

Hans Uijen



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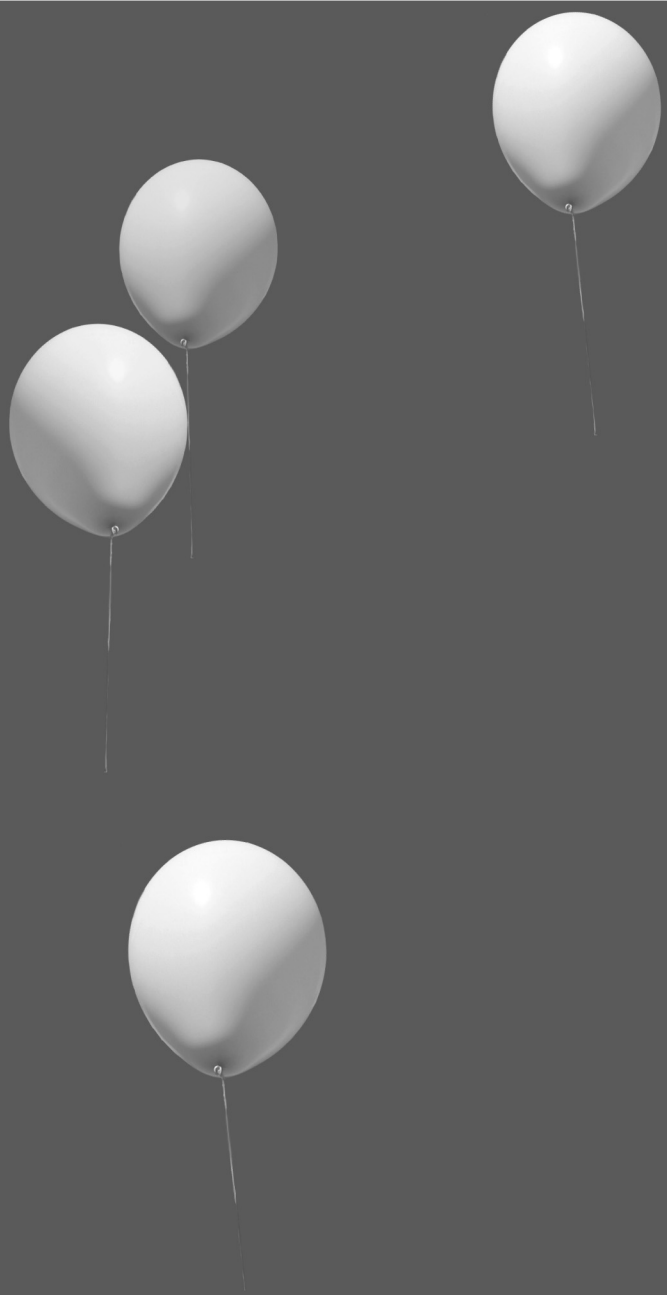

INTRODUCTION

Nowadays, although considerable attention is paid to chronic conditions and preventive medicine in adults, less attention is paid to common complaints and diseases in children in general practice.[1,2] Studies of morbidity patterns in children in general practice are important to gain insight into the health of the future population. Respiratory symptoms and diseases are the most frequently occurring common complaints and diseases in children. Surveillance of respiratory diseases in childhood and monitoring of common treatment strategies in general practice are important to identify and monitor problems and priorities, changes over time, and newly emerging issues.

In the total spectrum of respiratory disease and its management in children in general practice, many questions and topics still need attention: ranging from disease incidence rates, to diagnostic strategies, therapeutic decision-making and referral rates.

Respiratory symptoms and diseases in the general population

As stated above, respiratory tract symptoms and diseases are common in children in the general population.[3] Respiratory problems can be divided into symptoms and diseases of the upper respiratory tract (ENT problems, including cough, earache, sore throat, otitis media, tonsillitis) and the lower airways (as cough, wheezing, dyspnoea, pneumonia, bronchitis, asthma). More than 80% of all illnesses in children are dealt with by parents without using professional healthcare services.[4] Children consult their general practitioner (GP) in about 10% of all illness episodes and, [4] of this low proportion, respiratory symptoms account for about 25% of all consultations of children in general practice.[5] Therefore, GPs generally see only the 'top of the iceberg' in relation to respiratory complaints.[6,7]

Exactly why and when parents and their children decide to consult their GP for respiratory symptoms is unknown. Moreover, children (and/or parents) and the GPs seem to have different expectations about the consultation.[8,9] For example, patients (to a greater extent than GPs) regard respiratory tract symptoms as a serious problem, and generally believe that consulting a GP is necessary because antibiotics or other medication prescribed by the GP are an essential step in the treatment of respiratory infections.[9] In contrast, GPs know that most respiratory symptoms are self-limiting and most respiratory symptoms do not need antimicrobial treatment. Studies in adults show that older age, worry, and being cued by others to consult, are correlated with consulting the GP for respiratory symptoms and diseases.[10] However, the child-related and GP-related determinants influencing GP consultation for respiratory symptoms by children are largely unknown.

Respiratory symptoms and diseases in general practice: incidence, diagnosis and management

Some studies have reported a decreasing trend of GP consultation rates for respiratory symptoms and ENT problems, such as tonsillitis.[11,12] Incidence rates of respiratory symptoms and diseases in children in Dutch general practice are scarce and outdated. Considering the decreasing time trends in other countries, the question arises whether incidence rates for respiratory symptoms and diseases in children in the Dutch population are also changing. More recent data are needed in order to plan care in general practice, to allocate resources, and to predict referrals and hospital admissions in children with respiratory symptoms or diseases. To obtain relevant data, the focus must be on the incidence rates of respiratory symptoms and diseases that occur most frequently in children, i.e. otitis media, otitis media with effusion, sinusitis and tonsillitis.

For the diagnosis and management of respiratory symptoms and diseases GPs are supported by evidence-based guidelines and, in case of lack of evidence, consensus-based guidelines. In the Netherlands, the Dutch College of General Practitioners has issued guidelines on acute otitis media, serous otitis, sore throat, (rhino)sinusitis, tonsillitis, and asthma.[13-6] Generally, these guidelines state that the diagnosis of respiratory tract infections should predominantly be based on history and physical examination.

Most of the guidelines are reluctant to recommend antibiotics, and antibiotic treatment is only warranted in small groups of high-risk patients or in specific circumstances. GPs in Europe and the USA are encouraged to reduce their prescribing of antibiotics to diminish or prevent resistance of pathogens for antibiotics.[17-19] In the Netherlands,[20,21] antibiotics are prescribed in about one third of the respiratory episodes, while in other European countries and in the USA antibiotics are prescribed in more than half of all respiratory episodes.[22,23] Compared with other countries, in the Netherlands antibiotics are less frequently prescribed.[24] In the USA the rate of antimicrobial prescribing overall, and for respiratory infections in children younger than 15 years, decreased between 1990 and 2000 from about 800 to 500 per 1,000 children.[22] In spite of the relatively lower antibiotic prescription rates by GPs in the Netherlands, it is unknown whether in the last decade Dutch GPs also show a trend of decreasing use of antibiotic prescriptions for respiratory symptoms and diseases.

Recommendations for drug treatment in children with asthma have changed over the last 20 years and many related guidelines have been issued and/or revised. The Global Initiative for Asthma (GINA) recommends a stepwise approach with different asthma medications based on control of the asthma symptoms.[25] The guidelines for childhood asthma issued by the Dutch College of General Practitioners correspond with the GINA

guidelines.[26,27] In these guidelines, bronchodilators (reliever medication) and corticosteroids (controller medication) play the most important role in the treatment of children with asthma in general practice.

Before the age of 6 years it is not possible to make a firm diagnosis of asthma.[28,29] Therefore, most asthma guidelines make a distinction between asthma therapy for children younger and older than 6 years of age. Zuidgeest et al. found a higher variance in GPs' prescription patterns for children younger than 6 years compared with older children.[30] Asthma medication prescriptions can be classified as intermittent (1 or 2 per year) or continuous (≥ 3 per year) prescriptions for bronchodilator alone, corticosteroid alone, or a combination of both. Information about prescription patterns of asthma medication by GPs, the possible effect of the child's age on this pattern, and whether differences exist in GP and child characteristics in relation to the prescription of intermittent and continuous asthma medication, can help to develop effective strategies to optimize the prescribing of asthma medication in children with asthma.[31]

Nowadays, inhaled medications are preferred because they deliver the active agent directly to the airways.[25-27] Asthma and other chronic airway diseases can be effectively treated by inhaler therapy.[32] Inhaler devices come in a variety of types, such as metered dose inhalers (MDI) or dry powder inhalers (DPI). Irrespective of the type of inhaler device used, the outcome of inhaler therapy largely depends on appropriate use of the inhaler. Appropriate use primarily involves a correct inhalation technique, because a poor technique reduces drug deposition in the lungs.[33] Moreover, the more mistakes that are made in the inhalation technique, the lower the beneficial effect on lung function.[34] Little is known about the current situation regarding the appropriate use of inhalers by children in the Netherlands. It essential to determine the level of knowledge of children and their parents associated with the correct use of the inhaler, and to identify inconsistencies between the actual use of inhalers compared with the prescriber's advice on inhaler use.

For the development of guidelines for childhood asthma, GINA and the Dutch College of General Practitioners used (among other sources) evidence synthesized in systematic reviews of the Cochrane Collaboration. For many years, disodium cromoglycate (DSCG) has been recommended as maintenance treatment for childhood asthma. Its use decreased after 1990 when corticosteroids became popular, but it is still used in many countries. The discrepancy between guidelines, and the debate on the role of DSCG which led to its withdrawal as first-line maintenance treatment in young children in some countries, was the rationale to update the review on the efficacy of inhaled DSCG as maintenance treatment for chronic childhood asthma.

Referring children with respiratory symptoms and diseases to medical specialists

When children with respiratory problems are referred to specialised care it is generally for ENT problems, bronchitis, bronchiolitis and asthma.[35] In the Netherlands, the GP acts as a gatekeeper for specialised care. In general, access to specialist care is limited to those patients who are referred because the GP considers referral as the appropriate subsequent step within this disease episode of the patient. A considerable decrease in referrals for ENT problems in Dutch children was found between 1987 and 2001.[36] It is difficult to uncover trends for referring children to an otorhinolaryngologist and paediatrician, because studies either have too few subjects, or are restricted to referrals to a single outpatient clinic.[37-38] To facilitate planning of daily care in Dutch general practice insight into recent trends of referrals to specialized care can be helpful.

SCOPE OF THIS THESIS

As mentioned earlier, many questions about respiratory diseases in children in general practice are still open, and our goal was to find some answers. The general aim of this thesis is to provide information for optimizing the care for children with respiratory symptoms and diseases in general practice. We provided epidemiological data on respiratory symptoms and diseases in children, and examined GPs' management with regard to medication prescribing and referrals to specialists for these children.

Based on these considerations the following research aims were formulated:

1) to explore characteristics of children, their parents and their GPs that are correlated with consulting a GP for cough, sore throat or earache;
2) to examine trends in incidence, antibiotic prescribing and referrals (from 2002 to 2008) with respect to five common ENT problems in children aged 0-17 years;
3) to assess prescription patterns, intermittent and continuous asthma medication, in children with physician-diagnosed asthma in general practice;
4) to evaluate the knowledge among Dutch children and their parents regarding asthma inhaler therapy, and to assess the appropriateness of its use among children aged 0-12 years;
5) to review the literature on efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma;
6) to examine respiratory morbidity in general practice and subsequent hospital admission patterns in children aged 0-17 years.

DATA SOURCES USED IN THIS THESIS

The study aim was achieved by analysing data from the second Dutch National Survey of General Practice, the Netherlands Information Network of General Practice, the Dutch National Medical Registration, and the Cochrane Central Register of Controlled Trials.

Second Dutch National Survey of General Practice (DNSGP-2)

During a one-year registration period (2001), 195 GPs in 104 practices throughout the Netherlands participated in the data collection. Routinely recorded data from the electronic medical records of 82,053 children aged 0-17 years were used, concerning all physician-patient contacts, drug prescriptions and referrals during these 12 consecutive months. The participating GPs were representative of all GPs in the Netherlands. The DNSGP-2 study has been described in detail elsewhere.[39]
In the Netherlands, general practices have a fixed patient list, all non-institutionalized inhabitants are listed in a general practice, and GPs have a gatekeeping role for specialized care. The patients enlisted in the participating practices were comparable to the general Dutch population with respect to age, gender, and type of healthcare insurance.

All diagnoses were coded using the International Classification of Primary Care (ICPC).[40] Additional information on patients and GP characteristics was collected through questionnaires.

Netherlands Information Network of General Practice (LINH)

During a seven-year observation period (2002 to 2008), 135 general practices throughout the Netherlands participated in the collection of the data used in this thesis. The patients enlisted in the participating practices are comparable to the general Dutch population with respect to age, gender, and type of healthcare insurance.[41]

Data on all physician-patient contacts, prescriptions and referrals during the study period were extracted from the electronic medical records of all children aged 0-17 years listed in the participating practices. Diagnoses were coded using the International Classification of Primary Care (ICPC).[40] Only practices that met predefined criteria for accuracy and completeness were included in the analyses. Over the seven years the number of participating practices ranged from 71 to 86. The included practices are considered representative for all Dutch practices regarding urbanisation level, practice type (single-handed or group practice) and region.[42]

Dutch National Medical Registration

The Dutch National Medical Registration contains information on all admissions (225,000 per annum) to all teaching and general hospitals in the Netherlands. Patient

characteristics such as date of birth, gender, postal code, and diagnostic and therapeutic interventions are registered.[43] Admission and discharge diagnoses and dates, including date of death during hospitalisation are also registered. All diagnoses in the National Medical Registration are coded by trained coding clerks using the International Classification of Diseases (ICD-9).[44]

Cochrane Central Register of Controlled Trials

For our systematic review of cromoglycate as maintenance therapy for childhood asthma, we used the Cochrane Central Register of Controlled Trials (Clinical Trials; CENTRAL). This database contains approximately 500,000 records of (randomised) controlled trials.[45] CENTRAL records include the title of the article, information on where it was published (bibliographic details) and, in many cases, a summary of the article.

About 60% of the records in CENTRAL are taken from MEDLINE. Also, each Cochrane Review Group maintains and updates a collection of controlled trials relevant to its own area of interest, these are called 'Specialized Registers'.

OUTLINE OF THIS THESIS

Chapter 2 explores which characteristics of the children, their parents and their GPs are correlated with consulting a GP for cough, sore throat or earache.
Chapter 3 examines trends in incidence, antibiotic prescribing and referrals in the period 2002 to 2008 of five common ENT problems in children aged 0-17 years.
Chapter 4 examines prescription patterns, and use of intermittent and continuous asthma medication in children with physician-diagnosed asthma in general practice.
Chapter 5 evaluates the knowledge among Dutch children and their parents regarding asthma inhaler therapy and appropriateness of its use.
In the systematic review described in **chapter 6**, we determine the efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma.
Chapter 7 examines respiratory morbidity in general practice and subsequent hospital admission patterns in children aged 0-17 years.
Chapter 8 discusses results of the study and presents implications for practice and recommendations for future research.

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Characteristics of children consulting for cough, sore throat, or earache

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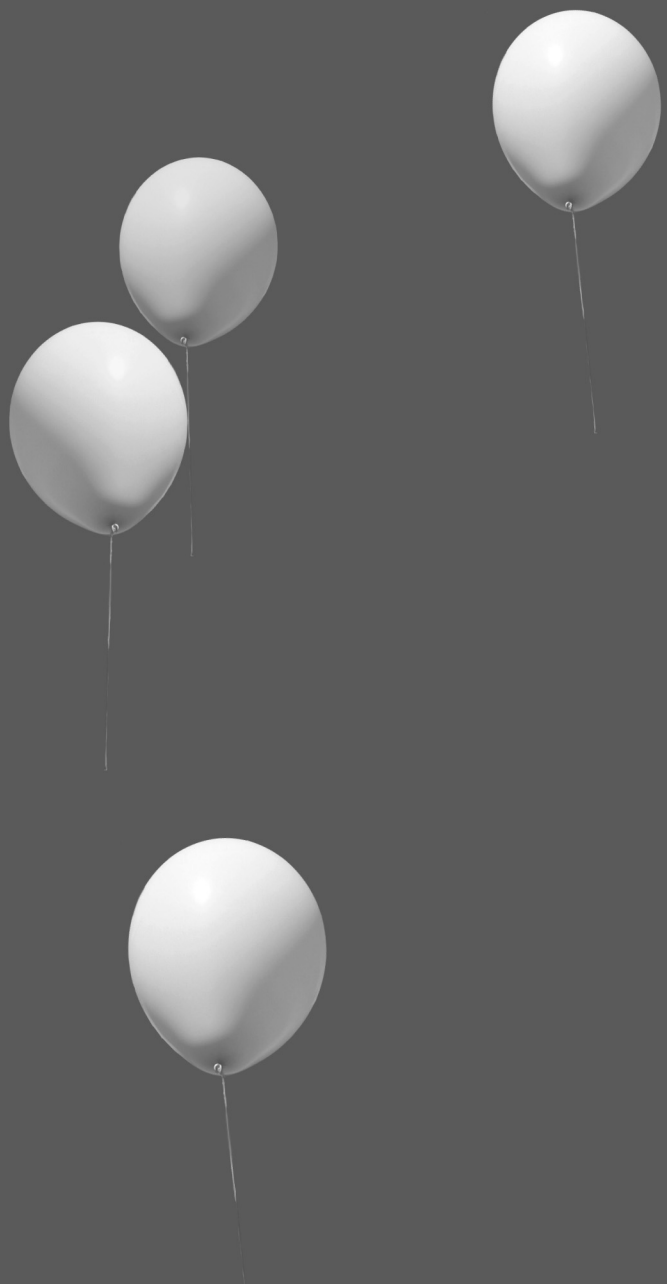


Uijen JHJM, van Duijn HJ, Kuyvenhoven MM, Schellevis FG, van der Wouden JC. Characteristics of children consulting for cough, sore throat, or earache. *British Journal of General Practice* 2008;58:248-54

ABSTRACT

Background

General practitioners (GPs) are often consulted for respiratory tract symptoms in children.

Aim

To explore characteristics of children, their parents and their GPs that are correlated with consulting a GP for cough, sore throat or earache.

Design of the study and setting

Second Dutch National Survey of General Practice (DNSGP-2) with a health interview and an additional questionnaire. Children aged 0-17 years registered with 122 GPs in Dutch general practice.

Methods

Characteristics of patients and their GPs were derived from the DNSGP-2 health interview and a questionnaire, respectively. Characteristics of the illness symptoms and GP consultation were acquired by means of an additional questionnaire. Data were analysed using multivariate logistic regression.

Results

Of all children who completed the questionnaire, 550 reported cough, sore throat or earache in the two weeks preceding the interview and 147 of them consulted their GP. Young children more frequently consulted the GP for respiratory symptoms, as did children with fever, longer duration of symptoms, those reporting their health to be 'poor to good', and living in an urban area. When parents were worried, and when a child/parents were cued by someone else the GP was also consulted more often. GP-related determinants were not associated with GP consultation by children.

Conclusions

This study emphasizes the importance of establishing the reasons for consulting the GP in children with respiratory tract symptoms. When GPs are aware of possible determinants of the decision to consult a GP, more appropriate advice and reassurance can be given regarding these respiratory symptoms, which are generally self-limiting.

INTRODUCTION

Respiratory tract symptoms such as cough, sore throat and earache are common in children.[1] Most illnesses in children are resolved without involving the professional healthcare system. Children consult their general practitioner (GP) in only 11% of all illness episodes,[2] while respiratory symptoms account for a quarter of the consultations by children in general practice.[3]

Respiratory tract symptoms generally have a viral cause and are self-limiting.[4-7] The Dutch guidelines accordingly recommend that GPs should provide adequately information to parents and children.[8-10] Children (and/or parents) and GPs seem to have different expectations for consulting a GP. Contrary to what many GPs believe, patients consult a GP primarily for information and reassurance rather than for a prescription for medication.[11,12]

Patients (more than GPs) regard respiratory tract symptoms as serious, and generally believe that consultation of a health professional is necessary for these symptoms.[13] Although inconsistent with the previous observation many adult patients believe that antibiotics are necessary to treat respiratory infections. Van Duijn et al. found that adult patients suffering from respiratory symptoms for longer than two weeks more frequently visited their GP when they were cued by others,[14] in addition, patients who perceived their symptoms as more serious, and those who were unaware of the self-limiting nature of respiratory symptoms more frequently visited their GP. Although these determinants have been studied in adults, it is unknown whether parents and their children have the same expectations regarding GP consultation for a child's respiratory tract symptoms.

Although van Duijn et al. found no association between GP-related determinants and illness behaviour in case of respiratory tract episodes,[14] others reported that GP-related characteristics (such as GP's age and gender) are correlated with consultation behaviour.[15-17]

Less is known about which GP-related determinants may influence GP consultation for respiratory tract symptoms among children. Therefore this study explored determinants of a GP consultation with respect to children, their parents and their GP with regard to consulting a GP for cough, sore throat or earache.

METHODS

Design

The data used in this study were derived from the Second Dutch National Survey of General Practice (DNSGP-2), which was performed by the Netherlands Institute for Health Services Research (NIVEL) in 2001.[18]

To establish which factors determine consultation of the GP by children suffering from respiratory symptoms we compared the characteristics of 1) children reporting these symptoms in a health interview and subsequently consulting their GP, with 2) children who also reported these symptoms but did not consult their GP. For these two groups, we also compared GP characteristics to determine whether or not they might be related to consultation behaviour.

Second Dutch National Survey of General Practice

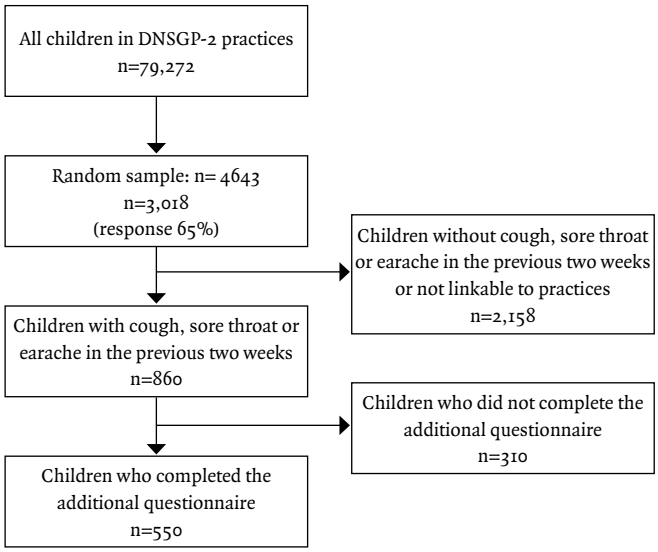
During a one-year study period, 195 GPs in 104 practices throughout the Netherlands participated in the data collection. In the Netherlands, general practices have a fixed patient list, all inhabitants are listed in a general practice, and GPs have a gate-keeping role for specialized care. The patients enlisted in the participating practices were comparable to the general Dutch population with respect to age, gender, and type of health insurance. Data also included all prescribed medication.

For the current analysis, data from 23 practices were excluded because data were incomplete, or linking additional child questionnaires (see below: patients) to GPs failed. We included data from children of 81 practices with 122 GPs (figure 1). When comparing these 122 GPs with all 7,676 Dutch GPs no significant differences were found for gender, age, and degree of urbanisation. Single-handed GPs were relatively underrepresented (34% vs. 43%, p=0.04) among the participating GPs.

Health interview

An all-age random sample of approximately 150 listed patients per full-time equivalent GP was selected and approached to participate in a health interview; [19] the response rate was 65%. The interviews were performed at the patient's home by trained interviewers, and the interviews were evenly distributed over four consecutive 3-month periods. A total of 3,018 children (aged 0-17 years) participated in the health interview (Figure 1). The following personal characteristics were derived from these data: age (years), gender (male vs. female), level of education of the parents (highest education of both parents; dichotomised into lower secondary school or less vs. more than secondary school), type of health insurance (public vs. private), degree of urbanisation of the patient's residence (rural vs. urban), ethnic origin (non-native vs. native), self-reported health (poor,

FIGURE 1 Selection of the study population (aged 0-17 years) from the Second Dutch National Survey of General Practice (DNSGP-2)



moderate or good vs. very good or excellent), and if the child had ever been diagnosed as having asthma (no vs. yes). For all children younger than 12 years, a proxy interview was carried out with a parent; children aged 12-17 years were interviewed personally.

For all people approached for the health interview, respondents and non-respondents did not differ with respect to age, gender and health insurance.

Patients

Children who had recently (the 2 weeks preceding the interview) suffered from cough, sore throat or earache (n=860) were asked to complete an additional questionnaire (response rate 64%). They were asked about the duration of symptoms (more or less than 2 weeks), whether they consulted their GP (either by telephone, visit to the practice, or home visit) for these symptoms during the 2 weeks preceding the interview (no vs. yes), presence of fever (no vs. yes), whether they were cued by their partner (only for parents), by parents, or by others to consult the GP (no vs. yes), if they had used over-the-counter medication (no vs. yes), and whether the parents worried that their child was suffering a serious illness (no vs. yes).

GP characteristics

Characteristics of all 122 GPs were obtained via a mailed questionnaire. Assessed were: age (years), gender (male vs. female), average number of patient contacts per day, single-handed practice (no vs. yes), self-reported use of national GP guidelines (once a week or less vs. more than once a week), seeing pharmaceutical representatives (an indicator of prescribing behaviour; no vs. yes), reluctance to prescribe new drugs (entirely disagree, disagree vs. hesitation, agree and entirely agree), and whether they were involved in GP training (no vs. yes). We also calculated the number of antibiotics prescribed by GPs for respiratory tract infections per 1000 patients of all ages during the one-year study period.

Data analysis

Data of 550 children were included in the analysis. Because only children aged 12-17 years were personally interviewed, the two age groups (0-11 and 12-17 years) were also analysed separately. Patient characteristics were compared using the χ^2-test.

The main outcome measure was whether or not the child with respiratory tract symptoms consulted their GP. Patient and GP characteristics as independent variables, and consulting the GP for respiratory symptoms as dependent variable, were first analysed bivariately. All above-mentioned patient and GP characteristics that were associated with GP consultation (with $p<0.20$) were included in the multivariate logistic regression analysis. Multicollinearity tests were performed to identify unacceptably high (> 0.80) correlations between the independent variables. For the multivariate analysis the significance level was $p=0.05$. Analyses were conducted with the SPSS package, version 11.0.

The multivariate analysis was repeated taking into account the multilevel structure of the data, with children clustered within practices, using the SAS package version 8.2, procedure GENMOD.

RESULTS

Patient characteristics are presented in Table 1. Young children (0-4 years) more frequently had respiratory symptoms (cough, sore throat or earache) in the previous two weeks than older children ($p= 0.01$). Girls more often reported respiratory symptoms than boys ($p = 0.009$). Type of health insurance and degree of urbanisation did not differ between all interviewed children and those with recent respiratory symptoms. Children with respiratory symptoms more often reported their health to be ‘poor to good’ than ‘very good’ or ‘excellent’.

TABLE 1 Characteristics of all children interviewed, children with recent symptoms (cough, sore throat or earache), children who consulted their GP for these symptoms, and children who did not consult

	All children interviewed (n=3018)	Children with recent symptoms (n=550)	Children with recent symptoms who consulted their GP (n=147)	Children with recent symptoms who did not consult their GP (n=403)
Age in years				
0-4 (%)	768 (25.4%)	173 (31.5%)	53 (36.1%)	120 (29.8%)
5-11 (%)	1327 (44.0%)	220 (40.0%)	65 (44.2%)	155 (38.5%)
12-17 (%)	923 (30.6%)	157 (28.5%)	29 (19.7%)	128 (31.7%)
Gender (% female)	46.9	52.9	46.3	55.3
Level of education parents (% low education)	14.1	10.4	14.3	8.9
Type of health insurance (% public insurance)	57.6	56.7	61.2	55.1
Urban (%)	50.9	51.8	62.6	47.9
Ethnicity (% native Dutch)	90.8	89.5	87.1	90.3
Self-reported health (% poor to good)	40.1	47.3	63.9	41.6

TABLE 2 Characteristics of the participating general practitioners (n=122)

Age mean (SD) in years	47.4 (6.1)
Gender (% female)	21.3
Single-handed practice (%)	33.6
Practice size (mean and SD)	2330 (589)
Full-time equivalent (mean and SD)	0.88 (0.17)
Number of daily contacts mean (SD)	29.7 (11.9)
Consulting GP national guidelines more than once a week (%)	54.9
GP trainer (%)	49.2
Seeing pharmaceutical representatives (%)	57.4
Reluctant to prescribe new drugs (%)	92.6
Number of antibiotic prescriptions/1000 patients (mean and SD)	265.8 (132.1)

About 27% of the children with recent respiratory symptoms consulted their GP. Children aged 0-4 years consulted the GP more often than older children (p=0.02), and children who had public health insurance were more likely to consult the GP. Children living in an urban area were overrepresented in the group of children with recent symptoms who consulted their GP, and the latter group more often reported their health to be 'poor to good' (p<0.001).

