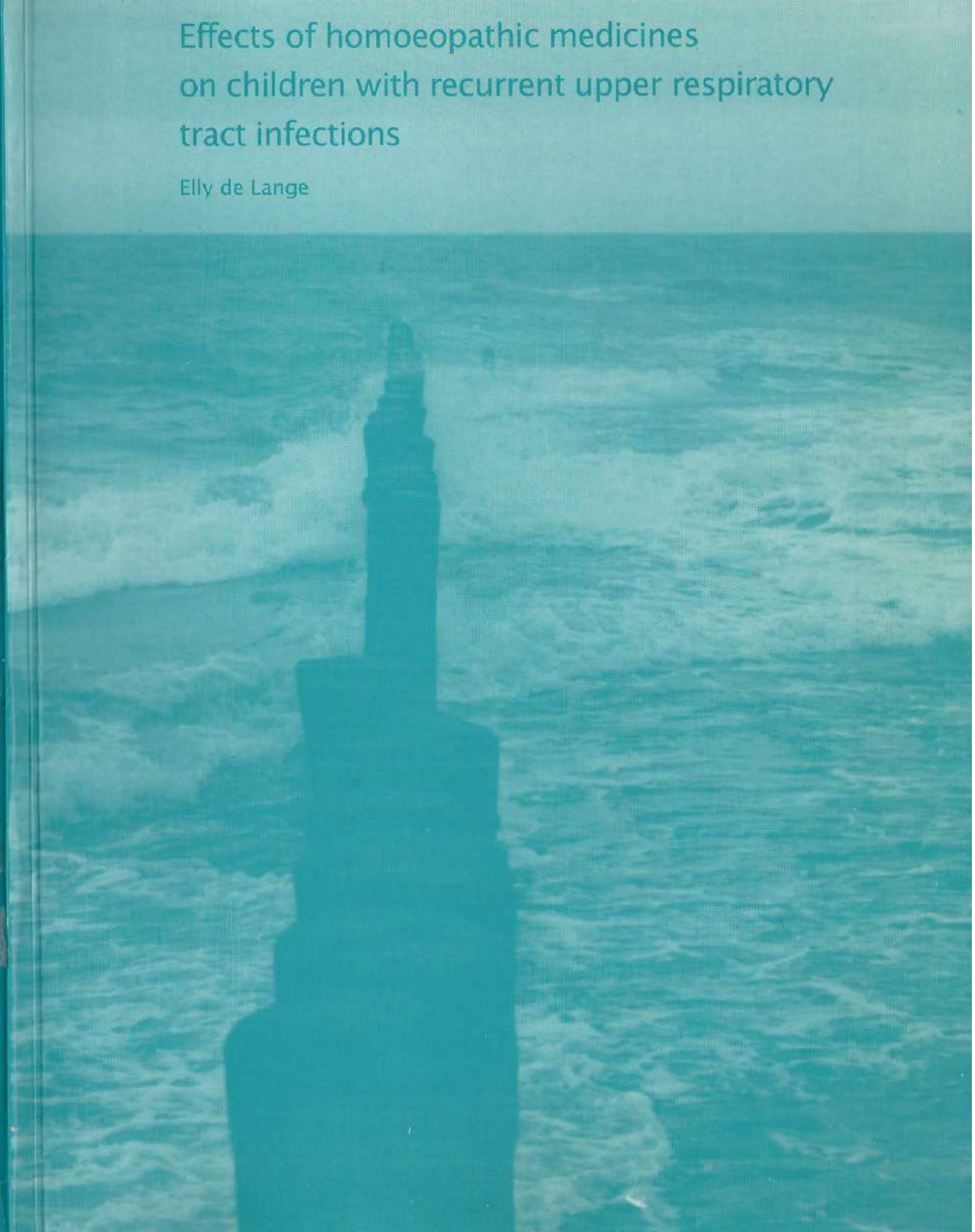
Effects of homoeopathic medicines on children with recurrent upper respiratory tract infections

Elly de Lange



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EFFECTS OF HOMOEOPATHIC MEDICINES ON CHILDREN WITH RECURRENT UPPER RESPIRATORY TRACT INFECTIONS

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door

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geboren te Oud-Beijerland

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CONTENTS

INTRODUCTION

At the Vrije Universiteit in Amsterdam a randomised placebo-controlled double blind clinical trial was performed to study long term effects of individually prescribed homoeopathic remedies on the health of children suffering from frequent upper respiratory tract infections. The first patient was enrolled in the trial on the 16th of March 1987 and the last patient completed participation in January 1992.

In this thesis respiratory tract infections and related subjects are described in *chapter 1*, homoeopathy is described in *chapter 2* and the study is described in the *chapters 3*, *4* and *5*.

I FREQUENT UPPER RESPIRATORY TRACT INFECTIONS

1.1 Introduction

Upper respiratory tract infections (URTIs) are very common, particularly in children.

The upper respiratory tract is continuously and extensively exposed to inhaled environmental air which contains a variety of gasses and particles among which are irritants, potential allergens and micro-organisms. Although the respiratory tract is protected by effective mechanisms to purify inspired air, it is, apart from the mouth, the most common site of infections in man. Pathogenic respiratory agents are spread both by air and contaminated objects and reach the airway of the host through inhalation or by the object-hand-nose route. Whether or not contamination is actually followed by infection, depends upon the interaction between agent and host. Number and virulence of the pathogens on the one hand and host defence mechanisms on the other, determine the outcome.[1 2] If infection does follow, the course of the disease is determined by the same factors, plus the effects of intervention. Although most upper respiratory tract infections heal spontaneously and completely, without any lasting structural damage, they may cause patients considerable discomfort.[3]

A myriad of microbes (viruses, bacteria, and others) may cause upper respiratory tract infections. It has been estimated that roughly 90% of upper respiratory tract infections are of viral origin.[4] Most clinical syndromes are a-specific: several pathogens may cause the same clinical syndrome, whereas one particular respiratory microbe may cause quite different clinical syndromes in different individuals. The characteristics of both the virus and the host play a role in the localisation (primary site and extent) of the infection: for instance, the size of the virus, the optimal temperature for its growth, the immunity of the host and anatomic characteristics of his respiratory tract.[5] The latter two are age dependent. The degree of constitutional disturbance caused by the infection is generally age dependent too. Since viral infections damage, at least temporarily, the mucosal lining and other defence mechanisms, they may be complicated or succeeded by bacterial infections.

Although respiratory infections are very common in children, some children are much more susceptible than others. This study focuses on these vulnerable children, who suffer from excessively frequent upper respiratory tract infections. In

order to define 'excessive frequency' data on frequencies of upper respiratory tract infections in children were looked for in the literature. Other questions addressed were: What is the average duration of upper respiratory tract infections in children? What factors are known to enhance the contraction of respiratory infections? Do children with frequent upper respiratory tract infections but without detectable underlying disease have other common characteristics apart from frequently being ill from respiratory infection?

In this chapter some epidemiologic studies on incidences of URTI in children are compared. Information on duration, complications and recurrence rates of respiratory infections are extracted from some other studies. Risk factors for respiratory tract infections are reviewed. Some explanations of the frequent occurrence of respiratory tract infections in childhood are given.

Then several authors' definitions of recurrent upper respiratory tract infections in children are compared. Attention is paid to factors that are related to the frequent recurrence of upper respiratory infections in a subgroup of children. Problems associated to frequent upper respiratory tract infections are discussed. Prophylactic interventions in children with frequent upper respiratory tract infections are reviewed. The anatomy and physiology of the upper respiratory tract, the known respiratory pathogens and the distinguished clinical syndromes of upper respiratory tract infections are reviewed because knowledge thereof contributes to the appropriate treatment of and care for susceptible children.

1.2 Occurrence of upper respiratory tract infections in children

The incidence of upper respiratory tract infections in western communities has been investigated in several prospective epidemiologic studies conducted from the forties onwards. Data from three studies are presented here. Prospective epidemiologic studies in non-western countries among people living in poor conditions have been performed more recently. There are no recent Dutch data available on incidences of respiratory infections in the general population. Instead recent data on consultation-rates for respiratory infections in general practice will be given. Consultation-rates, however, only give a rough indication of incidences, since for many respiratory infections the general practitioner is not consulted. Real incidences can therefore be expected to be much higher.

Most of the epidemiologic studies measured incidences and mean attack rates per person-year in dynamic populations of families. Little data are available on individual recurrences. A Dutch cohort study conducted in a general practice in a rather closed community in the late fifties provided individual recurrence-rates. These data cannot be applied to modern Dutch society unreservedly. A recent Dutch study provided data from which estimates of the proportion of modern Dutch children suffering from recurrent acute otitis media were calculated. Children with recurrent acute otitis media constitute a great proportion of all children with recurrent upper respiratory tract infections. These estimates therefore give an idea of the magnitude of the problem of recurrent upper respiratory tract infections in Dutch children nowadays.

1.2.1 Incidences of respiratory infections per child-year in different studies

Long-term studies of groups of families were performed to observe dynamic patterns of health and illness in their natural setting.[6] On the whole, the methods of data-collection vary in the different studies, however, diaries were used in most of them. The definitions of various types of upper respiratory tract infections differed in most studies. Some studies fail to even give any definition at all. These differences make comparisons difficult, if not impossible. However, data from the several studies give some idea of the attack rate of respiratory infections in children.

Tecumseh, 1965-1971

In Tecumseh, Michigan, USA, respiratory illnesses in families with children were studied during a period of six years, from 1965-1971. Participating families represented a cross-section of the community.[7] Each family remained in the study for the course of one year. A total of 4905 residents participated. Each week the families were contacted by telephone to determine whether or not an illness had occurred. Illnesses were divided into syndrome categories on the basis of reported symptoms. Respiratory illnesses were divided into 5 sub-categories: lower respiratory illness, upper respiratory illness, laryngopharyngeal illness, cough and earache. The mean number of *respiratory illnesses* per year was 6.1 for infants under 1 year, 5.7 for children aged 1 and 2 years, 4.7 for the 3 and 4 years olds, 3.5 for children aged 5 up to and including 9 years.[8] Upper respiratory illnesses constituted 60.9% of all respiratory illnesses in infants younger than 1 year, 61.8% in the 1-4 years olds and 54.4% in children aged 5 to 9 years.

Cornell Family Illness Study, Manhattan, 1962-1965

In the Cornell Family Illness Study 448 Manhattan families were studied from 1962-1965.[9] Each family was observed for an average of 45 weeks. A weekly questionnaire requested daily information on 14 acute symptoms. On the basis of

ADDENDUM 17.1

Overzicht van alle voorgeschreven homeopathische middelen in de gehele a + b + c-groep

Frequency Tabulation

REMEDY	comp.	oer	D3	D4	D6	D12	D30	D60	D200	D1000	TOTAAL
ABROT.		-	1	-	-	-	-	-	-	-	1
ACON.		-	-	-	3	-	-	-	-	-	3
AGRA.		-	1	-	2	-	-	-	-	-	3
ALL-C.		-	-	-	6	-	-	-	-	-	6
ALOE		-	-	-	3	-	-	-	-	-	3
ANT-C.		-	-	-	3	-	-	-	-	-	3
ANT-T.		-	-	-	2	-	-	-	-	-	2
APIS		-	-	-	10	-	-	-	-	-	10
ARN.		2	-	-	1	1	1	-	-	-	5
ARS.		-	-	-	-	4	4	1	-	-	9
ARS-I.		-	-	-	6	4	-	-	-	-	10
BAF	3	-	-	-	-	-	-	-	-	-	3
BAR-C.		-	-	-	2	1	-	-	-	-	3
BAR-I.		-	-	-	2	-	-	-	-	-	2
BELL.		-	-	-	108	1	-	-	-	-	109
BIOFORC		2	-	-	-	-	-	-	-	-	2
BRY.		-	-	-	6	-	-	-	-	-	6
CALC-I.		-	-	-	-	-	1	-	-	-	1
CALC-P.		-	-	-	20	10	5	2	1	-	38
CALC-S.		-	-	-	1	-	-	-	-	-	1
CALC.		-	1	-	47	29	19	7	4	-	107
CALEN.		3	-	-	-	-	-	-	-	-	3
CAPS.		-	-	-	2	-	-	-	-	-	2
CAUST.		-	-	-	-	6	-	-	-	-	6
CHAM.		-	-	-	10	3	3	-	-	-	16
CHIN.		-	-	-	1	-	-	-	-	-	1
CHLOR.		-	-	1	-	1	-	-	-	-	2
CINNB.		-	-	-	1	-	-	-	-	-	1
COCC.		-	-	-	6	-	-	-	-	-	6
COFF.		-	-	-	1	-	-	-	-	-	1
COR-R.		-	-	-	2	-	-	-	-	-	2
CYPR.		-	-	-	4	-	-	-	-	-	4
DROS.		-	-	2	4	-	-	-	-	-	6
DULC.		-	-	-	1	-	-	-	-	-	1
ECHI-P.		5	-	-	-	-	-	-	-	-	5
ELAPS		-	-	-	-	1	-	-	-	-	1

Overzicht van alle voorgeschreven homeopathische middelen in de gehele a + b + c-groep (vervolg)

Frequency Tabulation

REMEDY	comp.	oer	D3	D4	D6	D12	D30	D60	D200	D1000	TOTAAL
FERR-P.		-	15	3	13	1	-	-	-	-	32
GRAPH.		-	-	-	-	2	-	-	-	-	2
HEP.		-	-	-	-	30	3	3	-	-	36
HYDR.		-	-	-	1	-	-	-	-	-	1
HYOS.		-	-	-	1	-	-	-	-	-	1
IGN.		-	-	-	2	-	-	-	-	-	2
IP.		-	-	-	42	1	-	-	-	-	43
KALI-BI.		-	-	-	13	1	-	-	-	-	14
KALI-C.		-	-	-	-	1	-	-	-	-	1
KALI-CHL.		-	-	-	1	-	-	-	-	-	1
KALI-M.		-	-	-	15	2	-	-	-	-	17
KALI-S.		-	-	-	14	1	-	-	-	-	15
LACH.		-	-	-	-	2	3	-	-	-	5
LYC.		-	-	-	1	9	8	1	-	-	19
MED.		-	-	-	-	-	-	-	1	-	1
MERC.		-	-	-	23	4	2	1	1	-	31
MERC-C.		-	-	-	-	1	-	-	-	-	1
NAT-M.		-	-	-	-	-	1	-	2	-	3
NAT-S.		-	-	-	-	3	-	-	-	-	3
NUX-V.		-	-	-	3	1	2	-	-	-	6
NYSIKIN	1	-	-	-	-	-	-	-	-	-	1
PASSI.		2	-	-	-	-	-	-	-	-	2
PHOS.		-	-	-	-	3	22	5	3	-	33
PULS.		-	-	-	44	17	18	5	2	-	86
RUMX.		-	-	-	1	-	-	-	-	-	1
SABIN.		-	-	-	1	-	-	-	-	-	1
SIL.		-	-	-	32	24	15	4	3	-	78
SPONG.		-	-	-	15	-	-	-	-	-	15
STRAM.		-	-	-	4	-	-	-	4	-	8
SUL-I.		-	-	-	7	-	-	-	-	-	7
SULPH.		-	-	-	-	5	86	37	24	1	153
TARAX.		-	1	-	-	-	-	-	-	-	1
THUJ.		-	-	-	-	-	13	2	1	-	16
TUB.		-	-	-	-	-	-	-	20	-	20
TUSSIST	1	-	-	-	-	-	-	-	-	-	1
VARIO.		-	-	-	-	-	-	-	1	-	1
TOTAAL	5	14	19	6	487	169	206	68	67	1	1042

reported symptoms five syndromes were defined as combinations of cojoint symptoms.

On average the *common cold* was experienced 6.1 times per child-year in children aged 0 up and including 4 years and 3.8 times in children aged 5 up and including 9 years. *Rhinitis* was experienced 0.7 times per child-year in the youngest group and 0.4 times in children from 5 to 9 years old. *Coughs and/or sore throats* were more frequently encountered in children from 5 to 9 years old: the average frequency in this age-group was 0.9 episodes per child year and in the children under 5 years 0.5. [10]

Cleveland, 1948-1950

In Cleveland, USA, a group of 61 families with children (yielding a total of 292 individuals) belonging to the higher socio-economic layers of society was studied over a 3-year period, from 1948-1950. [11] Illness was defined as the presence of one single symptom. 'Common respiratory illnesses' included the common cold, rhinitis, laryngitis, bronchitis and other respiratory illnesses of undifferentiated type. 'Specific respiratory infections' included tonsillitis and pharyngitis, pneumonia and influenza. Otitis media was categorised under the rubric 'other infections'. The incidence of *common respiratory illnesses* in children was: infants under 1 year on average 6.9 per child-year, children aged 1 and 2 years 8.4, aged 3 and 4 years 8.3, from 5 up to and including 9 years 6.6. [12]

Manila, Philippines, 1985-1987

From 1st April 1985 to 31st March 1987 a prospective cohort study of respiratory tract infections in children less than five years of age took place among the poorest families of Metropolitan Manila, the Philippines. Data were collected by weekly interviews in which information on symptoms and signs of respiratory infection was obtained by trained nurses and medical technologists. Children with cough were considered to have acute lower respiratory tract illness, which was further differentiated into degrees of severity by the most severe manifestations recorded. The incidences of acute upper respiratory tract infections per child year were 5.1 for children aged 0 - 5 months, 6.4 for 6-11 months, in the second year of life 6.5, in the third 5.6, in the fourth 5.3 and in the fifth 4.7. The incidences of acute lower respiratory tract infections per child year were 0.6 for children aged 0 - 5 months, 0.9 for 6-11 months, in the second year of life 0.8, in the third 0.5, in the fourth 0.4 and in the fifth 0.2. [13]

Summing up and comment

The studies differ in types of population, living-conditions, methods of data-collection and definitions.

The Tecumseh study included ear-ache as well as lower respiratory infections in 'respiratory tract infections'. The Cornell-data include the categories common cold, rhinitis, and cough or sore throat. In Cleveland, where the wealthiest families were studied, just one symptom was sufficient to gain the predicament 'illness' but the syndromes tonsillitis, pharyngitis, pneumonia, influenza and otitis media were not included in 'common respiratory illnesses'. The data from Manila concern upper and lower respiratory tract infections in children from the poorest families.

Upper respiratory tract infections account for the greatest part of recorded incidences of respiratory tract infections. In the Cleveland study, the incidence of 'common respiratory diseases' decreases sharply after the sixth birthday.

1.2.2 Consultations of the general practitioner for respiratory infections

In the Continuing Registration of Morbidity in General Practice (Nijmeegs Universitair Huisartsen Instituut) 6 Dutch general practitioners in 4 practices (total practice population of 12000 individuals) register their diagnoses of all the patients who consult them. [14] For this registration the entries from the E-list of the International Classification of Diseases is used. No definitions are given of criteria for the several clinical entities.

Incidence is here defined as the number of new cases a year in 1000 patients who consulted their general practitioner. The incidences in the period 1982 till 1987 are presented in *table 1.1* and the incidences in various age-groups in the period 1987 till 1991 are presented in *table 1.2*.

In the period 1982 till 1987 the general practitioner (GP) was consulted for 1.2 acute upper respiratory tract infections per child-year for the 0 to 4 years olds, 0.7 for the 5 to 9 years olds and 0.4 for the children aged 10 to 14. In the period 1987 till 1991 the GP was consulted for less upper respiratory tract infections in children: in the 0 to 4 year olds for 0.9 acute upper respiratory tract infections per child-year and in the 5 to 14 year olds for 0.3.

1.2.3 Recurrence rates

Pel, a general practitioner in Zeeland, the Netherlands, conducted a longitudinal survey in his practice in the town of Middelburg from 1951 to 1959. [15] He monitored one hundred and sixteen children of his own practice from birth until their fifth birthdays. All 116 children belonged to different families. A diary was kept

Table 1.1 *Incidences of respiratory tract infections and symptoms in the Continuing Registration of Morbidity in General Practice from 1982 till 1987*

	incidences in several age-groups		
	0-4	5-9	10-14
• coryza without fever	505.7	272.3	167.9
• catarrh with fever	262.2	139.9	96.9
• acute otitis media	218.4	117.1	27.3
• earache	5.2	5.7	1.8
• acute sinusitis	2.8	8.8	8.3
• acute tonsillitis	151.1	104.3	54.6
• sore throat	0.0	0.0	0.4
• cough	1.7	1.0	0.2
• mastoiditis	0.3	0.3	0.2
• glue ear	19.7	38.2	14.4
• hypertrophy tonsils/adenoid	42.8	27.0	3.0

Table 1.2 *Incidences of respiratory tract infections and symptoms in the Continuing Registration of Morbidity in General Practice from 1987 till 1991.*

	0-4		5-14	
	male	female	male	female
• coryza without fever	344	429	137	175
• catarrh with fever	308	291	74	75
• acute otitis media	177	160	71	61
• acute sinusitis	3	1	5	14
• acute tonsillitis	45	44	21	31
• mastoiditis	0	0	0	0
• glue ear	82	75	55	55

for every child by his or her parents. In this diary the child's complaints and diseases of other members of the family were documented. The general practitioner visited the family every 6 weeks to work through the notes with the parents. His data provide a rough indication of the magnitude of recurrent respiratory infections in young children in that period, although the population studied probably was not representative of Dutch children from 0 to 5 years old in the fifties.