TABLE 3 Percentages of children with recent symptoms (cough, sore throat or earache) who consulted their GP for these symptoms and children who did not

	% Children with recent symptoms who consulted their GP (n=147)	% Children with recent symptoms who did not consult their GP (n=403)	p-value $\chi 2$, df=1
Duration of symptoms > 2 weeks (% yes)	73.2	28.8	<0.001
Presence of fever during reported symptoms (% yes)	41.5	21.6	<0.001
Cued by others to consult GP (% yes)	34.7	1.0	<0.001
Over-the-counter medication (% yes)	60.5	59.3	0.79
Worried child is suffering a serious illness (% yes)	42.1	9.3	<0.001
Self-reported diagnosis asthma (% yes)	25.2	11.2	<0.001

GP characteristics are presented in Table 2. The mean age of the GPs was 47 years, less than a quarter was female, and the majority was practising in an urban area. The mean number of daily contacts was around 30, and most of the GPs reported regular use of the national GP guidelines. Almost 50% was a GP trainer, a small majority saw pharmaceutical representatives, and most GPs were reluctant to prescribe new drugs.

Table 3 provides an overview of the patient factors related to GP consultation. Children who consulted their GP more often had symptoms which lasted longer than 2 weeks and more often reported having fever, than children who did not consult. When parents or children were cued by others to contact the GP, they more frequently consulted their GP (34.7% vs. 1.0%). As stated above, for children aged under 12 years of age a proxy interview was carried out; all parents who felt cued to consult the GP were cued by their partner. For children older than 12 years the questionnaire was answered by the children themselves; and this group were cued by their parents. Children of worried parents consulted their GP more frequently.

Determinants for consulting GP

The results of the multivariate analyses are presented in Table 4 (all children together, and the two subgroups separately). Multicollinearity testing did not reveal any unacceptably high correlations between the independent variables. None of the correlations was above 0.30, and most were close to zero.

For all children, seven determinants for GP consultation emerged. Younger and urban children with upper respiratory symptoms more often consulted their GP. Children who reported their own health as 'poor to good' consulted their GP twice as often as children reporting their health as 'very good' or 'excellent'. Symptoms lasting

TABLE 4 Determinants for consulting a GP for recent cough, sore throat or earache for all children who completed questionnaires, children aged 0-11 years and children aged 12-17 years. Multivariate logistic regression analysis. Adjusted OR (95% CI)

	All children (n=550)	p-value	Children 0-11 years (n=393)	p-value	Children 12-17 years (n=157)	p-value
Age	0.91 (0.86-0.97)	0.002	0.99 (0.89-1.10)	0.90	1.05 (0.78-1.40)	0.77
Female gender	0.91 (0.55-1.52)	0.72	0.73 (0.42-1.27)	0.26	1.22 (0.46-3.26)	0.69
Urban living	2.01 (1.19-3.40)	0.009	2.19 (1.25-3.83)	0.006	1.31 (0.48-3.62)	0.60
Low education parents	0.73 (0.41-1.32)	0.30	0.70 (0.36-1.37)	0.30	0.69 (0.26-1.81)	0.45
Reporting own health as poor to good	2.23 (1.26-3.94)	0.006	1.73 (0.90-3.33)	0.10	4.00 (1.43-11.01)	0.008
Reporting presence of diagnosis asthma	1.39 (0.71-2.69)	0.34	1.52 (0.75-3.11)	0.25	1.41 (0.41-4.89)	0.59
Duration of symptoms more than 2 weeks	3.50 (1.98-6.19)	<0.001	3.80 (2.05-7.03)	<0.001	5.04 (1.69-14.99)	0.004
Fever	2.11 (1.22-3.64)	0.007	2.56 (1.42-4.61)	0.002	2.38 (0.79-7.13)	0.12
Parents worried (or child if ≥ 12 years)	4.95 (2.79-8.78)	<0.001	4.88 (2.61-9.12)	<0.001	2.77 (0.81-9.48)	0.10
Cued by others to visit GP	47.72 (15.34-148.48)	<0.001	12.34 (3.86-39.51)	<0.001	*	
GPs' age	0.98 (0.94-1.03)	0.40	0.98 (0.93-1.03)	0.36	0.99 (0.91-1.07)	0.78
Consulting GP national guidelines more than once a week	0.67 (0.40-1.12)	0.12	0.76 (0.44-1.31)	0.32	0.40 (0.15-1.03)	0.59

* *Not included in analysis: every child that was cued consulted the GP*

more than two weeks and presence of fever yielded an increased chance of GP consultation (ORs 2.1 and 3.5 respectively). Worried parents and those who were cued by other family members to consult a GP consulted their GP more often.

In the subgroup of children aged 0-11 years, fewer independent determinants were associated with GP consultation. Children who consulted a GP more frequently, more often had fever, respiratory symptoms lasting longer than two weeks, and more frequently lived in urban areas. Parents of these children were more frequently worried and cued to consult a GP with their child.

In the subgroup of children aged 12-17 years, the two independent determinants 'reporting own health as moderate to poor' and 'longer duration of respiratory symptoms' were related with GP consultation. This subgroup was analysed without the determinant 'cued to consult the GP' because every child in this age group who was cued did in fact consult the GP.

None of the GP characteristics was associated with the consulting pattern of the children and their parents. Multilevel analyses, taking clustering of children at practice level into account, yielded very similar results.

DISCUSSION

Summary of main findings

Younger children more often consulted their GP for respiratory symptoms than older ones. Children with fever and respiratory symptoms that lasted longer than two weeks, more often consulted their GP. GPs were more frequently consulted when the parents were worried and when children/parents were cued by other family members. Children with respiratory symptoms living in urban areas consulted more often than children in rural areas. Fever and longer duration of respiratory symptoms were associated with consulting behaviour, whereas GP-related characteristics were not associated with parents' decision to consult.

Strengths and limitations of this study

This study uses data that were derived from the Second Dutch National Survey of General Practice (DNSGP-2). These unique data allowed us to assess the role of both child and parent factors, as well as GP characteristics, on consulting behaviour for respiratory tract symptoms.

Characteristics of the GP and patient sample are comparable with the general Dutch population.[19] Only single-handed practices were relatively underrepresented; however, because this item was not related to the study outcome it is probably not a major limitation. Our results can therefore be assumed to represent daily primary care and consultation behaviour in the Netherlands.

Although we separated the children in two age groups, driven by the different way of data collection in the health interview, within each age group differences may exist.

In the additional questionnaire, parents and children were asked whether or not they had consulted their GP. Self-reports are vulnerable to recall bias. Because the recall period was only two weeks, we assume that this bias was relatively small.

Comparison with the literature

A relationship between age and consultation rates was earlier reported by Holme.[20] Bruijnzeels et al. found that younger children (0-4 years old) were taken twice as often to the GP than older children (10-14 years).[2] Our study yields similar results; with every yearly increase in age the risk for a child with respiratory symptoms to consult the GP

decreases by 9%. In accordance with Hay et al. we found that fever plays an important role in consulatation.[21] In contrast with our study in which urban children more frequently consulted their GP with cough, sore throat and earache, others found no relation with the degree of urbanisation.[2]

Van Duijn et al. reported that age, longer duration of symptoms, and having respiratory co-morbidity positively influences GP consultation among adults with upper respiratory tract symptoms.[14] Adult patients who were worried about the seriousness of their respiratory symptoms consulted a GP earlier, and the same was found for those who were cued by others to visit a GP.[14,22] Our study showed similar findings for children aged 0-17 years old.

The literature is inconclusive as to whether GP characteristics are associated with GP consultation by children and parents. In the current study no GP-related determinants were found for GP consultation, as was reported earlier for adults.[14] In another study, GP characteristics were associated with prescribing antibiotics for upper respiratory tract infections.[23] Others found the same association,[24-26] which might be explained as follows: patients generally know the prescription pattern of their GP and this may, in turn, affect GP consultation rates. However, in contrast to these studies, our study combined both patient viewpoints with respect to a specific respiratory tract infection (RTI) and GP characteristics. Williamson et al. reported that prescribing antibiotics for middle ear disease probably increased reattendance.[27] In our study no association was found between the number of antibiotics prescribed by GPs for RTI per 1000 patients and GP consultation. Probably this difference can be explained by the larger amount of antibiotic prescriptions in the United Kingdom.

Being cued by a family member to consult the GP is a well-known phenomenon in daily practice. In the present study parents cued each other, and older children were cued by their parents; this strong association between 'cueing by family members' and GP consultation confirms the findings of Cardol et al. about family influence on healthcare utilisation.[28]

Implications for clinical practice

This study emphasizes the importance of adequately exploring the reasons for consulting the GP. For example: are children and/or parents worried about the child's respiratory symptoms? are they cued by another family member? is the fever or duration of symptoms the reason for consulting the GP? Most symptoms of cough, sore throat and earache have a viral cause and a self-limiting character. When GPs gives attention to the possible reasons for consultation, they will be able to give more appropriate advice and reassurance to children and parents for these specific symptoms.

In conclusion, this study shows that children with younger age, fever, longer duration of upper respiratory tract symptoms, living in an urban area, parents and children who worry about symptoms, reporting their own health as 'poor to good', and those who are cued by other family members more frequently consult their GP. Knowledge about these determinants will enable GPs to provide appropriate and timely advice and reassurance.

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ENT problems in children in Dutch primary care: trends in incidence rates, antibiotic prescribing and referrals 2002-2008

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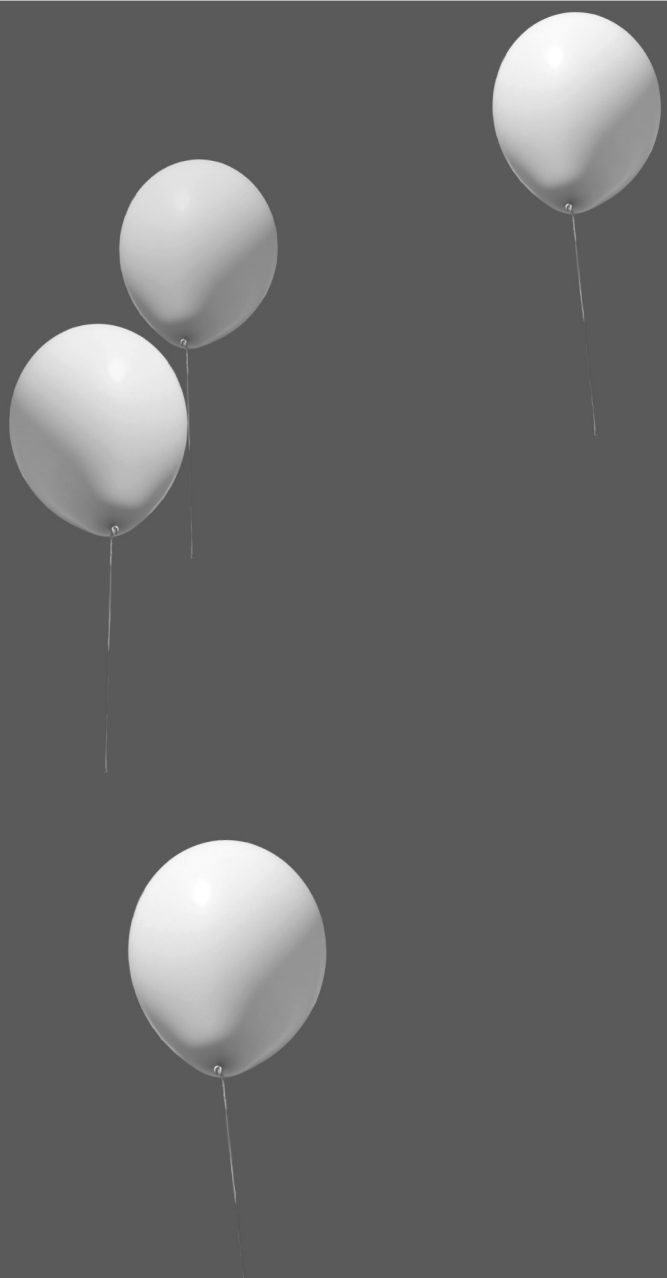


Uijen JHJM, Bindels PJE, Schellevis FG, van der Wouden JC. ENT problems in children in Dutch primary care: trends in incidence rates, antibiotic prescribing and referrals 2002-2008. *Submitted*

Background

Ear, nose and throat (ENT) problems are common in childhood and important reasons to visit the general practitioner.

Aim

To examine trends in incidence rates, antibiotic prescribing and referrals of five common ENT problems in children.

Design, setting, and methods

Netherlands Information Network of General Practice (LINH), a nationally representative general practice database. 50,000 children, aged 0-17 year, registered in Dutch general practice over the period 2002-2008.
Incidence rates were calculated and trends were analyzed using linear regression analysis, with incidence rates per age group, proportion treated with antibiotics and referrals as dependent variables and year of observation as independent variable.

Results

In general, incidence rates of acute otitis media, serous otitis, sinusitis, tonsillitis and tonsil hypertrophy remained stable over the period 2002-2008. An increasing trend was observed for serous otitis media in children aged 0-4 years (RR=1.04, $p<0.001$). A decreasing trend was observed for sinusitis in children aged 5-11 and for tonsillitis in children aged 11-17 years (RR 0.99, $p<0.001$ and RR 0.94, $p<0.001$, respectively). Antibiotics were prescribed in 10-60% of the diagnoses. An increasing trend of antibiotic prescription was found for acute otitis media (beta=0.07, $p<0.001$), mainly on account of amoxicillin. Although antibiotic treatment of tonsillitis remained stable, pheneticillin prescriptions showed a downward trend (beta= -0.10, $p<0.001$). First-choice antibiotics were prescribed in >80% of the cases.

Conclusions

This study showed remarkably stable trends in incidence rates, antibiotic prescribing and referrals of common ENT problems. The low proportion of antibiotic treatment in ENT problems did not show negative consequences.

INTRODUCTION

Ear, nose and throat (ENT) problems such as otitis media, serous otitis media (glue ear), sinusitis and tonsillitis are common in childhood and important reasons for parents and children to visit the general practitioner (GP).[1] In the Netherlands cough, sore throat and earache together account for nearly 25% of the consultations of children in general practice.[2-4] Treatment options for ENT problems in general practice include watchful waiting, medication for symptomatic relief and antibiotics or referral to an otorhinolaryngologist or pediatrician.

For planning of health services and guideline development, recent data on incidence rates, antibiotic use and referrals are important.

Only a few studies have examined the incidence rates of ENT problems in children in general practice over time.[5] In some countries a decreasing trend of GP consultations for respiratory symptoms and ENT problems (e.g. tonsillitis) was found.[1,5] Considering these time trends we were interested in the long-term incidence rates for ENT problems in children in the Dutch population.

In the last 10 years the Dutch College of General Practitioners published several evidence-based guidelines for the management of ENT problems, i.e. for acute otitis media,[6] serous otitis media,[7] sinusitis,[8] tonsillitis and tonsil hypertrophy.[9] These new or revised guidelines might have changed GPs' management, e.g. antibiotic prescribing or referral. Most of these guidelines are cautious about recommending antibiotics; however, when antibiotics are still needed because of clinical symptoms, small-spectrum penicillin is advised for tonsillitis, tetracycline or broad-spectrum penicillin for sinusitis, and a broad-spectrum penicillin for acute otitis media. No antibiotics are advised for serous otitis media and tonsil hypertrophy. In accordance with European GPs, family physicians in the USA were further encouraged to reduce their prescribing of antibiotics.[10-12] In the few studies available, the trend of prescribing antibiotics for ENT problems showed a decrease or a stabilisation.[1,5] However, a drawback of these studies is that the prescriptions rates were calculated for all respiratory symptoms together and not specified by separate diagnoses.

When children are referred to specialized care it is generally for ENT problems.[4] In the Netherlands the GP acts as a gatekeeper for specialized care, so access to this care is mostly limited to those patients who are referred by their GP. In the past, a considerable decrease of referrals for ENT problems was found in Dutch children in a 14-year period. Compared to 1987, in 2001 the population-based referral rate for acute otitis media was 72% lower (the referral rate decreased from 6.9 to 1.9).[13] Information on trends in referring children to an otorhinolaryngologist and pediatrician is scarce. Moreover, study populations were either small or restricted to referrals to a single outpatient clinic.[14,15]

The present study used a national general practice database to explore trends over the years 2002-2008 in incidence rates, antibiotic prescribing and referral to a medical specialist of five common ENT problems in childhood.

METHODS

We derived data from the electronic medical records of Dutch general practices participating in the Netherlands Information Network of General Practice (LINH).[16,17]

Netherlands Information Network of General Practice

During the 7-year registration period (2002-2008), 135 general practices throughout the Netherlands participated in data collection. In the Netherlands, general practices have a fixed patient list, all inhabitants are listed in a general practice, and GPs have a gate-keeping role for specialized care. The patients enlisted in the participating practices are comparable to the general Dutch population with respect to age, gender, and type of healthcare insurance.[16]

Data on all physician-patient contacts, prescriptions and referrals during the study period were extracted from the electronic medical records of all children aged 0-17 years listed in the participating practices. Diagnoses were coded by the GP using the International Classification of Primary Care (ICPC).[18] Only practices that met predefined criteria for accuracy and completeness were included in the analyses. Over the 7 years the number of participating practices ranged from 71 to 86. The included practices are considered representative for all Dutch practices regarding urbanisation, gender, age and region. Single-handed practices are slightly underrepresented

Study population

The total number of children in the participating practices ranged from 53,137 to 62,862 per observation year. Over the 7 years, the percentage of boys was around 51%; the percentage of children aged 0-4 years was around 28%, children aged 5-11 years around 33%, and children aged 12-17 years around 39%.

Outcomes

The first outcome measure was the annual incidence rate of acute otitis media (ICPC code H71), serous otitis media (H72), sinusitis (R75), tonsillitis (R76) and tonsil hypertrophy (R90). For each diagnosis the children were divided into three age groups: 0-4, 5-11 and 12-17 years.

Incident cases were defined as cases with at least 30 days without GP practice attendance for the same problem before the current consultation with this diagnosis. For the diagnoses serous otitis media and tonsil hypertrophy we used a period of 90 days. Incidence rates were calculated per 1,000 person-years.

The second outcome measure was the annual proportion of cases in which oral antibiotics were prescribed in the first consultation for each of the five diagnoses under study. The third outcome measure was the annual proportion of cases referred in the first consultation to an otorhinolaryngologist or pediatrician for these ENT problems.

Statistical analysis

We calculated incidence rates per 1,000 children per year using the annual mid-time population size as the denominator and the number of incident cases as numerator. Trends were analyzed by Poisson linear regression analysis using the incidence per age group as the dependent variable and the years as independent variable. This allows the change to be expressed in relative risk (RR) per year (significance level $p=0.05$). We corrected for multiple testing with the step-down Bonferroni method.

Percentages prescribed antibiotics and referrals were calculated using the incident cases as the denominator, and the number of antibiotic prescriptions and referrals, respectively, as numerator. Trends were analyzed by linear regression analysis using number of antibiotics or referrals as the dependent variable and the years as independent variable. Reported here are beta values with significance level set at $p<0.05$.

RESULTS

Incidence rates

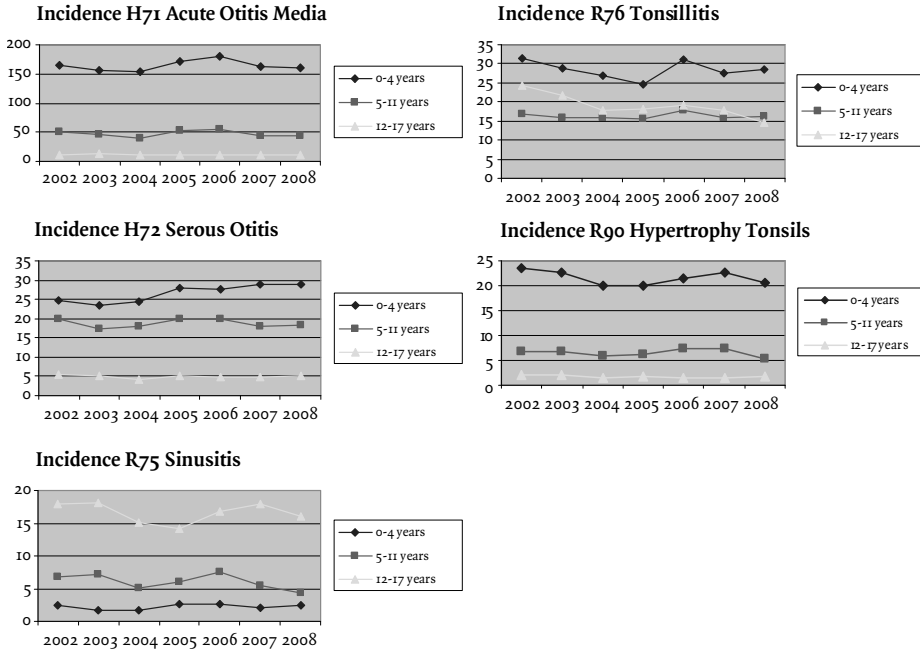
Figure 1 shows the incidence rates of acute otitis media, serous otitis media, sinusitis, tonsillitis and tonsil hypertrophy presented in general practice over the years 2002-2008.

Acute otitis media and tonsil hypertrophy are diseases of the younger child (0-4 years). Sinusitis showed higher incidence rates in the older (12-17 years) age group. Tonsillitis and serous otitis media is more common in children aged 0-4 years, but also in the older age groups.

The incidence rates ranged from about 2 per 1,000 for sinusitis to about 150 per 1,000 for acute otitis media. Due to varying ranges of the incidence rates, the scale of the vertical axis in Figure 1 was adjusted for the five diagnosis groups.

Most incidence rates remained stable, with three exceptions. An increasing trend was found for serous otitis media in children aged 0-4 years old with a relative risk (RR) of 1.04 ($p<0.001$). Decreasing incidence rates were found for sinusitis in children aged

FIGURE 1 Incidence rates (by age group) for Acute Otitis Media (H71), Serous Otitis Media (H72), Sinusitis (R75), Tonsillitis (R76), and Hypertrophy Tonsils (R90) for 2002-2008



5-11 years (RR=0.95, p=0.001) and for tonsillitis in children aged 11-17 years (RR=0.94, p<0.001).

Antibiotic prescriptions

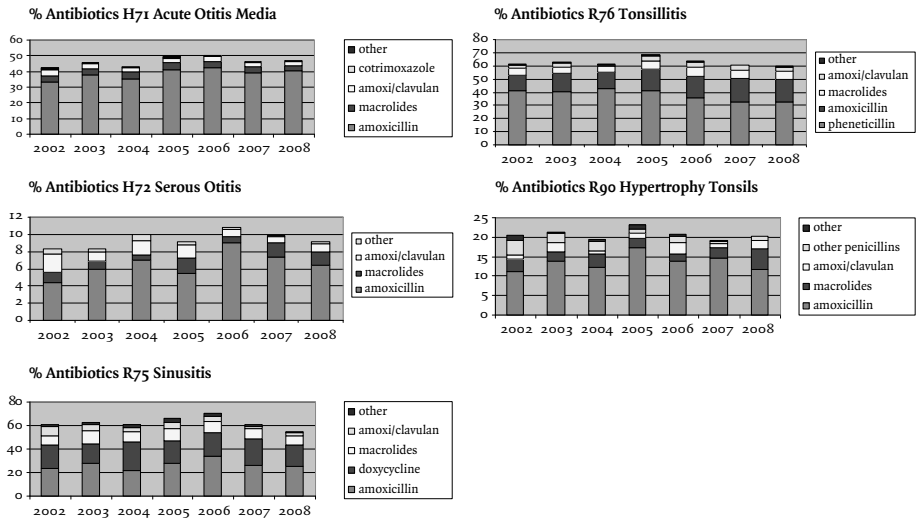
Figure 2 shows in which proportion of the incident cases oral antibiotics were prescribed during the first consultation, throughout the 7-year period.

For sinusitis and tonsillitis the percentage of antibiotic prescribing in the first consultation was nearly 60%. The antibiotic prescribing percentage for acute otitis media was nearly 50%, followed by tonsil hypertrophy with 20% and serous otitis media with 9%.

Over the whole period, in children with acute otitis media, amoxicillin was most often prescribed (in about 80% of all antibiotic prescriptions). Macrolides were prescribed in 10% of all antibiotic prescriptions.

For children with sinusitis the antibiotics of first choice (doxycycline and amoxicillin) were prescribed in 38% and 43% of the prescriptions, respectively. Macrolides followed in 13% of the prescriptions.

FIGURE 2. Percentage antibiotic prescriptions in children with Acute Otitis Media (H71), Serous Otitis (H72), Sinusitis (R75), Tonsillitis (R76), and Hypertrophy Tonsils (R90) for 2002-2008



For children with tonsillitis, pheneticillin, the antibiotic of first choice, was prescribed in 63% of the prescriptions in the first consultation. For this diagnosis, amoxicillin was prescribed in 22% and macrolides in 8% of the antibiotic prescriptions.

For each diagnosis the change in antibiotic prescribing (beta) over the consecutive years was calculated. For serous otitis media, sinusitis and tonsil hypertrophy no significant change was found. For acute otitis media an increase was seen, i.e. an increase in antibiotic prescriptions in general, with a beta of 0.03 ($p<0.001$). Of this increase in antibiotic prescriptions, most was accounted for by amoxicillin (beta=0.07, $p<0.001$). For tonsillitis the change in all antibiotics over the subsequent years was not significant; however, the percentage of the antibiotic of first choice, pheneticillin, decreased with a beta of -0.10 ($p<0.001$).

Referral to otorhinolaryngologist or pediatrician

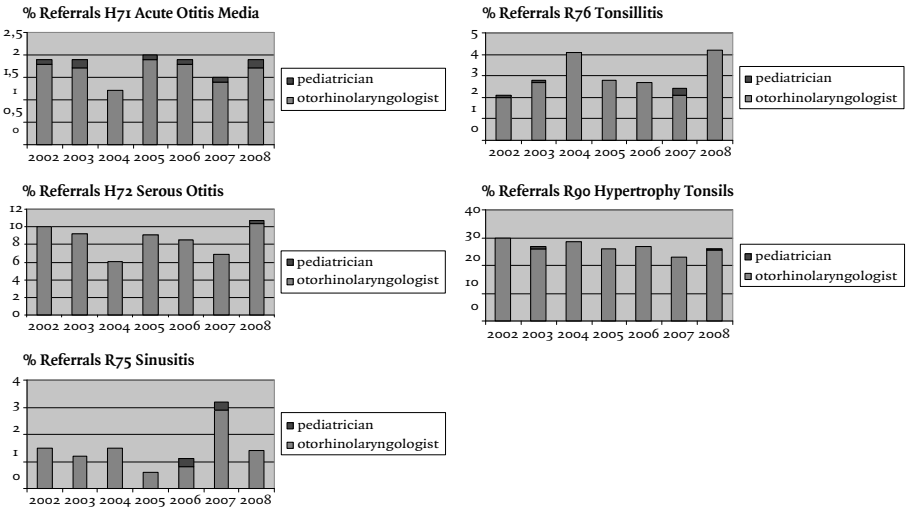
Figure 3 shows in which percentage of the incident cases of acute otitis media, serous otitis media, sinusitis, tonsillitis and tonsil hypertrophy over the years 2002-2008 the GP referred the child to a specialist.

The referrals ranged from 1% of the incident cases of sinusitis to 30% of the incident cases of tonsil hypertrophy.

The GPs most often referred young children aged 0-4 years with acute otitis media, serous otitis and tonsil hypertrophy.

None of the diagnoses showed a significant trend in referrals over the 7-year period.

FIGURE 3 Percentage referrals to otorhinolaryngologist or pediatrician in children with Acute Otitis Media (H71), Serous Otitis (H72), Sinusitis (R75), Tonsillitis (R76), and Hypertrophy Tonsils (R90) for 2002-2008



DISCUSSION

In this large study population the incidence rates of acute otitis media, serous otitis media, sinusitis, tonsillitis and tonsil hypertrophy in children were remarkably stable over the years 2002-2008. An increasing incidence rate was found only for serous otitis media in children aged 0-4 years, and a decreasing incidence was found for sinusitis and tonsillitis in children aged 5-11 years and 12-17 years, respectively. Prescription of antibiotics for the five diagnosis groups also remained stable and relatively low with 10-60% prescriptions in the incident cases over the 7-year period. Exceptions were increasing antibiotic prescription (mostly on account of amoxicillin) for acute otitis media and a decrease of pheneticillin for tonsillitis. Stable trends were also found for referrals to an otorhinolaryngologist or pediatrician for ENT problems in children.

Strengths and limitations of the study

The major strength of this study is the use of unique data over a 7-year period from a large national network of practices: the Netherlands Information Network of General Practice. The study population allowed to calculate incidence rates for five ENT diseases. Characteristics of the study population are comparable to the general Dutch population, and the GP sample is comparable to the national GP population.[16] In the present study we chose to use only the first contact in an episode for ENT problems to calculate antibiotic

prescriptions and referrals. In this way the GP's management will not have been affected by a previous contact in the same episode.

Single-handed practices were somewhat underrepresented; however, because this item is not related to our study outcomes it is not considered an important limitation. The results can be assumed to represent regular primary care and consultation behavior in the Netherlands.

A limitation of our study is that not all referrals and prescriptions were linked to an ICPC code by the GPs. Each year some ICPC codes (3-5%) are missing for antibiotic prescription and referral to a specialist. This could lead to underestimation of prescriptions and referrals; however, there is no reason to believe that higher rates would influence our conclusions or that the absence of codes is selective for the treatment of ENT problems.

Comparison with other studies

Over the past 10 years decreasing consultation rates of ENT problems in general practice have been reported in Europe and the USA,[1,5,20-22] which might reflect a decrease of 'real' incidence in the general population. However, the present study does not confirm a considerable decline in ENT problems during 2002-2008. Incidence rates for the various age groups showed only a slight increase for serous otitis media, and a slight decrease for sinusitis and tonsillitis. For the remaining ENT problems, in the various age groups no positive or negative trends in incidence rates emerged.

The question arises as to how reliable the methods used to compare data have been in the past. In the present study we used the same method throughout the 7-year period.

A comparative study among 26 European countries showed that Dutch GPs prescribe the lowest amount of antibiotics in children.[23] In the present study, the percentage antibiotic prescriptions is relatively low: 50% in acute otitis media, and 60% in sinusitis and tonsillitis. Guidelines vary across western-European countries. For example, a Scandinavian guideline recommends to treat acute otitis media primarily with antibiotics in all children. In contrast, the Dutch guideline recommends to prescribe antibiotics in selected cases of acute otitis media, e.g. those at risk for complications or with symptoms persisting for >3 days.[6,24] The question then arises whether Dutch GPs under-treat children with ENT problems. However, because referral rates remained low, in our opinion these low antibiotic prescription rates do not represent under-treatment. On the other hand, GPs can help reduce overuse of antibiotics for ENT problems in children.[10-12] It seems that there is still room for improvement with regard to prescribing antibiotics.

In the present study, in more than 80% of the cases the GPs prescribed a first-choice antibiotic. Assuming that GPs prescribed macrolides as an alternative for penicillin (in

case of penicillin allergy or intolerance) the percentage correct antibiotic prescribing would increase by 10% to more than 90%. This is a remarkable result in contrast with another study in which GPs prescribed more broad-spectrum antibiotics for inappropriate diagnoses.[25] A disturbing trend is the decline in prescribing small-spectrum penicillins, a first-choice antibiotic for tonsillitis.

In 2005-2007 three Dutch guidelines were revised, i.e. acute otitis media, tonsillitis and sinusitis; all adjustments emphasized a reluctance to prescribe antibiotics.[6,8,9] In the present study, however, we found no effect of these guideline adjustments. Surprisingly, we found antibiotic prescriptions for serous otitis media and tonsil hypertrophy: 9% and 20%, respectively. These GPs apparently disregarded the guidelines and incorrectly prescribed antibiotics for these diagnoses. For these GPs there is an opportunity for improvement.

Although the vast majority of ENT problems in children presented in general practice are managed by GPs themselves, some treatment involves referral to an otorhinolaryngologist or pediatrician. Most referrals to the otorhinolaryngologist concerned an (adeno)tonsillectomy. It is well known that tonsillectomy rates vary considerably between countries.[26] In the Netherlands, an important decrease in ENT referral rate was found between 1987 and 2001.[13] In the present study no significant trends in ENT referrals in children aged 0-17 years were found during the period 2002-2008.

In summary, the present study provides a comprehensive, up-to-date and representative overview of incidence rates, antibiotic prescribing and referrals for ENT problems in children aged 0-17 years in general practice. We found remarkably stable trends in incidence rates, antibiotic prescribing and referrals of ENT problems in Dutch general practice over a 7-year period.

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Asthma prescription patterns for children: can GPs do better ?

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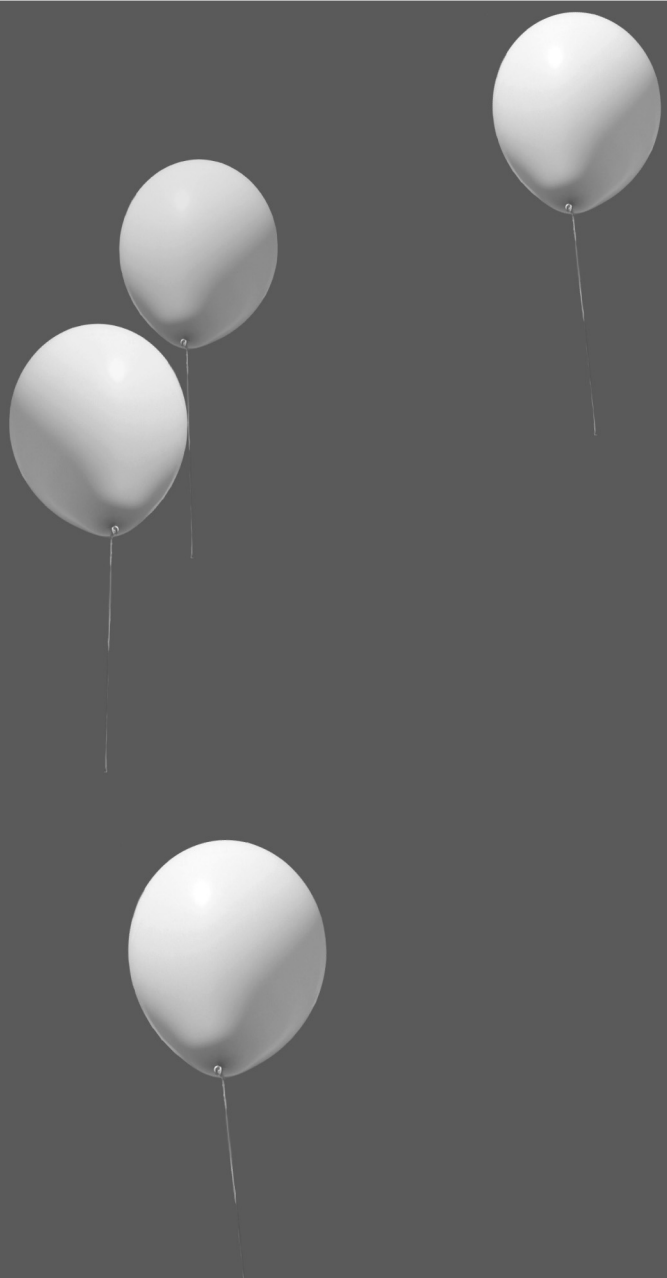

Uijen JHJM, van der Wouden JC, Schellevis FG, Willemsen SP, van Suijlekom-Smit LWA, Bindels PJE. Asthma prescription patterns for children: can GPs do better? *In press, European Journal of General Practice*

ABSTRACT

Background

Assessing prescription patterns of asthma medication for children is helpful to optimize prescribing by general practitioners (GPs). The aim was to explore prescription patterns in children with a doctor-diagnosed asthma in general practice and its determinants.

Methods

We used the Second Dutch National Survey of General Practice (DNSGP-2) with children aged 0-17 years registered in 87 general practices. Data on children with at least one asthma prescription were included in the analysis. Prescription rates and prescription of continuous (≥ 3 prescriptions/year) versus intermittent asthma medication were calculated. Data, including several GP characteristics, were analysed using multivariate logistic regression accounting for clustering within practices.

Results

During one year, 16% of the children received no prescription despite an asthma diagnosis was recorded during a consultation. Of the 2,993 children receiving asthma prescriptions, 61% received one or two prescriptions, and 39% received three or more. Prescribing behaviour for asthma medication varies widely between practices. Continuous medication with a bronchodilator and/or a corticosteroid was prescribed in 22% of children. One in five children receiving continuous medication were prescribed a bronchodilator only. In 7.5% of the prescriptions other medications than bronchodilators or corticosteroids were prescribed for asthma. None of the child and GP determinants had an independent effect on prescribing continuous versus intermittent medication.

Conclusions

In general practice the annual number of asthma prescriptions per child is relatively low. One in 20 children is prescribed bronchodilators only continuously indicating room for improvement. Child and GP characteristics cannot be used for targeting educational efforts.

INTRODUCTION

Patterns of medication for children with asthma have changed over the last 20 years and many related guidelines have been issued. The Global Initiative for Asthma (GINA) recommended a stepwise approach with different asthma medications based on control of the asthma symptoms.[1] The guidelines for childhood asthma issued by the Dutch College of General Practitioners correspond with the GINA guidelines.[2,3] In these guidelines, bronchodilators (reliever medication) and corticosteroids (controller medication) play the most important role in treating children with asthma in general practice.

Nowadays, inhaled medications are preferred because they deliver the active agent directly to the airways.[1-3] Antibiotics and cromones are not recommended for the treatment of childhood asthma in general practice. [4-8]

Before the age of 6 years it is not possible to make a firm diagnosis of asthma.[9,10] Therefore, most asthma guidelines make a distinction between asthma therapy for children less than/older than 6 years of age. However, one study showed that ≤50% of all children receiving asthma medication had a registered diagnosis of asthma, and that asthma medication is frequently prescribed at an early age to children who at an older age did not have asthma.[11] In addition, a higher variance in general practitioners' (GPs) prescription patterns exists for children younger than 6 years compared with older children.[12]

In the aim to develop effective strategies to optimize the prescribing of asthma medication for children with physician-diagnosed asthma,[13] the present study examined prescription patterns of asthma medication by GPs, the possible effect of the child's age on this pattern, and whether differences exist in GP and child characteristics in relation to the prescription of intermittent and continuous asthma medication.

METHODS

Second Dutch National Survey of General Practice

Data used in this study were derived from the most recent nationwide study DNSGP-2, conducted in 2001 by the Netherlands Institute for Health Services Research (NIVEL).[14] During a one-year registration period, 195 GPs in 104 practices throughout the Netherlands participated in the data collection. In the Netherlands, general practices have a fixed patient list, all inhabitants are listed in a general practice, and GPs have a gate-keeping role for specialized care. The patients enlisted in the participating practices were comparable to the general Dutch population with respect to age, gender, and type of health care insurance.

During the registration year, GPs (who were intensively trained in medical coding) recorded data on all contacts, including face-to-face consultations, telephone contacts and repeat prescriptions. When a patient presented two health problems within one consultation, these were coded separately. GPs were instructed to code contact diagnoses according to the International Classification of Primary Care (ICPC) and medical drug prescriptions were coded according to the Anatomical Therapeutically Classification (ATC) coding system.[15,16] In the registration year, for all 79,272 listed children (aged 0-17 years) the GPs issued 146,816 prescriptions. The participating GPs constituted a representative sample of the total population of Dutch GPs according to age of the GP, region, and location of the practice (rural/urban); the only exception is that single-handed GP practices were underrepresented.[14] This study was carried out according to Dutch legislation on privacy.

For the present analysis, data from 17 practices were excluded: in 9 practices data were incomplete and in 8 practices less than 20 asthma prescriptions for children were issued during the registration year - we assumed that GPs had failed to adequately record the ICPC code R96 (asthma). From the remaining 87 practices (174 GPs), data of all children (0-17 years) with physician-diagnosed asthma (ICPC R96) were selected. No attempts were made to validate this diagnosis.

Patients

In the present study, all contacts resulting in a prescription related to asthma were used to assess the proportion of children who used asthma medication, and to assess the prescription patterns of the GPs. For the registration period, we calculated the number of children receiving: 1) bronchodilators only (ATC: R03A, R03CC), 2) corticosteroids only (ATC: R03BA, H02AB), 3) the exclusive combination of bronchodilators and corticosteroids, and 4) other respiratory medication only (i.e. without bronchodilators and/or corticosteroids).

We considered distinguishing between short-acting and long-acting bronchodilators, but preliminary data-analysis revealed that the latter constituted only about 5% of prescribed bronchodilators. Therefore, these two categories were combined.

We classified the children in two age groups (0-5 and 6-17 years) and by sex. Asthma medication prescriptions were classified as intermittent (1 or 2 per year) or continuous ($\geq$ 3 per year) ones.

GP characteristics

Characteristics of all GPs were obtained through a mailed questionnaire. Data were collected on age, sex, degree of urbanisation (rural versus urban), single-handed practice or

not, practice size (number of listed patients), workload (number of patients per full-time equivalent GP), self-reported use of national guidelines (once a week or less versus more than once a week), whether they were involved in GP training, seeing pharmaceutical representatives, and reluctance to prescribe newly introduced drugs (entirely disagree and disagree versus hesitation, agree and entirely agree).

Data analysis

Data on all children with a diagnosis of asthma during the consultation were included in the analysis. The prescription pattern was analysed for all children (0-17 years) and for the two age groups (0-5 years and 6-17 years).

To assess which GP characteristics were associated with prescribing continuous asthma medication, Alternating Logistic Regressions (ALR) were used to estimate the associations of interest. [17] ALR alternates between Generalized Estimated Equations (GEE) to estimate the effect of the potential risk factors adjusted for the effect of clustering at the practice level, and logistic regression analysis to estimate the pair-wise odds ratios (ORs) between two children that belong to the same practice. In this way we corrected for possible clustering of children within practices.

Analyses were conducted with SPSS (version 15.0) and SAS (version 9.1).

RESULTS

Overall prescription rates for asthma in children

During the one-year registration period the diagnosis asthma was recorded for 3,562 children attending the participating general practices (4.3% of all children 0-17 years); of these, 16% received no prescription during one year despite an asthma diagnosis and 84% (n=2,993) received at least one prescription for asthma. A total of 8,740 prescriptions for asthma were issued for these children. The mean number of prescriptions for asthma per child/per annum was 2.9 (median 2, range 1-27 per child/annum). In addition, 6,686 contacts with the general practice resulted in a prescription for asthma.

Of the 2,993 children receiving an asthma prescription, 36% received only one prescription, 25% received two, and 39% received three or more prescriptions.

Table 1 shows which types of asthma medication were prescribed by the GPs in contacts with children with asthma by age category (0-5 and 6-17 years) and by sex. Of all contacts which resulted in an asthma prescription, a bronchodilator was prescribed in 53% and a corticosteroid in 51%. Antibiotics were prescribed in 4% and anticholinergics, leukotriene antagonists (LTRAs), mucolytics and cromones were seldom prescribed. More

TABLE 1 Type of asthma medication (%) prescribed in contacts with children (aged 0-17 years) with asthma (n=6,686 contacts resulting in a prescription)

	0 - 5 years			6 - 17 years			All children
	Boys	Girls	Total	Boys	Girls	Total	
Total number of contacts	**1,850**	**1,086**	**2,936**	**2,023**	**1,727**	**3,750**	**6,686**
Type of asthma medication prescribed during consultation							
Bronchodilators	47.6%	46.0%	47.0%	55.4%	59.4%	57.2%	52.8%
Corticosteroids	57.0%	53.8%	55.8%	49.6%	46.0%	48.0%	51.4%
Antibiotics	4.9%	5.0%	4.9%	3.0%	2.1%	2.6%	3.6%
Anticholinergics	2.9%	3.1%	3.0%	1.1%	1.3%	1.2%	2.0%
Leukotriene antagonists	0.2%	0.3%	0.2%	1.0%	1.1%	1.0%	0.7%
Mucolytics	0.4%	0.5%	0.4%	1.0%	0.5%	0.7%	0.6%
Cromones	0.3%	0.3%	0.3%	0.2%	1.2%	0.6%	0.5%

Sum of proportions >100%, because during a consultation more than one prescription could be issued

bronchodilators were prescribed in the older than in the younger age group (57% versus 47%, respectively; p<0.001). In contrast, more corticosteroids were prescribed in the younger than in the older age group (56% versus 48%, respectively; p<0.001). Antibiotics and anticholinergics were relatively frequently prescribed to children under 6 years of age (p<0.001).

Variation between general practices

Regarding the proportion of children prescribed a bronchodilator alone, the distribution of practices had a 25th percentile, median and 75th percentile of 19%, 28% and 36%, respectively. Related data for corticosteroids alone were 11%, 18% and 24%, respectively, and for the combination of a bronchodilator and a corticosteroid 5%, 9% and 15%, respectively.

Prescribing intermittent or continuous asthma medication

Table 2 shows the type of asthma medication, intermittent (1-2 prescriptions/year) and continuous (≥ 3 prescriptions/year) prescribed for children aged 0-5 years and 6-17 years during the registration period. A bronchodilator only was prescribed in 35% of the children, a corticosteroid only in 24%, a combination of bronchodilator and corticosteroid in 33%, and in 7.5% of the children only other respiratory medication (i.e. without a bronchodilator and/or corticosteroid) was prescribed.

TABLE 2 Type of asthma medication prescribed for children aged 0-5 years (n=1,398) and 6-17 years (n=1,595) during the one-year registration period

	0-5 years			6-17 years			0-17 years
Total number of children	**Boys n=860**	**Girls n=538**	**Total n=1398**	**Boys n=876**	**Girls n=719**	**Total n=1595**	**All children n=2993**
Number of prescriptions							
1			38%			35%	36%
2			26%			23%	25%
3			36%			41%	39%
Medication type							
Intermittent medication (1 or 2 prescriptions per medication type)							
Bronchodilators only	31.7%	32.3%	31.9%	30.4%	30.2%	30.3%	31.0%
Corticosteroids only	20.1%	21.2%	20.5%	17.4%	15.3%	16.4%	18.3%
Bronchodilators + Corticosteroids	22.2%	18.6%	20.8%	22.0%	20.9%	21.5%	21.2%
Continuous medication (≥ 3 prescriptions per medication type)							
Bronchodilators only	1.9%	3.2%	2.5%	5.1%	6.9%	6.0%	4.4%
Corticosteroids only	6.3%	6.7%	6.4%	5.0%	5.2%	5.1%	5.7%
Bronchodilators + Corticosteroids*	11.4%	9.1%	10.5%	12.9%	13.3%	13.1%	11.9%
Only other respiratory medication (i.e. without bronchodilators and/or corticosteroids)	6.4%	8.9%	7.4%	7.2%	8.2%	7.6%	7.5%

* *≥ 3 prescriptions bronchodilators and/or ≥ 3 prescriptions corticosteroids*

During the registration year, of all children prescribed a bronchodilator alone 72% received only one prescription, and of all children prescribed corticosteroids alone 54% received only one prescription (data not shown).

Overall, medication was prescribed continuously in 22% of the children. In one in five of these, 4.4% of all children, only bronchodilators were prescribed.

Younger children (0-5 years) less frequently received a bronchodilator prescription for continuous use than older children (boys 1.9% versus 5.1%, p<0.001; girls 3.2 versus 6.9, p<0.001); for continuous corticosteroid prescriptions no differences were found.

Table 3 presents data on the general practices. The mean age of the GPs was 46 years, most were male (76%), and the majority (62%) had a practice in an urban area. Two-thirds trained GP trainees; in most practices GPs saw pharmaceutical representatives, and most GPs (88%) were reluctant to prescribe new drugs.

Table 3 Characteristics of 174 general practitioners (GPs) in 87 general practices

Mean age of GPs, years (SD)	46.5 (5.5)
Sex of GP (% male)	76.3
Urban (%)	62.1
Single-handed practice (%)	49.1
Practice size, mean (SD)	4,272 (2,333)
Workload (number of patients per full-time equivalent GP) (SD)	2,666 (481)
Consulting general practice national guidelines more than once a week (%)	52.7
GP trainer (%)	67.1
Seeing pharmaceutical representatives (%)	74.1
Reluctant to prescribe new drugs (%)	88.2

Determinants for intermittent or continuous bronchodilator and/or corticosteroid prescription

The multivariate logistic regression (Table 4) shows that none of the child or GP characteristics had an independent effect on prescribing intermittent versus continuous medication. The ORs were estimated for both age groups separately. Except for a very small effect (OR=1.01) for prescribing continuous asthma medication by male versus female GPs in children aged 6-17 years, no differences in determinants were found.

Table 4 Relation between GP and child determinants, and prescribing continuous (≥ 3 prescriptions/year) asthma medication for children aged 0-5 years and 6-17 years with asthma (n=2,993). Multivariate logistic regression analysis

	Children 0-5 years (n=1398) OR (95% CI)	p-value	Children 6-17 years (n=1595) OR (95% CI)	p-value
Age child	1.07 (0.99-1.17)	0.09	0.99 (0.95-1.03)	0.78
Female child	0.99 (0.69-1.29)	0.95	1.13 (0.85-1.41)	0.33
Age GP	1.00 (0.96-1.05)	0.56	0.98 (0.95-1.02)	0.34
Male GP	1.00 (0.99-1.01)	0.06	1.01 (1.00-1.01)	0.02
Urban practice	1.17 (0.98-1.38)	0.66	1.08 (0.94-1.22)	0.23
Single-handed practice	1.41 (0.96-2.61)	0.15	0.73 (0.53-1.15)	0.09
Workload (1,000 patients/fte*)	1.00 (0.99-1.01)	0.82	1.00 (0.99-1.01)	0.94
Consulting general practice national guidelines more than once a week	1.00 (0.99-1.01)	0.99	0.99 (0.99-1.01)	0.89
GP trainer	1.00 (0.99-1.01)	0.21	1.00 (0.62-1.38)	0.99
Seeing pharmaceutical representatives	1.00 (0.99-1.01)	0.38	1.00 (0.99-1.01)	0.94
Reluctant to prescribe new drugs	1.00 (0.99-1.01)	0.38	1.00 (0.99-1.01)	0.10

* *full-time equivalent GP*

DISCUSSION

During the one-year registration period, over 60% of the children received only 1 or 2 prescriptions for asthma. In over 50% of the prescriptions the GP prescribed a bronchodilator or a corticosteroid; in only 7.5% of the children were other types of respiratory medication prescribed. In accordance with the Dutch GP Guideline,[3] the proportion of prescribed antibiotics, mucolytics and cromones was very small. In 22% of all children, bronchodilator and/or corticosteroids were prescribed by the GPs on a continuous basis. A bronchodilator only was prescribed continuously in almost 5% of the children. None of the child or GP-related determinants had an independent effect on prescribing intermittent or continuous medication.

Strengths and limitations of this study

The present study used data derived from the DNSGP-2.[14] The strength of this unique representative study is that it provides information on a relatively large group of children, and their GPs, in a country in which GPs act as gatekeepers to secondary care, and appropriate guidelines are disseminated. Therefore, our results can be assumed to represent the daily prescription behaviour among Dutch GPs for childhood asthma.

Although the data we used are several years old, we do not believe this is a major limitation. The outcome would not differ greatly when more recent data would have been available.

A possible limitation is the exclusion of GPs who failed to adequately record the ICPC code asthma specifically in children. It is known that some GPs are reluctant to label symptoms as asthma; however, despite the immaturity of the diagnosis asthma, medication is often prescribed.[11] These children with potential asthma, but without physician-diagnosed asthma, were not included in the present study and enabled us to study a more homogenous population.

On the other hand, in the present study an asthma diagnosis as registered by the GP was accepted as a valid diagnosis. However, this may not accurately reflect the actual number of asthmatic children in the study population, because some GPs may make the diagnosis asthma too easily or provisionally label the child as asthmatic. This is supported by the fact that some children received only one prescription during a whole year, and 16% received no medication despite an asthma diagnosis.

The registration period for asthma medication was set at one year and the prescription pattern within this time frame was analysed. However, prescriptions issued shortly before the registration period may have affected subsequent prescribing.

Comparison with the literature

In the present study 1,398 prescriptions were issued for all children aged 0-5 years, and 1,595 prescriptions for the larger group of children aged 6-17 years. This relatively large amount of prescriptions in the younger age group could be explained by the higher GP consultation rates of younger children than older children for respiratory complaints.[18]

GPs generally treat children with mild or moderate asthma.[1,19] In the present study this is supported by the large amount of children with only 1 or 2 prescriptions. The current guidelines recommend a two-step approach for asthma medication: start with a bronchodilator and add a low-dose inhaled corticosteroid when symptoms have failed to disappear or have worsened.[1-3] Single prescriptions, which could be tentative, were more common for bronchodilators (72%) than for corticosteroids (54%). The majority of prescriptions were for a bronchodilator only (31%), corticosteroid only (18%) and a combination of both (21%) for children with asthma of all ages and sex. These percentages are similar to those found in Germany.[20]

Inhaled corticosteroids are the most effective drugs for controller therapy in children and the cornerstone for continuous asthma medication.[1-3] The continuous asthma medication group in our study consisted of a high proportion of corticosteroids alone and in combination with bronchodilators (80%). In the light of current asthma guidelines,[1-3] prescribing bronchodilators alone in 20% of the children with continuous asthma medication (4.4% of all children) is unexpectedly high and suggests room for improvement. This finding of relatively high continuous bronchodilator prescriptions was also found in two recent primary care studies in the UK.[21,22] Most likely, these children also need inhaled corticosteroids.

At the time of our study, LTRAs were not used widely, which is however in line with a recent study in primary care in the UK.[22] LTRAs provide clinical benefit in children but generally less than low dose corticosteroids.[23,24]

One would expect older children to have a clearer diagnosis of asthma and therefore receive more corticosteroids continuously than children aged 0-5 years.[11,12,25,26] However, in the present study a different picture emerged, suggesting either undertreatment of the older group or overtreatment of the younger group.

Because asthma guidelines have long been available, we expected that medication other than bronchodilators and corticosteroids would be prescribed in a minority of cases.[1-3] Indeed, in only 7.5% of the children was 'other' medication prescribed for asthma, with a low percentage (3.5%) for antibiotics. Age and sex of the child had no independent effect on prescribing continuous versus intermittent bronchodilator and/or corticosteroid medication. Our finding that sex was not associated with prescribing continuous asthma medication is in contrast to other reports.[20,27] We also expected GP determinants to be associated with prescribing continuous asthma medication.

Zuidgeest et al found the variance in prescribing patterns among GPs for children under 6 years of age to be higher than for older children.[12]

The results of the present study imply that GP characteristics cannot be used for targeting education on prescription patterns.

Implications for clinical practice and research

It is noteworthy that during the one-year registration period many GPs issued only 1 or 2 asthma prescriptions per child. Future studies should establish whether these children do in fact need only 1 prescription, or whether they are undertreated and might benefit from more prescriptions, or from a combination of a bronchodilator and a corticosteroid.

The wide variation in prescribing behaviour between general practices also needs further investigation. Prescribing a bronchodilator as continuous medication is not recommended by any guideline. GPs should be aware of this type of over-prescribing in the asthmatic child.

In conclusion, the present study shows that in general practice the number of prescriptions per child issued for asthma is relatively low. The prescribing behaviour for bronchodilators and corticosteroids varies widely. Twenty percent of children receiving continuous prescriptions were prescribed bronchodilators only (4.4% of all children), indicating room for improvement. No specific child or GP characteristics can be used for targeting education on prescription patterns.

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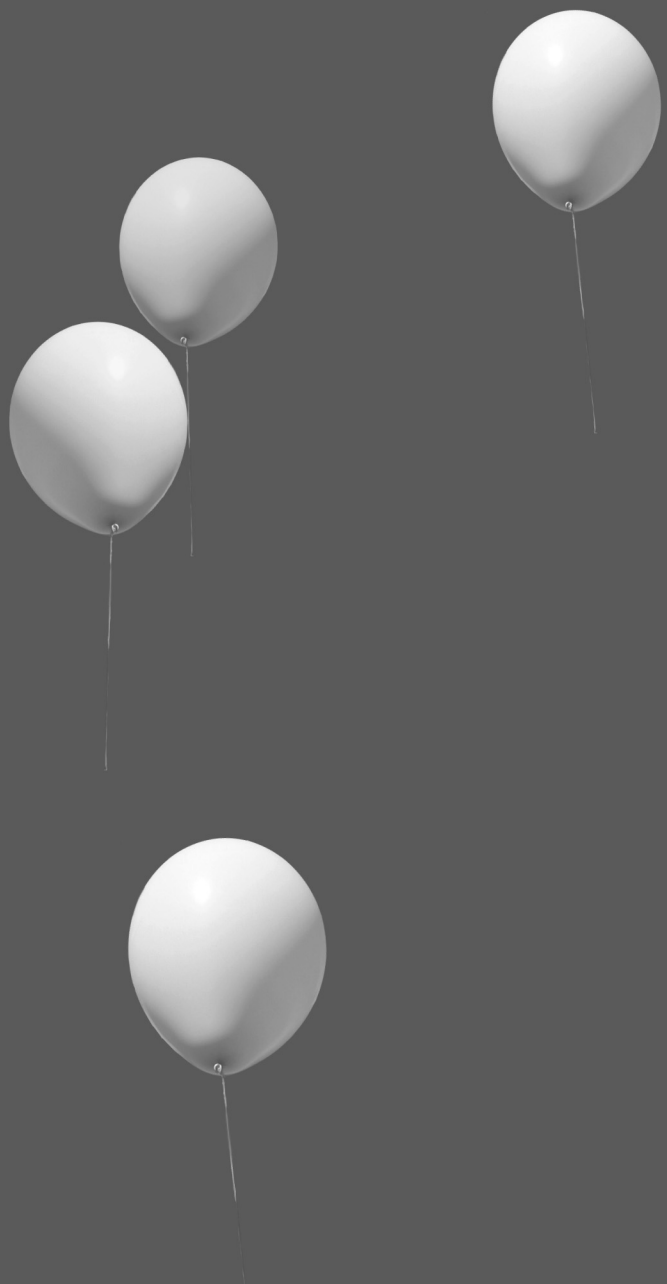
Adequate use of asthma inhalation medication in children: more involvement of the parents seems useful

5



Uijen JHJM, van Uijthoven YJW, van der Wouden JC, Bindels PJE. Adequate use of asthma inhalation medication in children: more involvement of the parents seems useful. *BMC Research Notes* 2009;2:129

Background

Asthma and other chronic airway diseases can be effectively treated by inhaler therapy. Inhaler therapy depends on appropriate use of the inhaler. This study evaluates the knowledge among Dutch children and their parents regarding asthma inhaler therapy and appropriateness of its use.

Findings

Five general practices selected all children aged 0 to 12 years on asthma inhalation medication. Children demonstrated inhaler use and were interviewed with their parents. 46 subjects were enrolled; mean age 5.5 years (SD 3.4) years; 26 (57%) were boys. Of the children using one inhaler only, 70% used the inhaler as indicated and of those using more than one inhaler 46%. On average 2.6 mistakes were made during demonstration of the technique, and 2 mistakes were reported in the interview. In total, 87% of the parents decided when and how the inhaler had to be used. Spacer cleaning was performed correctly by 49%; 26% reported a correct way of assessing how many doses were remaining.

Conclusions

Dutch children make essential mistakes related to inhaler use that are easy to avoid. We recommend a better explanation and demonstration of the technique, and recommend involvement of the parents during instruction.