From his data Pel calculated the mean number of common colds in different age-periods: in the first year of life the mean number of common colds was 3.1, in the second 4.3, in the third 4.0, in the fourth 3.6 and in the fifth 3.5.

Children who had many colds in their first year of life, tended to continue to have many colds in subsequent years. This is in accordance with the results of Miller's follow-up study: he also found that the number of respiratory infections children suffered from in their first year of life was positively related to the frequency of respiratory infections which they experienced in the succeeding years. [16]

Apart from uncomplicated colds, Pel recorded 'other respiratory tract infections' to which he added: pharyngitis, laryngitis, sinusitis, bronchitis and bronchopneumonia and furthermore: febris e causa ignota, otitis media, angina and flu. He does not give any criteria for the particular diagnoses.

Pel observed a mean of 5.5 episodes per child of all these types of respiratory infections during the first 5 years of life. The incidence gradually increased with age and was highest in the age-group of 4 year olds (*table 1.3*).

Two percent of the children in Pel's cohort suffered during their first five years of life on average from more than of 2.8 episodes of 'other respiratory infections' a year and 8% from more than 2.4 (*table 1.4*).

Table 1.3 *Mean number of all 'other respiratory infections' in one year in the several age-periods in Pel's study*

the first year of life	0.3
the second year of life	0.8
the third year of life	1.1
the fourth year of life	1.4
the fifth year of life	1.8

Because of differences in living-conditions and life-styles, the proportion of contemporary Dutch children suffering from frequent upper respiratory tract infections is apt to be different from the proportion in Pel's study. Appelman and Claessen estimated that nowadays 5.4% of the total Dutch population of 12 years and younger is otitis-prone, i.e. suffer from recurrent otitis media. [17] A large proportion of children with frequent upper respiratory tract infections is otitis-prone. It may be assumed therefore that the proportion of Dutch children under 12 who suffer from frequent upper respiratory tract infection nowadays is at least 5.4%.

Table 1.4 *Distribution of numbers of episodes of 'other respiratory infections' per child in the first 5 years of life in Pel's study (n = 116)*

absolute number of r.i.	percentage of children
0-2	22
3-5	35
6-8	23
9-11	11
12-14	6
>14	2

1.2.4 Duration and complications

In a prospective study Wald and her colleagues collected data on the duration and complications of upper respiratory tract infections in a cohort of healthy children in Pittsburg from birth till the age of 30- 36 months using health diaries and fortnightly structured interviews by telephone (1985-1989).[18] There were 392 child-years observed over the 3-year period.

In this study they defined a simple upper respiratory infection as the presence of nasal discharge or nasal congestion with or without a cough. A complicated upper respiratory infection was defined as a simple upper respiratory infection accompanied by otitis media or sinusitis which had been reportedly confirmed by a physician. An illness was considered to be resolved when the child no longer had symptoms and the activity level was normal. An illness episode was counted as new when symptoms occurred at least 3 days after the stated time of the resolution of a previous episode. When an illness lasted more than 30 days and extended into the next month it was counted as a new illness. Nearly 7 upper respiratory tract infections per child-year were recorded. Of all recorded respiratory tract infections, 29.2% were complicated by otitis media. The mean duration of a URTI varied between 6.6 days for the 1- to 2-year-old children in home care and 8.9 days for the children younger than 1 year in day care.

Recorded mean durations of upper respiratory tract infections in children in the Cornell Family Illness Study and the Tecumseh Study ranged from 6 to 10 days and durations were shorter in children older than 5 years than in those younger than 5 years.[7 11]

Shah and his colleagues estimated the average total number of person-days of respiratory symptoms experienced by children in one year from the data of the Cornell Family Illness Study in Manhattan. Children from 0 up to and including 4 years old experienced respiratory symptoms on 70.1 days a year (nearly 20% of the time) and children from 5 up to and including 9 years on 41.8 days a year (11.4% of the time).[3]

1.2.5 Risk factors and prognostic factors for upper respiratory tract infection

Various factors are found to influence the risk of contracting upper respiratory tract infections and several factors influence the risk of the infection to run an abberant course.

The incidence of acute respiratory infections is highest in the cold season.[19] This does not apply to angina: the incidence of angina is equally distributed over the year. The incidence of otitis media is highest in winter and early spring.[20]

The incidence of respiratory infections is higher in children from parents with a lower socio-economic status.[21 22] Housing probably plays an important part in this association.[23]

Crowding favours the transmission of pathogens. Infections tend to spread more easily in dense populations. Members of large families have more respiratory tract infections per person per year than members of smaller families.[11 23] Day-care for small children increases the risk of respiratory infections[24-30], but for these children medical attention is sought for illnesses of a lesser degree of severity as than for children who stay at home.[31 32]

Air pollution and active or passive smoking increase the risk of respiratory infections and complaints of the respiratory tract.[33-41] Inhalation allergy may increase vulnerability to respiratory tract infections.[42-44]

Stress increases the risk of respiratory tract infection[45] and affects the functioning of the immune system.[46]

Inadequate diet reduces resistance against infections.[47] Deficiencies of the vitamins A and D weaken the epithelial barrier and protein-deficiency reduces the production of immunoglobulines.[48] Iron-deficiency also diminishes defence against infection.[49]

Breast fed infants in developed countries seem not to have fewer respiratory infections than bottle fed ones, but the severity of the illnesses may be less.[50-52] Prolonged breastfeeding (longer than six months) does have a protective effect against acute purulent otitis media.[27 53] Bottle feeding in a lying position increases the risk of otitis media.

Several studies have identified family history of middle ear disease as an important risk-factor for recurrent otitis media.[33 54 55]

Children suffer from upper respiratory tract infections more often than adults. The first child in a family usually contracts respiratory infections at a later age and less frequently than subsequent siblings. Otitis media is most prevalent in infants and young children and is much less common after the age of 6 to 7.[12 56] At young age, the incidence of otitis media is slightly higher in males than in females.[22]

1.3 Explanations for young age as a risk-factor

Young age has a profound influence on the risk of contracting a respiratory infection. The frequency of respiratory tract infections usually declines after the sixth birthday. Social factors modify this association; the first child in a family usually contracts respiratory infections at a later age and less often than subsequent siblings. The eldest child of the family reaches his or her peak in the frequency of respiratory tract infections during the period that he or she mixes with other children, either at school or in the creche.[57]

The most important cause of the high frequency of respiratory tract infections in small children is probably the relative incompetence of their immunesystem. In the first years of life a child meets many pathogens to which he or she subsequently learns to produce anti-bodies. After five years, the child's immune-system is equipped to combat many pathogens more rapidly and efficiently.[58]

Another cause of the high frequency of respiratory tract infections is the high exposure rate to pathogens at schools and in creches because of crowding.[29] The high passing-rate of the pathogens within school- and creche-communities possibly makes them also more virulent, able to cause more severe illness.

Apart from the functioning of the immune-system, anatomic factors play a key role in the clinical course of respiratory disease: the diameter of the air-passages is relatively small in children and this interferes with draining mechanisms. The anatomical characteristics of the Eustachian tube in children probably play a role in their vulnerability to middle ear infections: the tube has a more horizontal course, is shorter and wider than in adults and ends more distally in the nasopharynx. These factors facilitate pathogens to enter the middle-ear cave.[59]

1.4 Recurrent upper respiratory tract infections in children

1.4.1 Definitions

What is the borderline between a 'normal' and an excessively high frequency of infection episodes? There is no straightforward answer to this question.[60-62] Not only the frequency in a defined period of time, but also the total time span the child has been suffering from the episodes, as well as their duration and severity and the age of the child must be taken into account in answering this question. Recurrent infections should be differentiated from chronic infections with acute exacerbations and from recurrent manifestations of allergy.[1 63] Recurrent infections are separated by intervals of full resolution. This may however, be difficult to assess.

In the literature the criteria which authors use to define excessively frequent bouts of upper respiratory tract infections vary. Most studies supporting either medical or surgical prophylaxis for recurrent otitis media have used entrance criteria of three or more episodes of acute otitis media within six months, or four or more episodes in one year.[64] Children who suffer very frequent middle ear problems are called 'otitis-prone' by some authors.[65-67] Feldman refers to recurrent otitis media when there are more than three episodes per year, and to recurrent streptococcal sore throats when their frequency is greater than four episodes per year.[68] The eligibility for the Pittsburgh trial on the effect of tonsillectomy for recurrent throat infection, was: seven or more episodes in the preceding year, five or more in each of the preceding two years, or three or more in each of the proceeding three years.[69]

1.4.2 Susceptibility to URTI

Recurrent upper respiratory tract infections are generally not indicative of a serious underlying systemic disorder if no infections in other tracts occur, and therefore these do not usually require extensive laboratory investigation.[70-72] It may be sensible though, to check for anaemia, as frequent infections promote anaemia, and anaemia again, makes people more vulnerable to infections.

Infrequent systemic causes of recurrent respiratory tract infections are: mucoviscoidosis, ciliary dyskinesia and immunodeficiencies, for instance IgG subclass deficiency.[73 74] In case of these underlying anomalies, the lower respiratory tract is usually involved too. Local anatomic anomalies such as palatoschisis increase the individual's vulnerability to infections of the upper respiratory tract. Atopic children seem to be more vulnerable to respiratory tract infections than children who do not suffer from atopy.[44]

In children with recurrent otitis media, a familial predisposition for this condition in childhood is frequently encountered. [12 55 58] The mechanism of this susceptibility is however still unclear. Children who experience their first otitis media before their first birthday, run a greater risk of recurrences than children who experience their first episode of otitis at an older age. [75 76]

Recurrent sore throats are seen mainly in children aged 9 to 10 years and also in adolescents. The condition seems to be worsened by maternal smoking. [39]

Several, yet unknown factors might contribute to an increased constitutional susceptibility to respiratory infections. We may not yet be able to detect minor immunodeficiencies or retardation in the ripening of the immunesystem. Unfavourable conditions (extrinsic risk factors) may worsen an individual constitutional susceptibility. Infection with certain pathogens at a young age may predispose to increased susceptibility to respiratory tract infections at a later age. But on the other hand, susceptible children may contract infections with these pathogens at a younger age than non-susceptible children. Iatrogenic damage might even add to the risk of recurrences of respiratory infections; repeated courses of antibiotics, for instance, might cause a shift of bacteria on the mucous membranes to more potential pathogens or might diminish IgA concentrations on membranes. [77]

Söderström and his colleagues followed 41 schoolchildren who had recurrent respiratory tract infections as preschoolers and 29 children of the same age and socio-economic background. [62] They collected data through diary reports by parents and medical consultations. During the two years of follow-up, a greater number of episodes of respiratory tract infection and a longer mean duration of such episodes were reported in the children with recurrent bacterial respiratory infections as preschoolers as compared with the controls. The annual recurrence rate of respiratory infections decreased with age among the children with recurrent episodes as preschoolers, whereas in the control group the incidence remained consistently low. Acute otitis media was the predominant bacterial respiratory tract infection in pre-schoolers, and acute tonsillitis in school-age children. The children with recurrent bacterial respiratory infections as preschoolers also had more other diseases. The authors conclude that their findings suggest that certain children are susceptible to respiratory tract infections and other illnesses over a rather long period of years. These findings are in accordance with the clustering of morbidity that was found in a follow-up study of children. [78] This tendency might even go on into adult life. A study among Swedish men in their sixties, revealed that men who suffered from otitis media in their youth had more health problems in their adult life than men who did not suffer from otitis media at a young age. [79]

Söderström compared prevalences of various diseases in families of children with frequent respiratory tract infections and children who did not suffer from these problems. [60] Diseases occurred more frequently in the families of children with recurrent respiratory tract infections and this particularly applied to cardiovascular diseases. These findings suggest that children who are susceptible to upper respiratory infections frequently belong to vulnerable families.

1.4.3 Related problems

Recurrent upper respiratory tract infections in a child may give rise to several related somatic, psychological and social problems.

One of the consequences may be prolonged hearing loss. Several studies have shown a correlation between the number of episodes of upper respiratory tract infection and otitis media with effusion. [81-85] Children who suffer from recurrent acute otitis media have an increased risk of otitis media with effusion. [86] Otitis media with effusion, also known as serous otitis media, is characterized by the accumulation of fluid in the middle ear behind an intact tympanic membrane without distinct local or general signs of an infection. [87] Chronic middle ear effusion however, is found not to be sterile, as previously hypothesized. [88] Microbiological examinations are positive in 20-75%. [89 90] It is not yet clear, whether otitis media with effusion predisposes to acute otitis media or acute otitis media predisposes to otitis media with effusion, or whether both are two different expressions of the same underlying process.

In most children otitis media with effusion is a self-limiting problem. [91 92] In 7-9% of children with otitis media with effusion though, episodes last from several months to several years. [93]

Otitis media with effusion causes hearing loss which, if prolonged, endangers the social, linguistic and cognitive development of the child. [94-98]

Frequent respiratory tract infections may lead to hypertrophy of adenoids and subsequently to (partial) obstruction of the choanae, mouth breathing [99 100], snoring, hyponasal speech and in extreme cases even to the obstructive sleep apnoea syndrome, alveolar hypoventilation and cor pulmonale.

If the adenoid causes severe obstruction or is chronically infected, adenotomy reduces morbidity and complaints. [101 102] Tonsillar hypertrophy less often causes severe obstruction which compels the removal of the palatal tonsils. [103]

Respiratory tract infections in children often causes stress in their families [104 105] and conversely, stress in families may promote respiratory tract infections in children. [106]

Frequent illness in a child may provoke fear, worry and insecurity in parents and consequently they may behave over-protectively towards their offspring. [107] The reactions of the parents are likely to influence the health of their child in some way. [108] The way in which parents react to a problem of their child not only depends on the nature and magnitude of the particular problem, but also on the personality of the parents, their experiences and their circumstances. The decision of whether or not to seek professional medical advice, for instance, is not only based on the severity of the symptoms, but also (or maybe even more so) on the emotional state of the parents and the advice of neighbours, family and friends and former experience with members of the medical profession. [109-111]

It has been suggested by some authors that minor respiratory symptoms in children may just serve as a smokescreen to seek help for other problems, that parents may use the simple symptoms of their child to gain entry into the consulting room of their general practitioner in order to gain his or her attention for another, embarrassing predicament or a problem that they find difficult to formulate. To what extent this really is the case, is difficult to find out. Others state that the parents of children with a high number of visits to their general practitioner for respiratory complaints were, generally, not more action-prone in the case of respiratory complaints than other parents. [112]

It seems evident however, that parents who wrestle with personal problems, may not be able to cope at the same time with the stresses and strains of caring for a child with respiratory problems, even if these are judged to be 'mild' by medical professionals. A study by Howie revealed a correlation between high use of antibiotics for children with recurrent respiratory tract infections and the high use of psychotropic drugs by their mothers. [113] It may be hard to cope with an ill or listless child during the day and meanwhile do the work that has to be done, while the nights are also being disrupted.

1.4.4 Intervention and management

Several methods of intervention to prevent recurrences, thereby disrupting the cycle of infections, have been proposed and studied. The three main prophylactic measures are: passive and active immunization and chemoprophylaxis. A fourth measure promoted by some physicians and many laymen, is the employment of homoeopathic remedies, which is the subject of our present study. Furthermore, surgical procedures are employed to combat focal infections and to reduce certain negative effects of recurrent infections.

Advice and support are necessary constituents of the care of all children with recurrent URTI and might have a favourable effect on the recurrence rates.

In a double-blind placebo-controlled study conducted by Christensen, active immunisation with pneumococcal vaccine was shown to have only a small positive effect on the recurrence rate of upper respiratory tract infections in children aged between 2 and 5 years. In smaller children, no positive effect on the recurrence rate was found. [114] Polyvalent pneumococcal vaccine has little or no effect on the overall rate of acute purulent otitis media in children. [115-117]

Passive immunization has many hazards and drawbacks and its efficacy in children with recurrent upper respiratory tract infections has not been demonstrated. [118-120] In the case of isolated IgG subclass deficiency human immunoglobulin is sometimes given. [121]

Several controlled studies of chemoprophylaxis have demonstrated efficacy in the prevention of acute symptomatic purulent otitis media. [66 122 123] However, chemoprophylaxis has its own hazards, i.e.: the emergence of resistant strains of bacteria and the possible side-effects of the drugs. [124-126] In case of acute rheumatic fever, which nowadays occurs infrequently, chemoprophylaxis is always employed to prevent new ß-haemolytic streptococcal infections.

Homoeopathic physicians claim a great success of homeopathic remedies in preventing recurrences of infections. This study focuses on their effect in children with recurrent upper respiratory tract infections. Information on homoeopathy is given in *chapter 2*, the homoeopathic method is described in *chapter 3* and the results are presented in *chapter 4*.

Surgical procedures are employed to clear chronic focal infections and to repair long lasting damage of respiratory infections.

Maw's randomised study with a 3 year follow-up showed a beneficial effect from removal of the adenoid in children suffering from glue-ear. [127 128] As already noted under the heading 'related problems', adenotomy reduces morbidity and complaints if the adenoid causes severe obstruction or is chronically infected. [103] Tonsillectomy is performed in recurrent tonsillitis. [129] However, indications for tonsillectomy and adenotomy are still a controversial subject. [130]

In a child with persistent glue ears the insertion of tympanostomy tubes improves hearing, prevents accumulation of effusion and allows the mucous membrane to recover. [131-133] If tubes have to be placed more than three times, some specialists prefer not to replace them but instead to supply the patient with a hearing-aid and to regularly examine the patient. [134]

Treatment with transmyringeal tubes has also been shown to reduce the number of episodes of acute otitis media in most otitis-prone children. [135-136]

Advice and support

Careful examination, a clear medical explanation and the mental support of the child and his or her parents helps them to cope with the health problems and thereby reduces stress.[71] Reduction of stress might lead to a reduction of recurrences, but as far as we know, there is no evidence from investigations on this possible relationship.

Advice on adequate nutrition seems important in this group of children as inadequate nutrition enhances vulnerability.

Damage to the child's development by recurrent URTI and their sequelae should be prevented. Special attention should be payed to the child's linguistic development. The risk for impaired linguistic development may be reduced by compensatory measures.

If children must undergo surgery, it is very important to provide them with good psychological preparation for the event. Children should be accompanied by familiar people (e.g. parents) during their stay in hospital in order to reduce the psychological trauma that the experience may induce.[137 138]

1.5 Anatomy and physiology of the upper respiratory tract

The respiratory tract and its various appendages (sinuses, middle ear) form an anatomical continuity from nose to lungs.[139] The respiratory tract serves respiration: the uptake of oxygen for metabolism from the environmental air and the excretion of carbon-dioxide, a product of metabolism. This exchange takes place in the alveolar system, where the interface between environmental atmosphere and the internal vascular system is found. The rest of the respiratory tract forms the conducting passage for ventilation. In the air-passages inspired air is conditioned: purified, brought to body temperature and saturated with water.

The respiratory tract is traditionally divided into the upper respiratory tract (from nose to larynx), the middle respiratory tract (larynx and trachea) and the lower respiratory tract (the bronchial and alveolar system). The upper respiratory tract consists of the nose and its appendages, the pharynx and the glottis.

The respiratory tract and its appendages are derived from the endodermal lining of the embryologic foregut.[140]

1.5.1 The muco-ciliary clearance mechanism

The muco-ciliary clearance mechanism is one of the major defences of the respiratory tract.[141 142]

The epithelium of the mucous membrane of respiratory tract is in most sites ciliated columnar epithelium. This type of epithelium is called respiratory epithelium. It contains ciliated cells and non-ciliated cells. Among the non-ciliated cells there are mucus-secreting (goblet) cells. Submucosal glands however, produce most of the mucus in the respiratory tract.

The epithelium is covered by a 'mucus blanket' which consists of an inner layer of serous fluid and an outer layer of mucus. This 'mucus blanket' is continuously transported by the cilia of the ciliated epithelial cells towards the pharynx. The ciliary movement consists of a vigorous, rapid and effective stroke during which the cilia are rigid, and a less vigorous, less rapid recovery stroke during which the cilia are relatively limp. The velocity of the movement of the mucus differs in the various parts of the respiratory tract. In the trachea, the average velocity is estimated as 10-24 mm/min, in the nose 4.5-7.0 mm/min, in the pharyngotympanic tube 0.7-1.1 mm/min and in the bronchioli 0.5-2.0 mm/min. There is a great inter-individual variability and a small intra-individual variability in the velocity of the mucusblanket.[143]

Most air-borne particles out of the inspired air are suspended in the mucus and removed to the oropharynx by the ciliary transport mechanism. From the oropharynx the mucus disappears into the stomach by swallowing. Most micro-

organisms cannot survive in the acid contents of the stomach. Only particles smaller than 2 μm are likely to reach the terminal portion of the airway.