INTRODUCTION

Asthma and other chronic airway diseases can be effectively treated by inhaler therapy.[1] Inhaler devices come in a variety of types, such as metered dose inhalers (MDI) or dry powder inhalers (DPI). Irrespective of the type of inhaler device used, the outcome of inhaler therapy largely depends on appropriate use of the inhaler.

Appropriate use primarily involves the correct inhalation technique. A poor inhalation technique reduces drug deposition in the lungs;[2] moreover, the more mistakes made in the inhalation technique the lower the beneficial effect on lung function.[3] From adults it is known that 89% of the patients make at least one mistake in the inhalation technique.[4] Also children face difficulties in using an inhaler. A study among Taiwanese children showed that none of the children had a perfect inhalation technique,[5] a Dutch study reported that even after instructing children the overall inhalation technique remained poor.[6] In contrast, a study from Malta showed that only 17% of children using an MDI with a spacer device had a poor technique.[7]

Appropriate inhaler use also involves actual use compared with the advised regimen of the prescriber. Several studies have shown that, even with adequate inhaler use (between 50 and 80% of prescribed doses), compliance with inhalation corticosteroids (ICS) is far from perfect.[8-12] Overuse of bronchodilators has also been reported and some parents confuse the corticosteroid inhaler (for maintenance therapy) with the bronchodilator inhaler (to be used in case of symptoms).[13-14]

Little is known about the current situation regarding the appropriate use of inhalers by children in the Netherlands. Therefore the purpose of this study is to determine the level of knowledge of children and their parents associated with the correct use of the inhaler. We also wanted to identify inconsistencies between use of inhalers compared with prescriber advice on inhaler use.

METHODS

Subjects

We included all children aged from 0 to 12 years who had been prescribed inhalation medication in the last three months. For this reason, the electronic patient files were searched for patients who had been prescribed relevant medication using the ATC codes R03A (adrenergics) and R03B (other drugs for obstructive airway diseases, including ICS).[15] A convenience sample of five Dutch general practices in both rural and urban areas was invited to participate.

Data collection

The general practitioner (GP) sent parents of the children a letter with an informed consent form, a request to participate, and an answer form that had to be returned to the investigators. Subjects that responded positively were visited at home during the period April to July 2007 by a well-trained investigator who observed the inhalation technique and held a face-to-face interview.

Questions on the inhalation technique were posed to the children themselves if they were aged five years and older; if they were younger the parents answered these questions. Additional general questions were always answered by the parents.

Assessing appropriate use

The investigator assessed the child's inhalation technique using an inhaler specific checklist adapted from the checklists of the Dutch Asthma Foundation.[16,17] Children were asked to demonstrate their inhalation technique and any mistakes were written down. Essential mistakes were identified.[17] These involved preparing or loading the device prior to inhalation; slow continuous inhalation (MDI) or deep forceful inhalation (DPI); waiting too long before inhaling a spacer after activating the MDI; and incorrect spacer mask use.

In order to exactly compare inhalation technique itself with knowledge on inhalation technique, the investigator administered a second questionnaire after the child had demonstrated the inhalation technique.

Finally the parents were asked how they assessed the number of remaining doses and how they cleaned the device. Both questionnaires can be found in the appendix.

Assessing actual use compared with prescribed daily dose

After the interview, the pharmacy prescription labels of the inhalation medication were collected. With permission of the parents, the information written on the prescription label was copied. If the label was no longer available the parents were asked to provide written consent to obtain the prescription details from the GP.

Data analysis

All data were analysed with SPSS version 11.0. All analyses were descriptive.

RESULTS

Response and inhaler use

All five practices agreed to participate and a total of 162 children were selected from the electronic medical files. A reply was received from 56 subjects (34%), of which 10 (16%) refused to participate. The most frequent reason for refusal (among responders) was that the inhalation medication was no longer used. Two subjects refused because of a stressful situation at home. The 46 subjects (28%) enrolled had a mean age of 5.5 (SD 3.4) years. Thirty (65%) were aged five years or older. Twenty-six (57%) of the subjects were boys. Twelve (26%) of the children lived in an urban region, while 34 (74%) lived in a rural area. Most children (n=41; 89%) used an MDI in combination with a spacer device, four children (9%) used a DPI and only one child (2%) used an MDI without a spacer. Thirty-three children (72 %) used a bronchodilator in combination with an ICS, the remaining children used either a bronchodilator (n=12; 26%) or an ICS (n=1; 2%).

Inhalation technique

Because two very young children refused to demonstrate their inhalation technique, demonstration data are available for only 44 of the 46 children. Table 1 summarizes the three most frequently made mistakes during the demonstration of the technique and the three most frequent incorrect answers. One child made no mistakes during the demonstration.

Not shaking the inhaler before use was the most frequently made mistake (n=9; 20%) during the demonstration; and "When I need two doses, I can activate MDI twice before starting to inhale through spacer" was the most frequently noted incorrect answer (n=19; 43%). Each child made on average 2.6 mistakes (range: 0 – 7) in demonstrating, and on average 2 mistakes (range: 0 – 5) were noted on the questionnaire.

TABLE 1 Essential mistakes during demonstration of inhalation technique and in questionnaire (n = 44)

Type of mistake made in demonstration of technique	*n*	*(%)*
Forgot to shake inhaler before use	9	(21)
Waiting >5 sec before inhaling spacer after MDI activation	8	(18)
Not pressing spacer mask on face	8	(18)
Type of mistake made in questionnaire on technique		
Activating MDI twice before inhaling through spacer, when two doses are needed	19	(43)
Not rinsing the mouth after using ICS inhaler	4	(9)
Making less than five inhalations through spacer	3	(7)

Actual use of inhalers compared with prescribed use

Pharmacy prescription labels were available from 32 children. Twenty of the 32 children (63%) used the inhaler as indicated on the prescription label. All children having one inhaler used their inhaler as indicated on the prescription label. Of the children having two inhalers, only 39% used both their inhalers as indicated on the label. The following mistakes were made: three children used their bronchodilator 'as needed' instead of daily. Five children used their bronchodilator daily instead of 'as needed'. Four children were using their ICS 'as needed' and one child did not use the prescribed bronchodilator.

Education

Of all parents, 42 (91%) had received some instruction about the inhalation technique; this instruction was clear for 41 of them. Of these 42 parents, 19 (45%) had received instruction at the pharmacy, 11 (26%) at the general practice, 7 (17%) at the hospital, 4 (10%) had more than one source of instruction, and 1 (2%) had received instruction from friends or family. There was no relationship between the different sources of education and mistakes related to inhalation technique or therapy adherence.

Decision concerning inhaler use

In total, 87% of the parents decided when and how the inhaler had to be used. The mean age of their total of 40 children was 4.9 (SD 3.2) years. The six children, who decided themselves when and how they used the inhaler, had a mean age of 8.5 (SD 1.8) years. There was no significant difference between both groups regarding mistakes.

Inhaler management

Table 2 summarizes the parental reports on assessing an inhaler for remaining doses of the drug. We considered the following categories to be correct: looking on counter of inhaler; spraying on dark background; if inhaler floats in water, it is empty; and counting remaining doses with agenda. The reports of 12 of the 46 subjects (26%) were correct.

Table 3 shows the parental reports on cleaning the spacer. We considered only cleaning the spacer with soap, and letting it dry in the air to be correct. Of the 41 subjects (49%) using a spacer, 20 (49%) reported to clean it correctly.

DISCUSSION

Despite decades of experience with inhaler therapy, a variety of mistakes concerning therapy adherence, the inhalation technique, and mistakes in the handling of spacer and

Table 2 Parental report on assessing remaining doses (n = 46)

Method used	*n*	*(%)*
Correct		
Looking on counter	3	(7)
Spraying against dark background	4	(9)
If inhaler floats in water, it is empty	2	(4)
Counting remaining doses using agenda	3	(7)
Incorrect		
Feeling inhaler weight while shaking	9	(20)
Listening to inhaler while shaking	4	(9)
Spraying in the air	13	(28)
If inhaler sinks in water, it is empty	1	(2)
Not assessing at all	7	(14)
Total	46	(100)

Table 3 Parental report on cleaning spacer (n=41)

Method used	*n*	*(%)*
Correct		
Soaping inhaler, dry in air	20	(49)
Incorrect		
Soaping inhaler, dry with towel	15	(36)
Cleaning inhaler in dishwasher	2	(5)
No cleaning at all	4	(10)
Total	41	(100)

device were made by Dutch children. The important role of the parents in all of these aspects is highlighted in this discussion.

Therapy inconsistency

To determine therapy inconsistency we compared the reported use with the pharmacy prescription label, in our opinion the most appropriate source for comparison. The use of more than one inhaler was most frequently the reason for inappropriate use. Parents decide when and how the inhaler is to be used for most of the children, which confirms their important role in compliance with inhaler therapy. Noteworthy is that four children only used their ICS in case of symptoms, although ICS are a long-term maintenance therapy and should be administered daily.

Inhalation technique

We found that many subjects did not shake their inhaler (c.f. Kamps et al).[6] However, despite their mistake, most subjects knew that the inhaler had to be shaken before use. On the other hand, nineteen subjects did not know that it is recommended to activate the MDI once, inhale the first dose of drug, and then activate the MDI again for a second dose.[16]

Most of the parents received the instruction either at the pharmacy or the general practice, emphasizing that both organisations play an important role in educating parents about the inhalation technique.

Inhaler management

Most parents reported an incorrect method of assessing an inhaler for remaining doses. Most of them spray in the air to see whether the inhaler still contains gas. Fifteen subjects reported that they clean and dry their spacer with a towel. This is incorrect because the generated static load will prevent the drug from leaving the spacer for the first few inhalations.[16] Four subjects reported that they never cleaned their spacer.

Is every mistake a failure?

Dutch children and their parents make a variety of mistakes when using an inhaler. However, despite the mistakes made, none of the children included in this study had severe asthma symptoms. It is therefore important to further investigate the effect of both the inhalation technique and the therapy consistency on asthma control. Especially ICS have become very potent in the last decade and even with a less correct inhalation technique relief of symptoms might be achieved.

Strengths and limitations

This present study has several potential limitations. Although our strategy of using self-reports may not be ideal, no feasible alternative is available.[8,10,12] During the technique demonstration, some of the younger children became shy, which probably influenced their inhalation technique. The limited number of general practices and pharmacies may have affected the results. The proportion of responders, although low, is not uncommon in this setting.[18] As responders were probably more compliant, given their interest in the study, the overall compliance and inhaler technique might be even worse than our results suggest.

Strength of the present study is that the children were visited at home allowing them to demonstrate their inhalation technique in a familiar environment. We also explored knowledge on the inhalation technique and use, and combined these findings with the prescription.

CONCLUSIONS

Children and their parents still make a variety of mistakes when using an inhaler. Concerning the inhalation technique, some easy to avoid mistakes were made, e.g. shaking and activating twice an inhaler before use. Therapy adherence was not optimal, especially when more than one inhaler was prescribed. In addition, mistakes were made related to cleaning the spacer and assessing the inhaler for remaining doses.

Practice implications

Inadequate knowledge of when and how to use prescribed medication is one of the major barriers in achieving asthma control.[19] It is important that the GP give appropriate and written instruction to the parents, who play a prominent and important role in compliance with therapy of their children.

First of all, the inhalation technique should be clearly explained and well demonstrated. Preferably, this should be checked again during follow-up appointments to correct mistakes. Therapy regimen should be discussed, particularly when more than one inhaler is prescribed. An explanation of the difference between maintenance therapy and rescue medication is essential. We recommend further studies into the effect of education and monitoring on the appropriateness of inhalation technique in children (c.f. Haynes et al.[20]).

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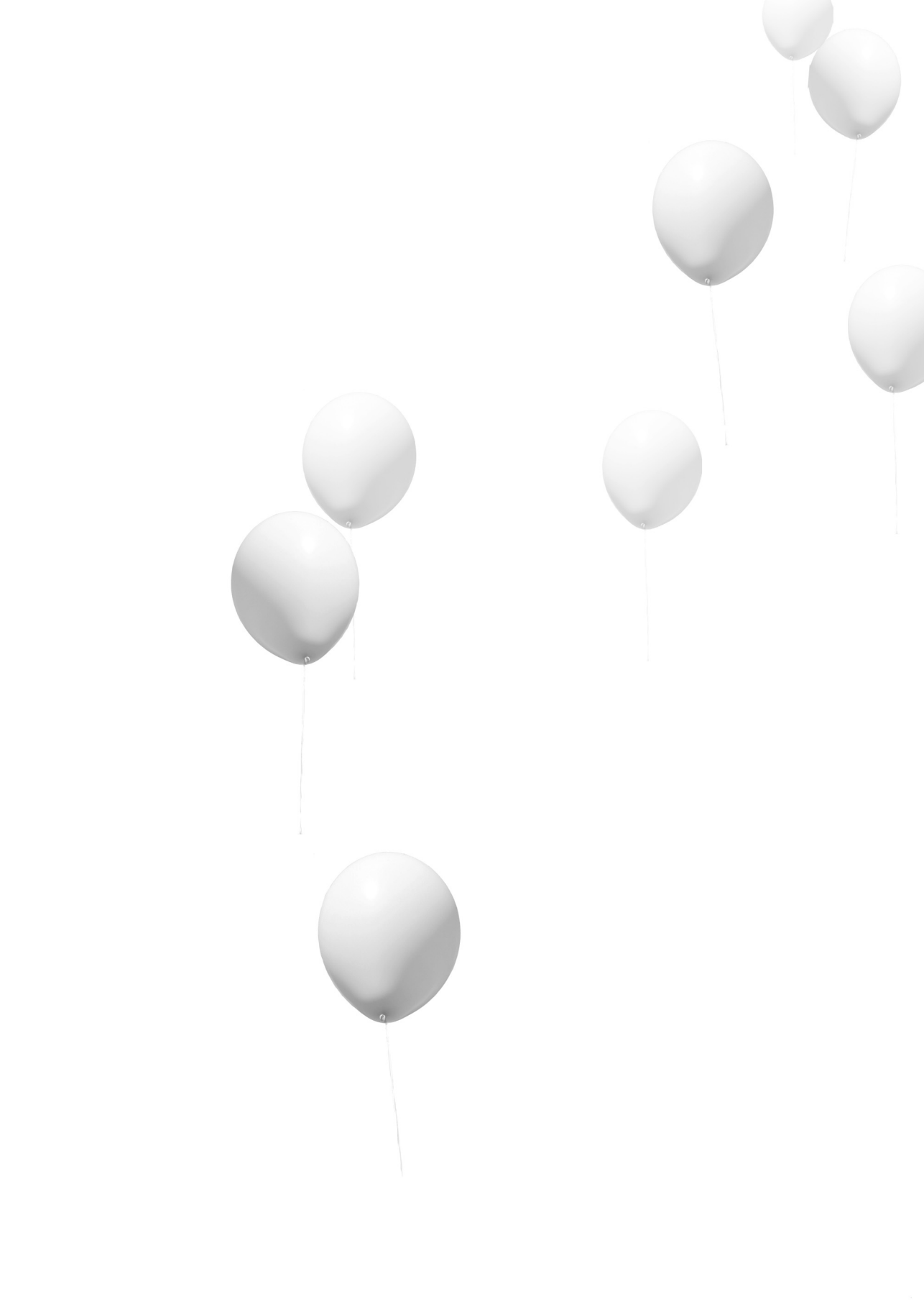


APPENDIX

Inhalation technique questionnaire and general questionnaire items

Inhalation technique questionnaire items:

- Should the inhaler be shaken before use?
    - Yes
    - No
- Where on the face should the inhaler / the mask be placed?
    - Mouth
    - Nose
    - Both
- Should the mask firmly fit the face?
    - Yes
    - No
- How many doses should be brought into the spacer?
- At what speed does your child need to breath through the inhaler / the spacer?
    - Quick (< 2 seconds)
    - Normal (2 – 5 seconds)
    - Slow (> 5 seconds)
- How many times should your child breathe in and out through the inhaler / the spacer?
- When in need of multiple doses, how are these doses applied?
    - Initially bring all the doses in the spacer, then start the inhalation process.
    - Bring one dose in the spacer, then start inhalation process. Bring another dose in the spacer, and then repeat the inhalation process.
- Does your child need to rinse the mouth after inhaling?
    - Yes
    - No

General questionnaire items:

- Who provided instructions regarding the inhalation technique?
    - General practitioner
    - Pharmacy
    - Hospital
    - Somebody else
    - No instructions
- Was the inhalation technique checked during a follow-up appointment?
    - Yes
    - No
- Did you read the information leaflet provided with the inhaler?
    - Yes
    - No
- How do you assess the inhaler(s) for remaining doses?

  .....
- How do you clean the inhaler(s) or spacer?

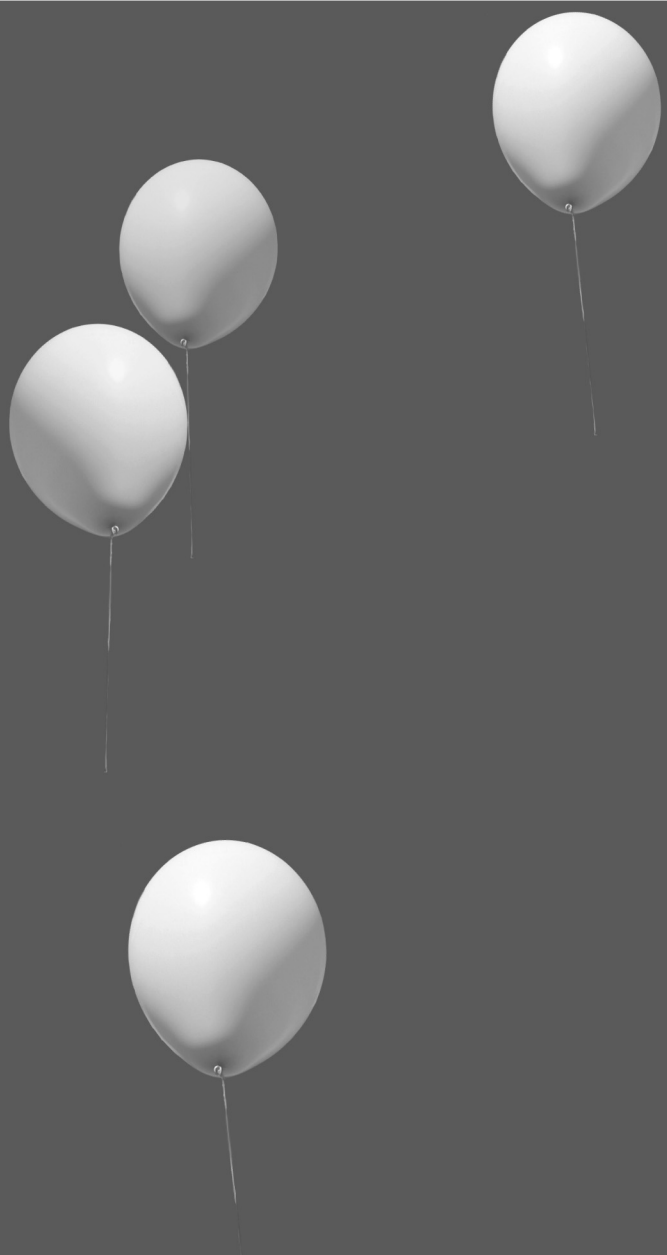
  .....
- When does your child use the inhaler(s)? For example daily or as needed?

  .....
- Who decides when the inhaler has to be used: you or your child?

  .....

Inhaled sodium cromoglycate for asthma in children – a systematic review

6



Van der Wouden JC, Uijen JHJM, Bernsen RMD, Tasche MJA, de Jongste JC, Ducharme F. Inhaled sodium cromoglycate for asthma in children – a systematic review. *Cochrane Database Systematic Reviews* 2008, Issue 4. Art. No.: CD002173

Background

Sodium cromoglycate has been recommended as maintenance treatment for childhood asthma for many years. Its use has decreased since 1990, when inhaled corticosteroids became popular, but it is still used in many countries.

Objectives

To determine the efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma.

Selection criteria and analysis

All double-blind, placebo-controlled randomised trials, which addressed the effectiveness of inhaled sodium cromoglycate as maintenance therapy, studying children aged 0 up to 18 years with asthma. Two authors independently assessed trial quality and extracted data. We pooled study results.

Results

Of 3500 titles retrieved from the literature, 24 papers reporting on 23 studies could be included in the review. The studies were published between 1970 and 1997 and together included 1026 participants. Most were cross-over studies. Few studies provided sufficient information to judge the concealment of allocation. Four studies provided results for the percentage of symptom-free days. Pooling the results did not reveal a statistically significant difference between sodium cromoglycate and placebo. For the other pooled outcomes, most of the symptom-related outcomes and bronchodilator use showed statistically significant results, but treatment effects were small. Considering the confidence intervals of the outcome measures, a clinically relevant effect of sodium cromoglycate cannot be excluded. The funnel plot showed an under-representation of small studies with negative results, suggesting publication bias.

Conclusions

There is insufficient evidence to be totally sure about the efficacy of sodium cromoglycate compared with placebo as maintenance therapy in childhood asthma.

BACKGROUND

Since the late 1960s, disodium cromoglycate (DSCG) has been used as maintenance treatment for children with moderate asthma, although the precise mechanism of action is still not fully understood. No serious side effects have been reported in trials, but cases of dysuria, urticaria, bronchospasm, angio-oedema and anaphylaxis have been ascribed to the use of DSCG, once with death as a result (Lester 1997; Leynadier 1985).

In the early 1990s, many guidelines recommended use of DSCG. Gradually, corticosteroids have come to the fore as first choice maintenance therapy (BAG 1997; Ernst 1996), or were recommended alongside DSCG for mild persistent asthma (NIH 1997). Other guidelines continued to recommend DSCG as first choice in young children (Sly 1997). The most recent revisions of the GINA and NIH guidelines (GINA 2005; NIH 2002) consider the role of DSCG in children to be limited. Inhaled glucocorticosteroids are the first choice; DSCG is only recommended as one of the alternative treatment options for children with mild persistent asthma. Canadian guidelines no longer recommend DSCG as maintenance therapy for children, nor do British guidelines for children aged 5 to 12 years (Becker 2005; BTS 2003, page i20).

The long-term side effects of asthma treatment with inhaled steroids in early childhood are not clear. Nevertheless, there is concern that treating very mild cases of asthma with inhaled steroids may have an adverse effect on the balance between risk and benefit. A Cochrane review has shown an effect of inhaled beclomethasone on linear growth in children (Sharek 1999). Therefore, physicians involved in the treatment of asthma in children may still prefer sodium cromoglycate as first choice maintenance treatment.

The use of DSCG has decreased since 1990, while the use of inhaled corticosteroids is increasing. The discrepancy between guidelines and the debate on the role of DSCG, which led to its recent withdrawal as first line maintenance treatment in young children in some countries, was the rationale to review the efficacy of inhaled DSCG as maintenance treatment for chronic childhood asthma.

Objectives

To determine whether there is evidence for the efficacy of inhaled sodium cromoglycate as maintenance treatment in children with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

All double-blind, placebo-controlled, randomised clinical trials, which addressed the effectiveness of DSCG as maintenance therapy.

Types of participants

Children aged 0 up to 18 years with asthma in all settings (general practice, emergency departments, outpatient departments, hospitalised). We only included studies including both children and adultswhen results for children were presented separately. When the number of children in these studies was less than five, we did not include the study.

Types of interventions

Inhaled sodium cromoglycate, delivered via any device: nebulised, by Spinhaler or by metered dose inhaler, with or without holding chamber. We only included trials that compared DSCG with placebo. No co-interventions were permitted other than rescue medication as needed.

Types of outcome measures

Primary outcomes

The primary outcome measure was the difference in percentage of days without asthma symptoms, between placebo and cromoglycate treatment.

Secondary outcomes

- Symptom scores (day cough, day wheeze, daytime asthma score, day activity, night cough, night wheeze, night-time asthma score, sleep disturbance, overall symptom/ severity score)
- Auscultation score
- Preference of patients/parents and clinicians
- Overall success rate
- Bronchodilator use, use of oral steroids, hospital admission
- Side effects

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and hand searching of respiratory journals and meeting abstracts (please see the Airways Group Module for further details).

Additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2009), MEDLINE (January 1966 to October 2009) and EMBASE (1979 to October 2009) were also conducted. For MEDLINE and EMBASE we used the Cochrane sensitive search strategy to select all RCTs (Dickersin 1994) and in all databases, we used the following search terms: cromolyn* OR dscg OR cromoglycate* or cromoglicate* OR cromone* or intal*.

Searches are current to October 2009.

Searching other resources

We contacted the pharmaceutical company manufacturing DSCG (Rhone-Poulenc-Rorer, formerly Fisons plc, Loughborough, UK), checked bibliographies of retrieved trials and contacted primary authors of trials published after 1990 for any additional trials.

Data collection and analysis

Data extraction and management

Two authors extracted data. When using symptom scores, most studies used a scale of 0 to 3 points; where a different scale was used we transformed the mean and standard deviation for our purposes. We calculated confidence intervals for the treatment effect (difference in symptom score) for individual studies assuming a t-distribution.

Assessment of risk of bias in included studies

Two authors independently scored the methodological quality of all trials using three sets of criteria: Chalmers (Chalmers 1981), Jadad (Jadad 1996) and the Cochrane criteria for concealment. A third author determined the final decision if there was lack of consensus. Trials in which one of the authors was involved were also scored by an impartial author. We did not contact authors of the trials for confirmation of methodology and data extraction, because most of the studies were performed many years ago and we considered it unlikely that this would provide further useful information. When updating the review in 2007, a 'Risk of Bias' table was added.

Dealing with missing data

If no standard error of the treatment effect of a particular outcome measure was available, and could not be calculated, we imputed it from a study with a similar design (cross-over or parallel) (cf Follman 1999). If more than one study was available for imputation, we selected the largest study, unless this choice would lead to inconsistencies with the results in the original study (e.g. when the authors reported no significant difference, but the imputed data would change this). In that case the second largest study was taken.

Data synthesis

We computed pooled estimates of the treatment effect and the pooled 95% confidence intervals (CI), combining parallel and cross-over studies (Elbourne 2002). For cross-over studies we used the results of paired analyses, extracting treatment effect, standard error and within patient correlation between DSCG and placebo period (rho) from papers. When rho was not given, we imputed this in the same way as stated above for missing standard errors. We tested for homogeneity (Dersimonian 1986). When heterogeneity was found ($P < 0.05$), we did not use the fixed-effect model to compute a pooled estimate and confidence interval, but only used the random-effects model (Dersimonian 1986). To investigate causes for heterogeneity, we evaluated the influence of study characteristics (year of publication, mean age of children, method of delivery, asthma severity of the study population, methodological quality, doses per day and duration). Assessment of asthma severity was based on the description of the study population in the papers. As there was no single outcome measure available for all studies, we selected those outcomes for which at least 10 studies were available. To include as many studies as possible in the funnel plot (see below) and the meta-regression analysis, we combined various outcome measures that used a similar scale, taking the first available from overall symptom score, day wheeze, day cough, day activity and daytime asthma score.

For all study characteristics except asthma severity, we used univariate and multivariate meta-regression analysis (Fleiss 1993), weighing observations by the reciprocal of the square of the standard error of the mean difference between placebo and DSCG. Thus, all pooled outcomes are presented as weighted mean differences (WMD). Study characteristics were either entered as categorical (design, type of delivery) or as continuous (publication year, quality score, etc.). For asthma severity, we used the asthma score in the placebo group (or period) as study characteristic. Because this measurement is subject to measurement error as much as the outcome variables are, ordinary regression analysis is inappropriate, as this technique only assumes measurement error in the outcome variable. Therefore, we used an analysis technique called functional

relationships (Nagelkerke 1992) to evaluate the influence of asthma severity of the study population on the outcome for cough, wheeze and overall symptom score.

We performed all analyses using SPSS version 10 for the initial review.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses when outcome data were available from at least 10 studies, using the following characteristics for subgroup identification: asthma severity (moderate versus severe), health care settings (hospitalised/institutionalised versus other settings), type of delivery (nebulised versus other), age (using a mean age of five years as the cut-off point), duration of follow up (using three months follow up as the cut-off point) and methodological quality (for Jadad's scoring system three points or higher versus lower; for Chalmers' summated items the 13 best studies versus the remaining studies).

To explore heterogeneity further and visualise possible publication bias, we constructed a funnel plot of the effect estimate (delta) against the precision (Egger 1995), using the same combination of outcome measures as for meta-regression analysis. The precision of a trial was defined as one divided by the standard error. The symmetry of the funnel plot was tested using a significance level of 0.10 (Egger 1997).

RESULTS

Description of studies

Results of the search

Searching the literature databases resulted in retrieval of over 3500 titles (MEDLINE: 1500; EMBASE: 1400; Cochrane Airways Group Trials Register: 850 titles). We read about 200 papers in full; 65 of these were evaluated by two authors according to a structured inclusion criteria form. The final set consisted of 24 papers, reporting on 23 studies. For one study, two papers were published reporting on different outcome measures (Yuksel 1992). Update searches were conducted in November 2006 and October 2007. These identified 181 titles, which were screened, and 10 were obtained as full papers for further assessment. None of these fulfilled our inclusion criteria, but several were added to the list of excluded studies. An updated search in October 2008 did not identify any new studies for consideration in the review. For the sake of brevity in this chapter we present only the most important results. More details are provided in the publication of this study in *Cochrane Database of Systematic Reviews.*

Included studies

Most of the included studies were European (13 studies, nine of which were from the UK) or North American. Two were from Israel, three from Japan and one from Thailand. All but three papers were written in English. One study was in Norwegian (Dalene 1977), the other two in Japanese (Kobayashi 1970; Mikawa 1986).

The studies were published between 1970 and 1997. Twelve studies were published in the 1970s, eight studies in the 1980s, and four in the 1990s.