1.5.2 The nose

The functions of the nose are air-conditioning (i.e. purification, humidification and warming of inspired air), regulation of the resistance of the inspired air, olfaction and provision of vocal resonance for speech.

The nose consists of two nasal cavities separated by the nasal septum. Each nasal cavity is subdivided into three parallel meatus by three turbinates (shelf-like structures): the superior, middle and inferior meatus. The nasal turbinates divert the incoming air-stream. [141 144]

The nasal cavities are connected with the nasal sinuses through ostia and small ducts. The frontal, maxillary, and anterior ethmoid sinuses open into the middle meatus, the sphenoid and posterior ethmoid cells open into the superior meatus. The anterior third of the nasal cavity, the vestibule, is lined with non-keratinizing squamous or transitional epithelium, the remainder, except for the olfactory area, is lined with ciliated pseudo-stratified columnar epithelium.

The nasal mucosa is highly vascular with abundant arterio-venous anastosmoses and cavernous sinusoids, particularly over the turbinates. The vasculature is capable of intermittent engorgement, causing an increase in nasal resistance to air flow. Its smooth muscle is primarily under sympathic nervous control.

Air entering the nostrils is first filtered through the hairs in the vestibule. Big suspended particles are deposited in this anterior part, most smaller particles are removed by the mucociliary transport mechanism. All particles of 5 μm or more in diameter, about half of the particles of 2-3 μm in diameter and no particles of 1 μm or less in diameter are filtered out by the nose.

1.5.3 The paranasal sinuses

The paranasal sinuses are, like the nose, lined with ciliated respiratory epithelium which are continuous with the respiratory epithelium in the nasal cavity. [145] They are situated around the nose and adjoin the orbits and anterior cranial fossa and comprise the maxillary and ethmoid, the frontal and sphenoid sinuses. The frontal and sphenoid sinuses are not clinically significant until late childhood.

The frontal sinuses, situated in the frontal bones, are extremely small or absent at birth, fairly well developed by 10 years of age and fully developed by 20 years of age. Each drains into the anterior middle meatus.

The maxillary sinuses also drain into the middle meatus. The roof of the maxillary sinus borders the orbita and the floor of this sinus is closely related to the three molar teeth. The maxillary sinuses are present in the newborn and grow in lateral and caudal direction until the age of 15 years.

The ethmoidal sinuses are thin walled cavities between the upper parts of the nasal cavities and the medial walls of the orbit. The anterior and middle ethmoidal sinuses drain into the middle meatus, the posterior ethmoidal sinuses drain into the superior meatus. The ethmoidal sinuses are already partly present in babies and are fully developed by the age of 12 years.

The sphenoidal sinus lies behind the distal part of the nasal cavity and immediately below the pituitary, and it drains into the superior meatus. The sphenoidal sinus starts growing into the os sphenoidale by the age of 4 years. It is fully developed by the age of fifteen.

1.5.4 The pharynx

The pharynx is a passageway which serves two systems: the respiratory and the digestive system, and is also important for speech.

The pharynx, which is funnel shaped and broadest in its upper end, is situated behind the nasal cavities and the mouth and above the larynx. Three parts of the pharynx are defined: the nasopharynx, the oropharynx and the hypopharynx. In the newborn the nasopharynx, oropharynx and hypopharynx form a straight tube. In the adult, the nasopharynx and oropharynx almost form a right angle. [146] Around the nasopharynx and the oropharynx is a ring of lymfoid tissues (Waldeyer's ring).

The nasopharynx lies behind the nasal cavities, above the level of the soft palate and contains in its lateral walls the openings to the Eustachian tubes. It connects the nasal cavity and the oropharynx. The nasopharynx is lined with ciliated respiratory epithelium. In the mucous membrane of the roof of the nasopharynx lies the nasopharyngeal tonsil or adenoids, a collection of lymphoid tissue, covered with pseudostratified ciliated respiratory epithelium. It increases in size after birth up to the age of 6 or 7 years after which it usually begins to atrophy. The enlargement of the adenoids in young children is related to immunologic responses to infections. There is an increase in the number of cells in the parenchyma. [147]

The oropharynx reaches from the soft palate to the upper border of the epiglottis. Its lateral walls consist of the palatopharyngeal arches and the palatine tonsils. The oropharynx is lined with stratified squamous epithelium. The free surfaces of the palatine tonsil, including the tonsillar crypts, are also covered with stratified squamous epithelium. The palatine tonsils increase in size during the first five years of life and their involution begins at puberty.

On its anterior aspect, the hypopharynx includes the inlet of the larynx with a small recess, the piriform fossa on each side of the laryngeal orifice. It is lined

with stratified squamous epithelium.

The entrance of the respiratory and digestive system is guarded by a circular band of lymphoid tissue: Waldeyer's ring.[148] Waldeyer's ring plays an important part in the immunologic defense of the respiratory and digestive tract.[148-151] Its anterior and lower part is formed by the lingual tonsil, its lateral portions are formed by the palatine tonsils and the lateral pharyngeal band of follicles, its posterior and upper part is formed by the adenoids. The pharyngeal lymphoid tissue has no afferent lymph channels. Numerous efferent lymphatics drain from the tonsillar tissue to the superior cervical lymph nodes. The tonsils contain B lymphocytes capable of producing all major classes of immunoglobulins as well as T lymphocyte subsets and various antigen presenting cells.[152]

1.5.5 The pharyngo-tympanic or Eustachian tube

The Eustachian tube connects the nasopharynx to the middle ear. It is directed upwards, backwards and outwards from its opening in the lateral wall of the nasopharynx towards its opening in the anterior wall of the tympanic cavity.

In newborn children the pharyngo-tympanic tube is wider, shorter and more horizontal in direction than in adults and its pharyngeal opening lies in a more caudal position.[153] These anatomical differences probably contribute to the susceptibility of young children to middle-ear infections (see *1.3*).

The epithelium of the Eustachian tube is of the ciliated type, varying from simple columnar at the tympanic end to pseudostratified near the nasopharynx.

The Eustachian tube has three main functions relating to the middle ear: regulation of air pressure in the middle ear, drainage of middle ear-secretions into the nasopharynx and protection of the middle ear from nasopharyngeal sound pressure and secretions.[154] The tube opens intermittently due to the contraction of the tensor veli palatini muscle during swallowing. Active muscular opening function was found to be deteriorated in children during upper respiratory tract infection.[155] Obstruction (mechanical, functional or both) or increased patency of the Eustachian tube usually causes middle ear problems.[156]

1.5.6 The middle ear

The middle ear cavity has the form of a biconcave disc. The mucous membrane of the middle ear cavity is continuous with the mucous membrane of the Eustachian tube and the mastoid antrum. In the anterior-inferior part of the tympanic cavity the epithelium is respiratory in type (ciliated columnar). Above and behind this level the epithelium is of a single non-ciliated cuboidal type. In the antrum and peri-antral cells, the epithelial cells become reduced to a single row of flattened squamous cells.

The tympanic membrane consists of three layers: the outer epithelial layer which is continuous with the skin of the auditory canal, the middle fibrous layer and the inner mucosal layer.

1.6 Host defence mechanisms

An infection occurs when pathogenic micro-organisms penetrate into the tissues of the host and are able to survive and replicate there. This means that during infection, the offensive power of the micro-organism (determined by number and virulence) is initially greater than the defensive power of the host. If the host conquers the invaded micro-organism healing subsequently follows. If the host is not able to eliminate the micro-organism, a carrier-state, a chronic infection, or even death may result.

Man has several defence-mechanisms against pathogenic micro-organisms that work closely together.[157 158] The defence mechanisms of the upper respiratory tract include mechanical protection[159] (aerodynamic filtration in the nose, ciliary movement, swallowing, sneezing, coughing), protection provided by the activity of the normal bacterial flora, non-specific biochemical protection (lysozyme, mucopolysaccharide, etc), and immunological protection (secretory IgA, complement, macrophage, etc).[160] Another classification of the human respiratory defences distinguishes three barrier-lines against infection: the first line is the epithelial barrier, the second line is the non-specific or innate immunity and the third line is the specific or adaptive immunity.[161 162]

1.6.1 The first line of defence

In the respiratory tract, the first line of defence is formed by the respiratory epithelium with the muco-ciliary clearance mechanism which is described above.

Particles with a diameter greater than 1 μm are trapped in the mucus blanket and transported towards the oropharynx from where the mucus disappears into the stomach, in which most pathogens are unable to survive. Since viral upper respiratory tract infections result in transient loss of cilia, they may cause impaired mucociliary clearance for several weeks. This most especially applies to infections caused by influenza viruses.

The mucus on the epithelium contains several substances produced by the second and third defence-lines which prevent the growth of pathogenic micro-organisms: lactoferrin which binds iron so that pathogens cannot get enough iron to permit growth, lysozyme which destroys the cell walls of Gram-positive pathogens, and secretory IgA which prevents the adhesion of recognised pathogens to

the epithelium and inhibits the absorption of bacterial toxins. Secretory IgA also agglutinates bacteria and partially suppresses their multiplication. [163-165] Further detail about secretory IgA will be given in the section about the third line of defence.

During viral infections interferon is formed by infected cells. Interferon prevents the replication of the virus in other cells and is a non-specific defence-mechanism.

Pathogens are also prevented from adhesion by commensals which have colonised the various parts of the respiratory tract. [166 167] Very few micro-organisms are found in the lower respiratory tract of the healthy. [160] In the upper respiratory tract various commensals are found in different sites.

However, in many healthy persons potentially pathogenic bacteria are also found in the nose and throat. They have a commensal-like relationship with the host who is called 'carrier'. Haemophilus influenzae [168] and Streptococcus pneumoniae are often found in the throat of healthy persons and Neisseria meningitidis is also regularly detected. [169]

1.6.2 The second line of defence

When a micro-organism breaches the epithelial barrier and reaches the subepithelial tissues, it encounters the second line of defence which is formed mainly by the complement system, phagocytic cells and natural killer cells.

Apart from these defence mechanisms, the intercellular tissue fluids do not favour settlement and replication of pathogens. There is little free iron available for replication of pathogens and the continuing stream of tissue-fluid takes microbes to the regional lymphnodes.

The complement system is a complex enzyme-system present in the serum. When it is activated, it mediates and amplifies inflammatory response (release of vasoactive substances from mast-cells, leucotaxis), immune reactions (opsonisation) and lysis of viruses, infected cells and certain bacteria.

The complement system can be activated by antigen-antibody complexes (classical pathway) and by many bacterial products and viruses (alternative pathway). The first activated enzyme splits the next component in the pathway and so on. The progressive increase in the number of molecules of successive components produces a cascade reaction. One single molecule of activated C1 generates thousands of molecules of the later components, the final response is thus greatly amplified. The complement sequence is however controlled by a number of built-in safety devices and inhibitors. Moreover the activated components have a short half-life and do not spread throughout the body.

Phagocytic cells include polymorphonuclear leucocytes (particularly neutrophils), blood monocytes and macrophages including tissue histiocytes; they are all derived from the same stem cells.

The neutrophil leucocyte has a brief life-span (its circulating half-life is 7 hours), is metabolically active and demonstrates marked chemotaxis to some bacterial products, complement-components and products of the inflammatory processes. Blood monocytes assume the characteristics of macrophages when they leave the blood circulation and reach inflammatory sites. Macrophages live longer than neutrophils and can resynthesize lysosomal enzymes and successively attack phagocytosed micro-organisms or debris from the infective process. They also cooperate with cells of the lymphoid immune system.

The process of phagocytosis is greatly enhanced by the presence of specific IgG and IgM and non-specific complement. This phenomenon is known as opsonisation.

Macrophages are triggered by micro-organisms to produce monokines called interleukin-I. [170] Interleukin-I stimulates the release of neutrophil leucocytes from the bonemarrow into the blood, it stimulates the metabolism of the neutrophils, activates the B- and T-lymphocytes and stimulates the production of proteins in the liver and of prostaglandin E2 in the hypothalamus. [171 172] Prostaglandin E2 affects temperature regulation by the hypothalamus which results in a rise of the body temperature. Rise of body temperature probably has a favourable effect on the host's recovery from the infectious process, for it activates the immunologic reactions and inhibits the growth of many micro-organisms. [173 174]

Natural killer cells are immunologically non-specific leukocytes with the capacity to kill virus-infected cells.Their exact role in viral infections has not yet been established.

1.6.3 The third line of defence

The third line of defence consists of specific immune mechanisms: humoral and cell-mediated immunity. [175 176] Humoral immunity involves the production of antigen-specific antibodies by plasma cells derived from B-lymphocytes [177] and cellular immunity is provided by T-lymphocytes.

B-lymphocytes ripen in the bone marrow, they constitute 5-15% of the circulating lymphocytes, tending to accumulate in the lymphoid follicles and germinal centres of the lymph nodes and also in the white pulp of the spleen. The final product of B-cell differentiation is the plasma cell which, under certain conditions, produces

immunoglobulin in response to an antigen.

Five classes of immunogobulins have so far been discovered in man: IgM, IgG, IgA, IgE and IgD. [178] Four subclasses of IgG have been identified [179], of which subclasses IgG2 and IgG4 seem to be the most important in defending the body against infections. [121 180 181]

IgA is produced by plasma cells (derived from B lymphocytes) in the subepithelial tissues in response to an antigen and is transported through the epithelial lining of the mucous membrane. IgA is provided with a secretory piece by these epithelial cells. Secretory IgA only has an effect on the pathogen that triggered its production. Secretory IgA plays an significant role in the defence against respiratory pathogens.

T-lymphocytes are responsible for cell-mediated immunity and are also necessary for some humoral responses (T-helper cells which modulate B-cell response). In addition, T-cells produce soluble factors called lymphokines which trigger inflammatory reactions.

T-lymphocytes originate from the same stem cell as B-lymphocytes, but they have migrated the thymus and undergone its modifying influence. They constitute 85-95% of peripheral blood lymphocytes and are present in lymph nodes and the spleen. There are different subsets of T-lymphocytes: T-helper cells, T-suppressor cells and cytotoxic T-cells.

Immune response can be divided into three stages.

In the first stage (induction), the antigen is recognised as being foreign. Non-lymphocytic mononuclear cells act as antigen presenting cells and present the antigen to T-lymphocytes.

The second stage includes the production of antibodies and/or T-cells. In response to the recognised foreign antigen, the T-cells undergo clonal expansion and the B-cells expand and mature to plasma cells that produce specific antibodies.

Finally, in the third stage, the process of antigen elimination takes place through antigen-specific effector T-lymphocytes and antibodies.

When reinfection occurs, the immunological memory allows rapid production of specific antibody and rapid proliferation of T lymphocytes. [182]

1.7 Micro-organisms

It has been estimated that more than 90% of acute respiratory tract infections are primarily caused by non-bacterial agents. [4 183] More than 200 non-bacterial agents etiologically related to acute respiratory infections have been identified. Different viruses can produce identical syndromes and the same virus can produce different syndromes. [184] Severity of the illness is generally related to previous experience with the virus. [185 186]

Viral respiratory tract infections can be complicated by secondary bacterial infections. [187] Bacteria, however, are infrequently the primary invaders. Examples of primary bacterial infections are pertussis and streptococcal tonsillitis and lobar pneumonia.

Other micro-organisms that can cause respiratory tract infections in man are mycoplasma pneumoniae, chlamydiae and rickettsiae.

The viruses, bacteriae and other microorganisms that are most frequently isolated in respiratory tract infections shall be described, apart from the etiologic agents of systemic infections with a strong involvement of the respiratory tract, such as pertussis, measles, influenza and glandular fever.

1.7.1 Viruses

Respiratory viruses are transferred from one host to the next by either airborne transmission (myxoviruses and coronaviruses) or handborne transmission (rhinoviruses and adenoviruses) or a combination of both (enteroviruses).

Rhinoviruses are chiefly responsible for the common cold: about 50% of common colds are caused by rhinoviruses. [188] In children, rhinoviruses can occasionally cause lower respiratory infection. [5] The rhinovirus replicates with maximum efficiency at a nasal temperature which is 33 to 34°C. More than 113 serologic types have been detected. A rhinovirus-infection does not give immunity against other serologic types of the rhinovirus. Transmission of rhinoviruses mainly takes place via contaminated subjects. [189]

It is estimated that the coronavirus causes up to 30% of common colds. [190 191] Influenza viruses may, in some individuals, cause localised respiratory tract infections instead of influenza. This applies particularly to influenza-C viruses. Para-influenza viruses are associated with croup in small children. The initial infection may cause a febrile respiratory disease, often with involvement of the lower respiratory tract, while later infections cause only mild upper respiratory tract symptoms.

The respiratory syncytial virus (RSV) is a threatening respiratory pathogen for young children. [192] The respiratory syncytial virus can cause serious disease in in-

fants: croup, bronchitis, bronchiolitis and pneumonia. In older children and adults, RSV may cause mild upper respiratory tract infections and otitis media. [193]

Adenoviruses cause respiratory tract infections, often pharyngitis combined with conjunctivitis, also bronchitis and pneumonia with structural damage to the bronchi (bronchiectasies). Acute pertussis-like paroxysmal cough has also been attributed to adenovirus-infection. Adenoviruses produce viraemia. After the acute stage, they stay in the body of the host as a latent infection. Outbreaks of adenovirus-infections occur mainly in institutions like military recruit-camps. [194]

Coxsackieviruses have been identified in herpangina (group A) and in febrile respiratory infection with cough and nasal discharge (group B).

ECHO viruses can cause mild upper respiratory tract infections as well as enteric infections.

The herpes simplex virus is one of the agents that may cause acute pharyngitis accompanied by vesicles or ulcers; although it more often causes vesiculous stomatitis in children. A first infection is dangerous for very small children since it may affect the central nervous system, resulting in a fatality.

The cytomegalovirus may cause pneumonia.

The Epstein Barr virus causes tonsillopharyngitis in infectious mononucleosis.

Table 1.5 *Viruses in acute respiratory tract disease in man*

Orthomyxoviruses:
Influenzaviruses types A, B, C.
Paramyxoviruses:
parainfluenzaviruses types 1, 2, 3, 4.
measles virus
respiratory syncytial virus
Picornaviruses:
rhinoviruses
enteroviruses
coxsackieviruses
ECHOviruses
Herpesviruses:
herpes simplex viruses types 1, 2
herpes varicellae viruses
cytomegalovirus
Epstein Bar virus
Adenoviruses
Coronaviruses

1.7.2 Bacteriae

In the following, the most commonly found bacteria in upper respiratory tract infection shall briefly be described. [195] Pathogens are also often isolated from the upper respiratory tract of healthy children. [196 197]

Haemophilus influenzae is a small gram-negative pleomorphic bacillus found in encapsulated and nonencapsulated forms. Virulent H.influenzae posess a type-specific capsular polysaccharide of which 6 distinct antigenic types have been identified: a through to f. [198] Strains of type b cause serious invasive infections like meningitis, epiglottitis, orbital cellulitis, buccal cellulitis, arthritis, osteomyelitis, pericarditis and, more rarely, endocarditis. Nonencapsulated Haemophilus cause sinusitis, otitis, bronchitis and pneumonia. Otitis media in children is frequently caused by non-typable haemophilus influenzae. [199-201]

Streptococcus haemolyticus is considered to be an important pathogen in throat infections [202 203], thus it will be discussed more elaborately in the following.

Streptococci are gram-positive cocci with characteristic colonial morphology. The classification of streptococci is based on two characteristics: the type of haemolysis produced on blood agar and the cell-wall carbohydrate (the last according to Lancefield's grouping system lettered A-H and K-V).

The streptococci secrete toxins and enzymes such as streptokinase, deoxyribonuclease, streptolysin S and O, hyaluronidase and erythrogenic toxin.

Type-specific M surface proteins and erythrogenic toxins stimulate the production of specific antibodies. A person who is infected with a given type of streptococcus develops antibodies against strains of the same type only. Antitoxic immunity is, however, group- rather than type-specific.

The optimal temperature for growth of the streptococcus is 37° C and it is inhibited at temperatures above 40° C. This implies that a fevered host provides unfavourable conditions for the streptococ.

Streptococci circulate in families and close communities [204] and by circulating they possibly increase in virulence. Healthy people can be carriers: streptococci live on their pharyngeal mucous membrane, but do not penetrate into their tissues. Carriers are the chief source of pathogenic streptococci. The streptococci are spread by airborne droplets formed during sneezing and coughing and are transmitted directly to the next host by inhalation of the contaminated droplets, or indirectly by touching contaminated objects and subsequently transfering the micro-organisms by the hands to the nose.