The age range of the children in the included studies varied considerably. Eleven studies included children not older than four years of age. In one study (Easton 1973) the age of the children was not specified. Before 1977, none of the studies included children below the age of four.

Most of the studies had a cross-over design. Four were parallel group studies. The cross-over studies typically were divided into two periods of three or four weeks treatment, with sometimes a washout period in between. In some of the cross-over studies, the first two weeks of each period weIn nine studies the study drugs (DSCG or placebo) were nebulised. Nine studies used dry powder in capsules, most often with the Spinhaler as device, but sometimes without a device being mentioned. In five studies the drugs were administered as aerosols with a spacer and sometimes a facemask.

In several papers it was not clear whether and what concurrent medication was permitted during the trial. We included these studies. Compliance with the therapy regimen was only discussed in a minority of papers.

Most of the studies were carried out in a hospital setting, usually with outpatients. For several studies, no information about the setting could be found. Based on the authors' affiliations, we assumed that these were hospital outpatients. Only one study recruited patients in general practice (Tasche 1997).

Regarding asthma severity, most of the studies included children that would be classified as having moderate or severe asthma by current standards (e.g. GINA 2005). Many children had one or more hospital admissions for asthma in the past. The three studies with probably the largest proportion of mild asthmatic children were Edmunds 1980; Furfaro 1994 and Tasche 1997.

The size of the trials varied between 10 and 232 participants. Only two trials included more than 100 children (Mikawa 1986; Tasche 1997). As can be expected, the parallel-group trials had larger patient groups than the cross-over trials (parallel group trials had on average 131 participants versus 26 for cross-over studies). Altogether, the 23 studies included 1026 participants.

The length of the period during which the children used either active medication or placebo in the trials varied from three weeks to 26 weeks. For 15 studies (of which

14 had a cross-over design), this was three or four weeks, while only two studies had a duration of over 10 weeks (Cogswell 1985; Tasche 1997).

Several study characteristics were strongly correlated. Dose (corrected for type of delivery), method of delivery, year of publication, age of children and length of treatment period showed Pearson correlations up to 0.75.

The variety of outcome measures on which data were reported was large. Likewise, for most outcome measures only few studies reported comparable data. The outcome measures that were reported most often were asthma scores (10 studies), daytime wheeze scores (10 studies), daytime cough scores (nine studies) and bronchodilator use (10 studies). Several studies reporting on hospital admittance and steroid use provided insufficient information to be included in the pooled results.

Excluded studies

Excluded studies were either not blinded, not randomised, not placebo-controlled, did not concern the appropriate age group, or investigated the effectiveness of DSCG in exercise induced asthma. One study (Kraemer 1993) was misclassified and hence erroneously included in the first version of the review: this trial was removed from this update.

Risk of bias in included studies

The methodological quality, as assessed by two scoring methods, varied considerably (see Table 1; Table 2). Only one study attained the maximum score of five points on the Jadad list (Mikawa 1986). The proportion of items fulfilled on Chalmers's list varied between 24 and 79% (mean 44% (SD 11.9)). Of the papers reporting cross-over studies, only few stated explicitly that the sequence of both treatments had been randomised. In the analysis, we assumed they were.

When updating the review in 2007, 'Risk of Bias' tables were produced, and a summary table was added to this review (Figure 1). For further explanation of this table, see the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8 (Higgins 2008).

For several items (sequence generation, allocation concealment, selective reporting and other sources of bias), only few studies provided a clear answer. The proportion of question marks (for which the study reports do not provide enough information) is high. Blinding was considered to be adequate for all studies, which is no surprise, as this was an inclusion criterion. Several studies inadequately reported on incomplete outcome data or reported selectively. None of the studies attained the maximum score for 'withdrawals', and 20 of the 23 studies scored less than 50% on this item (Table 1).

TABLE 1 Methodological quality scores according to Chalmers

Study	Selection & reject log	Randomisation & concealment	Blinding	Therapy regimens	Withdrawals	Compliance	Numbers & Statistics	Timing	Total score (%)
Maximum score study	6	13	23	6	7	6	24	10	95 (100%)
Bertelsen 1986	1	3	12	3	3	0	6	3	31/95 = 33%
Cogswell 1985	1	10	13	4	3	1/3	9/22	2	43/91 = 47%
Collins 1971	2	7	18	6	0	0	3	3/9	39/94 = 41%
Dalene 1977	2	2	16	4	3	1	3/20	2	32/91 = 35%
Easton 1973	1	4	17	5	1	0	4/16	3	35/87 = 40%
Edmunds 1980	0	4	14	0	1	2	6/20	2	29/91 = 33%
Furfaro 1994	3	13	13	5	4	3	11	4	56/95 = 59%
Geller 1982	1	4	16	2	3	0	6/20	2	34/91 = 37%
Geller 1983	2	6	18	3	4	1	5/19	2	41/90 = 46%
Glass 1981	0	4	14	2	0	1	6	2/9	29/94 = 31%
Henry 1984	0	0	16	3	0	0	2	2/9	23/94 = 24%
Hiller 1975	2	10	18	4	3	0	5/18	2/9	44/87 = 51%
Hiller 1977	0	10	14	4	3	0	2/18	1/9	34/87 = 39%
Hyde 1970	1	6	13	4	3	0	6/18	5/9	38/87 = 44%
Kobayashi 1970	2	4	16	5	3	0	13/19	2	45/90 = 50%
Limburg 1971	1	4	13	5	3	0	11/23	8	45/94 = 48%
Matthew 1977	0	4	13	4	3	0	3/16	2	29/87 = 33%
Mikawa 1986	3	4	16	5	2	0	721	6	43/92 = 47%
Shioda 1970	3	6	18	4	2	0	5	4	42/95 = 44%
Smith 1970	2	4	16	6	3	0	4/21	8	43/92 = 47%
Tasche 1997	6	11	20	3	6	3	21	5	75/95 = 79%
Tuchinda 1974	1	5	19	6	3	0	11/15	4	49/86 = 57%
Yuksel 1992	3	4	16	5	3	0	5/21	3/9	39/91 = 43%

Footnote: "/" means denominator adapted because items non-applicable.

TABLE 2 Methodological quality scores according to Jadad's criteria

Study	Randomisation	Randomisation detail	Double-blind	Blinding details	Withdrawals	Total
Bertelsen 1986	1	0	1	0	1	3
Cogswell 1985	1	0	1	1	1	4
Collins 1971	0	0	1	1	0	2
Dalene 1977	1	0	1	0	1	3
Easton 1973	1	0	1	0	0	2
Edmunds 1980	1	0	1	0	0	2
Furfaro 1994	1	1	1	0	1	4
Geller 1982	1	0	1	1	1	4
Geller 1983	1	0	1	1	1	4
Glass 1981	1	0	1	0	0	2
Henry 1984	0	0	1	0	1	2
Hiller 1975	1	0	1	0	1	3
Hiller 1977	1	0	1	1	1	4
Hyde 1970	0	0	1	1	1	3
Kobayashi 1970	1	0	1	0	1	3
Limburg 1971	0	0	1	1	1	3
Matthew 1977	1	0	1	1	0	3
Mikawa 1986	1	1	1	1	1	5
Shioda 1970	1	0	1	0	1	3
Smith 1970	1	1	1	0	1	4
Tasche 1970	1	0	1	0	1	3
Tuchinda 1974	0	1	1	1	1	4
Yuksel 1992	1	0	1	0	0	2
Yuksel 1993	1	0	1	0	1	3

Effects of interventions

Study outcomes have been summarised in Table 3. The table gives pooled point estimates for the difference between DSCG and placebo (i.e. DSCG minus placebo), and confidence intervals, assuming homogeneity (fixed-effect) and heterogeneity (random-effects).

Symptoms

Only four studies provided results for the percentage of symptom-free days: our primary outcome measure. In all but one of the studies (Cogswell 1985), the confidence interval included the point of no difference. Pooling the results revealed no significant difference between DSCG and placebo (WMD 6.76% favouring DSCG, 95% CI -2.18 to 15.70), random-effects model.

FIGURE 1 Methodological quality summary: review authors' judgments about each methodological quality item for each included study

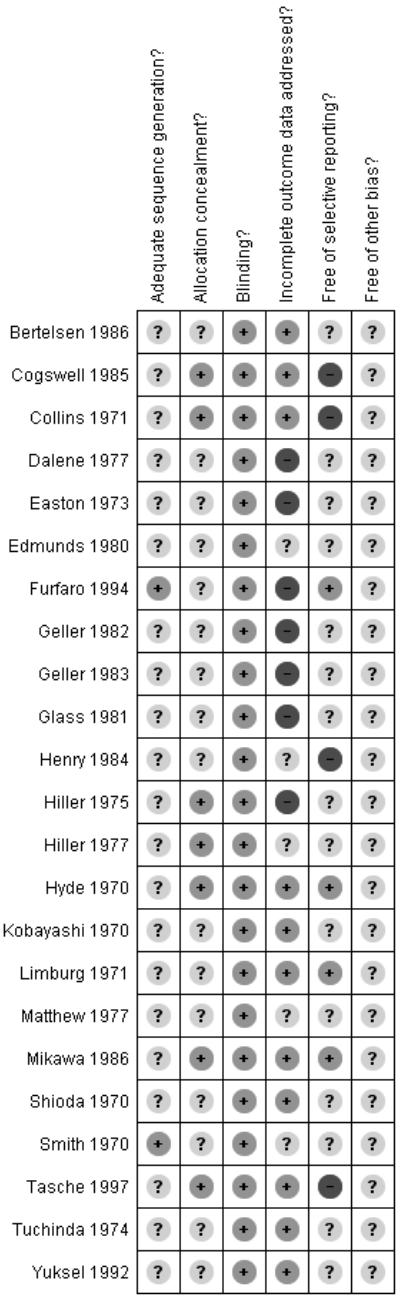


TABLE 3 Summary of pooled results

Outcome	Number of studies	P homogeneity test	Mean (CI) FEM	Mean (CI) REM	Pooled OR cross-over
Percentage of symptom-free days	4	0.06	3.57 (-1.18 to 8.32)	6.76 (-2.18 to 15.70)	—
Day cough score	9	< 0.001	—	-0.18 (-0.32 to -0.04)	—
Day wheeze score	10	0.01	—	-0.11 (-0.19 to -0.03)	—
Daytime asthma score	2	0.02	—	-0.30 (-0.71 to 0.10)	—
Day activity	4	0.08	-0.13 (-0.19 to -0.03)	-0.16 (-0.27 to -0.05)	—
Night cough	5	0.10	-0.19 (-0.27 to -0.12)	-0.25 (-0.39 to -0.11)	—
Night wheeze	3	0.15	-0.29 (-0.48 to -0.10)	-0.32 (-0.59 to -0.05)	—
Night-time asthma score	2	0.01	—	-0.26 (-0.59 to 0.06)	—
Sleep disturbance	3	0.43	0.02 (-0.03 to 0.08)	0.02 (-0.03 to 0.08)	—
Overall symptom/severity score	10	< 0.001	—	-0.22 (-0.34 to -0.09)	—
Auscultation score	2	0.74	-0.39 (-0.81 to 0.04)	-0.39 (-0.81 to 0.04)	—
Fraction preferring DSCG (patient/parent)	3	0.98	0.72 (0.62 to 0.82)	0.72 (0.62 to 0.82)	—
Fraction preferring DSCG (clinician)	2	0.48	0.81 (0.71 to 0.90)	0.81 (0.71 to 0.90)	—
Success rate (ln (OR) DSCG/ placebo)	2	0.88	1.16 (0.60 to 1.71)	1.16 (0.60 to 1.71)	—
Bronchodilator use (doses per day)	10	< 0.001	—	-0.24 (-0.42 to -0.07)	—
Steroid use (ln (OR) DSCG/ placebo)	2 (parallel only)	0.58	-0.24 (-1.07 to 0.57)	-0.24 (-1.07 to 0.57)	—
Steroid use (ln (OR) DSCG/ placebo)	5 (cross-over only)	NA	NA	NA	0.08 (0.002 to 0.056)
Hospital admittance (ln (OR)) DSCG/placebo	2 (parallel only)	1.0	0.07 (-1.08 to 0.94)	0.07 (-1.08 to 0.94)	—

A variety of other symptom and hindrance scores was found. We present the results for outcome measures for which at least two studies provided data. Here we describe the results for the symptom scores with the largest number of studies: day cough score

(nine studies), day wheeze score (10 studies), and overall symptom/severity score (10 studies).

For daytime cough, the difference between placebo and DSCG favoured DSCG in all but one study (Bertelsen 1986). The confidence intervals included the point of no difference for seven out of the nine studies. Pooling the results (random-effects model because of heterogeneity) did result in a statistically significant difference between placebo and DSCG favouring DSCG (WMD -0.18, 95% CI -0.32 to -0.04).

For daytime wheeze the pooled results show a small but significant difference favouring DSCG: a difference of -0.11 (WMD) on a scale of 0 to 3 (95% CI -0.19 to -0.03; random-effects model).

Mean overall symptom scores favoured DSCG in direction in six out of ten studies. The 95% confidence intervals of four of the studies included the point of no difference. Pooling the results (test of homogeneity rejected, hence random-effects model) showed an overall mean difference of -0.22 symptom score points (WMD), favouring the DSCG group (95%CI -0.34 to -0.09), hence statistically significant.

Use of other medication

The use of bronchodilators was reported in ten studies. Seven of these reported a difference in favour of DSCG. Five of the studies had confidence intervals excluding the point of no difference. Pooling the data (null hypothesis of homogeneity rejected) resulted in an overall estimated difference of -0.24 daily doses (WMD) favouring the DSCG group (95% CI -0.07 to -0.42, random-effects model), which is statistically significant.

Steroid use in case of exacerbations was also addressed as an outcome measure: systemic or inhaled, or sometimes unspecified. Seven studies provided these data. Only one study (Shioda 1970) found a significant difference. The pooled results did not show a significant difference (OR 0.76, 95% CI 0.34 to 1.72).

Hospital admission

Hospital admission was reported in three studies. None of these found a significant difference between DSCG and placebo. Pooling the results of the parallel studies did not result in a significant difference (OR 0.93, 95% CI 0.40 to 2.56).

Lung function parameters

Thirteen studies assessed lung function parameters. Eight of these reported no statistically significant difference between DSCG and placebo groups/periods, sometimes without providing exact figures. The variety of parameters, methods used, time of day tests were performed and the way they were presented made it impossible to pool data. Five of the

13 studies reported differences to be statistically significant for one or more lung function parameters (Geller 1983; Hiller 1975; Limburg 1971; Matthew 1977; Yuksel 1992).

Side effects

Twelve studies did not report on side effects (Table 4). The reported side effects of DSCG and placebo in the other 11 studies were mild and of short duration (minutes to a few days). Overall, differences between DCSG and placebo were small.

Subgroup analysis

Subgroup analyses were performed for four outcome measures: day time wheeze (10 studies), overall asthma symptom/severity score (10 studies), bronchodilator use (10 studies) and a combination of outcome measures using the same scale (19 studies, see 'Data collection and analysis'). For day time wheeze and for bronchodilator use, the differences between subgroups were either not significant or one of the groups contained only one or two studies. For the asthma symptom/severity score, the age of the children and duration of follow up showed statistically significant differences. Studies that included children with a mean age lower than five showed less effect than studies that (also) included older children (estimate of difference between DSCG and placebo -0.06 (95% CI -0.15 to 0.02) versus -0.30 (95% CI -0.49 to -0.11), favouring DSCG, P = 0.03). The three studies that had at least three months follow up showed less effect than the eight shorter studies (0.04 versus 0.27, favouring DSCG, P = 0.01).

The combined outcome measure showed subgroup differences for way of administration of the drug, hospitalisation, age and duration of follow up. Studies that applied nebulised DSCG showed less effect than studies that used other methods of administration (0.08 versus 0.32 on a 0 to 3 point symptom scale, P = 0.01). Studies in hospitalised patients showed less effect than studies in other patients (0.08 versus 0.34, P = 0.01). Subgroup analyses for age and for duration of follow up both showed differences of the same magnitude and in the same direction for the combined outcome measure as reported above for asthma symptom/severity score.

The subgroup analyses for the above mentioned four outcome measures were also performed separately for studies with higher methodological quality (see 'Data collection and analysis' for cut-offs). Comparing the results of this subgroup of studies to the overall results revealed only minor differences, in the same direction as in our primary analysis, sometimes more in favour of the subgroup of better quality studies.

The same analyses were done excluding cross-over studies that did not take account of period effects (or did not report they did). For the asthma symptom score (five studies) the pooled difference was -0.06, with 95% CI (-0.16 to 0.03) (random-effects model). For bronchodilator use (four studies) the pooled difference was -0.05 doses

TABLE 4 Side effects reported in included studies

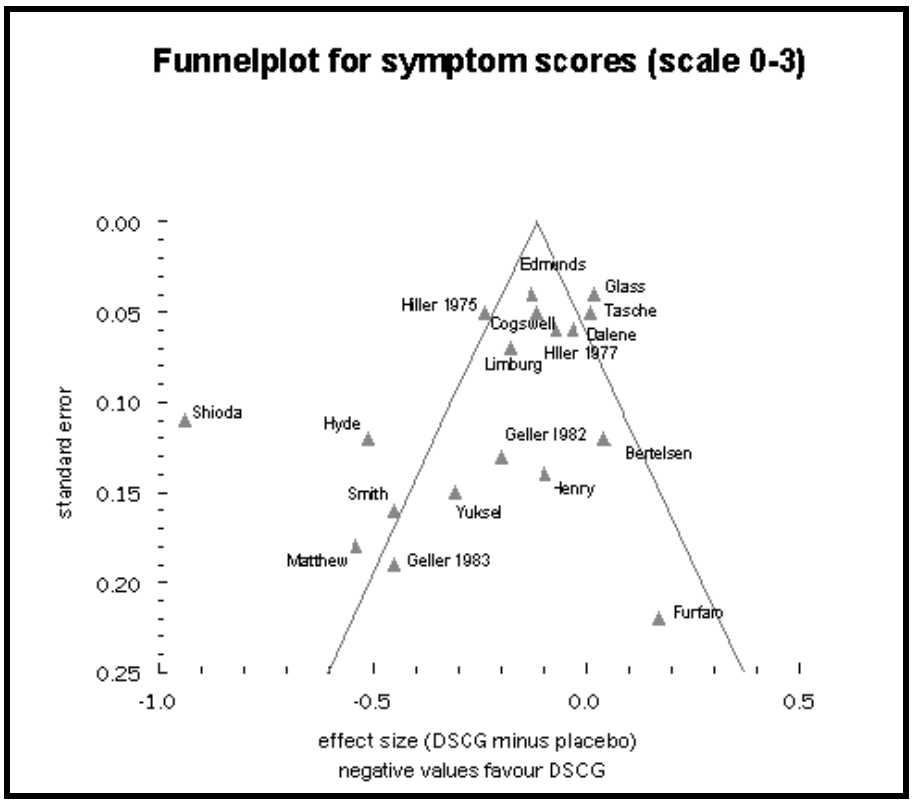
Study ID	Side effects DCSG	Side effects placebo
Bertelsen 1986	Eczema oral (1) Cough (1)	Cough (3)
Cogswell 1985	Not mentioned	Not mentioned
Collins 1971	Bitter taste (20) Cough (11) Dry mouth (4) Dizziness (2) Nausea (2) Sore throat (0) Headache (2)	Bitter taste (13) Cough (1) Dry mouth (2) Dizziness (0) Nausea (0) Sore throat (1) Headache (0)
Dalene 1977	Not registered	Not registered
Easton 1973	Not mentioned	Not mentioned
Edmunds 1980	Nausea, vomiting, abdominal pain, headache 5%	Nausea, vomiting, abdominal pain, headache 5%
Furfaro 1994	Not mentioned	Not mentioned
Geller 1982	Not mentioned	Not mentioned
Geller 1983	None	Throat irritation (1)
Glass 1981	Well-tolerated	Well-tolerated
Henry 1984	Not mentioned	Not mentioned
Hiller 1975	Not mentioned	Not mentioned
Hiller 1977	Not mentioned	Not mentioned
Hyde 1970	Duration mild side effect less than 5 minutes Throat irritation (4) Headache (1) Brief coughing (4) Wheezing (2)	Cough (1) Wheezing (1) Headache (1)
Kobayashi 1970	No side effects	No side effects
Limburg 1971	Cough (2)	Cough (1)
Matthew 1977	Not mentioned	Not mentioned
Mikawa 1986	Mild nausea (1)	Mild nausea (1) Mild sore throat (1)
Shioda 1970	Mild Perioral dermatitis (3) Headache (1)	None
Smith 1970	Not mentioned	Not mentioned
Tasche 1997	Mild side effects (40) Eczema mask (5) Cough after inhalation (9)	Mild side effects (33) Eczema (0) Cough after inhalation (1)
Tuchinda 1974	No side effect experienced	No side effect experienced
Yuksel 1992	Not mentioned	Not mentioned
Yuksel 1993	Not mentioned	Not mentioned

(-0.12 to 0.02) (fixed-effect), the random-effects model gave -0.08 (-0.19 to 0.04), all not statistically significant. Both these outcomes are smaller than found for the whole group of studies. For the combined outcome measures (see 'Data collection and analysis') nine studies provided data. The mean difference was -0.20, with random-effects, 95% CI -0.49 to 0.09.

Funnel plot

For the funnel plot, showing the mean difference in effect between DSCG and placebo treatment against precision of the study, we could include 19 studies. The symmetry test gave a value of -1.95 for the constant (SE 1.12, P = 0.09), which means that the hypothesis of symmetry was rejected. Especially imprecise (small or heterogeneous) studies with results favouring placebo were under-represented (Figure 2).

FIGURE 2.



Meta-regression analysis and functional relationships

Seven study characteristics showed relationships with the (combined) outcome variable ($P < 0.25$). As only 19 studies provided data for this combined outcome measure, the power of a meta-regression analysis would be very low. Furthermore, several study characteristics were strongly related to each other (e.g. age, publication year, and method of administration of DSCG). Hence, we decided to refrain from the planned analysis.

There was no influence of placebo symptom level on study outcomes (day cough, day wheeze, overall severity score and bronchodilator use), assessed by means of functional relationships.

DISCUSSION

Summary of main results

This systematic review, involving 1026 children in 23 trials performed between 1970 and 1997, provides conflicting evidence regarding the superiority of DSCG over placebo in children with asthma. There is no evidence to support the superiority of DSCG over placebo in the percentage of symptom-free days, the main outcome of this review, although this is limited by the small number of trials reporting on this outcome.

For several secondary outcomes, especially symptom scores and bronchodilator use, we found significant group differences between DSCG and placebo, favouring DSCG. The overall treatment effect for these outcomes appears to be quite small, with a mean difference of 0.2 to 0.3 symptom score on a scale from 0 to 3 and less than ¼ puff per day for bronchodilator use. However, considering the confidence intervals of the outcome measures, a clinically relevant effect of sodium cromoglycate cannot be excluded.

For mild persistent asthma, evidence is only available for children below the age of four. For this subgroup, we can rule out important benefit in terms of symptom scales but not in terms of symptom-free days. We cannot rule out the possibility that DSCG is of benefit in children above the age of four.

Overall completeness and applicability of evidence

Although DSCG has been advocated as maintenance treatment for mild to moderate asthma, and nowadays only for mild persistent asthma (GINA 2005), nearly all trials were hospital based, and included children with moderate to severe asthma. Three studies appear to have included a considerable proportion of children with mild asthma (Edmunds 1980; Furfaro 1994; Tasche 1997). The study by Edmunds showed positive outcomes on four outcome measures but was methodologically weak. The two other

studies had negative conclusions, i.e. DSCG was not more effective than placebo. Both studies were carried out in young children (below the age of four). Studies in children above the age of five found more favourable effects than studies in children below that age.

In nine studies, the drug was administered with a nebuliser. Spinhalers were used in eight studies. Metered dose inhalers with spacer devices, nowadays the preferred method of administration for young children, were used in only two studies (Tasche 1997; Yuksel 1992). The method of administration, a critical factor in delivery of drugs to the lungs, was a predictor of outcome (combined outcome measure): studies that used nebulisation showed less effect than studies that used other methods.

The year of publication of the study and the age of the children turned out to be strongly related. In multivariate analysis, results proved to be instable, sometimes favouring age, sometimes publication year. It is impossible to disentangle these two factors: in the early days of DSCG, studies were carried out in older children and only after 1977 did studies start to include children below the age of four.

Quality of the evidence

Heterogeneity of study results is apparent for several outcome measures. The methodological quality of the studies, especially regarding sequence generation and concealment of allocation, was often impossible to assess (see 'Risk of Bias' table Figure 1), and varied considerably for other aspects.

The absence of small trials favouring placebo, as shown in the funnel plot, indicates possible publication bias. This bias is likely to result in an overestimation of the efficacy of DSCG, especially because when applying a random-effects model the small positive studies we included received a relatively large weight.

Potential biases in the review process

It has been questioned whether the (difference in) percentage of symptom-free days should be the primary outcome measure, given the fact that only a minority of studies included this (see Feedback (Edwards et al)). However, we believe that the choice of primary outcome measure should not be driven by availability, but by clinical relevance. We feel supported by national and international guidelines, where the aim of the treatment of asthma focuses on leading a normal life with few or no complaints.

Lung function parameters could not be aggregated due to incomplete reporting of data.

Agreements and disagreements with other studies or reviews

The effects of treatment with DSCG have been reviewed previously. As early as 1974 a narrative review was published in JAMA (Dykes 1974), based on data provided by the

manufacturers, but giving no references to published data. Edwards 1994 examined the evidence for the anti-inflammatory action of DSCG in adults and children in a large number of controlled and uncontrolled studies but it is unclear how these were selected. Hoag 1991 summarised studies on the effect of DSCG on bronchial hyperreactivity in adults and children. Schweitzer 1994 discussed the role of DSCG in children below two years of age and concluded that evidence was lacking; this conclusion was shared by Carlsen 1996. Holgate 1996 reviewed recent trials with metered dose inhalers in children and adults and discussed challenge studies, therapeutic studies, and the long-term effects of DSCG. Other reviews were Berman 1983; Carlsen 1996; Church 1985; Kuzemko 1989; Shapiro 1985; Storms 2005. None of the reviews mentioned above were systematic, assessed the methodological quality of studies or tried to quantify treatment effects. With the exception of Schweitzer 1994, all of these reviews came to conclusions in favour Our group published a systematic review of inhaled DSCG as maintenance therapy in children in 2000 (Tasche 2000). The current review differs from the previous one in several respects. Seven studies that were included in the previous review were excluded in this one, either because of different exclusion criteria, especially regarding continuous use of steroids (Crisp 1974; Fox 1972; Hyde 1973; Miraglia 1982; Sly 1970), or because we initially overlooked the fact that the placebo drug contained isoprenaline and hence was not a true placebo (Silverman 1972; Smith 1968). The current review included six studies that were not included in the previous one, because of more thorough searching and the withdrawal of language restrictions (Easton 1973; Dalene 1977; Kobayashi 1970; Mikawa 1986; Smith 1970; Tuchinda 1974). Another important difference is that the previous review only considered symptom scores for cough and wheeze as outcome measures. The overall results of the previous and the first version of the current review are similar. For the 2007 update, changing our focus for the pooled results from the tolerance interval to the random-effects model interval has slightly affected the interpretation of our results in favour of DSCG. For this review, we excluded Kraemer 1993, for reasons mentioned above.

The funnel plot was similar to the one published in our earlier review (for 'wheeze'), although a different outcome was used in order to include as many studies as possible (Figure 2). As we have put forward before, when discussing our previous review (Tasche 2000; Tasche 2001), publication bias may be an explanation for the asymmetry. More specifically we think it is possible that small studies that did not find a beneficial effect for DSCG may not have been submitted to journals, or may not have been published.

In order to appreciate the results of this review in the context of other relevant treatments for childhood asthma, we refer to several recently published Cochrane reviews (Adams 1999; Arnold 2008; Guevara 2006; Gøtzsche 2008; Manning 2008; Seddon 2006; Sridhar 2006).

The possibility of publication bias could be further explored by trying to obtain information about studies that have been performed but were never published. However, since most studies we traced were published more than 20 years ago, and expecting unpublished studies to be at least as old, this does not appear to be a very promising endeavour.

This review only addressed DSCG as maintenance therapy in childhood asthma. Other studies have investigated the role of DSCG in attenuating exercise-induced bronchoconstriction, but we are unaware of a systematic review comparing DSCG to placebo for this condition. Indirect evidence from two systematic reviews in this area suggests that DSCG may be beneficial in both adults and children (Kelly 2003; Spooner 2003).

CONCLUSIONS

Implications for practice

A considerable number of trials has been performed. Together, they show heterogeneous effects for DSCG compared to placebo as maintenance therapy for childhood asthma. Given the strong indication of publication bias, the small overall treatment effect, and the pooled confidence intervals including zero for our primary outcome measure and several others, we conclude that it is not justified to recommend DSCG as first line maintenance therapy in childhood asthma. This recommendation is further supported by the availability of alternatives with proven effectiveness, i.e. inhaled corticosteroids. For mild persistent asthma evidence is only available for children below the age of four. For this subgroup, there is no good evidence that DSCG is much more effective than placebo. We cannot rule out the possibility that DSCG is of benefit in older children.

Implications for research

Given the place of DSCG in current guidelines, the lack of studies in children from age four onwards with mild persistent asthma is surprising. A large parallel study in this group, of high methodological quality and extended follow up (at least six months), could fill this gap. Preferably, such a study should not only compare DSCG to placebo, but also contain a study arm with low dose inhaled steroids. As the primary outcome measure we would recommend symptoms, either as a symptom score or as a percentage of symptom-free days. Given ongoing concern about the side effects of inhaled steroids, such a study should also address secondary outcomes like growth, adrenal function and bone density. Leukotriene-modifying drugs would be another class of drugs that could be compared to DSCG.

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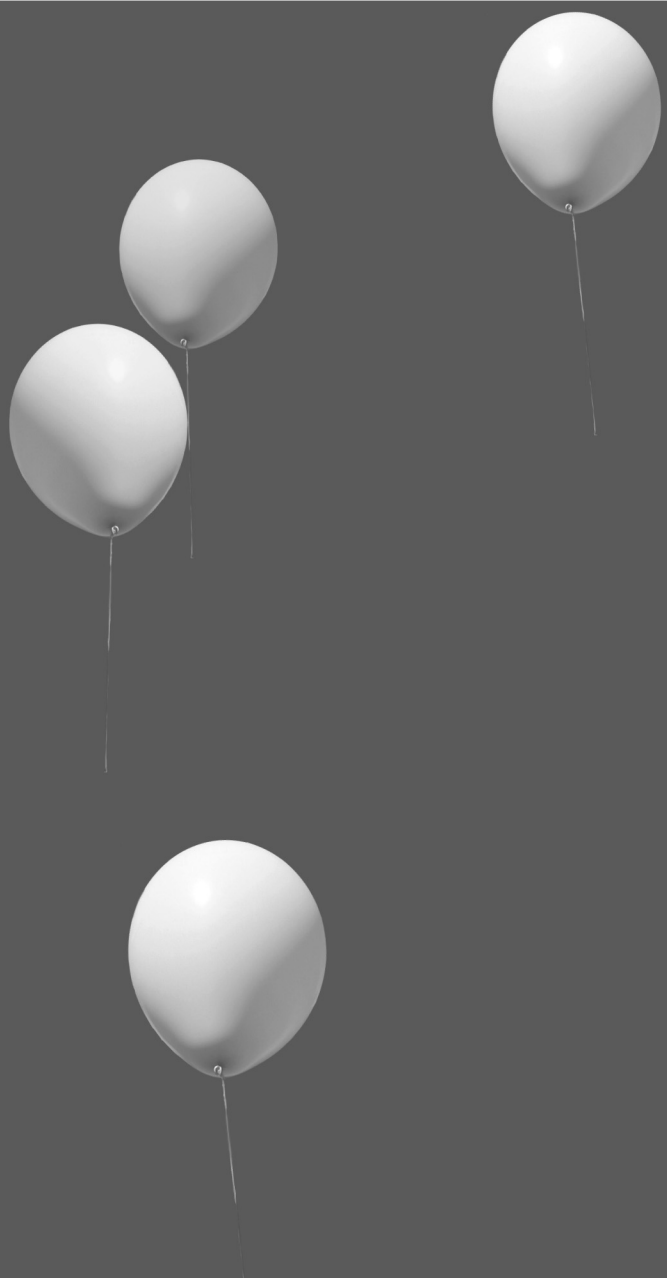
Low hospital admission rates for respiratory diseases in children

7



Uijen JHJM, Schellevis FG, Bindels PJE, Willemsen SP, van der Wouden JC. Low hospital admission rates for respiratory diseases in children. *BMC Family Practice* 2010;11:76

Background

Population-based data on hospital admissions for children aged 0-17 years concerning all respiratory diseases are scarce. This study examined hospital admissions in relation to the preceding consultations in general practice in this age group.

Methods

Data on children aged 0-17 years with respiratory diseases included in the Second Dutch National Survey of General Practice (DNSGP-2) were linked to all hospital admissions in the Dutch National Medical Registration. Admission rates for respiratory diseases were calculated. Data were analysed using multivariate logistic regression.

Results

Of all 79,272 children within the DNSGP-2, 1.8% were admitted to hospital for any respiratory diagnosis. The highest admission rates per 1000 children were for chronic disease of tonsils and adenoids (12.9); pneumonia and influenza (0.97); and asthma (0.92). Children aged 0-4 years and boys were admitted more frequently. Of children with asthma, 2.3% were admitted for respiratory diseases. For asthma, admission rates varied by urbanisation level: 0.47/1000 children/year in cities with ≤ 30,000 inhabitants, 1.12 for cities with ≥ 50,000 inhabitants, and 1.73 for the three largest cities (p=0.002). Multivariate logistic regression showed that within two weeks after a GP consultation, younger age (OR 0.81, 95% CI 0.76-0.88) and more severe respiratory diseases (5.55, 95% CI 2.99-8.11) predicted hospital admission.

Conclusions

Children in the general population with respiratory diseases (especially asthma) had very low hospital admission rates. In urban regions children were more frequently admitted due to respiratory morbidity. For effectiveness studies in a primary care setting, hospital admission rates should not be used as quality end-point.

BACKGROUND

Respiratory symptoms account for about 25% of consultations for children in general practice.[1] Respiratory tract infections are the leading cause of childhood hospital admission,[2-4] which is often an unpleasant experience for the child and their parents. Data on hospital admissions for children aged 0-17 years concerning the total spectrum of respiratory diseases are scarce. Generally, data on a specific age group (e.g. preschool children) or on a specific respiratory disease (e.g. asthma) are reported.[5-7] Most admission data are hospital based,[8] but the catchment area and hence the denominator for calculating these hospital admission rates is often not known. Primary care data linked with hospital admission registration data can be useful for allocating resources, to plan hospital care, to predict admissions for children from general practice, and studies conducted in primary and specialised care might benefit from these data.

In recent decades various factors have influenced morbidity patterns in children with respiratory diseases. For example, the introduction of inhalation therapy with bronchodilators and corticosteroids for the treatment of asthma, guidelines recommending a restrictive policy towards prescribing antibiotics for respiratory symptoms,[9,10] vaccination programmes against respiratory diseases (e.g. influenza and *Streptococcus pneumoniae*), and demographic changes such as population growth and the influx of ethnic minorities.[11,12] Therefore, this study investigated morbidity and hospital admission patterns for respiratory diseases in children at the turn of this century. Linking the data of a large national survey of general practice with admission data from the national medical registration enabled us to determine hospital admission rates and risk factors for hospital admission for children aged 0-17 years who presented with various respiratory diseases in general practice.

METHODS

Data were derived from the most recent nationwide study, the Second Dutch National Survey of General Practice (DNSGP-2) conducted in 2001 by the Netherlands Institute for Health Services Research (NIVEL).[13] The Dutch National Medical Registration, maintained by the Dutch Centre for Health Care Information, was asked to provide data on all admissions of all children included in the DNSGP-2 database.

Second Dutch National Survey of General Practice (DNSGP-2)

During the one-year registration period (i.e. 2001), 195 general practitioners (GPs) in 104 practices throughout the Netherlands participated in data collection. In the Netherlands, general practices have a fixed patient list, all inhabitants are listed in a general practice, and GPs have a gate-keeping role for specialized care. The patients enlisted in the participating practices were comparable to the general Dutch population with respect to age, gender, and type of healthcare insurance.

Data on all physician-patient contacts, prescriptions and referrals during the 12 months were extracted from the electronic medical records of all children aged 0-17 years listed in the participating practices. All diagnoses were coded using the International Classification of Primary Care (ICPC).[14] For the current analysis, data from 14 of the 104 practices were excluded because data were incomplete due to suboptimal recording quality. Therefore, the study included 90 practices with a total of 79,272 children.

Dutch National Medical Registration

The National Medical Registration contains information on all admissions (225,000 per annum) to all (teaching and general) hospitals in the Netherlands. Patient characteristics such as birth date, gender, postal code, and diagnostic and therapeutic interventions are registered. Admission and discharge dates, and cause of death during hospital admission are also registered. All diagnoses in the National Medical Registration are coded by trained coding clerks using the International Classification of Diseases (ICD-9).[15] Admissions for respiratory diseases are defined according to the ICD-9 (see Appendix). For the present study, we focussed on the principal diagnoses, and categorized these diagnoses into seven groups: nasopharyngitis, laryngitis and sinusitis (ICD 460-464, 472, 473, 476), acute upper respiratory infections (ICD 465), acute bronchitis and bronchiolitis (ICD 466), chronic disease of tonsil and adenoids, peritonsillar abscess (ICD 474-475), pneumonia and influenza (ICD 480-487), asthma (ICD 490-496), and other diseases of respiratory system (ICD 470, 471, 477, 478, 488, 507, 510-519). In case of multiple admissions we only included the first admission during the registration period.

Linking National Medical Registration to DNSGP-2

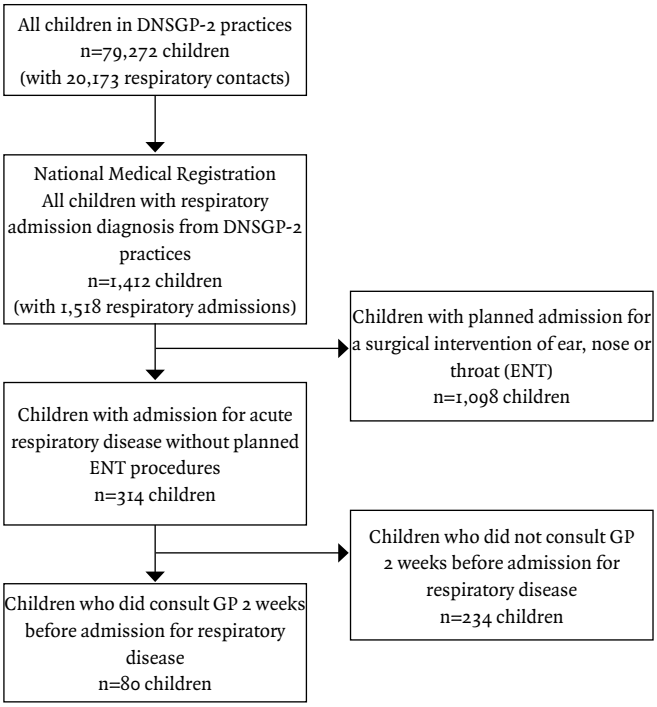
Patients in both databases were linked through the combination of date of birth, sex and the four-digit postal code.[16]

The DNSGP-2 included 79,272 children aged 0-17 years. During the 2001 registration period, for these children a diagnosis of a respiratory disease was registered 20,173 times by the GPs during a first contact of an episode. During the same period, the National Medical Registration contained 1,518 admissions for all respiratory diagnoses

for the 1,412 children in the DNSGP-2. Figure 1 shows the selection process for the study population.

For the identification of determinants predicting hospital admission for an acute respiratory illness, we assumed that hospital admissions for ear, nose or throat (ENT) problems (ICD 474 and 475) were planned hospital admissions for surgical interventions. These planned ENT admissions were excluded.

FIGURE 1 Selection of the study population (aged 0-17 years) from the Second Dutch National Survey of General Practice (DNSGP-2) matched with hospital admissions for respiratory illness (Dutch National Medical Registration)



Characteristics of patients and GPs

The following characteristics were derived from the computerized patient files of DNSGP-2: age and sex of the child; season in which the GP consultation occurred (October-March versus April-September); severity of the respiratory complaint or disease [severe (R02 Shortness of breath/dyspnoea; R76 Tonsil abscess; R77 Laryngitis/tracheitis acute; R78 Acute bronchitis/bronchiolitis; R81 Pneumonia; R82 Pleurisy/pleural effusion; R96 Asthma) versus not-severe (all other diagnoses)]; single-handed practice, or not. The degree of urbanisation of the patients' living area was derived from the general practice

postal code and categorized into four classes: 'less than 30,000 inhabitants', '30,000-50,000 inhabitants', 'more than 50,000 inhabitants', and 'the three largest Dutch cities Amsterdam, Rotterdam and The Hague'.

Statistical analysis

Data on all hospital admissions for respiratory diagnoses in children aged 0-17 years were analysed. Admission rates for respiratory diseases per 1,000 children were calculated using the population size in the denominator and the number of admissions as numerator. Differences in admission rates were tested with Chi-square tests (significance level p=0.05). To model the probability to be admitted, after a GP contact within two weeks before admission, a logistic regression model with a random practice effect was estimated and multivariate odds ratios (OR) were calculated. It was not possible to include a random effect for an individual besides the practice-specific effect. However, fitting slightly simplified models showed that the omission of this determinant had only a negligible effect on the ORs and their confidence intervals.

RESULTS

General characteristics

During the one-year registration period, of the 79,272 children aged 0-17 years 1,412 (1.8%) were admitted to hospital for any respiratory diagnosis. Of these 1,412 children, 54.4% was male. Overall, 63.5% was aged 0-4 years, 24.8% 5-9 years, and 11.7% aged 10-17 years.

In total, 11% of the GP consultations were registered outside normal office hours (between 8 AM and 17 PM) or in the weekend.

Of all admitted children, 38.2% lived in an urban community of ≤ 30,000 inhabitants, 19.2% in a community of 30,000-50,000, 35% in a community of ≥ 50,000 inhabitants (excluding the 3 largest Dutch cities), and 7.6% lived in the three largest cities.

During the registration period, 94% of the 1,412 children were admitted once for a respiratory diagnosis, 61 children were admitted two times, 14 children three times, 3 children four times, and 2 children were admitted five times (a total of 1,518 admissions).

Distribution of children and admissions by respiratory diagnosis group

Table 1 shows that the majority of children (73%) were admitted with a chronic disease of tonsils, adenoids and/or peritonsillar abscesses. Of the remaining six respiratory diagnosis groups, each group accounted for about 5% of all admissions. Among these,

TABLE 1 Number of admissions and duration of hospital stay per diagnosis for children aged 0-17 years

ICD codes*	Diagnoses	No. of children (%)	No. of admissions (%)	Duration of hospital stay in %		
				≤24 hours	2-7 days	≥8 days
460-464, 472, 473, 476	(Acute + chronic) nasopharyngitis, laryngitis, tracheitis, sinusitis	62 (4.1)	66 (4.2)	48	50	2
465	Acute upper respiratory infections	58 (3.9)	60 (4.0)	10	74	16
466	Acute bronchitis and bronchiolitis	50 (3.3)	51 (3.4)	0	70	30
474-475	Chronic disease of tonsils and adenoids, peritonsillar abscess	1098 (73.2)	1075 (70.8)	87	12	1
480-487	Pneumonia and influenza	80 (5.3)	87 (5.7)	3	71	26
490-496	Asthma	77 (5.2)	101 (6.7)	7	70	23
470, 471, 477, 478, 488, 507, 510-519	Other diseases of respiratory system	75 (5.0)	78 (5.2)	31	57	12
Total		1500 (100) #	1518 (100)	26	58	16

* SEE Appendix
# TOTAL number of children is higher than 1,412 because some children had more than one diagnosis

pneumonia and influenza (5.7%) and asthma (6.7%) were the most frequent reasons for admission.

The diagnostic categories 'chronic diseases of tonsils, adenoids and peritonsillar abscess', 'nasopharyngitis, laryngitis and sinusitis', and the remainder group 'other respiratory diagnoses' had the most admissions and discharges within 24 hours (87%, 48% and 31%, respectively). Most children with 'acute upper respiratory infections', 'pneumonia and influenza', 'acute bronchitis and bronchiolitis', and 'asthma' had a hospital stay of 1-7 days (74%, 71%, 70% and 70%, respectively). A longer hospital stay of 8-30 days was seen in children with 'acute bronchitis and bronchiolitis', 'pneumonia and influenza' and 'asthma' (30%, 26%, 23%, respectively).

Admission rates by diagnosis

The highest admission rates per 1000 children were for 'chronic disease of tonsils and adenoids', 'pneumonia and influenza', and 'asthma' (12.9, 0.97, and 0.92, respectively) (Table 2). Boys were admitted more frequently than girls. In all groups, admission rates

TABLE 2 Admission rates for respiratory diseases per 1000 children

	All	Gender			Age				Urbanisation				
Diseases (ICD codes)		Male	Female	p-value	0-4 years	5-9 years	10-17 years	p-value	< 30,000	30,000 – 50,000	>50,000 excl. the 3 largest cities	3 largest cities	p-value
Nasopharyngitis, laryngitis, sinusitis (460-464, 472, 473, 476)	0.75	0.71	0.80	0.64	1.33	0.44	0.56	<0.01	0.68	0.96	0.78	0.52	0.66
Acute upper respiratory infections (465)	0.71	0.97	0.43	<0.01	2.17	0.13	0.08	<0.01	0.59	0.32	0.93	1.38	0.02
Acute bronchitis, bronchiolitis (466)	0.61	0.59	0.63	0.85	2.00	0.09	0	<0.01	0.47	0.57	0.71	1.04	0.34
Chronic disease of tonsil and adenoids, peritonsillar abscess (474-475)	12.86	12.96	12.75	0.79	26.90	13.84	2.75	<0.01	12.55	13.13	13.34	11.74	0.70
Pneumonia and influenza (480-487)	0.97	1.28	0.65	<0.01	2.79	0.22	0.22	<0.01	0.71	0.57	1.46	1.38	0.01
Asthma (490-496)	0.92	1.28	0.55	<0.01	2.46	0.44	0.20	<0.01	0.47	1.27	1.12	1.73	<0.01
Other diseases of respiratory system (470, 471, 477, 478, 488, 507, 510-519)	0.90	1.06	0.73	0.10	1.29	0.40	0.96	<0.01	0.82	0.57	1.12	1.21	0.24
TOTAL	17.72	18.85	16.54	0.03	38.94	15.56	4.77	<0.01	16.29	17.39	19.46	19.00	0.08

were significantly higher among children aged 0-4 years (39/1000) than in older age groups (5-9 years: 16/1000; 10-17 years: 4.8/1000).

Children with 'acute upper respiratory infections', 'pneumonia and influenza' and 'asthma' were significantly more frequently admitted to hospital when living in a more urbanised region. In total, 3,417 children in the DNSGP-2 database consulted their GP for asthma and 77 (2.3%) of these children were admitted to hospital. The admission rate for asthma in rural areas was 0.47 per 1000 children per year; in suburban areas it was 1.27; in urban areas it was 1.12; and for the 3 largest cities the admission rate was 1.73 (p=0.002).

Of all children admitted with a respiratory diagnosis, one died in hospital. This was an 8-month-old child admitted with pneumonia (ICD 486) who had a severe underlying neuromuscular disease.

Of the 1,412 children, 323 (23%) children had 396 admissions for an ICD diagnosis that we considered not to be planned (Figure 1).

Distribution of diagnoses and GP consultation

Of the 80 children who consulted their GP two weeks before hospital admission, a higher percentage of children were admitted with 'nasopharyngitis, laryngitis, tracheitis, sinusitis', 'bronchitis and bronchiolitis' and 'pneumonia and influenza' compared with children who did not consult the GP (Table 3). In the group of 234 children who did not consult the GP two weeks before hospital admission, two differences showed significance. A lower percentage of children in this group were admitted with acute

TABLE 3 Distribution of diagnoses for all children with admission for acute respiratory disease without ENT procedures (n=314), for children who did consult GP two weeks before admission for respiratory disease (n=80) and for children who did not consult GP two weeks before admission for respiratory disease (n=234)

ICD codes	Diagnoses	All children (%) (n=314)	Children who consulted GP (%) (n=80)	Children who did not consult GP (%) (n=234)
460-464, 472, 473, 476	(Acute + chronic) nasopharyngitis, laryngitis, tracheitis, sinusitis	29 (9.2)	10 (12.5)	19 (8.1)
465	Acute upper respiratory infections	55 (17.5)	15 (18.8)	40 (17.1)
466	Acute bronchitis and bronchiolitis	49 (15.6)	19 (23.8)	30 (12.8)
480-487	Pneumonia and influenza	78 (24.8)	23 (28.7)	55 (23.5)
490-496	Asthma	73 (23.3)	6 (7.5)	67 (28.6)
470, 471, 477, 478, 488, 507, 510-519	Other diseases of respiratory system	30 (9.6)	7 (8.7)	23 (9.7)

bronchitis and bronchiolitis (p=0.02) and a higher percentage of children were admitted with asthma (p<0.001).

Determinants predicting hospital admission for respiratory diseases

Table 4 shows the adjusted ORs obtained from the logistic regression model. The multivariate logistic regression showed that younger age and more severe respiratory diseases predict a hospital admission in the two weeks after GP consultation. None of the other included determinants had an independent effect on hospital admission.

TABLE 4 Relation between child and GP determinants and hospital admission for respiratory disease (n=95 GP contacts two weeks before admission). Multivariate logistic regression analysis

	Relative probability of hospital admission within 2 weeks after GP consultation (n=95) OR (95% CI)	p-value
Age of child (years)	0.81 (0.76-0.88)	<0.001
Sex:		
Boy	1.14 (0.63-1.66)	0.55
Girl	(ref)	
Season:		
October-March	1.18 (0.64-1.73)	0.56
April-September	(ref)	
Severity:		
severe	5.55 (2.99-8.11)	<0.001
not severe	(ref)	
Urbanisation:		
rural	0.96 (0.40-1.52)	0.89
suburban	0.92 (0.20-1.64)	0.84
urban	(ref)	
Practice:		
not single-handed	0.75 (0.34-1.16)	0.30
single-handed	(ref)	

DISCUSSION

In this nationally representative study population, admission to hospital for a respiratory diagnosis occurred in only 1.8% of children. Children aged < 4 years with respiratory diagnoses were admitted more often. Admission rates for acute respiratory tract infections, pneumonia and influenza, and asthma were higher in urban regions than in rural areas. Admissions for asthma were not common, i.e. about 0.1% of all children, and

2.3% of all children who consulted their GP with asthma. Many of the admissions were planned (77%), mostly for ENT procedures. Children with upper respiratory infections, pharyngitis, sinusitis, bronchitis and pneumonia consulted their GP relatively more often in the two weeks before admission. In contrast, children with asthma and other diseases consulted their GP less often before admission. Younger age and a more severe respiratory disease predicted hospital admission in the two weeks after the GP consultation.

The major strength of this study is the use of unique data from a large national survey and the linking of these data to the Dutch National Medical Registration. The study population allowed to calculate admission rates for all respiratory diseases. Characteristics of the study patients are comparable to the general Dutch population, and the GP sample is comparable to the national GP population.[17] Single-handed practices were somewhat underrepresented; however, because this item is not related to study outcome it is not considered an important limitation. The results can be assumed to represent regular primary care and consultation behaviour in the Netherlands.

About 11% of the GP consultations were registered outside normal office hours or in the weekend. Although this may entail some underrepresentation, we don't believe this limits generalizability.

We could not test the assumption that all admissions for ICD codes 474 and 475 were planned. However, over 99% of these admissions were for ICD code 474, which concerns chronic disease of tonsils and adenoids. In the Netherlands, the vast majority of admissions under this diagnosis is due to planned (adeno)tonsillectomy.

2.3% of all children who consulted their GP for asthma were admitted to hospital. The denominator of this proportion underestimates the true number of asthmatic children since not all asthmatic children (mainly children suffering from intermittent asthma) may have consulted their GP within the study period.

Although the data we used are several years old, we do not believe this is a major limitation. The outcome (low admission rates) would not differ greatly when more recent data would have been available. We used the most recent nationwide study for answering our research question.

The present study provides insight into the large differences in disease profiles for children treated in general practice or in hospital. For example, in general practice 5% of the presented respiratory problems concern pneumonia.[18] In contrast, 25% of the children with a respiratory problem were admitted to hospital with pneumonia (Table 3). On the other hand, 17% of children admitted to hospital suffered from acute upper respiratory infections compared with 32% of the children in general practice. The relative contribution of asthma was about 22% in both general practice and in hospital.[18] The

considerable difference in disease presentation of children consulting GPs or hospital physicians was reported by Hodgkin in his classic work dating from 1978.[19]

Of the 314 children with an unplanned admission to hospital, only 25% attended general practice with respiratory complaints two weeks before admission. Of the 234 (75%) children who did not consult the GP two weeks before admission, 45% did not visit their general practice at any time during the one-year registration period. We assume that these children were already receiving specialised care.

Children with acute upper respiratory infections, pneumonia, influenza and asthma were admitted to a hospital significantly more often when living in an urbanised region. This might be due to greater air pollution in urban regions. The impact of air pollution on respiratory admissions and asthma has been reported in Canada and Italy.[20,21] Another explanation could be the availability of hospitals in urban regions.

Gender and age differences are common in hospitalization rates for respiratory diseases.[22,23] In the present study we also found that younger children and boys were admitted more often than older children and girls.

The finding that children with more severe illness are more likely to get admitted, is not surprising. More surprising is that no other determinants turned out to be related to admission.

The present study found very low admission rates for respiratory diseases, especially for asthma. Hospital admission is often used as quality parameter.[24,25] The low admission rates in our study show that it may be necessary to reconsider the use of hospital admission as a quality parameter for asthma treatment, and that for effectiveness studies in primary care settings admission rates should no longer be used as a quality end-point.

CONCLUSIONS

Children in the general population with respiratory complaints/diseases had very low hospital admission rates. There is a large difference in the scope of work of GPs and specialists in relation to respiratory diseases in children. In urban regions children were more frequently admitted with upper respiratory infections, pneumonia, influenza and asthma. Finally, we suggest that for effectiveness studies in a primary care setting the hospital admission rate should not be used as quality end-point.

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APPENDIX

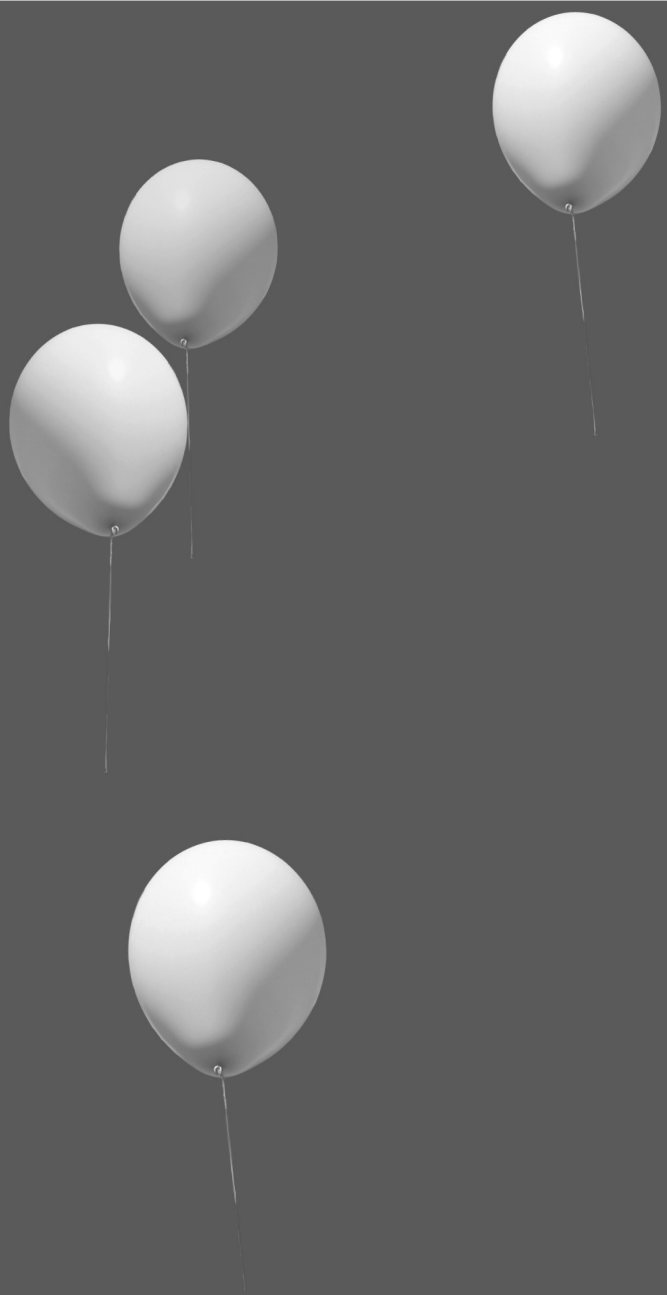
ICD-9 codes used to select all children admitted with a respiratory diagnosis:

460 acute nasopharyngitis
461 acute sinusitis
462 acute pharyngitis
463 acute tonsillitis
464 acute laryngitis and tracheitis
465 acute upper respiratory infections of multiple or unspecified sites
466 acute bronchitis and bronchiolitis
470 deviated nasal septum
471 nasal polyps
472 chronic pharyngitis and nasopharyngitis
473 chronic sinusitis
474 chronic disease of tonsils and adenoids
475 peritonsillar abscess
476 chronic laryngitis and laryngotracheitis
477 allergic rhinitis
478 other diseases of respiratory tract
480 viral pneumonia
481 pneumococcal pneumonia
482 other bacterial pneumonia
483 pneumonia due to other specified organism
484 pneumonia in infections diseases classified elsewhere
485 bronchopneumonia, organism unspecified
486 pneumonia, organism unspecified
487 influenza
488 influenza due to identified avian influenza virus
490 bronchitis, not specified as acute or chronic
491 chronic bronchitis
492 emphysema
493 asthma
494 bronchiectasis
495 extrinsic allergic alveolitis
496 chronic airway obstruction, not elsewhere classified
507 pneumonitis due to solids and liquids
510 empyema
511 pleurisy

512 pneumothorax
513 abscess of lung and mediastinum
514 pulmonary congestion and hypostasis
515 post inflammatory pulmonary fibrosis
516 other alveolar and parietoalveolar pneumopathy
517 lung involvement in conditions classified elsewhere
518 other diseases of lung
519 other diseases of respiratory system

General discussion

8



INTRODUCTION

In daily practice general practitioners (GPs) are often consulted by children with respiratory symptoms and diseases. Not surprisingly, health care for children with respiratory symptoms and diseases has changed during the past decades. Various factors are reported to influence morbidity patterns in children with respiratory diseases: for example, the introduction of guidelines recommending a restrictive policy towards prescribing antibiotics for respiratory symptoms,[1,2] inhalation therapy with bronchodilators and corticosteroids for asthma,[1] vaccination programs against respiratory diseases (e.g. influenza and *Streptococcus Pneumoniae*), and demographic changes such as population growth and the influx of ethnic minorities.[3,4]

In this chapter we discuss the main findings of this thesis, as well as methodological issues, and place their relevance and implications in a broader context. Finally, some directions for further research are presented.