Group A ß-haemolytic streptococci are responsible for a large variety of diseases in childhood, including tonsillitis, scarlet fever and erysipelas. These

diseases range in severity from trivial to life-threatening. They often give rise to constitutional symptoms, fever and the production of purulent material.

Age seems to be an important factor in the clinical syndrome caused by streptococci. In infants younger than 6 months streptococci can cause a syndrome that may be almost indistinguishable from the common cold [43]: mucopurulent nasal discharge with excoriation of the nares and irregular rises in temperature. The acute symptoms may last for 1 week and the nasal discharge for up to 6 weeks. In older babies and toddlers streptococci may cause nasopharyngitis with purulent discharge which is often complicated by sinusitis or otitis media. The anterior cervical lymph nodes are usually enlarged and quite tender. This may be accompanied by a low grade fever which may continue for as long as 8 weeks. In children aged 3 to 12 years, streptococci usually cause tonsillitis and scarlet fever. Scarlet fever manifests very acute symptoms: fever 39-40°C, vomiting, sore throat, headache, chills, malaise, abdominal pain. Within 12-48 hours after onset, the familiar skinrash appears. In older people streptococci may provoke a much less fierce and characteristic syndrome.

Late complications of streptococcal infection are rheumatic fever and acute glomerulonephritis. These complications develop after a latent period of 1-3 weeks. Nowadays their incidence is low. [205] They may follow inapparent, subclinical infections as well as severe infections and their incidence is not related to the severity of the initial infectious disease.

The treatment of every patient who is possibly having a streptococcal infection with penicillin is controversial. Advocates of penicillin treatment emphasise the prevention of rheumatic fever, whilst others suggest that the risks of penicillin treatment may exceed the risk of complicating rheumatic fever. [206] Patients who have suffered from acute rheumatic fever are given continuing penicillin prophylaxis. [207] Acute glomerulonephritis is probably not prevented by penicillin treatment. Antimicrobial treatment does reduce the risk of transmission.

Streptococcus pneumoniae is a gram-positive cell surrounded by a polysaccharide capsule. [208] The capsule acts as a protective shell against phagocytes and is a significant factor in the virulence of the organism.

Pneumococci are common inhabitants of the normal upper respiratory tract. A viral respiratory tract infection predisposes the respiratory tract to invasive pneumococcal infection. The same applies to the inhibition of mucociliary function by allergy, irritants and other agents.

Pneumococci are responsible for most bacterial pneumonias. In children they also cause otitis media, mastoiditis and sinusitis and infrequently meningitis, cellulitis, peritonitis, arthritis, osteomyelitis, endocarditis and pericarditis. [209]

Branhamella catarrhalis, also named Neisseria catarrhalis, has emerged as a human pathogen in the past decade. In 1970, a new genus, Branhamella, was named in honour to Dr. Sarah Branham. [210] The organism is the third most common cause of otitis media in contemporary children. [211,212] It is also found in sinusitis. [213] It may protect itself as well as other micro-organisms from the action of penicillin by producing bèta-lactamase.

1.7.3 Other organisms

Other organisms include mycoplasms, rickettsiae and chlamydiae.

Mycoplasms are ubiquitous, free living organisms found in many animals and plants. [214] They are unable to synthesize a cell wall but they can grow on cell-free media. Mycoplasms contain RNA as well as DNA. Mycoplasma pneumoniae cause respiratory disease in man, most particularly they cause atypical pneumonia, but also mild upper respiratory tract infection, bronchitis, bronchiolitis, bronchopneumonia and myringitis bullosa. [215] The organisms remain extracellular, but they exert a toxic effect that interferes with ciliary function of respiratory epithelial cells and mucosal cell metabolism.

Rickettsiae are obligate intracellular gramnegative bacteria that multiply in arthropod vectors; the blood eating habits of these vectors involve their vertebrate host in the complex life cycle of these microorganisms. [4]

Coxiella burnetti may also cause atypical pneumonia.

Chlamydiae are small intracellular obligate parasites which posess a cell wall and contain both RNA and DNA. Chlamydia psittaci may cause atypical pneumonia and Chlamydia pneumoniae may give rise to pneumonia as well as acute upper respiratory tract infections. [216]

1.8 Clinical syndromes of upper respiratory tract infection

Classification of a clinical syndrome caused by respiratory tract infection is not always easy. Since infection is a process, it is related to time and causes a changing syndrome. Respiratory infections develop and extend sequentially in an anatomical way. Depending on the date of examination, the same infection episode might, in fact, clinically be classified differently. Apart from these changes over time, inter-individual and intra-individual variation in perception and interpretation of symptoms can also yield differences in naming a syndrome. Individuals perceive and stress symptoms and signs in different ways; one's attention may centre on the symptoms or signs originating from one particular site. Apart from variation in naming the syndromes, there is a great variation in the management of upper respiratory tract infections in general practice.[217]

A description of four different clinical syndromes of upper respiratory tract infections based on anatomical grounds will be given below: the common cold (coryza), acute sinusitis, acute otitis media and acute tonsillopharyngitis.[4 218-223]

The clinical syndromes of middle respiratory tract infections (acute laryngitis and epiglottitis), lower respiratory tract infections (bronchitis, bronchopneumonia and segmental pneumonia) and agent-specific general infections like measles, influenza and mononucleosis infectiosa will not be described.

1.8.1 The common cold

Synonyms

coryza, acute catarrh, acute nasopharyngitis.

Definition

The common cold is a syndrome caused by a viral infection of the mucous membrane of the upper respiratory tract.[224 225]

Symptoms and signs

The pattern of symptoms varies between individuals but tends to be repetitive in separate episodes of the common cold in any given individual. The common cold usually causes sneezing and nasal discharge, which is at first watery and clear, but after a few days becomes mucopurulent. The nose may become blocked and the throat dry and sore. There may be an unproductive cough which can persist for weeks after the other symptoms have subsided, this occurs particularly in people who suffer from chronic non-specific lung disease (CNSLD). There may be impairment of hearing and also clicking noises in the ears due to oedema of the Eustachian tube's lining. In addition, the sense of smell is usually impaired. In children there may be fever and general malaise, and in adults headaches and facial aches are common. Conjunctivitis might also occur.

Examination of patients show inflamed and swollen nasal and pharyngeal mucous membranes and nasal discharge. The cervical lymph nodes may be slightly enlarged or tender.

Most common colds last from 6 to 10 days.

Differential diagnosis

The common cold must be differentiated from allergic rhinitis.[226] The common cold syndrome may also be the initial stage of a serious systemic infection such as meningitis, hepatitis or endocarditis.[227]

Pathogenesis

In the common cold, the mucous membrane of the upper respiratory tract is infected by a respiratory virus. The inflammatory reaction on the tissue damage includes: edema, hyperaemia, transudation and exudation. In the course of the common cold, there is an increase of serum globulins and substances of cellular origin in the nasal secretions.

Although the tissue damage is rapidly repaired, the mucociliary clearance mechanism may be disturbed for several weeks.[228]

Complications

A common cold can be complicated by secondary bacterial infection of structures in the upper respiratory tract: acute otitis media, acute sinusitis, or a descending infection like laryngotracheobronchitis. Individuals with CNSLD often experience an exacerbation of obstructive lung symptoms by bronchoconstriction and increased sputum production.

Immunity

Within a week after the onset of the viral respiratory infection, healthy persons develop specific antibodies to the causative viral strain. These antibodies provide highly specific protection against reinfection by the same viral strain during the following months, or even years. However, in spite of this protection, since a large number of different virus strains can cause common colds, colds tend to recur.

Etiology

The most frequently found agents are rhinoviruses (probably about 50%) and coronaviruses (probably up to 30%). Other agents are the influenza-C virus and the para-influenza-4-virus. Adenoviruses and influenzaviruses A and B and Mycoplasma pneumoniae, notorious agents of more serious infections, may simply cause a common cold in healthy individuals. Respiratory syncytial viruses and para-influenzaviruses 1,2 and 3, which may cause severe respiratory infections in young children, generally only cause a common cold in older children and adults. The coxsackie virus may also cause the common cold syndrome.

Therapy

There is, unfortunately, no specific therapy for common colds, although symptoms that seem ineffective in attaining elimination of the infection, can be alleviated. It seems advisable to ensure that the nasal passage is free, particularly in babies. Use of physiologic salt or suitable vasoconstrictive nose-drops for a limited period of time may be necessary to attain this. Steam inhalations can also be beneficial. If fever is alarming, or if pain is too bad, an analgesic such as paracetamol can be administered. Aspirin is not given, because it is believed that it might trigger the Reye syndrome.[229] However, fever in fact helps to combat the infection. Antitussives may be given in the event of a troublesome unproductive cough. Similarly, in productive coughs expectorants may be beneficial. Extra rest, humidification of room air and adequate fluid intake are all beneficial and probably promote healing. In homoeopathy, remedies are given according to the total symptom picture (see *chapter 2*). Little data on the effectiveness of these homoeopathic remedies are available yet. On the basis of current data there seems to be no role for antihistamines in the treatment of upper respiratory tract infections.[230]

Prevention

Careful personal hygiene, to avoid spread of virus-contaminated secretions, helps to prevent common colds. Immunoprophylaxis has been extensively investigated, but is not yet available.

1.8.2 Acute sinusitis

Definition

Acute sinusitis is an acute bacterial infection of the mucous membrane of one or several paranasal sinus(es), which usually occurs simultaneously with rhinitis.

Symptoms and signs

Sinusitis usually develops in the course of a common cold, particularly in children.[231,232] Symptoms of acute sinusitis are purulent nasal discharge, nasal congestion, a cough which increases in supine position, and mild or high fever. There may also be malodorous breath[233] and older children may complain of headache[234] increasing on stooping or facial pain and tenderness.

On physical examination, one sees swelling and erythema of the nasal mucosa and mucopurulent discharge from the middle meatus.

In adults, the clinical diagnosis can be supported by radiography, ultrasonography or by transillumination, but these diagnostic methods seem to be of limited value in children.[235] When microscopic examination of nasal secretions is performed, sheets of polymorphonuclear cells and bacteria are often found.

Pathogenesis

The mucous membranes which line the sinuses are continuous with the nasal mucous membrane. Any nasal viral infection will, to some extent, also affect the sinuses causing erosion of the lining epithelium. Edema and an increase of mucus-secretion may cause partial obstruction of the sinus ostia and stagnation of drainage. Secondary bacterial infection is promoted by loss of epithelium, ciliary dysfunction, impaired phagocytic activity and stagnation of drainage.[238]

Complications

Sinusitis can be complicated by an extension of the infectious process.[237-239]

The bronchial tree may become involved[240] and chronic sinus infection may aggravate chronic reactive airway disease.[241] Prolonged episodes of sinus-infection may lead to irreversible changes in the affected mucosal lining of the sinus. Serious complications of sinusitis include orbital, intra-cranial and osseous infections and cavernous sinus thrombosis.[242] These complications are fortunately rare.

Etiology

The most commonly found bacteria in sinusitis are Haemophilus influenzae, Streptococcus pneumoniae and Branhamella catarrhalis. Other agents are Streptococcus pyogenes, α-haemolytic streptococcus and anaerobes. Anaerobes play a crucial role in chronic sinusitis. Adenoviruses and parainfluenzaviruses have also been isolated from sinus-aspirates.

Therapy

The first measure to be taken in treating sinusitis is the promotion of drainage. One can try to achieve this by steam-inhalations and the use of topical nasal decongestants for a limited period of time.[243,244] Saline irrigations humidify the nasal mucosa, remove secretions and improve sinus drainage via mild vasoconstriction.[245] If these measures prove to be insufficient and if complaints are serious, an appropriate antibiotic must be given.[246] Puncture of the sinuses is sometimes applied in children older than 4 years. If orbital or cranial complications occur, immediate surgery and adequate antibiotic therapy are nessecary.

1.8.3 Acute otitis media

Definition and introduction

Acute otitis media is an acute infection of the mucous membrane of the middle ear with an acute onset and a duration of less than three weeks. It is characterised by changes of the tympanic membrane and often accompanied by earache, fever and general illness.[247] It usually follows a common cold.

The extent and severity of the process depend on the general state of health of the patient, his or her specific immunity and the virulence of the agent.

Epidemiology

Otitis media is most prevalent in infants and young children and is much less common after the age of 6 to 7.[22]

In an epidemiologic study in Boston, 498 children were followed during their first seven years of life. By the age of one year 62% of the children had had at least one episode of acute otitis media, at the age of three years this percentage was 83. At age one 17% of the children had already had three or more episodes of acute otitis media. The peak incidence of acute otitis media was at the second half year of life (age 6 months to one year).[77]

Symptoms

Acute otitis media may cause children considerable distress: otalgia, malaise, fever and diminished hearing.[248,249] Sleep is often disturbed by pain. Small children who cannot yet indicate what the trouble is may just be generally miserable, or ill with fever and may have diarrhoea with or without vomiting. They may bang their head or seize their ear and they prefer being held upright.[250] Middle ear infection must be ruled out in the examination of any child with a fever of undetermined origin.

Signs

The diagnosis is achieved by combining the symptoms with the findings of otoscopy relating to the colour of the tympanic membrane, its position and its degree of translucency.[251] In acute otitis media, the tympanic membrane is usually red and opacificated and may be bulging. A red tympanic membrane alone does not necessarily provide enough evidence for an otitis media: it can become red as the result of crying, or even blowing the nose. The normal tympanic membrane is translucent. Opacification of the drum indicates middle ear effusion, the thickening of the tympanic membrane or both. The tympanic membrane may rupture because of the pressure in the middle ear and then otorrhea will follow. In Anglo-saxon literature, the use of a pneumatic otoscope is advised to assess impaired mobility of the eardrum by effusion of the middle ear[252], but in the Netherlands this instrument is generally not used.[7,253]

Pathogenesis

Children usually develop an acute otitis media during the course of a common cold. The Eustachian tube is the portal of entry for the pathogenic organisms. The protective functions of an obstructed or abnormally patent Eustachian tube are compromised. If secretions cannot drain, multiplication of bacteria is enhanced.[254,255]

Complications

In most cases, otitis media is a self-limiting disease and serious complications are rare in Western countries today. Serious complications comprise intracranial complications and intratemporal complications and a protracted course, resulting in a chronic purulent otitis media which may give rise to irreversible sequelae. A late, mild complication is the persistent of an effusion in the middle ear.

Intracranial complications include meningitis, focal encephalitis, brain abcess, sinus thrombophlebitis, extradural abcess, subdural abcess and otic hydrocephalus. They occur more often in association with chronic suppurative otitis than with acute otitis media. However, since these complications cause serious damage, or even death, and rapid treatment can reduce damage considerably, one should be alert for them, even though they are nowadays uncommon. Any child with otitis media who develops persistent headache, nausea or vomiting or a new rise in temperature should be suspected of having an intracranial complication.

Intratemporal complications are mastoiditis, facial paralysis and suppurative labyrinthitis. Acute mastoiditis usually develops in the course of an ongoing otitis media with purulent discharge. The systemic symptoms may be masked by antibiotics. In severe mastoiditis there is pain, tenderness, edema and erythema of the postauricular area. When there is a subperiosteal abcess, the pinna is displaced inferiorly and anteriorly. Swelling and sagging of the posterior-superior canal wall may then be present. Immediate myringotomy and antibiotics are indicated and mastoid surgery is often required to prevent any further damage. Facial paralysis may occur as an isolated complication of acute otitis media. This condition requires myringotomy, parenteral antibiotics and rarely facial nerve decompression. Immediate surgery is required when facial paralysis develops in a child who has a chronic suppurative otitis media. Suppurative labyrinthitis is a serious condition that requires intense parenteral antibiotic treatment. Signs and symptoms are striking, including vertigo, nystagmus, tinnitus, hearing loss, nausea and vomiting.

If an acute otitis media does not heal in due time, it may turn into a chronic purulent otitis media, often with irreversible sequelae: atelectasis (collaps of the mesotympanum), perforation, granulation tissue, cholesterol granuloma, the very destructive cholesteatoma and ossicular discontinuity or fixation.

Otitis media acuta can have long-term sequelae. Middle ear effusions may persist for weeks or months after the acute phase of otitis media.[76,256,257] If the inflammation does not resolve in due time, it can cause longlasting impairment of hearing which may influence the communication and language development of the child as has already been mentioned before.[258]

Etiology

The commonest found pathogens are Streptococcus pneumoniae (25-50%) Heamophilus influenzae, mostly nontypable (15-25%), and group A beta-haemolytic streptococci (5-8%).[128,259] The nontypable Haemophilus influenzae generally causes a milder otitis media than the haemolytic streptococcus and the streptococcus pneumoniae.[260] In neonates middle ear effusions may contain gram-negative

enteric bacilli. Gram-negative organisms are also found in patients with persistent tympanic membrane perforations. Less common pathogens found include Branhamella catarrhalis, Staphylococcus aureus and Staphylococcus epidermis.

Therapy

Nowadays, in most instances, acute otitis media is a selflimiting disease, but in former times the disease was far more serious. The disease has become milder, probably because of the generally better health of children which is due to better socio-economic circumstances and the reduced virulence of the etiologic microbes. A policy of 'masterly inactivity' with careful observation of the patient and alleviation of pain by an analgetic antipyretic medicine is justified.[261-265] However, alertness is still necessary because the disease may follow an aberrant course and may still lead to serious complications. Children with recurrent acute otitis media are at greater risk of an abberant course than children who only occasionally suffer from acute otitis media.[266] Tympanostomy and/or the application of antibiotics or other measures may then be necessary.

Certain indications for an emergency myringotomy include: acute mastoiditis, labyrinthitis, facial nerve paralysis and intracranial suppurative complications. Other indications include: severe uncontrollable earache, unsatisfactory response to antibiotic treatment, otitis media in immunocompromised or critically ill persons and very young children.[195 247]

If the use of antibiotics is considered in acute otitis media, they must be active against the most prevalent pathogens: Haemophilus influenzae and Streptococcus pneumoniae. The drugs used must penetrate into the middle ear. Amoxicillin, erythromycin, sulfisoxazole and trimethoprim-sulfamethoxazole are the most commonly used antimicrobial drugs to combat acute otitis media.

1.8.4 Acute tonsillopharyngitis

Definitions

Tonsillitis is an inflammation of the tonsils, pharyngitis is an inflammation of the mucous membrane of the pharynx. The two are usually combined in children.

Symptoms

The most prominent symptoms of tonsillopharyngitis are usually the sore throat and pain on swallowing.[267] Small children however, do not complain about a sore throat or pain on swallowing, but instead refuse food and drinks. Besides pain there is usually malaise and fever and there may also be headaches. Children may complain about abdominal pain.

The duration of the illness is, in most cases, one week.

Signs

The tonsils are hyperaemic, swollen and sometimes covered with an exudate. The cervical glands are usually swollen.

In 'herpangina' caused by a Coxsackie group A virus, 5-10 ulcers can be seen on the anterior pillars of the fauces or on the soft palate. (A primary infection with Herpes simplex virus is usually characterized by stomatitis and gingivitis, rather than by tonsillopharyngitis.)

Complications

The tonsillar infections may spread into surrounding tissues and cause a peritonsillar infiltrate or abcess. Symptoms are severe and prolonged pain, fever and general malaise, and trismus. On examination one-sided swelling of the peritonsillar area and the palate and medial displacement of the tonsil are seen. Parapharyngeal spread of infection occurs very infrequently, but is a life-threatening complication which requires immediate surgery. The following symptoms can arise: fever, stridor, swelling in the pharynx and neck, trismus and torticollis.[268]

Etiology

Tonsillopharyngitis is often caused by a viral infection (adenovirus, Epstein Barr virus, Coxsackie group A virus) The most common agent, however, is a group A ß-haemolytic streptococ[269], notorious for its secondary auto-immune effects: acute glomerulonephritis and acute rheumatic fever.[270] It is difficult, if not impossible, to differentiate between the etiologic agents by their clinical appearance. The triad of purulent tonsillar exudate, fever and tender anterior cervical adenopathy is associated with a high risk of ß-haemolytic streptococcal infection, but many viral illnesses, including mononucleosis and adenoviral infection, show a very similar picture. Petechiae of the palate point to streptococcal infections.