Strengths and limitations of this research

The main aim of this study was to provide information for optimizing the care for children with respiratory symptoms and diseases in general practice. For this we used data of the second Dutch National Survey of General Practice (DNSGP-2),[5] the Netherlands Information Network of General Practice (LINH),[6] and the Dutch National Medical Registration (LMR).[7,8] These comprehensive databases have provided a considerable amount of important and useful data.

The strengths of the DNSGP-2 and LINH surveys are the large number of children included in the studies, the representativeness of the children in the study population and of the GPs participating in the study, and the fact that the GPs' diagnosis and management were directly derived from the GPs' records. DNSGP-2 is a large cross-sectional study covering a one-year period. The LINH is a comprehensive longitudinal study allowing to study trends. These surveys enabled us to identify determinants associated with the help-seeking behaviour of children and/or parents, and the GPs' management of respiratory symptoms and diseases in childhood.

An important drawback of the DNSGP-2 and LINH is the absence of information on the severity of the disease (episodes). This would provide more insight into differences in GPs' management of the disease, and into differences in morbidity data. Secondly, both surveys have a proportion of misclassifications regarding the diagnostic coding (approximately 3%) and not all referrals and prescriptions were linked to a diagnostic code by the GP. In addition, each year some diagnostic codes (3-5%) were missing for antibiotic prescriptions and referrals to a specialist. Although this could have resulted in an underestimation of prescription and referral rates, there is no reason to suspect that

this was a selective phenomenon and, therefore, this probably had no influence on the observed relationships.

The LMR contains information on all admissions of children to all teaching and general hospitals in the Netherlands. Admission and discharge diagnoses and dates, and date of death during hospitalisation, are also registered. Patients registered in both the DNSGP-2 and LMR were linked through the combination of date of birth, sex and the four-digit postal code. However, the linking of these databases has some limitations. First, the LMR only contains information on the children who were hospitalised. Attendance at outpatient clinics is not recorded in the LMR. Therefore, in the present study, the data reflect only the more severe (exacerbations of) respiratory diseases. Secondly, although Struijs et al. reported that the success of linking these databases may differ across diagnoses, they concluded that, overall, linking of the LMR and DNSGP-2 was satisfactory and can assumed to be representative.[7]

Despite these limitations, we conclude that the data analysed from these comprehensive databases are well able to represent consultation behaviour and management in daily general practice and hospitals in the Netherlands.

Help-seeking behaviour

An important finding, with consequences for primary health care for children, is the major role of cueing the parents in the process of help-seeking behaviour of children with respiratory symptoms and diseases. Parents cued each other, and children were cued by their parents, to consult the GP. This strong association between 'cueing by family members' and GP consultation confirms the findings of Cardol et al. regarding the influence of family on healthcare utilisation.[9] Van Duijn et al. and others showed that patients' views regarding the nature of the respiratory illness, its causes, its course, and possibilities to control it, play an important role in help-seeking behaviour and the patient-GP relationship.[10-11] Before the parents decide to consult their GP a whole decision-making process has already taken place.

Nowadays parents are better informed (e.g. by the Internet) and therefore feel more confident about dealing with respiratory symptoms themselves.[12] On the other hand, in daily practice, over recent decades GPs have experienced that patients visit them earlier for respiratory symptoms.[10,13-14] An explanation for this could be the decline of extended family relationships and the fact that nowadays both parents are likely to have a job. It can be hypothesised that parents make much less use of the knowledge of experienced family members, for example, the grandparents.

In this thesis we show that it is not the GP-related factors, but only the child-related and parent-related factors that are associated with the decision to attend general practice for

cough, sore throat and earache. Younger age was associated with consulting the GP for respiratory symptoms, as did children with fever, longer duration of symptoms, those reporting poorer health, and those living in an urban area. We studied the following GP related factors: age, gender, average number of patient contacts per day, single-handed practice or not, self-reported use of national GP guidelines, seeing pharmaceutical representatives (an indicator of prescribing behaviour), reluctance to prescribe new drugs and whether they were involved in GP training. Although we were unable to establish an association with GP-related factors, patients are generally aware of the routine of their GP regarding advice to return after a first consultation. Often patients are aware of the prescription pattern of their GP. This may, in turn, affect GP consultation rates. We did not specifically address these factors in our study. But it will be interesting to study them in more detail in future research and establish whether differences in consultation rates can be explained by these factors.

The long-term patient-doctor relationship is a cornerstone of the Dutch healthcare system, and often gives parents and their children a feeling of confidence and trust. This also enables the physician to choose for a 'watchful waiting' policy when appropriate.

The present study emphasizes the importance of adequately exploring the reasons for consulting the GP. For example: are children and/or parents worried about the child's respiratory symptoms, and were they cued by another family member? In case of self limiting respiratory symptoms and diseases reassurance and advice are usually sufficient. This is in line with previous findings of Cals e.a.[15] They found in a randomised controlled trial that 28% of 431 patients, with low respiratory tract infections, reconsulted during 28-days of follow-up. Patient reporting dyspnoea and concerns that persisted after the initial consultation independently predicted patient-initiated reconsultation. Not receiving antibiotics at index consultation was not associated with patient-initiated (re)consultation, suggesting that patients may be mainly seeking symptom relief or reassurance.[15] It is also known from patients with chronic pulmonary disease that dyspnoea contributes to discomfort and anxiety.[16] GPs need to be well aware that child and parent satisfaction depends not only on prescribing medication but also on carefully listening and examining the child. Although GPs have been taught to do this during their vocational training, it seems difficult to implement these questions in daily consultations.[17]

Improving the parent's knowledge about respiratory symptoms and the self-limiting nature of these symptoms can affect the consulting behaviour of the parents. Future research should establish whether this behaviour can be positively influenced by improving this knowledge. If help-seeking behaviour has in fact changed over recent years, we need to examine all the reasons why children with respiratory tract symptoms consult the GP. In this way GPs can become more aware of their own influence, and

of the child's and parents' motives to consult a GP, and thereby of the help-seeking behaviour of children and their parents.

Trends in epidemiology and management

As mentioned before, respiratory symptoms such as cough, sore throat, earache and wheezing are common in children. Parents deal with more than 80% of all illnesses in their children without the help of a healthcare professional.[18,19] Of all symptoms and diagnoses for which children and their parents attend general practice, respiratory symptoms and diseases account for 25%, skin diseases account for 23%, and musculoskeletal and digestive tract symptoms both for 10%. All other remaining reasons account for 42%.[12,18-20] Respiratory complaints include those of the upper respiratory tract (ENT problems, including cough, earache, sore throat, otitis media, tonsillitis) and the lower airways (as cough, wheezing, dyspnoea, pneumonia, bronchitis, asthma). Of all respiratory symptoms and diseases (final diagnoses) in children in general practice, 33% account for upper respiratory tract infections, 18% for cough, 8% for pneumonia and 5% for asthma.[19] Most respiratory symptoms in general practice are self-limiting and mostly have a viral cause.[21-23]

Depending on the type of research question we have to decide which incidence rates in which setting better reflect the presence of respiratory symptoms in children, e.g. incidence rates from an open population or from general practice.[24] Incidence rates in the open population reflect the actual occurrence of respiratory symptoms and diseases in children. This allows to examine the occurrence of respiratory symptoms in the population and which children subsequently consult the GP,[18] as we did in our study on the help-seeking behaviour of children with respiratory symptoms and diseases.

Because consultation in general practice is the entry point into the Dutch healthcare system, information regarding optimizing the care for children with respiratory symptoms and diseases should be collected in the general practice setting. Therefore, we calculated incidence rates for respiratory symptoms and diseases in a general practice population. For questions related to the provision of care, data which include the diagnosis of the GP are more valuable than data based on the patient's perceptions of the illness.[24]

Our study showed remarkably stable trends in the incidence rates of five of the most common ENT problems. Incidence rates for specific age groups showed only a slight increase for serous otitis media, and a slight decrease for sinusitis and tonsillitis. In contrast, other studies in Europe and USA showed decreasing consultation rates for ENT problems in general practice in the past decade.[25-29] Reasons for this decrease in other countries may be because there is a real decrease in occurrence,[24,30] or because the

self-management of children and their parents has changed. Depending on the actual reason, there may still be room for improvement in the Dutch incidence rates.

A strength of our study is the use of the same methodology over a seven-year period. Because our study provided a comprehensive, up-to-date and representative overview of incidence rates for ENT problems in children aged 0-17 years, in our opinion these figures are highly applicable for planning care and workload in general practice, and to predict referrals and hospital admissions for children.[22]

Contrary to what we expected, in the period 2002-2008, vaccination programs against respiratory diseases, and demographic changes such as population growth and the influx of ethnic minorities, have not influenced GP incidence rates for ENT diseases in children in the Netherlands. However, since most of the above-mentioned developments were introduced before the last decade we do not know whether a decrease in incidence took place (and ceased) before our study period started.

Our incidence rates do not provide any rationale to change the supply of health care provided by GPs. To assess the future need for respiratory health care in general practice, incidence rates in children of all ages (birth to 17 years old) should be monitored on a continuous basis. To plan future supply of care in general practice it is recommended to calculate incidence rates of respiratory diseases in general practice and to use annually collected longitudinal data over an extended period of time, rather than measuring the difference in incidence rates between two time periods.

Management of respiratory problems

GPs manage most of the respiratory symptoms and diseases of children themselves.[31] In our study we found very low referral and admission rates (18 admissions per 1,000 children in one year) for all respiratory diagnostic groups. Trends in referrals of common respiratory diseases (as otitis media, tonsillitis and sinusitis) were very stable and low over a seven-year period. Therefore, we conclude that the gatekeeping role of the GP for specialised care is adequate for children with respiratory symptoms and diseases in the Netherlands. For some treatments, referral to an otorhinolaryngologist or paediatrician is inevitable. Most referrals to the otorhinolaryngologist concerned an (adeno)tonsillectomy,[32] an intervention that GPs can not perform themselves.

When GPs decide to prescribe medication for respiratory symptoms and diseases, most will be either antibiotics or inhalation medication (for the latter, a reliever and/or controller medication). In our study we found low prescription rates for antibiotics for respiratory symptoms and diseases. The finding that Dutch GPs prescribe the lowest amount of antibiotics was also reported by Goossens et al. in their comparative study among 26 European countries.[33] National and international guidelines

advocate restrictive antibiotic prescription for respiratory symptoms and diseases in children.[1,34-38] As in other north European countries, Dutch GPs perform well in this respect, showing a low antibiotic prescription pattern. An explanation for different antibiotic prescription patterns could be the cultural differences across the European countries. In a study of cultural differences on coping with upper respiratory tract infections and using antibiotics, GPs in the Netherlands (a country with low antibiotic consumption) labelled most of these episodes of upper respiratory tract infection as common cold or influenza (in 70% of the cases), whereas Flemish GPs (a country with high antibiotic consumption) labelled most of their episodes as bronchitis and sinusitis (in 60% of the cases) and prescribed more antibiotics.[33,39]

Nevertheless, it remains important to select children at risk for complications and those for whom hospital admission might be needed. Indications for prescribing antibiotics are selected cases of acute otitis media (age < 6 months, worsening of disease) or patients with lower respiratory tract infections, e.g. those at risk for complications and with symptoms persisting for >3 days.[34,40] The question can arise as to whether Dutch GPs under-treat children with respiratory diseases. However, because referral rates remained low in seven consecutive years, together with low admission rates for respiratory diseases, in our opinion these low antibiotic prescription rates do not represent under-treatment.

We must be constantly aware of the increase in antibiotic resistance. Antibiotics are widely used by farmers and veterinarians. Moreover, Methicillin-resistant *Staphylococcus Aureus* (MRSA) constitutes a threat to the Dutch healthcare system.[41] Many years of a cautious restrictive policy of Dutch physicians has contributed to low MRSA resistance in the Netherlands. A clearly-defined policy by the Dutch government and policymakers to reduce antibiotic usage by veterinarians and farmers is necessary to further reduce the threat of increased antibiotic resistance.

In accordance with others, our study revealed low GP prescription rates (1 or 2 prescriptions/year) for asthma medication in children attending general practice with asthma.[42,43] In the Netherlands, GPs generally treat children with mild or moderate asthma themselves.[44] The current Dutch guidelines recommend a two-step approach for asthma medication: start with a bronchodilator and add a low-dose inhaled corticosteroid when symptoms have failed to disappear or have worsened.[1,38] Besides the fact that Dutch GPs treat children with mild or moderate asthma themselves, the current bronchodilators (and especially corticosteroids) may be so powerful that only low dosages of these medications are needed to relieve the asthma symptoms. Prescribing a bronchodilator as continuous medication is not recommended by any guideline. GPs

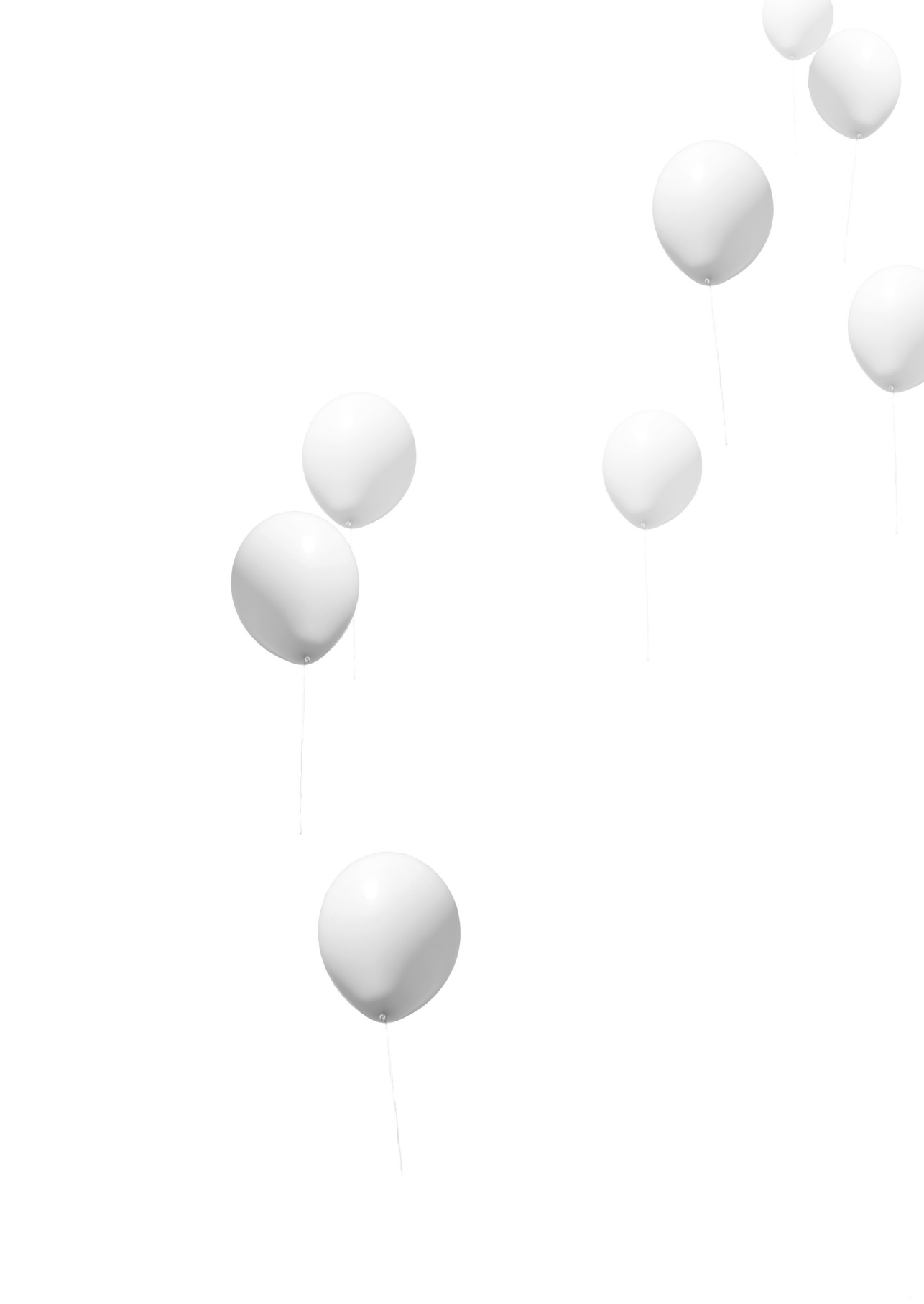
should be aware of this type of over-prescribing in asthmatic children and should add a corticosteroid if a bronchodilator is used on more than two days a week.

Improving the prevention and management of asthma is a high priority for primary health care in all countries. The Brussels Declaration advocates a plan of action to improve evidence-based asthma management, emphasising the importance of including evidence from real-life studies in treatment guidelines.[1,43,45-47] Inadequate knowledge of when and how to use prescribed medication is one of the major barriers to achieving asthma control.[47-50] It is important that the GP supplies appropriate and written instruction to the parents, who play a prominent role in maintaining compliance with therapy of their children. The inhalation technique should be clearly explained and well demonstrated. Preferably, this should be checked again during follow-up appointments to correct any mistakes. Therapy regimen should be discussed, particularly when more than one inhaler is prescribed. An explanation of the difference between maintenance therapy and rescue medication is essential.

In this thesis we conclude that there is insufficient evidence to draw a definite conclusion about the efficacy of sodium cromoglycate (DSCG) versus placebo. Many trials have been performed in the last 20 years. Publication bias is likely to have overestimated the beneficial effects of sodium cromoglycate as maintenance therapy in childhood asthma. Pooled results of systematic reviews give physicians the opportunity to assess the value of a treatment, in this case DSCG.

In general practice there are more examples of respiratory medication being used without clinical evidence whether it is in fact effective in young children. This is predominantly caused by the fact that most trials have been done in adults and not in (young) children. For example: how do corticosteroids and leukotriene antagonists compare with regard to effectiveness and side-effects in children with mild and moderate asthma in general practice?[47] What is the effect of bronchodilators in combination with corticosteroids on preschool children with persistent cough and wheeze in general practice?[48]

Finally, the impact of the children's and parents' comprehension of asthma, use of different treatment strategies, and concern about the side-effects of adherence to prescribed treatment need to be assessed. When GPs become more aware of the shortcomings in the comprehension and attitude of children and their parents in asthma therapy, this will enable them to improve the knowledge on asthma and its therapy, and to aim at attitude change with respect to asthma therapy when needed.[1,45,52,53]



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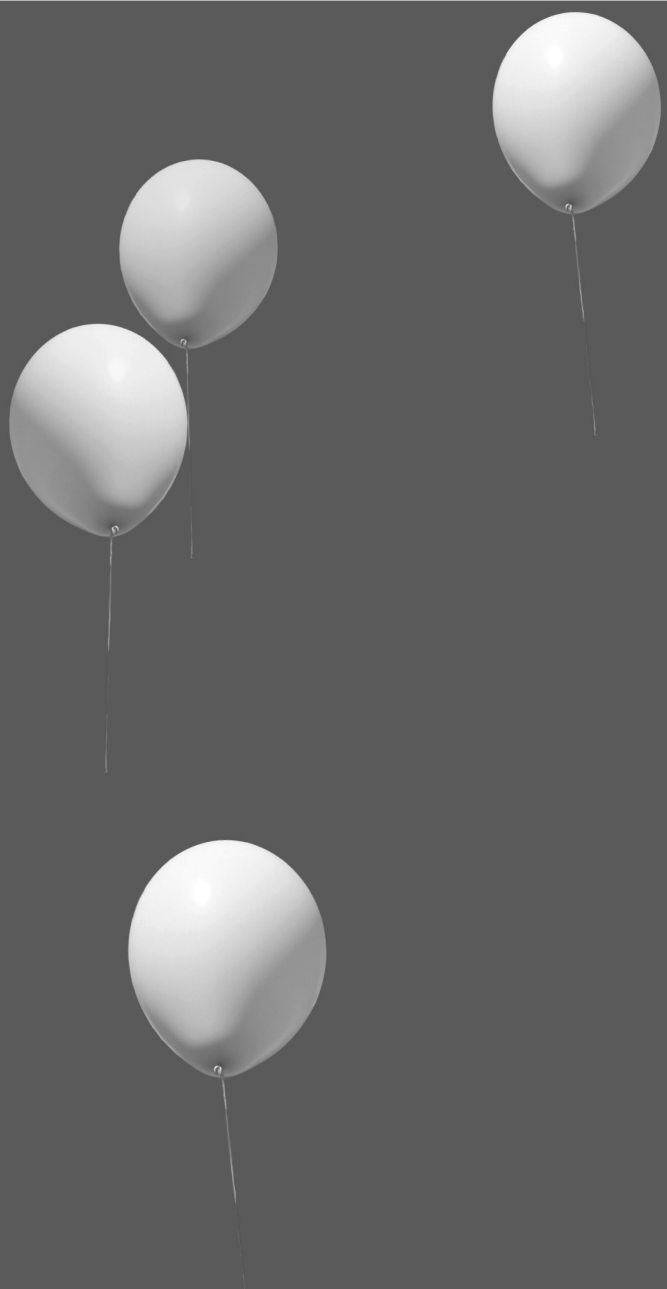
Summary



The work presented in this thesis covers various aspects of the epidemiology, diagnosis and management of various respiratory symptoms and diseases in children frequently encountered in general practice. These respiratory tract symptoms and diseases can be categorized into symptoms and diseases of the upper respiratory tract (ENT problems, including cough, earache, sore throat, otitis media, tonsillitis), and symptoms and diseases of the lower airways (e.g. cough, wheezing, dyspnoea, pneumonia, bronchitis, asthma). The general aim of this work was to provide information for optimizing the care for children with respiratory symptoms and diseases in general practice. We have provided epidemiological data about respiratory symptoms and diseases in children, and examined the general practitioners' (GPs) management with respect to medication prescribing and referring these children to specialist care. The study aims were achieved by examining data from the second Dutch National Survey of General Practice, the Netherlands Information Network of General Practice, the Dutch National Medical Registration, and the Cochrane Central Register of Controlled Trials.

Chapter 2 explores the characteristics of the children, their parents and their GPs that are correlated with consulting a GP for cough, sore throat or earache. For this study, data from the Second Dutch National Survey of General Practice (DNSGP-2) were used. Young children (aged 0-4 years) more frequently consulted the GP for respiratory symptoms compared to older children, as did children with fever, longer duration of symptoms, those reporting their health to be 'poor to good' as compared to 'very good or excellent', and those living in an urban region. Also, when parents were worried, or when the child/parent was cued by someone else, the GP was consulted more often. GP-related determinants did not appear to be associated with GP consultation by children.

We emphasize the importance of assessing the reasons for consulting the GP in children with respiratory tract symptoms in daily practice. When GPs are aware of the possible determinants of the decision to consult a GP, more appropriate advice and reassurance can be given regarding these respiratory symptoms, which are generally of a self-limiting nature.

Chapter 3 explores trends in incidence, antibiotic prescribing, and referrals during the period 2002-2008 for five common ENT problems in children aged 0-17 years. For this study, data were used from the Netherlands Information Network of General Practice, a nationally representative general practice database with data on over 50,000 children per year. In general, incidence rates of acute otitis media, serous otitis, sinusitis, tonsillitis and tonsil hypertrophy remained stable between 2002 and 2008. For some subgroups we found different trends. An increasing trend was observed for serous otitis media only in children aged 0-4 years. A decreasing trend was observed for sinusitis in children aged

5-11 years, and for tonsillitis in children aged 12-17 years. After diagnosis, antibiotics were prescribed in 10-60% of the cases. An increasing trend of antibiotic prescriptions for acute otitis media was found, mainly for the drug amoxicillin. Although the overall trend for antibiotic treatment of tonsillitis was stable, the number of prescriptions for pheneticillin showed a downward trend. First-choice antibiotics were prescribed in more than 80% of the cases.

Our conclusion was that trends in incidence rates, antibiotic prescribing and referrals for the five ENT problems were remarkably stable. The low proportion of antibiotic treatment rates for ENT problems did not lead to any negative consequences.

Chapter 4 examines prescription patterns, in particular intermittent versus continuous asthma medication, in children with physician-diagnosed asthma in general practice. For this study data from the DNSGP-2 were used. During the one-year study period (2001), 16% of the children received no prescription. Subsequently, data of all children (aged 0-17 years) with at least one asthma prescription were analysed. Prescription rates and proportions of children receiving continuous versus intermittent asthma medication were calculated. Data (including child and GP characteristics) were analysed using multivariate logistic regression techniques. Of the 2,993 children receiving asthma prescriptions, 61% received 1-2 prescriptions and 39% received 3 or more prescriptions. Continuous medication (i.e. 3 or more prescriptions) with a bronchodilator and/or a corticosteroid was prescribed in 22% of the children. Almost 20% of the children receiving continuous medication were prescribed a bronchodilator only. No child-related or GP-related characteristics had an independent effect on prescribing continuous versus intermittent medication.

It was concluded that in Dutch general practice the issue of asthma prescriptions per child/per annum is relatively low. Twenty percent of children receiving continuous prescriptions were prescribed bronchodilators only (5% of all children), suggesting room for improvement. No child-related or GP-related characteristics proved to be relevant for targeting educational strategies.

Chapter 5 evaluates the knowledge among Dutch children and their parents regarding asthma inhaler therapy and the appropriateness of its use among children aged 0-12 years using inhaler medication. In five general practices all children aged 0-12 years using asthma inhalation medication were selected. Of the children using one inhaler only 70% used the inhaler as indicated, and of those using more than one inhaler 46% used the inhaler correctly. On average 2.6 mistakes were made during demonstration of the technique, and two mistakes were reported during the study interview. In total, 87% of the parents decided (instead of the child) when and how the inhaler had to be used.

Spacer cleaning was performed correctly by 49% and only 26% reported a correct way of assessing how many doses were remaining.

Our conclusion was that children in the Netherlands make important mistakes related to inhaler use that are easy to avoid. We recommended a better explanation and demonstration of the technique, and more active involvement of the parents during the instruction.

Chapter 6 presents a systematic review on the efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma. Sodium cromoglycate has been recommended as maintenance treatment for childhood asthma for many years. Although its use has decreased since 1990 when inhaled corticosteroids became popular, it is still used in many countries. We updated our previous review for the Cochrane Collaboration. All double-blind, placebo-controlled randomised trials addressing the effectiveness of inhaled sodium cromoglycate as maintenance therapy, and studying children aged 0 up to 18 years with asthma, were included. Pooling of the results did not reveal any significant difference between sodium cromoglycate and placebo. However, considering the confidence intervals of the outcome measures, a clinically relevant effect of sodium cromoglycate cannot be excluded. The funnel plot indicated an under-representation of small studies with negative results, suggesting some publication bias. This may have overestimated the beneficial effects of sodium cromoglycate.

It was concluded that there is insufficient evidence to be totally sure about the efficacy of sodium cromoglycate compared with placebo as maintenance therapy in childhood asthma.

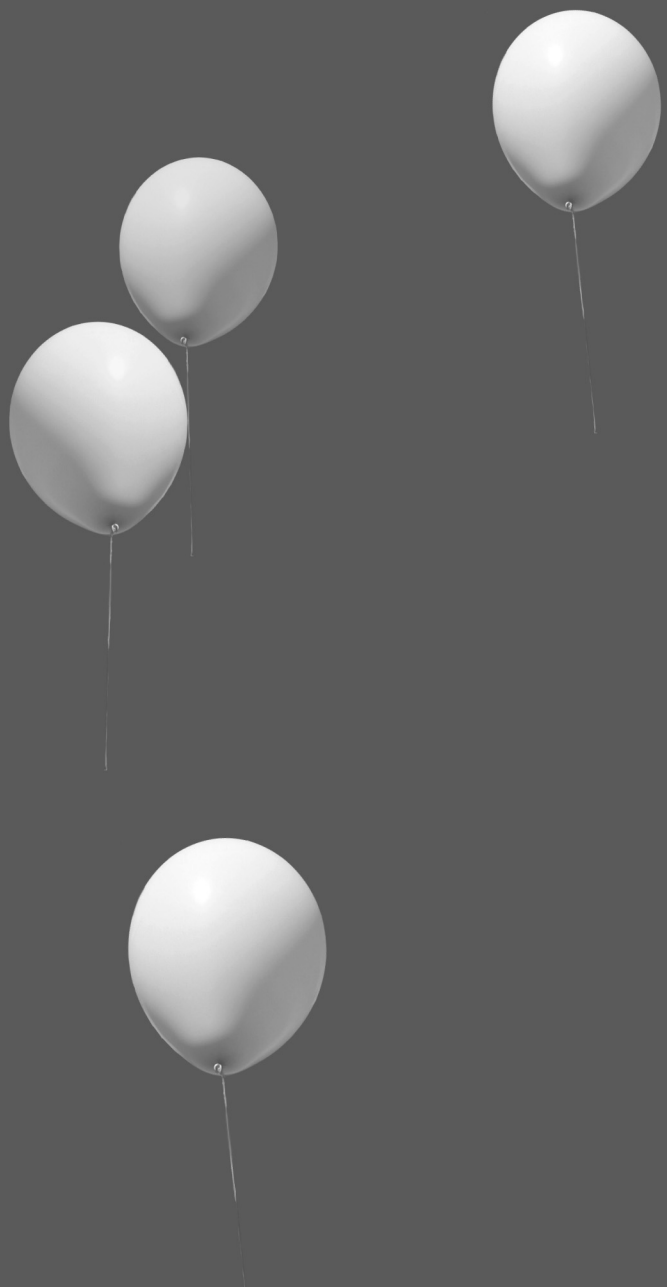
Chapter 7 examines respiratory morbidity in general practice and subsequent hospital admission patterns in children aged 0-17 years. Data on these children with respiratory diseases included in the DNSGP-2 were linked to all hospital admissions in the Dutch National Medical Registration. Of the 79,272 children whose data were analysed, 1.8% was admitted to hospital for any respiratory diagnosis in the year 2001. The highest admission rates were found for chronic disease of tonsils and adenoids, pneumonia and influenza, and asthma. Children aged 0-4 years, and boys, were admitted more frequently than children in the subgroups aged 5-9 and 10-17 years. Of all children with asthma, 2.3% was admitted to hospital for respiratory diseases. For asthma, admission rates were correlated with higher urbanisation level. Multivariate logistic regression analyses showed that within two weeks after a GP consultation, younger age and more severe respiratory diseases predicted hospital admission.