Diagnosis

In order to diagnose a streptococcal infection accurately, one must not only make a throat-culture but also compare antibody titres over time.[271 272]

Therapy

General measures to be taken are: rest and plentiful liquids. If a child refuses all drinks, he or she might still take fruit juice-ices. Adults are advised to gargle, but small children cannot perform this. If necessary an antipyretic-analgesic, preferably paracetamol, can be given.[273]

Antibiotics should not be given except on rare occasions.[274 275] Penicillin G used to be the first choice[276]: A streptococci are sensitive to penicillin and a small spectrum antibiotic produces less resistant strains of other germs and does not disturb the commensal flora as profoundly as broad spectrum antibiotics do. Penicillin was shown to be able to prevent the possible sequelae of streptococcal infections i.e.: suppurative complications and rheumatic fever. Penicillin could not reduce the risk of acute glomerulonephritis. Penicillin has been shown to reduce

the spread of the infection to other persons. Because of an increase in the prevalence of beta-lactamase producing microbes and encapsulated anaerobes in conjuncture with streptococcal infections, other antibiotics are possibly more appropriate today.[277]

The use of antibiotics, however, implies risks: sensibilisation of the user, the destruction of his commensal bacterial flora and the emergence of resistant strains. Early treatment of group A beta-haemolytic streptococcal infection with penicillin may enhance subsequent infections.[278] A further important issue is the degree of accuracy to which a quick diagnosis can be made. The clinical picture alone is insufficient for making an etiologic diagnosis; as already mentioned, a positive culture of a throat swab and evidence of a rise in antibody titres are necessary to confirm the diagnosis and this takes time.[278]

There is some agreement on the use of antimicrobial treatment of tonsillitis in the following instances.[280]

- An unusually severe clinical picture.
- Proven infections of ß-haemolytical streptococci in the same household.
- The patient being in close contact with susceptible and vulnerable people (and it therefore being important to eradicate the source of infection).
- Acute rheumatic fever in the past history.
- Acute glomerulonephritis in the past history.
- Vitium cordis.
- Peritonsillar infiltrate.
- Scarlet fever.

Finally, a remark on recurrences. In recurrent acute tonsillitis tonsillectomy must be considered[80] because the function of recurrently or chronically infected tonsils is changed.[151 281 282]

1.9 Summary

Respiratory tract infections occur frequently, especially in children, but a small proportion of children without a recognised underlying major disease are particularly susceptible. Most upper respiratory tract infections are of viral origin, but a secondary bacterial infection may deteriorate the clinical course.

Children between the ages of one to five years suffer on average from 4 to 8 colds and 1 episode of a more severe upper respiratory tract infection in one year, whereas susceptible children suffer from 3 or more of such upper respiratory tract infections during the same period.

Risk factors for respiratory tract infections are crowding, poverty, passive smoking, stress and inadequate nutrition, a risk factor for otitis media is a positive family history. Prolonged breastfeeding protects against acute otitis media.

With the advance of age the child's immune system becomes better equipped to combat pathogenic agents effectively and consequently the frequency of respiratory infections diminishes.

Several regimes have been applied to reduce infections in susceptible children: active and passive immunisation, chemoprophylaxis, surgery and homoeopathy.

The anatomy and physiology of the upper respiratory tract, the known respiratory pathogens and the distinguished clinical syndromes of upper respiratory tract infections were reviewed because knowledge thereof contributes to an appropriate treatment of and care for susceptible children.

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2 HOMOEOPATHY

2.1 Introduction and history

Homoeopathy is a polymorphic system of treating patients which was introduced by the nineteenth century German physician Samuel Hahnemann (1755-1843). It is based on the similia rule:
"To cure mildly, rapidly, certainly, and permanently, choose, in every case of disease, a medicine which can itself produce an affection similar to that sought to be cured!" [1]

In this chapter the development of Hahnemann's ideas and their practical application shall be reviewed. Then various concepts in homoeopathy shall be described. Finally some aspects of the practice of homoeopathy shall be expounded.

2.1.1 The origin: Hahnemann's work

Samuel Hahnemann studied medicine in Leipzig, Vienna and Erlangen, where he graduated in 1779. After graduating he wandered around, practising medicine as well as chemistry in several places.

In 1784 he openly criticised medical practice for the first time. [2] Medical practice in Hahnemann's days largely consisted of blood letting, purging and administering large doses of strong drug mixtures. Opium was abundantly used by doctors, as were arsenic and mercury. Hahnemann repeatedly critised the excessive bloodletting, the inhumane treatment of psychiatric patients, the use of compound medicines and the neglect of hygienic measures. [3 4] He rejected these practices [5], as well as the theorising in medicine. [6]

As a student, Hahnemann earned a living by translating scientific books and he was again occupied with translating while living in Stötteritz (1789-1792) where he did not practice medicine. Whilst translating the Scottish physician Cullen's Materia Medica, Hahnemann became acquainted with his explanation of the effect of Peruvian bark cinchona (which contains quinine) on intermittent fever (malaria). Cullen (1710-1790) attributed its effectiveness to its 'tonic effect on the stomach', but Hahnemann was unconvinced by this explanation and as an auto-experiment he took cinchona in order to examine its effects on himself. He subsequently developed symptoms of intermittent fever. It was this experience which led him to his hypothesis that a substance that can cause symptoms similar

to those of a disease, can also cure that disease. (In Latin: similia similibus curentur, ie: 'let like be treated by like'.)

Six years later he published this idea in an article entitled : "Versuch ueber ein neues Prinzip zur Auffindung der Heilkräfte der Arzneisubstanzen, nebst einigen Blicken auf die bisherigen" (1796) which appeared in a leading medical journal called the "Journal der praktischen Arzneykunde und Wundarzneykunst", published by C.W. Hufeland (1762-1836).[7]

In the period that followed his discovery, Hahnemann began to carry out experiments to test several substances on healthy volunteers and he called these experiments 'provings'. During a proving he gave his volunteers a particular substance and recorded all of the sensations and symptoms that they subsequently developed, which he ascribed to the action of the substance administered. The question whether these sensations and symptoms were actually generated by the substance that was tested or by other causes, was given only limited consideration. The study of medicines in healthy persons was already propagated by Von Haller (1708-1777)[8] and Jörg (1779-1856) also studied the effects of medicines on healthy persons.[9]

His next step was to administer a substance to a patient with symptoms which were similar to the symptoms that he recorded in his proving of that particular substance. Hahnemann was generally pleased with his results in treating patients in this way, but he observed that the patients' symptoms initially aggravated before they disappeared. He subsequently attempted to prevent these aggravations by reducing the doses of the substances that he administered to his patients. Hahnemann later (after 1821[10]) developed a special method for preparing medicines by stepwise dilution which he called 'potentisation'. He developed this method not only because he wanted to reduce doses, but also because he believed that thus prepared medicines would have a special power which he described as 'power released from matter'.[11]

Hahnemann put down the principles of his new therapeutic method in an article entitled "Heilkunde der Erfahrung" which was published in Hufeland's Journal in 1805.[12] The main points of this article were:

- The effects of medicines can be known only by means of experiments on healthy people;
- Medicines must be chosen for the similarity of the symptoms which they produce in healthy persons to the symptoms of the patient (the similia principle);
- Medicines are to be chosen only on the basis of the totality of the patient's symptoms;
- Medicines must not be given in mixtures;

- Medicines must be given in small doses to prevent initial aggravations of the symptoms;
- Medicines must not be repeated as long as the condition of the patient is still changing.

In this article he did not yet use the word 'homoeopathy', this was a term which he introduced in 1807.[13] The word homoeopathy is derived from the Greek and comprises two terms: 'homoios', which means similar and 'pathos' which means suffering, illness. In 1819 he coined the term 'allopathy', in the second edition of his book Organon, this term encompassed every mode of treatment apart from homoeopathy.

Hahnemann described his ideas about the correct treatment of patients more extensively in the first edition of 'Organon der rationellen Heilkunde' (1810). He produced six revised editions of this work and later retitled it 'Organon der Heilkunst'.

In his Organon Hahnemann expounded his theory on the action of medicines. Hahnemann assumed that an effective medicine causes an artificial disease which expels the original disease.[14] He attributed a double effect to medicines which comprised of a first, direct effect, due to the action of the medicine[15] and a subsequent, indirect effect, contrary to the first, due to the reaction of the organism.[16] The initial aggravation of symptoms after the administration of a medicine was compatible with his theory on the double effect of medicines.[17]

As a consequence, he reasoned that the use of medicines which as a direct effect cause symptoms which are contrary to the symptoms of the patient (contraria contrarii), should be rejected, particularly in chronic diseases.[18] He wrote that such medicines temporarily alleviate the complaints, but eventually worsen the disease.[19]

Between 1811 and 1821 Hahnemann published a six volumed work called 'Reine Arzneimittellehre' (Materia Medica Pura), which contained the results of his studies on the effects of medicines on healthy persons. He supplemented his research with reports of poisonings by the substances concerned.

Next Hahnemann published, between 1828 and 1839, a five volumed work called 'Die Chronische Krankheiten'(Chronic Diseases).[20] In this work he postulated a new theory on chronic diseases. He attributed chronic and recurrent diseases to three 'miasms': syphilis, sycosis and psora. The term miasm was in use in medicine in his day. The word miasm is derived from the Greek and means 'contamination'.[21] Hahnemann conjectured that these 'miasms' invaded through the skin, spread throughout the organism and subsequently produced chronic disease. According to Hahnemann, psora was the most prevalent miasm, very contagious and accounting for seven eights of all chronic diseases. He attributed

an enormous amount of symptoms to psora.[22] He believed that psora was the oldest miasma and that psora had increased in violence by passing many generations of people.[23 24]

Hahnemann had observed that in many patients symptoms recurred after a while, or were replaced by new symptoms, even if they were given a correct homoeopathic treatment, which temporarily took away their complaints. Unfavourable conditions could make the disease flare up and their health condition always worsened in the course of time.[25]

As a consequence of his miasm theory, Hahnemann warned strongly against the local application of medicines in skin eruptions: the correct homoeopathic medicine should be given internally as skin eruptions were only the outward signs of a systemic disease.[26] He believed that the suppression of symptoms by local applications drives the disease further inwards and ultimately troubles the patient further and renders psora ineradicable.[21 27] Hahnemann stressed that the totality of subsequent symptoms had to be taken into account in the choice of the similimum for chronically ill patients.

In 'Die Chronische Krankheiten' Hahnemann presented a group of new medicines to which he ascribed anti-psoric properties, for instance Sulphur, Silicea, Natrium muriaticum and Sepia. These medicines have probably not been as well proven as the medicines which Hahnemann describes in his 'Materia Medica Pura'.[28]

Whereas Hahnemann first rejected theorising in medicine, he now postulated this miasm theory. This miasm theory subsequently caused many disputes among homoeopathic practitioners.

According to the British homoeopathic physician Anthony Campbell, the miasm theory was a face-saver: "*Hahnemann had been forced to acknowledge that homoeopathy was not universally succesful, but he could not admit the thought that it was not a complete answer to disease, since he had invested too much of himself in it psychologically. The only way out of the impasse that he could find was to postulate the existence of a deep-seated, almost ineradicable, hydraheaded evil-psora.*"[21] Other homoeopathic authors stress that Hahnemann's miasm theory resulted in a more comprehensive approach towards chronically ill patients with more positive results.[29 30]

Throughout the years Hahnemann became more and more intolerant of other therapies until finally he did not allow his followers any deviation from his doctrines. His therapeutic system was an absolute system: the only right way of treating patients. Hahnemann did not balk from denouncing 'bastard homoeopaths'.[31]

Some homoeopaths accepted and elaborated his theories on dynamism and miasms ('classical homoeopathy'). Others subscribed to the similia rule only and left the dynamism and the miasm theory out ('critical scientific homoeopathy' or 'clinical homoeopathy').[32] The only common principle that Hahnemann conceived to which all homoeopaths refer is the similia principle.[33]

2.1.2 Spread and development

Hahnemann's Organon was eventually translated in several languages. It first appeared in French in 1824 (a translation from Von Brunnow)[34] and soon more translations followed. The new system spread over Europe (Austria, Italy, Hungary, Russia, Switzerland, The Netherlands, Belgium, England and Scotland, France, Spain) and was taken to America by Hering (1800-1880). In the various countries the system went through different courses of development. Generally speaking, the 'classical' stream became dominant in the USA and the 'critical scientific' or 'clinical' school prevailed in Europe, most particularly in Germany.

2.1.2.1 America

Homoeopathy flourished in the USA throughout the nineteenth century and many homoeopathic hospitals and colleges were founded during this period. However, after 1915 homoeopathy in North America declined.[35 36]

Two homoeopathic streams evolved in the USA: a 'critical scientific' stream which later merged with conventional medicine and a smaller, but more influential, 'classical' stream which laid great emphasis on vitalism and the miasm theory and extended and changed these ideas in important ways.[37]

The 'classical' stream was fused with Swedenborgianism, a religious movement started by Swedenborg (1688-1772).[38] The two very influential homoeopaths Hering (1800-1880) and Kent (1849-1916) were both Swedenborgians. Essential to Swedenborgianism was the belief in a mystical correspondence between the spiritual world and the visible world. Campbell writes the following about the fusing of Swedenborgianism and homoeopathy: "*Swedenborgianism and homoeopathy took to each other at once. Swedenborgians found in homoeopathy a medical system that perfectly complemented their religious attitudes, while homoeopaths found in Swedenborgianism a religious framework into which Hahnemann's ideas could expand freely.*"[39]

What especially appealed to the Swedenborgians was the divine inspiration of the similia principle that was claimed by Hahnemann and his vitalism, which included the potentisation doctrine and the miasm theory. The miasm theory was given another content though by the Swedenborgians: they considered miasms as moral taints passed from generation to generation.[37] The Swedenborgians believed that disease started in the human 'will' and 'understanding'. Kent writes:

"Thinking and willing establishes a state in man that identifies the condition he is in. As long as a man continued to think in which was true and held that which was good to the neighbor, that which was uprightness and justice, so long man remained upon the earth free from the susceptibility to disease, because that was a state in which he was created." [40] These ideas can today still be found in 'classical' homoeopathy. [41] In history taking and prescribing, Kent and his followers put great emphasis on 'mind symptoms' (see *3.4.2.1*).

2.1.2.2 Europe

Until recently, the 'critical scientific' stream of homoeopathy was dominant in Europe. (Homoeopaths who follow this stream prescribe remedies in low potencies, base their choice of the medicine primarily on the clinical diagnosis and they may in fact use several remedies simultaneously.)

This of course does not mean that every European homoeopath aligned himself to the 'critical scientific' stream, the prominent homoeopathic physician Leeser (1888-1964), for instance, certainly did not. An important exponent of the 'critical scientific' stream was the Hungarian Von Bakody (1825-1911) who examined the similarity of pathological lesions brought about by toxic substances and by natural diseases.

In Europe, the 'critical scientific' stream gradually lost ground in favour of 'classical' Kentian homoeopathy. [42] Kentian homoeopathy was brought to Europe from America in the first half of the twentieth century, its two promotors were Tyler (1875-1943) in Britain and Schmidt (1894-1987) in Switzerland. In the Netherlands, 'classical' homoeopathy has rapidly increased in popularity over the last ten years.

2.1.2.3 Contemporary homoeopathy

Homoeopathy is practised in many countries as a form of 'alternative' medicine. Homoeopathy has a legal status as a separate medical discipline in Great Britain and India. [43] In Sweden, on the other hand, the sale of all homoeopathic remedies has been forbidden. [44] It has been fairly popular in the Netherlands and after a decline in popularity (from about 1943 till 1980) there has been a renewed interest among both the public and among representatives of the medical profession. Homoeopathy is not only practised in human medicine but also in veterinary medicine. [45] [46] There is a large over-the-counter market for homoeopathy. [47] Througout the world there are several contemporary homoeopathic schools: several French schools [48], several South-American schools, the school of Dorcsi in Vienna and the school of Vithoulkas. [49] [50]

2.2 Concepts

In the following section several concepts in homoeopathy will be briefly discussed.

2.2.1 Disease, etiology and pathogenesis

Hahnemann rejected the classification of diseases into nosologic entities, instead he believed that disease is only to be known as the totality of symptoms:

"The unprejudiced observer is well aware of the futility of transcendental speculations which can receive no confirmation from experience. Be his powers of perspicacity even very great, he can take note of nothing in every individual disease, except the changes in the health of the body and of the mind (morbid phenomena, accidents, symptoms) which can be perceived externally by means of the senses; that is to say, he notices only the deviations from the former healthy state of the now diseased individual, which are felt by the patient himself, remarked by those around him and observed by the physician. All these perceptible signs represent the disease in its whole extent, that is, together they form the true and only conceivable portrait of the disease." (Organon, paragraph 6).

In 'classical' homoeopathy diagnosis and therapy coincide. Patients are not classified according to the disease from which they are suffering, but instead according to the remedy which they are thought to require. [51]

Homoeopaths have their own theories on etiology and pathogenesis. As outlined above, Hahnemann developed his miasm theory on the etiology of chronic diseases (see *2.1.1* and *2.2.5*). He also proposed that disease is generated by immaterial, 'dynamic' agents which affect the vital force (see *2.2.3*). Subsequent homoeopaths have expanded upon this hypothesis. In addition, they have assumed a fixed course of any disease. According to them, disease first affects the senses, then the functions and finally the structures of the body. [52] [53]

2.2.2 Similia principle

As described above (*2.1.1*), Hahnemann assumed a first and a second effect of medicines: the first effect was ascribed to the medicinal substance, the second to the reaction of the organism. He claimed that a medicine can only heal a disease when its symptoms resemble the symptoms which the medicine may cause as a first effect. Hahnemann supposed that the similimum provokes an artificial disease which expels the natural disease.

The similia principle is considered to be the central principle of homoeopathy. For some homoeopaths the similia principle is not less than a 'law of nature', whereas for others it is a rule of thumb to find a medicine that may be effective.

Homoeopathic physicians not only differ in the value which they attach to the

similia principle, but also in its interpretation and application. The character of this broad concept makes this unavoidable. The making of any kind of comparison implies a process of selection and ordering of facts since two phenomena often resemble each other in certain respects while they differ in others. [10]

2.2.3 Dynamism

In homoeopathy the term 'dynamic' means non-material and 'nearly spiritual'.

2.2.3.1 The vital force

Hahnemann believed that people are kept in a state of good health by their 'vital force' or 'dynamis' and that disturbance of this 'vital force' results in disease.
"In the healthy condition of man, the spiritual vital force (autocracy), the dynamis that animates the material body (organism), rules with unbounded sway, and retains all the parts of the organism in admirable, harmonious, vital operation, as regards both sensations and functions, so that our indwelling, reason-gifted mind can freely employ this living, healthy instrument for the higher purposes of our existence." (Organon, paragraph 9).

Hahnemann considered disease as well as potentised medicines to be dynamic in nature. Parallel to a vital force in human beings, Hahnemann assumed the existence of a 'healing principle' in substances. [54 55]

2.2.3.2 The potency theory

At first Hahnemann used material doses of medicines. He gradually reduced the doses, initially only to avoid too fierce aggravations [56], but later because he believed that, in the special process of preparing serial dilutions that he evolved, his medicines became more effective.

Hahnemann named his special method for preparing medicines by stepwise dilution and shaking 'potentisation'. By this term he indicated that he believed that his remedies became progressively more powerful by this process of preparing [57], that substance was replaced by power. Hahnemann became convinced that the vital force can best be restored by 'immaterial' medicines. [58] At the end of his life Hahnemann mainly used the C30 potencies (see for the meaning of C30 *2.3.3*). [59]

His followers, however went much further: the Russian general Korsakoff (1788-1853) made potencies as high as C1500 and American homoeopaths went further still, producing potencies as high as C1000 000. Homoeopaths call these potencies 'infinitesimal doses'. (Since preparation by hand was too time consuming, they invented all kinds of 'potentising machines'. [60]) Other homoeopaths stuck to low potencies and did not go any further than C6 or D6.

2.2.4 The action of small doses

'Classical' homoeopaths prefer non-material medicines [61] as they believe these to be truly beneficial, in contrast 'critical scientific' homoeopaths stick to the material world. They mainly prescribe low potencies and have several explanations for the action of small and extremely small doses, some of which will now be briefly described.

Some seek an explanation in a theory of the German psychiatrist Arndt (1835-1900) which is often referred to by homoeopaths as the Arndt Schultz law (1885). The theory can be summarised as follows: Small stimuli encourage life activity, medium to strong stimuli impede it and very strong stimuli stop it. A small dose of a substance is supposed to have an effect which is opposite to the effect of a large dose. [62]

Others seek an explanation in the sensitivity of diseased tissues. They suppose that diseased tissues are more sensitive to medicines than healthy tissues and therefore respond to very small doses, in contrast with healthy tissues. [63] Leeser explains this as follows: A small stimulus is more likely to evoke a response from processes already in disturbed equilibrium than from those in normal equilibrium. [64]

If the molecular theory is applied to high potencies, a specific effect cannot be explained. The chance that a dilution, in which the concentration of the original substance is 10^{-24} (this is in a C12 or a D24), contains any molecules of the original substance is virtually zero. 'Materialists' who prescribe high potencies either claim their effect but refrain from explanations, or seek natural explanations for their supposed action. Most of their hypotheses can be classified under the heading 'contamination hypotheses', the essence of which is a change of the properties of the solvent by the original substance from which the medicine is prepared through potentisation. [65 66]

2.2.5 Miasm theories

Hahnemann advanced the miasm theory by which he attributed chronic diseases to three miasms which invaded the body (see *2.1.1*). As outlined above this miasm theory was modified by subsequent homoeopaths. [21] Hering extended the miasm theory to all kinds of acute diseases. According to him, these acute diseases could leave long lasting ill-health. He treated patients in whom he supposed the negative influence of a former acute disease with potencies of disease products of that particular disease. These were called 'nosodes'.

Kent considered psora to result from a disorder in thinking, willing and acting (see *2.1.2.1*) [67]. Today miasm doctrines play a very important role in several

homoeopathic schools, but particularly in South-American schools and in the school of Vithoulkas. In these schools miasms are given a psychological meaning.

2.2.6 Symptom-shift

Based on the miasm theory, Hering postulated a theory about the progress of disease and healing: If disease progresses, it moves from outward structures to inward structures and from less vital to more vital organs. If healing takes place symptoms disappear in a particular sequence: from within outwards, from above downwards, from more vital to less vital organs and in the reverse order of their appearance. According to Hering, if symptoms disappear in a different sequence, there is no healing but mere palliation. [68]

2.2.7 Constitutional remedies

From ancient until recent times various schemes for the typological classification of people were designed and used in medicine. In homoeopathy such typological classifications play an important role. Homoeopathy employs the term 'constitutional prescribing' and, though there is no concensus about the exact meaning of the concept [69-72], one may say that a 'constitutional remedy' is a remedy that is prescribed mainly on account of the general mental and physical characteristics of the patient. [73]

Since mental and physical characteristics cannot be expected to suddenly appear in provings, constitutional prescribing seems to be incompatible with the similia rule. The concept of constitutional prescribing gradually entered homoeopathy which was originally supposed to treat patients with similia found in provings.

Constitutional prescribing plays an important role in various homoeopathic traditions: in 'classical' homoepathy as well as in German [74 75] and French homoeopathic traditions [76 77] and even in veterinary homoeopathy. [78] Constitutional medicines are especially used to treat chronic and recurrent health problems. Some views of homoeopaths on constitutional prescribing will now be presented.

Hahnemann only gives typological hints for the use of two homoeopathic remedies: Pulsatilla and Nux vomica. Thus in his work he advocated virtually no constitutional prescribing.

The first homoeopath who based his therapy on a constitution theory was Von Grauvogl (1811-1877). [51] He classified constitutions into three categories: hydrogenoid (people who were supposed to have an excess of water in the tissues), oxygenoid (people who were supposed to have an excess of oxygen in the tissues) and carbo-nitrogenoid (people who were supposed to have an excess of carbon and nitrogen). [79]

Kent's lectures on Homoeopathic Materia Medica [80] contain many typological descriptions as indications for the use of matching remedies, yet paradoxically, he wrote that he rejected the use of patient characteristics that were not described in provings for the choice of homoeopathic remedies. [81] For Kents' followers, however, constitution became most important. According to Blackie (1899-1981), homoeopaths noticed that persons with certain general physical and mental characterisics were more sensitive to a particular homoeopathic medicine than persons who lacked these characteristics. [82] They described these characteristics for many homoeopathic remedies, which they called 'polychrests' (medicines with a wide range of action) and they painted, as it were, the portraits of 'homoeopathic personalities'. [83-86]

Foubister (1902-1988) remarked that many patients cannot be typed and that constitution is not a static phenomenon: rather he found that it is liable to change in the course of a person's life. [87]

Ritter denounced the practice of typing patients since he thought that most patients cannot be forced into this system. [88] Van 't Riet suggested that several elaborate descriptions of 'homoeopathic personalities' are made up. [89]

Contemporary 'classical' homoeopaths stress the importance of general reaction-patterns of the patient, his or her mental characteristics and his or her 'peculiar' symptoms for the selection of the remedy, because they believe that these indicate the starting point of the disease process. But, to the contrary, local symptoms are considered to be of less importance in the choice of the remedy, for these are believed to be only the result of tissue changes brought about by the disease, rather than actual pointers to the cause of the disease. [90] Therefore they base their choice of the remedy on general reactions and mental characteristics of their patients, rather than on local symptoms, and this is called constitutional prescribing.

2.3 Practice

The practice of homoeopathy includes the tests of substances in healthy persons, called provings, the preparation of homoeopathic medicines and the homoeopathic treatment of patients.

2.3.1 Provings

Hahnemann began testing his medicines on healthy people: first himself, then members of his family and later also his followers. He first used tinctures of plants and insoluble substances in the form of 'first triturations' (1 part of a crushed mineral ground with 99 parts of lactose), though he did not give exact information on the doses he used. Later he advised the use of potencies of substances in provings.

Hahnemann's volunteers were not allowed to smoke, drink alcohol, tea or coffee, take pepper, ginger or strongly salted food. They had to record all symptoms they noticed in a notebook that they always carried with them and they were regularly interviewed by Hahnemann.[91] He processed the thus obtained data and compiled lists of all the recorded symptoms ordered according to the anatomical systems from which they were supposed to have arisen. Hahnemann was unaware of the possible effect of suggestion and did not account for this; later provers, however, did.[92 93]

In his 'Reine Arzneimittellehre' he describes 67 remedies. Later, in 'Die Chronische Krankheiten' he describes more remedies from the information derived from the recorded toxicology, from provings (though not performed by Hahnemann himself), and also from symptoms described by patients receiving drugs[94], although this was in fact against his own principle.[95]

During the second part of the nineteenth century provings were performed in Germany and Austria and the United States. Several kinds of substances were proved ranging from toxic to apparently inert substances. Very toxic substances included lead, arsenic and phosphorus, poisonous plants such as Belladonna and poisonous animal products such as snake venoms.[94]

Apart from a few dangerous nineteenth century provings, homoeopaths tended to prove substances in small doses in order to provoke so called 'micro-toxicologic' symptoms since they valued these most in prescribing.[96] Several substances were proved in potentised form, for instance, Natrium muriaticum (common salt).[97]

In the twentieth century, provings are still carried out on a small scale. In these provings placebo's are used part of the time in order to control for placebo symptoms when taking the substance to be tested.[28 98 99]

2.3.2 Data collections on homoeopathic medicines

Data derived from provings, toxicology and clinical experience are ordered in two ways: the materia medica begins with the remedies and record symptoms per remedy and the repertories start from symptoms and record remedies per symptom.

2.3.2.1 Materia Medica

Originally the Materia Medica included symptoms that developed in provings and involuntary poisonings. Later, however, homoeopaths added symptoms that had disappeared in patients who were treated with a particular substance. These were called 'clinical symptoms'. Often the origin of the symptoms was not indicated.[100 101] Later drugs that had not even been proved were included in the materia medica.[102] And personal characteristiscs of patients who reacted well to a particular medicine, were added. The first materia medica consisted of long lists of symptoms, later works contained vivid pictures of 'homoeopathic personalities,' the so called drug pictures. (see also 2.2.7)

Hughes (1836-1902) and Mezger (1891-1976) made an attempt to purify the materia medica by sifting out symptoms that had not occurred in provings.[97 103]

2.3.2.2 Repertories

Repertories are intended to be indexes on the materia medica, to be used as an aid in the homoeopathic treatment of patients. Homoeopaths look up the symptoms of their patient to find out which remedies match the symptoms and to what degree.

One of the earliest repertories was compiled by Von Bönninghausen (1785-1864).[104 105] The one that is still most widely used was compiled by Kent.[106] It is structured in a way that conforms to Swedenborgianism.[107] Contemporary homoeopaths are still instructed in the use of this instrument. Nowadays several computerised versions of Kent's repertory are available.[108]

2.3.3 Production of medicines

Rules for the preparation of homoeopathic medicines are laid down in Homoeopathic Pharmacopoeia's. Homoeopathic medicines are mainly prepared in homoeopathic drug factories.

Medicines are made from plants, animals or animal products, minerals and disease products. In case of vegetable remedies, fresh plants are prefered for preparing a tincture[109], mostly the whole of it, from root to flower. Most plants are collected in the flowering season.[110]

From the tincture, or crude substance, the potencies are produced by potentisation. In the case of soluble substances potentisation is a combination of serial

dilution (usually 1:10 or 1:100) and vigorous shaking.[111] Insoluble substances are first crushed and pounded and mixed with sugar of milk in the prescribed proportions to prepare the first so called 'triturations'. After a few steps the trituration is suspended in a solvent. Subsequently, the same method as for soluble substances is applied: stepwise dilution and shaking. Hahnemann probably learned this step-wise technique from alchemist monks.[112 113] As a young man Hahnemann became a Freemason. German Masonry in the late eighteenth century was affected by Rosicrucianism, which had close links to alchemy.[37]

Apart from the centisemal scale with dilution-steps of 1:100 , the decimal scale with dilution-steps of 1:10 and the quinquagintamillesimal scale with even greater dilution-steps are applied in potentisation (1:50 000).[114] The decimal method was introduced by Hering. In the last edition of the Organon, Hahnemann gives instructions for the preparation along the quinquagintamillesimal scale[115], a less straight-forward method which shall not be described here. Potencies are identified by a number indicating the number of dilution steps and a letter indicating the scale of dilution: C indicates the centesimal scale, D indicates the decimal scale, LM indicates the quinquagintamillesimal scale.[116]

Potencies are classified in three categories: low (tincture (ϕ) up to and including D6 or C3) , medium (higher than D6 or C3 up to and including D24 or C12) and high potencies (higher than D24 or C12). Potencies prepared along the quinquagintamillesimal scale usually range from LM 6 to LM 30 and are considered to be low and medium potencies, although the original substance is diluted out.[117]

2.3.4 Homoeopathic prescribing

As can be gathered from the great diversity in thinking among homoeopaths, there is a great diversity in the practice of homoeopathy. Some general policies that British and Dutch homoeopathic physicians are supposed to follow will be described.

Before the homoeopathic physician prescribes a remedy for a particular patient, he has to decide in the first place whether homoeopathy is indicated and in the second place whether homoeopathy is sufficient. Therefore an attempt to decide on a 'conventional' diagnosis must first be made.

After deciding to treat homoeopathically, the practitioner has to decide the type of homoeopathic prescription: an acute, a constitutional or an organotropic remedy. In order to decide this, the nature of the disease as well as the general ability of the patient to react to a homoeopathic medicine (vitality) is considered. In debilitated chronic patients homoeopathy is applied in a palliative way, not as a constitutional therapy.[118]

After chosing a remedy, the potency must be chosen.

Finally, the homoeopath will also inquire about any factors that can interfere with homoeopathic therapy and subsequently try to remove them.[119 120] Such factors vary from the habitual use of strong aromatic substances (for instance menthol), which are assumed to neutralize the action of homoeopathic remedies, to a continuing exposure to severe stress.

If necessary, homoeopathic treatment is combined with another therapy like surgery or psychotherapy.

2.3.4.1 Indications and contra-indications

Homoeopaths differ greatly in the extent to which they employ homoeopathy. Some always prefer homoeopathy and take refuge in other therapies at the last moment, when it cannot be avoided; i.e. in life threatening acute conditions or when structural damage has to be 'repaired'. Others only use homoeopathy if there seem to be no other possibilities. Many follow a policy somewhere between these two extremes.[121-123]

Some homoeopaths assume that homoeopathic treatment for subjective complaints, which in conventional medicine do not lead to a diagnosis, prevents more serious problems. They consider these non-specific complaints as the early signs of disease.[124] It seems evident that this opinion easily leads to the medicalisation of any unhappiness. However, at least in theory, homoeopaths will not treat any trivial complaint with their medicines: *"Small abberations of health should first be treated by a change in life-pattern." (Organon paragraph 150).* The threshold for the use of homoeopathic medicines, however, is lower than for the use of conventional medicines as homoeopathic medicines are considered to be safe and non-toxic. This leads easily to over-consumption, which also is encouraged by advertisements for mixtures of homoeopathic medicines which are promoted for minor ailments and promising stories in glossy magazines which are distributed by manufacturers or sellers of homoeopathic medicines.

Apart from not prescribing medicines for trivial acute complaints, Hahnemann would not prescribe medicines for chronic complaints that were obviously caused by harmful conditions or habits.[125] Instead of prescribing medicines, he would, if possible, advise the patient with regard to their circumstances or habits.

2.3.4.2 The choice of the remedy

In the paragraphs that follow some details will be given on the methodology of homoeopathic prescribing.

2.3.4.2.1 From symptoms to remedy

Firstly, an extensive and detailed history is taken and a clinical examination is performed to collect the symptoms and signs. [126-129]

Von Bönninghausen instructed homoeopaths to be as precise as possible in describing the symptoms of their patients in order to find the similimum. In pain, for instance, they must note the localisation and extension of the pain, the character of the pain such as sharp, stitching or dull, the circumstances that provoke, increase or decrease the pain, such as cold air or warm applications or a certain time of the day, and concomitant symptoms such as nausea. Homoeopaths pay special attention to alternating symptoms: for instance, stomach-ache alternating with aching joints. Circumstances that give relief or aggravation of symptoms are called modalities. The homoeopath will ask questions about the noticed influences of geographic residence and climate, seasons, weather (temperature, humidity, wind), activities, rest, time of the day or the year, hot and cold applications, food, emotions, surroundings and contacts with particular substances.

After collecting this information, the homoeopath appraises the symptoms: how pronounced are they, how characteristic and what is their relevance in terms of the homoeopathic system? Symptoms are ranked according to the philosophy of the prescriber and depending on the nature of the disease.

Hahnemann stressed the importance of unexpected [130] and mental [131] symptoms. In 'critical scientific' homoeopathy, mainly pathognomic symptoms are considered and modalities are added to find the appropriate medicine. In 'classical' Kentian homoeopathy non-pathognomic symptoms determine the choice of the medicine. [132] Kent distinguished several categories of symptoms: General versus particular, and common versus peculiar symptoms. General symptoms concern the whole person: I feel the cold very much, I am thirsty, I am irritable, I am upset, I perspire a lot, I lack confidence. Particular symptoms concern a part of the person: my leg hurts, my nose is running. Common symptoms are symptoms that can be expected in the given situation, for instance, fever with thirst. Peculiar symptoms are symptoms that are not expected in the situation given, for instance, fever without thirst. [133] Kent said that general and peculiar symptoms were more important for choosing a homoeopathic medicine than particular and common symptoms. According to Kent, the general mental symptoms are of the most import and these are followed in importance by 'peculiar' general somatic symptoms.

After the prominent symptoms are ranked they are looked up in a repertory and selected symptoms and matching remedies are tabulised with the appropriate scores. [134] This work is done much more quickly with computerised repertories. Repertorisation gives a clue to the choice of the remedy, but before the choice is finally made, the physician compares their drug-pictures as described in the Materia Medica to the symptom-picture of the patient. Then, at last, the remedy that best seems to suit the whole picture is chosen. At least three symptoms of the patient must correspond to the remedy. [135]

Instead of this painstaking process of collecting and ordering detailed information and the subsequent repertorising and comparing, many homoeopaths favour 'pattern-recognition' for choosing the homoeopathic remedy. [136]

2.3.4.2.2 Constitutional prescribing

In order to be able to choose a constitutional remedy for a patient, the doctor must collect information about the patient, his personal and medical history and the medical history of his ancestors and other family members.

2.3.4.2.3 Prescribing for acute medical problems

Some homoeopathic physicians find that in epidemics of acute diseases, the particular epidemic pattern usually overshadows individual variations found among patients. [137] Practitioners are advised to hand out to their patients the particular homoeopathic remedy that suits the epidemy. If this universal remedy fails to work in a patient, they are advised to look for another remedy for that patient. [138]

2.3.4.2.4 Organotropic prescribing

Organotropic remedies are thought to have an affinity with a particular organ, for instance, Crataegus to the heart, Carduus marianus to the liver, Chelidonium majus to the gallbladder, Berberis to the urinary organs.

It is also germane here to mention the so-called 'drainage-therapy': A contemporary of Hahnemann, Rademacher (1772-1850) taught that disease results from disfunctioning of various excretory organs and that medicines should be given to 'drain' them. In French homoeopathy certain homoeopathic medicines are administered in order to 'drain' particular organs. [139]

2.3.4.2.5 One or more remedies simultaneously?

Strict 'classical' homoeopaths always give only one remedy at a time.

Homoeopaths who are less 'classical' may give more than one remedy at once (this practice is called 'pluralism'), often a combination of a constitutional and an organotropic medicine. [140]

French homoeopaths give medicines in rapid alternation, for instance, different combinations of remedies in the morning, the afternoon and the evening.

'Complex homoeopaths' administer mixtures of organotropic medicines. These mixtures are also very popular in self-medication and are also prescribed by non-homoeopathic physicians.

2.3.4.3 The choice of the potency

The choice of the potency depends on the type of the medicine (acute, organotropic, constitutional), the toxicity of the substance from which the medicine is prepared, the assessment of the patient's ability to react to the medicine and the experience of the attending physician. [141]

Most authors distinguish between acute and chronic conditions in choosing the potencies, others refer in the first place to pathogenesis. Some authors give rather exact indications for the use of particular potencies in various health problems. [142]

In acute diseases Wheeler (1868-1946) advises low potencies [142]. Vithoulkas writes that in general lower ranges of potencies are used in acute illness and high potencies in chronic conditions. [143] If there is a close symptom resemblance between remedy and the totality of the patient's symptoms, Wheeler and Roberts both advise high potencies. Blackie tended to prescribe high potencies in chronic cases. [144] Köhler advises low potencies for organic diseases, medium for functional disturbances and high for psychiatric diseases. [145] In organotropic prescribing low potencies are used invariably. [146]

Poisonous substances are not prescribed in very low potencies.
For sensitive persons medium potencies are advised. In serious diseases in a debilitated patient high potencies are contra-indicated. There is a general tendency to advise novice homoeopaths against the use of high potencies. [147]

2.3.4.4 The repetition of the medicine

Hahnemann advised against repeating doses of the medicine as long as the condition of the patient is still changing. This policy is still followed by classical homoeopaths. *"The rule for repetition of the remedy is that you only repeat the dose when the effect of first dose has worn off, whether that is a matter of minutes, a matter of hours, days, weeks or months."* [148]

If the patient has to take the medicine for a longer period the potency has to be changed after a while. Hahnemann always changed the potency when prescribing the same remedy for the second or subsequent time. [149]

Several schemes for repetition related to potency have been published, but there is no standarisation of this aspect of homoeopathic therapy in the same way as there has not been for other aspects of homoeopathic practice.

There are tables available that roughly indicate how quickly particular medicines generally work and how long their effects usually last. [150]

2.3.4.5 Evaluation of the course of the disease

Homoeopaths pay great attention to the way in which the symptoms develop during the treatment. [151] [152] In the first place the homoeopath aims at improving the general feeling of well-being. Furthermore, he or she hopes that the symptoms change in a pattern which is considered to be favourable (see 2.6). If the symptoms alter in an unfavourable way, the homoeopathic physician reconsiders his or her prescription. [153]

2.4 Epilogue

Homoeopathy is a pluriform system in which the belief in the similia rule is common and central. This similia rule is interpreted and applied in a variety of ways. There are two mainstreams of thinking in homoeopahty, the 'classical' and the 'critical scientific' stream, and each of these has several schools. 'Classical' homoepathy has its own hypotheses (which it calls theories) on the nature and origin of disease and its own system of treating patients. Homoeopathy claims successes in several chronic health problems and one of these is the subject of the study that will be presented in the following chapters.

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3 METHODS AND PATIENTS

3.1 Purpose and design of the study

3.1.1 Purpose of the trial and research questions

The purpose of this trial was to study the intrinsic effect of homoeopathic medicines on children with recurrent upper respiratory tract infections (URTIs). The trial is thus meant to be explanatory. [1]

The research questions are:

1. To what degree do homoeopathic remedies (as compared to placebo's) affect the general sense of well-being of children who suffer from recurrent upper respiratory tract infections?
2. To what degree do homoeopathic remedies (as compared to placebo's) affect frequency, duration and severity of respiratory tract infections in children who suffer from recurrent upper respiratory tract infections?

3.1.2 Choice of the health problem studied

'Recurrent upper respiratory tract infections in children' provides appropriate subject matter to study the intrinsic effects of homoeopathic medicines, since it fulfills two necessary conditions; homoeopathic physicians consider recurrent respiratory infections in children to be a suitable indication for homoeopathic therapy, and their intended effects are measurable.

Homoeopaths consider homoeopathic medicines to be effective in the promotion of general good health and the prevention of new episodes of infection. Furthermore they consider children to be responsive to homoeopathic remedies. [2] However, the reported positive results of homoeopathic treatment of children with recurrent upper respiratory tract infections are not supported by evidence from controlled clinical trials. Campbell executed a retrospective study on the results of homoeopathic medicines in children with recurrent respiratory infections. His study indicated that most children improved under homoeopathic treatment, but conclusions about the intrinsic effect of homoeopathic medicines cannot be drawn from a retrospective descriptive study without a control group. [1] Such conclusions may only be drawn from the results of a prospective comparative trial of homoeopathic medicines versus placebos. [3]

The aim of the homoeopathic treatment is to improve the general health of the child and to reduce his or her vulnerability. Reduction of vulnerability will - provided that no unfavourable changes in circumstances occur - result in a decline of respiratory infections, i.e. a reduction of the frequency, extent and duration of upper respiratory tract infections, which can be measured. To measure a change in general health is somewhat more difficult, but not impossible.