It was concluded that children in the general population with respiratory diseases (especially asthma) have very low hospital admission rates. In urban regions children

were more frequently admitted to hospital due to respiratory morbidity. The extremely low admission rates imply that for effectiveness studies in a primary care setting, hospital admission rates should not be used as quality end-point.

Chapter 8 presents a general discussion on the strengths and limitations of the data from the second Dutch National Survey of General Practice (DNSGP-2), the Netherlands Information Network of General Practice (LINH), and the Dutch National Medical Registration (LMR). Finally, the results of the individual studies are placed in a broader perspective and implications for the future are discussed.

Samenvatting



Luchtwegsymptomen en -ziekten komen veelvuldig voor bij kinderen in de huisartsenpraktijk. We kunnen een onderscheid maken tussen symptomen en ziekten van de bovenste luchtwegen (o.a KNO problemen waaronder hoest, keelontsteking, middenoorontsteking) en symptomen en ziekten van de onderste luchtwegen (zoals longontsteking, bronchitis, astma). Dit proefschrift beschrijft diverse aspecten van de epidemiologie, diagnose, en behandeling van luchtwegsymptomen en -ziekten die frequent bij kinderen in de huisartsenpraktijk voorkomen.

De hoofddoelstelling van dit proefschrift was het leveren van nieuwe informatie waarmee de zorg voor kinderen met symptomen en ziekten van de luchtwegen in de huisartsenpraktijk verbeterd kan worden. Hiertoe hebben wij epidemiologische gegevens over luchtwegsymptomen en -ziekten bij kinderen geanalyseerd en de behandeling van de huisarts betreffende het voorschrijven van medicatie en de verwijzing naar een specialist onderzocht.

Gegevens zijn afkomstig uit de Tweede Nationale Studie naar Ziekten en Verrichtingen in de Huisartspraktijk, het Landelijk Informatie Netwerk Huisartsenzorg, de Landelijke Medische Registratie en het Centrale Register van gecontroleerde Trials van de Cochrane Collaboration.

In **hoofdstuk 2** onderzochten wij de kenmerken van kinderen, hun ouders en hun huisartsen die gecorreleerd zijn met het bezoeken van de huisarts voor hoesten, keelpijn en oorpijn. We gebruikten de gegevens van de Tweede Nationale Studie naar Ziekten en Verrichtingen in de Huisartspraktijk (NS2). Jonge kinderen (0-4 jaar) consulteerden frequenter de huisarts voor luchtwegsymptomen in vergelijking met oudere kinderen. Hetzelfde gold voor kinderen met koorts, langere duur van de symptomen, kinderen die hun gezondheid als 'slecht tot goed' in tegenstelling tot 'zeer goed en uitstekend' bestempelden, en die in een meer stedelijk gebied woonden. Als de ouders ongerust waren of wanneer het kind/ouder door een ander naar de huisarts werd gestuurd, dan werd de huisarts vaker geraadpleegd. Huisartsfactoren bleken niet samen te hangen met het raadplegen van de huisarts door kinderen.

We benadrukten dat het belangrijk is om de reden van komst voor kinderen met luchtwegklachten te exploreren. Wanneer huisartsen zich bewust zijn van de mogelijke factoren om de huisarts te raadplegen, zal meer passend advies en geruststelling gegeven kunnen worden voor deze luchtwegklachten, die meestal vanzelf over gaan.

In **hoofdstuk 3** onderzochten wij de trends in incidentie, het voorschrijven van antibiotica en verwijzingen bij kinderen van 0-17 jaar vanwege vijf veelvuldig voorkomende KNO problemen gedurende de periode 2002-2008. We gebruikten een landelijk representatief gegevensbestand van huisartsenpraktijken met gegevens van in totaal meer dan 50.000

kinderen. Over het algemeen bleven de incidentiecijfers tussen 2002 en 2008 stabiel voor acute otitis media, otitis media met effusie, sinusitis, tonsillitis en tonsil hypertrofie. Voor enkele subgroepen vonden we afwijkende trends. Een toenemende trend werd gezien bij 0-4 jaar oude kinderen met otitis media met effusie. Een dalende trend werd waargenomen voor 5-11 jaar oude kinderen met sinusitis en voor 12-17 jaar oude kinderen met tonsillitis. Antibiotica werden voorgeschreven bij 10-60% van de diagnosen. Er werd een toename van antibioticavoorschriften voor acute otitis media gevonden, wat grotendeels voor rekening van amoxicilline kwam. Ofschoon de algemene trend voor antibiotische behandeling voor tonsillitis stabiel was, liet het voorschrijven van feneticilline een afnemende trend zien. Antibiotica van eerste keuze werden in >80% van de gevallen voorgeschreven.

Wij concludeerden dat de trends voor incidentie, antibioticavoorschriften en verwijzingen voor vijf KNO problemen opmerkelijk gelijk bleven. De in verhouding lage percentages antibioticavoorschriften lieten geen negatieve consequenties zien.

In **hoofdstuk 4** onderzochten we voorschrijfpatronen voor kinderen met door de huisarts gediagnosticeerd astma met bijzondere aandacht voor aaneengesloten (d.w.z. ≥3 voorschriften) versus onderbroken astmamedicatie. We maakten gebruik van NS2 gegevens. Gedurende de eenjarige studieperiode kreeg 16% van de kinderen geen medicatie voorgeschreven. De gegevens van alle 0-17 jarige kinderen met tenminste één voorschrift voor astmamedicatie werden geanalyseerd. Voorschrijfcijfers en het percentage kinderen, dat aaneengesloten versus onderbroken astmamedicatie ontving, werden berekend. De gegevens (inclusief kind- en huisartskenmerken) werden geanalyseerd door middel van multivariate logistische regressie technieken. Van de 2993 kinderen met astma die een voorschrift kregen, ontving 61% 1-2 voorschriften en 39% 3 of meer voorschriften per jaar. Aaneengesloten medicatie met een bronchusverwijder en/of een corticosteroïd werd aan 22% van de kinderen voorgeschreven. Bij 20% van de kinderen die continue medicatie kregen voorgeschreven werd alleen een bronchusverwijder voorgeschreven. Geen van de kind- of huisartsfactoren had een onafhankelijk effect op het voorschrijven van continue versus onderbroken medicatie.

Wij concludeerden dat in de huisartsenpraktijk het aantal voorschriften voor astmamedicatie per kind per jaar relatief laag is. De 20% kinderen (5% van alle kinderen), die alleen bronchusverwijders als aaneengesloten medicatie kregen voorgeschreven, biedt ruimte voor verbetering in het voorschrijven van astmamedicatie.

In **hoofdstuk 5** onderzochten wij de kennis van 0-12 jaar oude Nederlandse kinderen en hun ouders over inhalatietherapie bij astma en het juiste gebruik daarvan. In vijf huisartsenpraktijken werden alle 0-12 jarige kinderen met astmamedicatie geselecteerd

om deel te nemen. Kinderen en ouders namen deel aan een interview en demonstreerden de inhalatietechniek. Van de kinderen die één inhalator gebruikten, deed 70% dat correct en van de kinderen met meer dan één inhalator voerde 46% de inhalatietherapie correct uit. Gemiddeld werden 2,6 fouten gedurende de demonstratie van de inhalatietechniek gemaakt, en twee fouten werden gerapporteerd in het interview. In 87% van de gevallen waren het de ouders (in plaats van het kind) die bepaalden wanneer en hoe de inhalator gebruikt moest worden. Het schoonmaken van de voorzetkamer werd in 49% van de gevallen correct uitgevoerd. Slechts 26% rapporteerde op een juiste wijze na te gaan hoeveel doses nog in de inhalator aanwezig waren.

We concludeerden dat Nederlandse kinderen essentiële fouten maken bij het gebruik van inhalatiemedicatie die gemakkelijk te voorkomen zijn. Onze aanbevelingen zijn een betere uitleg en demonstratie van de inhalatietechniek, en het meer betrekken van de ouders bij de inhalatie-instructie.

In **hoofdstuk 6** beschrijven we een systematische review naar de werkzaamheid van cromoglycaat in vergelijking met placebo als profylactische therapie van kinderen met astma. Cromoglycaat is gedurende vele jaren aanbevolen als onderhoudstherapie voor astma bij kinderen. In de jaren '90 nam het gebruik van cromoglycaat af doordat de corticosteroïden populair werden, echter het wordt in vele landen nog steeds gebruikt. We werkten onze eerdere review voor de Cochrane Collaboration bij. Alle dubbelblinde, placebogecontroleerde gerandomiseerde trials naar de werkzaamheid van geïnhaleerde cromoglycaat als onderhoudstherapie bij 0-18 jarige kinderen werden geïncludeerd. Het samennemen (poolen) van de resultaten liet geen significant verschil zien in werkzaamheid tussen cromoglycaat en placebo. Echter, bij het in ogenschouw nemen van de betrouwbaarheidsintervallen van de uitkomstmaten kan een klinisch relevant effect van cromoglycaat niet worden uitgesloten. De 'funnel plot' liet een ondervertegenwoordiging van kleine studies met negatieve resultaten zien, wat publicatiebias doet vermoeden.

Wij concludeerden dat er onvoldoende bewijs was om de werkzaamheid van cromoglycaat versus placebo onderhoudsbehandeling aan te tonen. De positieve effecten van cromoglycaat lijken te zijn overschat.

In **hoofdstuk 7** onderzochten we respiratoire morbiditeit in de huisartsenpraktijk en daarop volgende ziekenhuisopnamen bij 0-17 jarige kinderen. De gegevens van 0-17 jarige kinderen met luchtwegklachten uit de NS2 werden gekoppeld aan alle ziekenhuisopnames uit de Landelijke Medische Registratie. Van 79272 kinderen werden de gegevens geanalyseerd en van hen werd 1,8% in 2001 in het ziekenhuis opgenomen met een respiratoire diagnose. De hoogste opnamecijfers werden gevonden voor chronische ziekten van de tonsillen en het adenoid, pneumonie, influenza, en astma. Jonge (0-4

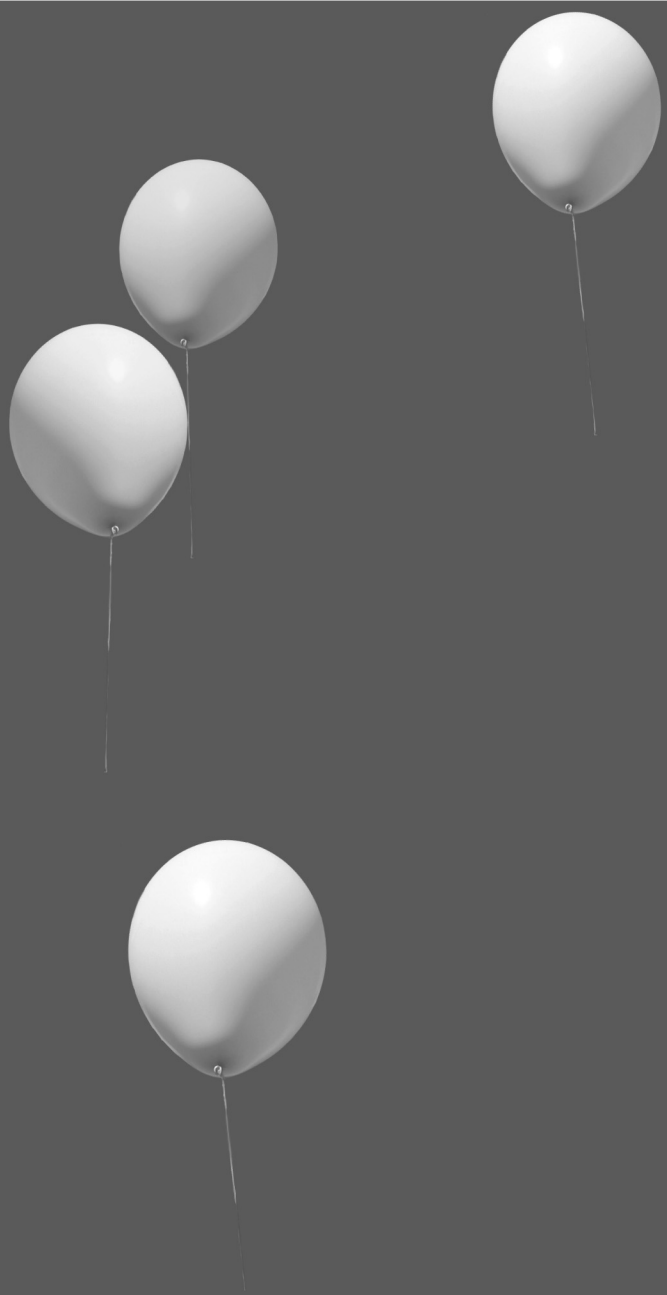
jarige) kinderen en jongens werden vaker opgenomen dan kinderen van 5-9 en 10-17 jaar oud en dan meisjes respectievelijk. Van de kinderen met astma werd ruim 2% opgenomen met een respiratoire ziekte. Voor astma hingen de opnamecijfers samen met hogere urbanisatiegraad. Multivariate logistische regressie liet zien dat, binnen twee weken na huisartsenbezoek voor een respiratoire aandoening, jongere leeftijd en meer ernstiger respiratoire ziekten een ziekenhuisopname voorspelden.

Wij concludeerden dat kinderen met respiratoire ziekten (in het bijzonder astma) in de populatie van de huisartsenpraktijk zeer lage opnamecijfers kenden. In meer stedelijke regio's werden kinderen relatief vaker opgenomen met respiratoire ziekten. De extreem lage opnamecijfers impliceren dat opnamecijfers voor respiratoire aandoeningen niet kunnen worden gebruikt als een indicator voor de kwaliteit van behandeling in de huisartsenpraktijk.

In **hoofdstuk 8** worden ter afsluiting een aantal algemene discussiepunten aan de orde gesteld. De sterke en zwakke kanten van de Tweede Nationale Studie naar Ziekten en Verrichtingen in de Huisartspraktijk, het Landelijk Informatie Netwerk Huisartsenzorg, en de Landelijke Medische Registratie worden belicht.

Tenslotte worden de resultaten van de studies uit dit proefschrift in een breder perspectief geplaatst.

List of publications



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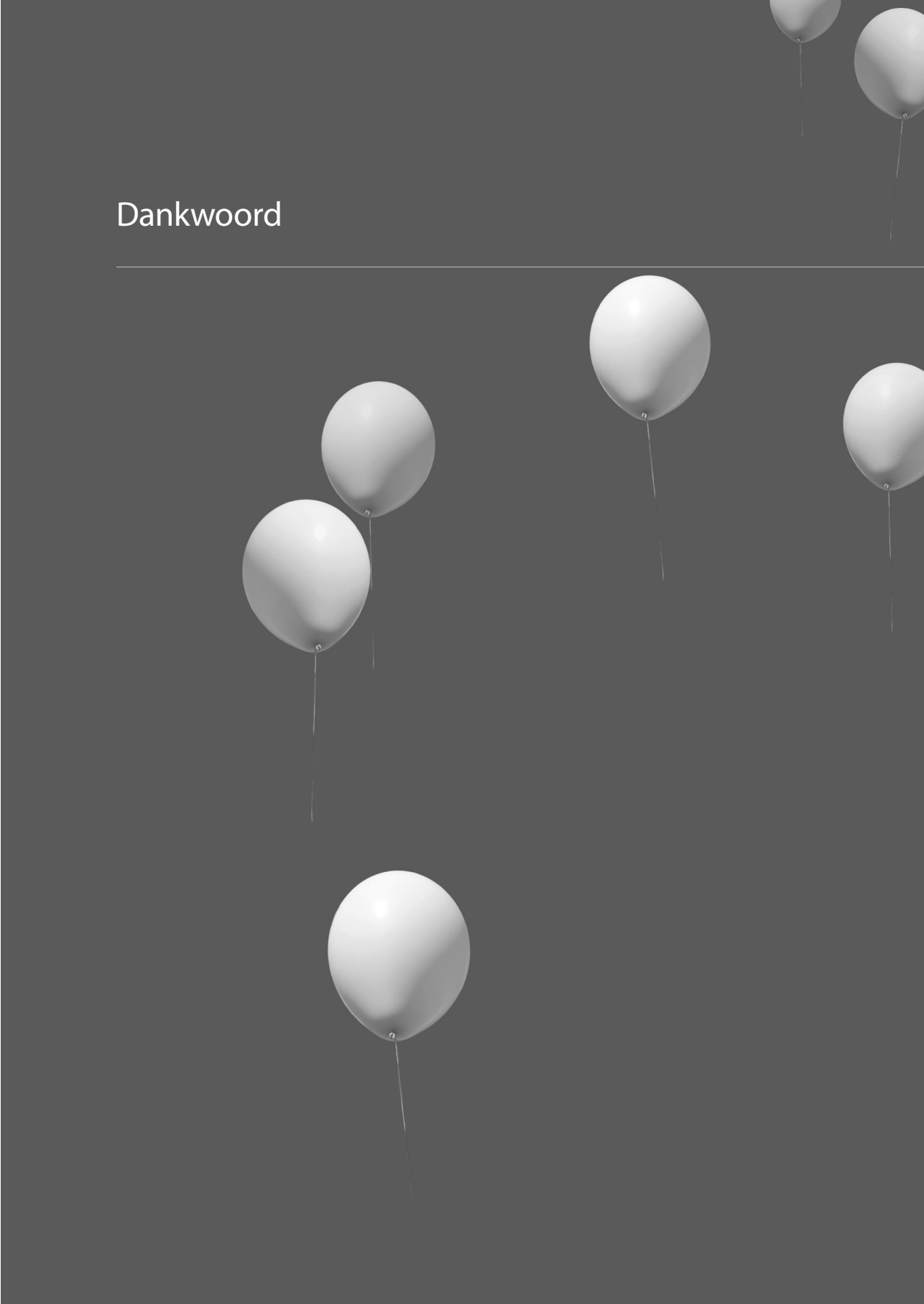
Dankwoord



Zonder dankwoord geen proefschrift. Het schrijven van een proefschrift kun je vergelijken met een lange hardloopwedstrijd. Spanning voor de start en in de beginfase het gevoel dat de finish nog heel ver weg is. Vragen gaan door je heen: kan ik het wel, zou ik deze afstand volhouden? Gedurende de wedstrijd zijn er dieptepunten (een moeizame analyse) of de man met de hamer (afwijzing van een artikel door een tijdschrift) en plots is er weer een hoogtepunt (geslaagde analyse of acceptatie van een artikel) met de bijbehorende euforie. En na gestaag doorlopen is de finish in zicht, je zet aan, versnelt, en haalt dan eindelijk met een opwindend gevoel de eindstreep.

Na afloop dient de wedstrijd te worden geëvalueerd en in dit dankwoord kijk ik terug op de mooie jaren die ik met het onderzoek op de afdeling huisartsgeneeskunde van het Erasmus MC Rotterdam heb beleefd. Wekelijks reisde ik met de trein vanuit Holten, aan de voet van de prachtige Sallandse Heuvelrug, naar het energieke en kleurrijke Rotterdam. Hoewel ik maar een dag per week op de Westzeedijk aanwezig was voelde ik me volledig opgenomen binnen de afdeling. Het waren leerzame jaren. In tegenstelling tot wat ik had verwacht, nam het gevoel van bescheidenheid ten aanzien van het verrichten van wetenschappelijk onderzoek eerder toe dan af. Ik heb meer respect gekregen voor de goede onderzoekers met wie ik omringd was. Ik heb bijzonder veel steun gekregen van vele mensen die ik in dit dankwoord van harte wil bedanken.

Zonder coach en leermeester geen promotie. Allereerst verdient mijn copromotor Hans van der Wouden veel dank voor de intensieve begeleiding en het onderwijs wat hij met veel enthousiasme aan mij gegeven heeft. Hans ontving me met open armen toen ik vroeg of er plaats was voor een huisarts uit het oosten van het land, die voor promotieonderzoek terug wilde naar het vertrouwde Rotterdamse nest. Door zijn deskundigheid, betrokkenheid en steun was ik in staat dit proefschrift te schrijven. Minstens zo belangrijk vond ik het grote plezier waarmee wij konden samenwerken, dat maakte de lange reistijd tot een draaglijk bezwaar.

Zonder goede promotoren geen proefschrift. Patrick Bindels wil ik bedanken voor zijn begeleiding en scherpe analyse van problemen gedurende het schrijven van deze dissertatie. Door nieuwe voorstellen wist hij meerdere malen een artikel of een analyse weer vlot te trekken. François Schellevis was vanuit het NIVEL betrokken bij mijn begeleiding. Zijn rustige en deskundige inbreng gaven mij altijd het vertrouwen dat het schrijven van dit proefschrift tot een goed einde zou komen.

Schrijven van een proefschrift doe je niet alleen. Geschikte statistische analyses worden gekozen en zo nodig aangepast. Tekst voor artikelen wordt gelezen, beoordeeld en herschreven tot dat het rijp is voor u als lezer. Graag wil ik, naast bovengenoemde begeleiders, mijn

andere medeauteurs bedanken: Roos Bernsen, Francine Ducharme, Huug van Duijn, Johan de Jongste, Marijke Kuyvenhoven, Lisette van Suijlekom-Smit, Marjolein Tasche, Yannick van Uijthoven, en Sten Willemsen. Ieder had zijn inbreng vanuit het eigen perspectief: huisarts, kinderarts, of statisticus.

Wetenschappelijk onderzoek is leuker op een gezellige afdeling. Met veel plezier werkte ik op de afdeling Huisartsgeneeskunde, mijn werkplek bevond zich op de Westzeedijk. Alle mensen waren bereid mij te hulp te schieten als ik tegen een vraag aanliep, die varieerde van een vraag over SPSS, Word of Excel tot waar ik de juiste drukker kon vinden. Zonder namen te noemen wil ik álle medewerkers hartelijk danken voor de hulp en gezelligheid.

Zonder rust en steun in de eigen huisartspraktijk geen promotiewerkzaamheden. Ik ben trots op de Maatschap Huisartsen Holten waarin ik met veel plezier werk. Mijn drie maten Rein van Couwelaar, Dieuwertje Leenaers en Frédérique Zweers-Talsma bedank ik voor de ruimte en begrip die zij mij gaven om deze uitdaging aan te gaan. Karo van der Hoek was de gehele periode mijn vaste waarnemer. Ik wil haar bedanken voor haar loyaliteit en goede werk. Katrien de Jong-Deschamps heeft mij ook regelmatig vervangen. Zij past heel goed in onze groep en ik ben blij haar in de nabije toekomst als maat te verwelkomen. Marie-Elise Bolt en Jacolien Drent zagen als huisartsen in opleiding regelmatig patiënten uit mijn praktijk.

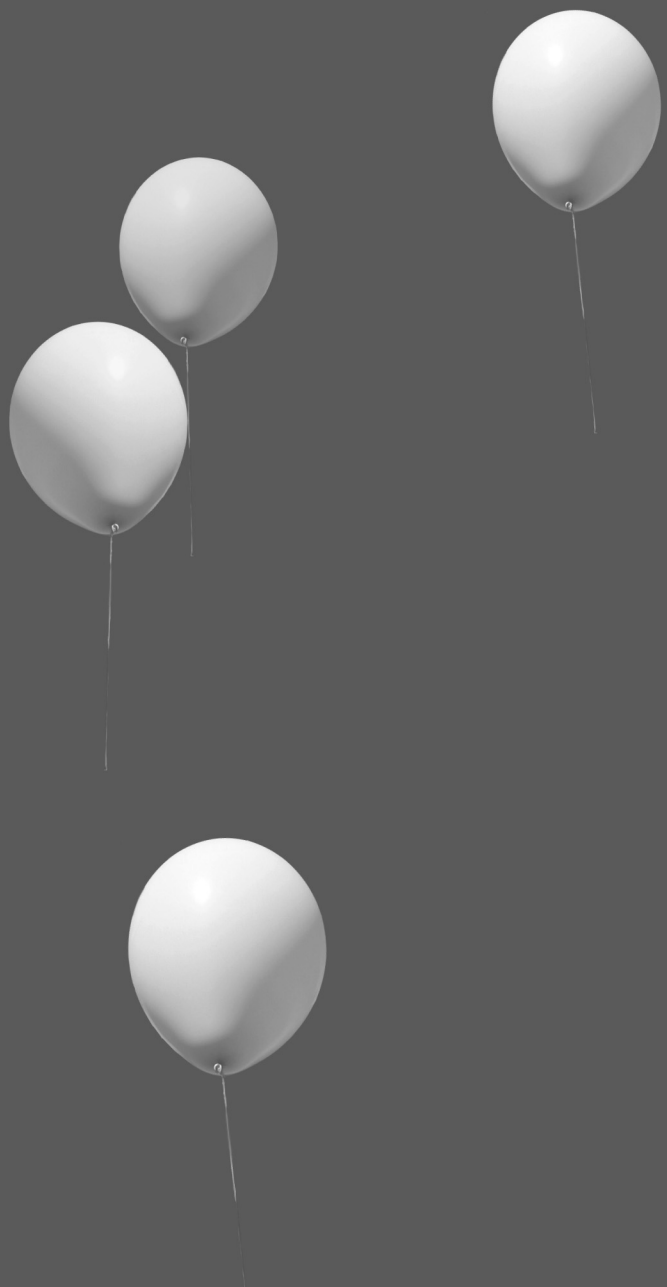
De assistentes en praktijkverpleegkundigen uit onze huisartspraktijk hebben de oneffenheden in de (patiënten)agenda en het gezamenlijke overleg altijd weer glad gestreken. Jennita Garritsen, Denny Kamphuis, Mariska Kuipers, Inge Kwintenberg, Nadine van Reen, Elly Schopman, Monique Slinkman, Liesbeth Stein, Monique Wichers, Andrea Winkel en Annet Wolfkamp: dank daarvoor!

Zonder paranimfen geen promotieplechtigheid. Een paranimf uit de werkkring en een paranimf uit het privéleven. Rein van Couwelaar is mijn collega waarmee ik met groot plezier veel plannen in de huisartspraktijk en de regio ten uitvoer breng. Met Hans Kaffener deel ik vriendschap en passie voor hardlopen.

Liefde en steun van het gezin geeft ruimte voor uitdagingen. Ik deel mijn leven met Marlies. Altijd staat zij achter mijn keuzes om mij verder te ontwikkelen. Mooi om te zien dat zij nu zelf de ruimte heeft om een nieuwe opleiding te volgen. Stijn, Madelief en Guus zijn onze prachtige kinderen. Ik bewonder hen om hun levenslust en veerkracht, en eerlijk gezegd ook wel om het geduld dat zij met mij hadden tijdens het schrijven van dit proefschrift.

Na de promotie wordt het tijd voor mijn eerste marathon, en, het kan niet anders: het wordt de marathon van Rotterdam.

Curriculum Vitae



Op 7 april 1966 werd Hans Uijen geboren in Delft. In deze stad doorliep hij de lagere school en het VWO aan het St. Stanislas College. In 1984 begon hij met de studie geneeskunde in Rotterdam, waar hij in 1992 cum laude het artsexamen behaalde.

Hierna werkte hij ruim een jaar als arts-onderzoeker bij de afdeling Huisarts-geneeskunde in Rotterdam om een onderzoek voor te bereiden naar de effectiviteit van cromoglycaat, als behandeling van astma bij kinderen. Alvorens de huisartsopleiding te beginnen was hij een jaar werkzaam als poortarts in het Schieland Ziekenhuis in Schiedam.

In 1994 tot en met 1997 volgde hij de huisartsopleiding in Rotterdam. Hij was in die tijd vicevoorzitter van het bestuur van de Landelijke Organisatie van Aspirant Huisartsen en adviserend lid van het algemeen bestuur van het Nederlands Huisartsen Genootschap.

In 1998 vestigde hij zich als huisarts in Holten. Hij was één van de oprichters van de Centrale Huisartsenpost Salland in Deventer en voorzitter van het bestuur, later gevolgd door het voorzitterschap van de Raad van Toezicht van de Stichting Dienstverlening Huisartsen Stedendriehoek (vier huisartsenposten). Daarnaast was hij bestuurslid van de District Huisartsen Vereniging Stedendriehoek.

In 2005 rondde hij de opleiding Management en Bestuur in de Gezondheidszorg aan de Universiteit van Tilburg met succes af.

In september 2006 startte hij zijn promotieonderzoek bij de afdeling Huisarts-geneeskunde aan het Erasmus MC te Rotterdam. In 2008 maakte hij deel uit van de congrescommissie van het NHG-congres 'Kijk op Kids: huisarts, kind en gezin'.

Hans Uijen is gehuwd met Marlies van Dartel, zij hebben drie kinderen: Stijn, Madelief en Guus.