It can be concluded that the problem 'recurrent upper respiratory tract infections in children' is suitable to study the intrinsic effects of homoeopathic medicines. This clinical trial examines the effects of homoeopathic medicines on respiratory infections as well as on the general health of children who are susceptable to respiratory infections.

3.1.3 Type of study

This study was designed as a randomised double-blind placebo-controlled clinical trial. Its methodology meets the current conventional standards of a clinical trial [4] as well as the requirements of proper homoeopathic practice; individually chosen homoeopathic remedies have been contrasted with individually chosen parallel placebo's.

The randomised double-blind placebo-controlled design was used because we were interested in the intrinsic effect of the homoeopathic medicines [1 5], not in the effect of the homoeopathic treatment as a whole. Study of the effect of the homoeopathic treatment as a whole requires a completely different study design.

In order to be able to measure the intrinsic effects of homoeopathic medicines, it is necessary to compare the development of the health-condition in a group of individuals who use the homoeopathic medicines with a group of individuals who do not. In order to make valid comparisons, all other conditions should be similar in both groups. Both groups should have similar ranges of prognosis on starting trial participation, and the assessments of the clinical course and other outcome phenomena should also be similar. Finally, the treatments must be similar in all respects apart from the medicines that are examined.

The best method to achieve prognostic comparability of the groups on starting trial-participation, is to allocate the different treatments to patients randomly. [6] The use of placebo and the 'blinding' of patients, doctors and assessors serves the purpose of comparability of treatment and assessment. Awareness of the nature of the received treatment influences the expectations of the patient and the doctor and thereby the effects of the treatment [6] as well as their behaviour, for instance where patient-compliance and the use of auxiliary treatments is concerned. Awareness also influences the assessment of the outcome as one tends to see

what one expects, or hopes, to see. These psychological phenomenona are ruled out by the application of placebos and blinding.

As mentioned earlier, the trial not only meets the current methodological requirements of a therapeutic experiment, but also the requirements of a proper homoeopathic approach, both in the prescription of remedies and the evaluation of the clinical course. Homoeopathy emphasizes the individualized approach of the patient and the assessment of the patient's general state of health in the long term, rather than of particular diseases or symptoms within a limited period of time.

The research design of the trial guaranteed the appropriate employment of homoeopathic remedies which were prescribed individually by a trained, qualified and experienced homoeopathic physician. The trial included the evaluation of an aspect of health that homoeopathic physicians consider to be very important: the patient's sense of well-being. [7] The length of the follow-up period (one year) was also, from a homoeopathic point of view, acceptable.

Before the study was carried out, it was presented to both a homoeopathic [8] and a general medical forum and relevant criticism was integrated in the protocol.

3.1.4 Source population

Since a child may have URTI in several sub areas (nose and paranasal sinuses, middle ear cavity and throat) simultaneously or subsequently [9], and homoeopaths consider the totality of the symptoms over a longer period of time, it would be erroneous to study only the infections of one subsystem, e.g. recurrent acute otitis media. Therefore children suffering URTIs in several sub areas were eligible for inclusion and effect-evaluation in this study comprised different types of URTIs in the several sub areas.

A proportion of the children with recurrent URTI also suffer from chronic non-specific lung disease (CNSLD). Children suffering from CNSLD were, however excluded from participation for two reasons: firstly, because many of these children require conventional medicines and secondly because inclusion of these children would interfere with the measurement of the outcome; the primary aims of the treatment of children who suffer from URTI and CNSLD differ from the primary aims of the treatment of children who only suffer from frequent URTI. [10]

Admissibility criteria (inclusion and exclusion criteria) consisted of the indications and contra-indications for the trial therapy (either placebo or verum) and any obstacles for the proper application of the trial intervention or the outcome-measurements.

Children were eligible for participation in the trial if in the preceding year

they had suffered from at least three episodes of illness caused by an upper respiratory tract infection (documented by the GP or the parents) or had suffered from two such episodes and, in addition, had a glue-ear at the time of the entry examination. They had to be at least one and a half years old and not yet ten years old.

Children were excluded from participation if they had undergone adenotomy and/or tonsillectomy, or had received a 'constitutional' homoeopathic treatment by a homoeopathic physician in the preceding 6 months.

They were also excluded if they were under regular medical care for any other chronic condition, if they had a congenital malformation of the respiratory tract or the heart, suffered from mental retardation or a neurological disorder, showed abnormal length-growth (outside the 3rd percentile) [11] or had ever suffered from rheumatic fever, endocarditis, myocarditis or nephritis.

Children with untreated dental caries at the time of the entry-examination were also not admitted to the trial, because such focal infection might influence the outcome phenomena.

Children whose parents were not fluent enough in the Dutch language to be able to understand and answer questionnaires adequately could not participate in the study and neither could children who did not exhibit three or more symptoms characteristic for a homoeopathic medicine (see *chapter 2, paragraph 2.3.4.2.1*).

3.1.5 Outcome phenomena

The outcome phenomena concerned general health and respiratory tract infections. The following aspects of the child's general health and sense of well-being were studied: energy, sleep, appetite, social behaviour and mood. Of the upper respiratory tract infections from which the child suffered during the year of participation, the frequency, duration and severity were studied in addition to the burden of the symptoms.

The operationalisation of these phenomena is described in *paragraph 3.5.1-3.5.8* of this chapter.

3.1.6 Study size

The size of the study population had to be sufficient to detect clinical relevant treatment differences. A minimal difference in improvement of 3 points on the questionnaire well-being was considered to be clinically relevant. It was calculated that this difference could be detected with a power of 90% and a significance level of 5% (double-sided) if there would be a total of 150 children in each treatment group.

3.1.7 Ethics

The use of placebos in our study was considered to be ethically justified because the children were not withheld any other prophylactic medication as a result of their participation in the trial whereas the efficacy of homoeopathic remedies was controversial.

The parents were informed about the nature of the trial and the procedures involved by way of written and oral information and their consent was confirmed by their signature on a form (see *addendum*).

If necessary, non-homoeopathic co-medication was provided by the child's own general practitioner or specialist (see *addendum*). [12]

3.2 Setting and patient recruitment

3.2.1 Setting

The study was carried out at the Free University pediatric outpatients clinic and the department of Theory of Medicine, Epidemiology and Biostatistics.

3.2.2 Recruitment of participants

We originally aimed at a study population of 300 children (for reasons see *3.1.6*) for the trial and with considerable effort we succeeded in attracting 175 suitable children. We also screened 154 children who could not be enrolled for reasons such as failing to meet the entrance criteria or refusal of informed consent. As a service to the participating families, we also cared for 27 siblings, even when they did not meet the entrance criteria and we did collect data of these children but these were not included in the analysis.

We began recruiting our subjects by informing all general practitioners in the greater Amsterdam area about the trial and requesting them to refer children who appeared to meet the admissibility criteria. They were regularly reminded of the trial in various ways: i.e. by visits, telephone calls and written memo's. However, as the influx of suitable patients continued to be smaller than expected, we decided to change our recruitment strategy. [13] We reasoned that more patients might be obtained if not only physicians, but also parents were directly informed about the study. Information leaflets about the trial were then distributed in playgroups and day-care centres. The response to this leafleting was good. Finally, the press payed attention to the trial: a woman's magazine mentioned the trial in its medical column and several local newspapers published an article about the project and this publicity was followed by a flood of responses.

These various ways in which participants were recruited may have had a different impact on parents and children from diverse backgrounds and so led to a greater heterogeneity of the study population. Fortunately, randomisation was balanced in time, so that this phenomenon affects the composition of both the placebo and the verum group to a similar degree.

3.2.3 Check of the admissibility-criteria and collection of baseline data

Early during the trial the GP who referred a child was required to fill in a questionnaire on the medical history of the child (see *addendum*). After the publicity, we sent written information about the trial on request and we enclosed a questionnaire that had to be answered and returned if parents wanted their child to participate. This questionnaire contained information on the age of the child, the duration of the problems, the frequency of respiratory infections in the previous year, applied interventions, other diseases and the condition of the child's teeth (see *addendum*).

Before an appointment for a first visit to the research team was made, this questionnaire was checked for admissibility of the child. If the child seemed to meet the admissibility criteria, he or she and his or her parents were invited for a first visit to the clinic, if not, the child's parents were provided with an explanation for the child's unsuitability for the study.

During the child's first visit to the research clinic an elaborate and detailed history was taken, clinical examination was performed and some laboratory tests were done (BSE, Hb, Ht, leucocytes, IgA, IgM, IgG) in order to exclude the possibility of, for instance, serious anaemia or major deficiencies in immunoglobulines. Laboratory tests for allergies (IgE, RAST) were only performed if the medical history or clinical examination indicated that an allergy might be present, for the purpose of advising the parents.

The medical history focused on the duration, nature and severity of respiratory tract problems, other medical problems, past history, family history, socio-economic circumstances, somatic and behavioral characteristics of the child. The child was examined by both the homoeopathic physician and the ear-nose-throat specialist. For inspection of the eardrums a microscope was used.

The information from the history, the physical examination and the laboratory tests was used to check admissibility and to choose the appropriate homoeopathic remedy. This base-line data were also used in the data analysis to check comparability of the groups on starting participation.

3.3 Intervention

3.3.1 Randomisation

When the child met the admissibility criteria and the parents gave informed consent to participation, the child was assigned randomly to either the verum or the placebo group by the pharmacist of the Free University Hospital by matching the child's consecutive reference number to the randomisation list made by the medical statistician. Randomisation was prestratified for age because symptom patterns change with the advance of age, and the following age groups were formed: 18 up to and including 23 months, 2 up to and including 5 years and 6 up to and including 9 years of age. Randomisation was balanced in time in order to achieve an even distribution of time-dependent variables over both intervention groups (verum and placebo). Time-bound factors were expected to influence the frequency and severity of upper respiratory tract infections as well as their medical management in addition to the type of children who participated in the trial.

3.3.2 Trial-interventions

3.3.2.1 General advice

Homoeopathic theory states that homoeopathic remedies should not be given if no attempt has been made to optimalize the patient's living-conditions. All parents were provided with written advice on adequate nutrition which is widely accepted in conventional as well as alternative medical practice (see *addendum*). Other advice was adjusted to the specific questions and problems; for instance, in the case of obvious allergies where the allergens could be avoided, the parents were informed about actions that could be taken.

3.3.2.2 Homoeopathic prescriptions

As already repeatedly stated, the objectives of administering homoeopathic medicines to children with recurrent respiratory infections are the improvement of general health and the prevention of new bouts of troublesome respiratory infections.

In homoeopathy, there is no such thing as one standard medicine for children with recurrent upper respiratory tract infections. In both clinical as well as classical homoeopathy so called 'constitutional' remedies are employed in long-lasting health problems as these are considered to be the most effective in the long run (see *chapter 2, paragraph 2.2.7*). The choice of a homoeopathic medicine is not solely based on the type of the medical problem (the conventional diagnosis), but

in the first place on the 'totality of symptoms' and most particularly on certain personal characteristics of the patient.

In this trial, the homoeopathic physician was not restricted in her choice of medicines. The homoeopathic physician chose medicines for each participating child on an individual basis and for each participating child several homoeopathic remedies could be prescribed over the year according to the actual clinical condition. The prescribed remedies were delivered either as a placebo or as a verum according to the treatment group to which the child belonged during the whole period of the child's participation.

The children were provided with their constitutional remedy as well as with remedies for 'respiratory emergencies' and, in some cases, they were given an organotropic remedy for longlasting nagging focal complaints.

During the trial the children's health was assessed by the prescribing homoeopathic physician at regular intervals and the homoeopathic prescriptions were adjusted according to the observed developments. This regular adjustment is customary in homoeopathic practice: treatment of chronic and recurrent diseases is a process in which the physician is guided by the reactions of the patient which are interpreted according to certain rules ('Hering's laws', see *chapter 2, paragraph 2.2.6*).

In German, French, Dutch and Anglo-Saxon literature much is written about 'constitutional remedies' for children. As a child changes in the course of his life, the constitutional remedy may change also.

Factors such as emotional, behavioral and physical characteristics, the type of disease the patient is suffering from, past history and family history are all taken into account when chosing a constitutional remedy. If it is not immediately obvious which constitutional medicine suits the patient, the repertory can offer help in the selection of the most appropriate remedy. (see *chapter 2, paragraph 2.3.2.2*).

Constitutional medicines that are frequently indicated in children with recurrent upper respiratory tract infections include: *Calcium carbonicum, Calcium phosphoricum, Sulphur, Lycopodium, Phosphorus, Silicea, Pulsatilla, Thuja, Tuberculinum and other nosodes.*

An elaborate and detailed history was taken and a clinical examination was performed to find the suitable remedies. We used the RADAR computer program, which is widely used by homoeopathic practitioners, to repertorise the symptoms of our patients.[14] The prescribed constitutional remedies are tabulised in the *addendum*.

Homoeopathy has at its disposal many 'acute remedies' for respiratory infections. The most popular are: *Allium cepa, Belladonna, Aconitum, Ferrum phosphoricum, Chamomilla, Pulsatilla, Kalium sulfuricum, Kalium bichromicum, Arsenicum jodatum, Sulphur jodatum, Drosera, Ipecacuanha, Tartarus emeticus, Spongia, Lachesis.* [15 16 17]

The selection of acute remedies for possible future episodes was based on the symptom-patterns of former episodes as described by the parents. The prescribed acute remedies are tabulised in the *addendum*.

Children who suffer from frequent upper respiratory tract infections often have longlasting sequelae, which we attempted to combat with organotropic remedies given during some time along with their constitutional remedy. This method is recommended by several British authors. [18]

For glue ears, for instance, several remedies are recommended [19]: *Kalium sulfuricum, Kalium muriaticum, Pulsatilla nigrans, Hydrastis canadensis* and for adenoid problems several others are commonly prescribed [20]: *Barium jodatum, Calcium jodatum, Agraphis nutans, Calcium phosphoricum*.

We administered organotropic medicines for glue-ears and enlarged adenoids. The prescribed organotropic remedies are tabulised in the *addendum*.

3.3.2.3 Follow up and adjustments of therapy

During return visits the homoeopathic physician evaluated the health of the children by means of scheduled history taking and physical examination. The prescription of homoeopathic medicines was then adjusted to the perceived developments in the following ways.

If the child generally seemed to feel better, the same constitutional remedy was continued, however, the dosage was adjusted: In case of steady improvement of the patient's health, the same medicine in the same potency was continued at greater intervals or the same medicine was given in a higher potency. If the child had been in very good health for some months, the administration of the constitutional medicine was stopped, as is customary in homoeopathy.

Homoeopathic theory states that shortly after a patient starts to take a homoeopathic medicine his or her complaints may worsen temporarily. If parents informed us by telephone that this had happened we advised them to interrupt the administration of the medicine until the child was better again. They then could start anew; if the reaction had been fierce, the medicine was given in another dosage or another potency, in the event of a mild reaction the same potency and dosage was administered.

If, after about six weeks, the health of the child had not changed at all, or if the child's condition had gradually worsened, the case was reevaluated which often led to a different constitutional remedy being chosen.

If we judged it irresponsible to treat a given condition with a trial medicine only, we advised the parents to consult their own general practitioner whom we informed about the child's condition (see also *3.3.4*). Trial personnel did not prescribe conventional medicines and did not refer a child for surgical intervention.

The use of homoeopathic medicines other than those supplied by the trial's organisation, was not allowed, because this would have interfered seriously with the experiment.

The consultation scheme was flexible, consultations took place whenever the patient's parents or the homoeopathic trial physician considered them to be necessary or desirable. Most children were seen at least 6 times during the year of follow-up. The homoeopathic physician could be contacted daily.
GPs were informed by letter after the child's first and last visit to the clinic.

3.3.3 Supply of trial medication and blinding

The trial medication was produced and supplied by V.S.M. Geneesmiddelen B.V. (drs. M.D. Dicke, pharmacist) and distributed to the patients by the Free University Hospital pharmacy (head: drs. A.C. van Loenen, pharmacist).

The personnel of the hospital pharmacy sent the medicines directly to the parents. They were the only persons who had access to information on the distribution of children over the placebo and verum groups.

After the trial had finished an independent person checked the records of both the producer and the supplier for potential mistakes in the dispatch of the correct substance, verum or placebo, to the children participating in the trial.

The placebo medication was in no way distinguishable from the verum. The code was not broken during the trial and remained so until all children had finished their participation and the scheme of analysis was fixed. The code was then half broken for the analysis, placebo and verum were given letter codes and coded information on the distribution of the children over both groups was given to the researchers. It was only after the data analysis was completed, that the code was completely broken.

3.3.4 Interventions outside the trial (co-medication and surgery)

During participation in the trial we tried to avoid the use of non-homoeopathic remedies as far as possible in order to avoid confounding, as well as disturbing

the action of the homoeopathic remedies. In order to achieve this, acute homoeopathic respiratory trial medicines were given to the parents to be administered when necessary and the homoeopathic physician of the trial was on call daily to advise the parents or the family doctors of participating children in the event of acute problems. Regular medicines were, of course, not withheld from the children if their need was really indicated, but they were not prescribed by the trial personnel. When the child required examination and advice for an acute respiratory tract infection or any other problem, the parents either consulted their own general practitioner or they contacted the homoeopathic physician in charge of the trial. If the homoeopathic physician of the trial considered other measures to be necessary, for example the use of non-homoeopathic medicines or a diagnostic test, she informed the child's own general practitioner, who then decided which course of action should be followed. The child's general practitioner reported his or her observations and interventions to the homoeopathic physician in charge of the trial.

Before the start of the trial, the GPs were requested to keep to certain directives when prescribing medicines to participating children (see *addendum*).

3.4.1 Data collection

Data ware collected in several ways. The main source of information were the parents of the children and information was also obtained from the physicians who were involved in the care for the children. In the following the data collections are listed.

1. The parent's diaries and the bi-weekly inventarisation of these diary notes by means of a structured telephone-interview.
2. The parents' answers to the questionnaire on child's well-being at the start of participation and after 26 and 52 weeks of participation.
3. Notes of the several physicians who were involved: the findings on scheduled examinations of the upper respiratory tract by the otolaryngologist at the first and last visits by the children to the research centre; the findings of the homoeopathic physician on scheduled history taking and examination of the children during their visits to the research centre; the prescribed remedies; the findings and interventions of the general practitioners and specialists. The latter were noted during the child's visits, in a booklet that the parents kept with them. The general practitioners also sent overviews of any consultations that occurred during the year of participation.
4. The parents' answers to our 'satisfaction-questionnaire', which they completed shortly after their child finished participation. The object of this questionnaire was to evaluate the practical conduct of the trial and find which practical aspects needed to be improved from the participants' point of view.

Data were put in a computerised database and all input was checked for mistakes.

3.4.2 Diaries

As we required information on frequently occurring symptoms during a year of intervention and follow up, we wanted to monitor the participating children as closely as possible. Their parents had the possibility to observe them nearly continuously, therefore we asked them to collect data for us, also realising however, that their personal involvement combined with the wide variety of their personalities, knowledge and attitudes towards their childrens' symptoms, would implicate a large inter-observer variability in measurement. This disadvantage does, however, in our opinion, not outweigh the advantage of continuous close observation. Parents kept a diary on the health of their child. They were telephoned every fortnight by a doctor who made an inventory of symptoms that had been noticed by

the parents. These regular telephone calls kept parents alert and involved in the trial and encouraged them to keep the diary up to date.

We specifically asked for information on the following symptoms: lack of energy, fever, tummy ache, headache, nasal discharge, nasal obstruction, sore throat, earache, ear discharge, hearing problems, cough, use of medicines, visits to doctors, absence from school and illnesses in the family.

Over the year the answers to our daily questions thus provided us with 365x15 data per child.

3.5 Outcome variables and analysis

3.5.1 Outcome measures

In this trial two health phenomena had to be operationalised before they could be measured: general well-being and respiratory infections. For general well-being a questionnaire was designed, for respiratory infections several scales based on diary data.

Respiratory infections cover a broad spectrum of courses varying from sub clinical disease to severe illness. The various clinically relevant consequences of recurrent respiratory infections in susceptible children may be categorised as transient, long-lasting and permanent discomfort and disability.

Repeated episodes of transient discomfort and disability as a result of acute respiratory infection occur in all these children. Longlasting discomfort and disability (like nose obstruction) as a result of a past infection or a continuing chronic focal infection (such as chronic adenoiditis) do occur in some of these children. Permanent disability as the result of permanent damage through serious complications of respiratory infections occurs seldomly.

In measuring effectiveness of treatment, transient discomfort and disability must be focused on in the first place. Rare complications are not liable to occur in a trial with a study population of a few hundred patients and therefore cannot serve as an outcome measure. They must, however, be described if they do occur during the trial.

Several scales were designed to measure the various aspects of respiratory infections in the trial: the episode scales, the day sum-scale, the chronicity scale, the operation scale, the antibiotic scale and the overall scale.

The episode scales were meant to be highly specific for episodes of illness caused by respiratory infection, and episodes are defined by combinations of general and local respiratory symptoms. A syndrome must contain symptoms of the respiratory tract as well as general symptoms in order to be labelled as an episode of respiratory infection.

The day sum-scale was designed as a measure of the burden of transient as well as long lasting symptoms (discomfort and disability) caused by respiratory infections. The specificity of the day sum-scale is low, since general symptoms caused by other diseases may also contribute to the score. It may be assumed that the contribution of other diseases to the mean day sum-scale of a year will be small in comparison to the contribution of respiratory infections as trial children

suffer frequently from respiratory infections. Moreover, respiratory symptoms were given much more weight in the day sum-scale than general symptoms to reduce disturbance caused by other diseases. General symptoms are though very important for the children. Therefore, the dimension of general symptoms ('malaise sum-scale') of the day sum-scale was also analysed separately and so were the other three dimensions ('ear, nose and throat sum-scales'). Therefore 'specific' information was not completely obscured in the day sum-scale. In addition, the general drawbacks of being frequently ill as a result of respiratory infections were also measured by the general well-being questionnaire.

The chronicity scale was designed as a measure of long lasting low grade symptoms.

Respiratory infections may have prompted interventions which in turn may have influenced respiratory infections. The use of antibiotics, adenotomies and tonsillectomies are most important in this respect. They were also used as outcome measures.

To summarise the various aspects of health in individual children and to correct for co-interventions an overall scale was designed.

It is most important that a scale really measures what it is intended to measure. In other words, it should be valid. As there is no gold standard for the quantitative measurement of the phenomena well-being and respiratory infections[21], it is difficult to assess the validity of scales. One has to take resort to 'face validity': do experts in the field of study consider the scale to be valid? A small panel of experts was consulted on the face validity of the first version of the episode scales and the day sum-scale. Their advice was incorporated into the definite scales. It is obvious though, that there is a strong unavoidable subjective element in the design of scales. Burden of suffering can hardly be measured in an 'objective' way. What is a burden to one person may be a slight inconvenience to another. Even if the measures were not entirely perfect, they were applied in the same way to the data of all children and subsequently the calculated scores of children from both treatment groups were compared. In fact, shortcomings of the scales affect outcome measures in both treatment groups.

In the following paragraphs the various outcome measures shall be described in greater detail.

3.5.2 The questionnaire on children's well-being

The general well-being questionnaire was designed for this trial to measure general well-being in a child. It covers five dimensions of health: sleep, energy, appetite, mood and social behaviour.[22] Answers are rated on a Likert scale.[23] For 4 of the 5 dimensions the score can vary between 3 and 15, for the dimension mood the score can vary between 4 and 16, this means that the total score can vary between 16 and 76. Two of the three questions on social behaviour are rela-ted to school or creche attendance. Because many children in the trial did not yet attend school or creche regularly, only one question of this dimension was answerable for these children. This dimension of the questionnaire was therefore left out of the analysis and this meant that the total score of the shortened questionnaire could vary between 13 and 61.

The difference between the score after 52 weeks follow-up and the baseline score for each individual patient indicates improvement or deterioration of well-being over the year.

The questionnaire was tested on 107 schoolchildren for test-retest reliability, which was acceptable.[24] However, before the start of the trial the score could not be tested for sensitivity to change (responsiveness) due to a lack of time.

3.5.3 Episode scales

The trial did not only concern the occurrence of separate respiratory and general symptoms, but predominantly the occurrence of patterns of overt respiratory infections. Hardly any single symptom (apart from purulent discharge) is specific to respiratory infection, but combinations of symptoms are much more specific and so are some signs of infection found by medical examination.

In this trial, a standardized physical examination of the patient during any acute respiratory infection could not be performed for practical reasons. Neither could GP's reports be used as a measure of respiratory tract infections for several reasons. The first reason is that no doctor is consulted during the majority of respiratory tract infections. The second reason is the evidence found in the literature for a great inter-, and less well documented, intra-doctor variability in the assessment of respiratory infections, particularly in the labelling of subentities like sinusitis, angina etc.[25,26] One of the causes of this assessment-variability is the unity of the respiratory tract. An infectious process in the respiratory tract often concerns several sub areas at the same time, or travels from one area to another, most particularly in children.[27] Any physical examination is time bound and can only indicate the patient's condition at the moment of examination.

The observations of the parents were not just recorded momentarily, but con-

tinually upon a daily basis. Thus information in our database is devided into daily parts. From these parts we reconstructed episodes of respiratory tract infection without trying to differentiate between the various subentities.

The reconstruction from the data on symptoms to episodes was done by means of two algorithms: the first algorithm concerned recognition, the second delimiting. Firstly, we defined criteria with regard to the presence of certain symptoms in particular degrees of severity which were to be met during at least one day in order to call the experienced distress an episode of respiratory infection. Then, we defined criteria for adjacent days to be included into the episode in order to (artificially) delineate the episode in time and measure duration.

After the definition of episodes, we counted the number of thus defined episodes that each child had during participation and the total number of days in the follow-up period during which the child was experiencing an episode. Then the episode-severity-score was computed by calculating the mean of the day sum-scores of each episode and next calculating the mean of these means, which served as the combined measure of severity of all episodes the child went through. In this combined measure of severity long and short episodes have equal weight so that short fierce episodes with a high mean day sum-scale contribute to the same degree to the combined measure of severity as long lingering episodes wih a low day sum-scale.

If the plain mean day sum-scale of all episode days had been taken as a measure of severity, the long episodes with low mean day sum-scores would have been given more weight.

The criteria which at least one day (*a 'peak-day'*) had to fulfill in order to name the experienced distress an episode of acute upper respiratory tract infection were:

listlessness or fever (rectal temperature ≥38 degrees Celsius)
plus
one or more of the following symptoms,
credited at least a moderate severity:
green nasal discharge
earache
sore throat
cough
or
ear discharge
or
one or more of the following symptoms,
credited at least a considerable severity:
transparent nasal discharge
nasal obstruction
cough

The criteria for *'adjacent days'* were less stringent, symptoms on these days were to be less severe than on 'peak-days'. 'Adjacent days' had to fulfill the following criteria in order to be reckoned to the episode:

listlessness or fever (rectal temperature ≥ 37,5 degrees Celsius)
plus
one or more of the following symptoms,
in less than moderate severity:
green nasal discharge
earache
sore throat
cough
or
ear discharge
or
one or more of the following symptoms,
credited moderate severity:
transparent nasal discharge
nasal obstruction
cough

The definition of adjacent days and peak days enabled us to delimit acute episodes in time. Beyond this defined limit, some local or general symptoms which did not meet the criteria for adjacent days could persist and either indicate the low grade persistence of the infection (with the agent still being present in the tissues), or the after effects of the infection which had already cleared. New episodes of respiratory infection cannot be distinguished from exacerbations of chronic focal infections by clinical symptoms alone. The symptoms which persisted after an episode were covered by the day sum-scale and the chronicity scale.

3.5.4 Day sum-scale

To condense information, a sum-scale for respiratory infections was computed for each day, based on the presence and degree of symptoms reported by the parents in the diaries. The day sum-scale has four dimensions consisting of symptoms of the nose, ear and throat and general symptoms respectively. The four dimensions could also be analysed separately.

Since we were interested in respiratory infections, dimensions of the upper respiratory tract were given greater weight than the dimension of a-specific, general symptoms which may have been caused by all kinds of other diseases, as outlined in *paragraph 3.5.1.*

Before deciding upon the differential importance of each symptom, we asked the advice of several experts in the field of general practice, paediatrics and otolaryngology. *Table 3.1* shows how much weight was given in the day sum-scale to the different symptoms. The scores for the separate symptoms is added to yield the day sum-scale. Symptoms of the respiratory tract can add to a maximum score of 42 (note that the several colours of nasal discharge are mutually exclusive), general symptoms of not being well can add up to a maximum score of 14. This makes that the day sum-scale can vary between 0 an 56. A score of zero indicates no complaints and a high score indicates many complaints.

For all participating children, the day sum-scale was computed for each day of follow-up for which diary data was available and, for each child, the mean of the day sum-scores of the whole period of follow-up was computed.

3.5.5 Chronicity scale

We tried to describe some characteristics of the symptom patterns over the year in various ways by looking at several aspects of illness. One aspect is the occurrence of acute episodes, another aspect is the persistence of symptoms. We tried to model persistent symptoms in a 'chronicity scale' which was derived directly

Table 3.1 *The day sum-scale*

Day sum-scale based on reported symptoms						
symptom						
	absent	present				
	absent	unspecified	slight	degree unknown	moderate	severe
green nasal dc	0	n.a.	0	4	8	8
clear nasal dc	0	n.a.	0	2	4	4
nasal dc colour ?	0	n.a.	0	2	4	4
nasal obstr.	0	n.a.	0	2	6	6
ear dc	0	6	n.a	n.a.	n.a.	n.a.
earache	0	n.a.	0	2	6	8
sore throat	0	n.a.	0	2	6	8
cough	0	n.a.	0	0	6	6
tummy ache	0	n.a.	0	1	2	3
headache	0	n.a.	0	1	2	3
listless	0	3	n.a.	n.a.	n.a.	n.a.
temp.	<37.5	unspecified	37.5 - 37.9	degree unknown	38-38.9	>38,9
	0	n.a.	1	3	4	5

n.a. = not applicable, d.c. = discharge
temp. = temperature, colour? = colour unknown

from the distribution of day sum-scores of a child and comprises the proportion of days with a medium day sum-scale.

We defined the chronicity score as the number of days on which the day sum-scale was greater than 6 and smaller than 15 divided by the total number of days for which the day sum-scale could be computed. In a formula: $a/(a+b+c)$, in which a is the number of days with day sum-scale of 7 up to and including 14, b is the number of days with day sum-scale greater than 14 and c is the number of days with day sum-scale smaller than 7.

The cut-off points for computing the chronicity scale were chosen after considering the scores that several symptoms and combinations of symptoms may produce.

3.5.6 Antibiotic scale

Parents reported daily on the use of any non-trial medicines. The diary notes were checked against the reports of general practitioners and specialists. All medicines were registered in a data base. For systematic antibiotics we recorded the reason for prescription as well as the type of substance prescribed.

Antibiotic courses were classified according to the reasons for prescription. Two prescription characteristics (respiratory versus non-respiratory and preventive versus therapeutic) were distinguished so that four categories were formed: for existing respiratory problems, to prevent respiratory problems, for existing other problems and to prevent other problems.

3.5.7 Operation scale

Any operation that the child underwent was recorded by the parent in the diary and reports from GP's who referred the children for an operation and from the consultants who performed the operations were also received. Both sources of information were referred to in the data base on operations.

Adenotomy and tonsillectomy were considered important indicators and modifiers of (frequent) respiratory infections.

3.5.8 Overall scale

To summarize the several relevant and interrelated aspects of the child's health during participation, we computed an overall scale out of the above described 'aspect scales' (*table 3.2*). The following measures were combined: mean day sum-scale, chronicity score, use of antibiotics, adenotomy and tonsillectomy, the score on the questionnaire on well-being at 52 weeks minus the score on the questionnaire on well-being at 0 weeks. To each of these aspects a summarising scale was designed and these aspect scales were added together to yield the overall scale.

Table 3.2 *The overall scale*

1	**Mean day-sum-score**	
	lowest quintile	0
	second	1
	third	2
	fourth	3
	fifth	4
2	**Chronicity score**	
	lowest quintile	0
	second	1
	third	2
	fourth	3
	fifth	4
3	**Score on the QWB at 52 weeks minus at 0 weeks**	
	lowest quintile	4
	second	3
	third	2
	fourth	1
	fifth	0
4	**Use of antibiotics**	
	no courses	0
	1 course	2
	2 courses	3
	3 or more courses	4
5	**Operations**	
	no adenotomy or tonsillectomy	0
	adenotomy and/or tonsillectomy	4

The distribution of the means of the day sum-scale, of the chronicity scores and of the sum scores on the questionnaire on well-being at 52 weeks in all 170 eligible randomised children were each divided into 5 quintiles. For each child, a 'summarising aspect score' was attached to each of the 'original aspect scores' according to its location in this distribution: a score of 4 was awarded to the 'original aspect score' if it was in the quintile that indicated the most severe condition, a score of 0 was awarded to the 'original aspect score' if it was in the quin-

tile that indicated the most favourable condition. Antibiotics and operations were dealt with in a different fashion. Antibiotics were scored according to the total numbers of courses the child had had during participation; three or more courses were scored 4, two courses 3, one course 2 and zero courses 0. We considered adenotomies and tonsillectomies to be relevant operations, these were awarded the score of 4. The overall scale was defined as the sum of the 'summarising aspect scores' and it ranges from 0 to 20 and a high score on the overall scale indicates many health problems.

A child who has, compared to the whole group of participating children, been doing well during follow-up, who had a low day sum-scale, no interventions outside the trial and an improvement on the well-being questionnaire, will have a low overall score. A child who did have interventions and subsequently a low day sum-scale, will have a medium overall score, as the improvement of the day sum-scale by the co-intervention is compensated for in the overall score. A child who did not at all do well, who was miserable over the year and had several co-interventions will have a high overall score.

3.5.9 Analysis of the outcome

Analyses were performed for the whole group as well as for the three age groups separately. Diary derived scores were computed for the whole year of follow up, as well as for the last nine months, as homoeopathic medicines need time to develop effect. The mean day sum-scores during the four quarters of the year were also analysed separately to look for a trend over the year. The four dimensions of the day sum-scale (ear, nose, throat and general symptoms) were also compared separately.

For differences in means and proportions 95% confidence intervals were computed, means were compared with Student's t test and proportions with a chi square tests and chi square tests for trend where appropriate. The level of significance was 5% (double-sided). When the value 'zero' is not included in the confidence interval, the difference is statistically significant at the 5% level (double-sided test).

Differences in means of scores are abstract and difficult to interpret. To facilitate interpretation ratios of means of scores are presented besides differences. These ratios express the magnitude of the mean score in the index group as a fraction of the magnitude of the mean score in the control group.

Finally, multiple linear regression models were used to estimate differences of means of several scores with a greater precision and adjusted for small differences of prognostic factors at the baseline. In a multiple regression model, the joint influence of variables on the outcome measure is analysed, taking account of possible correlations among them. In these models the dependent variables were the outcome scores and the independent variables were the type of therapy and several baseline measures.

Missing data were handled as follows: means were computed for the days on which data were available. Dimension scores in the questionnaire well-being were divided by the numbers of answered questions and multiplicated with the total number of questions that the dimension contained.

3.6.1 Numbers

The first patient was enrolled in the trial on the 16th of March 1987 and the last on the 13th of December 1990.

A total of 175 eligible children were enrolled and the age distribution is shown in *table 3.3*. Randomisation was pre-stratified in three age groups, for which the symbols A,B,C and ABC will be used. A is the group aged 2 to 5 years on entering the trial, B is the group aged 6 to 9 years upon entry to the trial, C is the group aged 18 to 23 months on entering the trial and ABC incorporates all eligible participating children.

Table 3.3 *The age distribution of the enrolled eligible participants*

Age-group	x	y	total
A 2-5 yrs	73	74	147
B 6-9 yrs	10	10	20
C 1,5-<2 yrs	4	4	8
ABC all ages	87	88	175

As a service to the participating families, we also cared for 27 siblings, even when they did not meet the entrance criteria. These children received the same type of trial medication (either verum or placebo) as their randomised sibling. These children are not included in the analysis as they were not randomised and a great deal of them did not even met the entrance criteria.

3.6.2 Discontinuation of trial therapy

Three children stopped trial therapy, but nevertheless their parents went on to collect information for the trial. The main reasons for discontinuation were the dissatisfaction of parernts and unfavourable changes in circumstances. Two children did not complete trial therapy because the parents were unsatisfied with the results and these children subsequently underwent an operation in the ear-nose-throat area (a girl from the x-group, aged 5, discontinued after 22 weeks and had ventilation tubes placed, a boy from the y-group, aged 4, discontinued after 23

Table 3.4 *Reasons for preliminary termination of participation (n=8)*

More than 26 weeks lost (data not in analysis)

code	wk	grp	reason	GP
A053	23	y	bad results and too much effort to go on.	yes
A094	5	x	bad results and regret (placebo not appreciated).	yes
A109	8	x	bad results and regret (placebo not appreciated).	no
B006	6	x	regret, parents prefer tonsillectomy.	yes
C008	16	y	regret, the possibility of placebo not appreciated.	no

Less than 27 weeks lost (data in analysis)

code	wk	grp	reason	GP
A082	29	y	bad results, had an operation performed.	yes
B012	29	x	bad results and too much effort to go on.	yes
A115	33	y	had to change address.	no

weeks when his tonsils and adenoids were removed). The third child, a boy from the y group, aged 3 on admittance, stopped visiting the clinic after 30 weeks because his mother could not cope any more, but she continued to answer the telephone interviews, albeit it irregularly.

The data from these three children which we collected during the whole year, was included in the analysis according to the 'intention-to-treat' principle. The 'intention-to-treat' principle means that all children remain in the group to which they were assigned by randomization in order to retain comparability of study groups obtained by randomization.

3.6.3 Loss to follow-up

Eight children were lost to follow-up sometime during the year that they should have participated. In most cases a variety of reasons played a role in the decision to stop. The parents of five children chose another therapeutic approach because they were unsatisfied with the results and in two of these five cases, the parent's uncertainty about the nature of the remedies (placebo or verum) contributed to their decision to withdraw their child.

The parents of two other children later regretted that their child had actually joined the trial and therefore withdrew; the parents of one child could not bear the thought that their child might receive the placebo in an acute episode of infection and the parents of the other child were unsatisfied, because, after joining and participating for several weeks, they felt that they had not chosen to the

participate themselves, but had instead been forced by their GP to join the trial while they preferred themselves a quick straightforward solution to their child's problems by tonsillectomy.

One child was lost to follow-up because his mother was forced to change address.

Table 3.5 *Distribution of reasons parents gave for terminating participation (n = 8)*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
bad results	2	2	1	0	0	0	3	2
regret	0	0	1	0	0	1	1	1
other	0	1	0	0	0	0	0	1
total	2	3	2	0	0	1	4	4

Children who completed less than 26 weeks follow-up were not included in the analysis of the outcome phenomena under study because there was little data available on them. They constituted only 5/178 (2.8%) of all participating children and were almost evenly distributed over the x and y group. We analysed the data of all children who completed the study and all children who participated in the trial for more than 26 weeks. For two of the three children who did not complete follow-up and whose available data were analysed, we could get hold of data on interventions outside the trial. However, no information on the further clinical course or outside trial interventions could be obtained of the child whose mother had to change address, as neither the investigators nor the GP had their new address. This boy was doing well before trial participation ended.

3.6.4 Patient characteristics

Age and gender

The age of the children on starting trial-participation varied between one and a half and nine years.

There were 90 boys and 80 girls in this study. The gender-distribution of both treatment groups was comparable.

Table 3.6 *Follow-up time lost and numbers of children whose data were analysed*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
lost weeks								
27-52	2	1	1	0	0	1	3	2
1-26	0	2	1	0	0	0	1	2
0	71	71	8	10	4	3	83	84
total	73	74	10	10	4	4	87	88
total analysed	71	73	9	10	4	4	84	86

Perinatal history

Four children had had a premature birth (before the 38th week), three in the x group and one in the y group. The mean birth weights were comparable in both treatment-groups.

Since breast-feeding may have an impact on later pathology, we enquired about the type of infant-feeding the child had had. No statistically significant differences in the numbers of children who had been breast-fed for at least three months were found between the two treatment groups.

Details of the upper respiratory tract infections

The age when, according to the parents, the complaints started differed substantially in the three age-strata. The median age at which the complaints began was 9 months for the youngest group of children, 1 year for the 2-5 years-olds and 2 years for the oldest group. Part of these observed differences might be due to recall-bias, but the differences might also indicate differences in the underlying pathological mechanisms and/or the exposure to respiratory pathogens. Therefore we analysed the results of the trial for the three age-groups separately as well as for the group as a whole.

The duration of complaints on entering the trial was greatest in the oldest age group, even though their complaints were reported to have begun at a later age than in the younger groups. The median duration of frequently recurring URTIs was 1 year for the group of youngest children, 2.4 years for the 2-5 years-olds and 4.7 years for the group of oldest children.

Table 3.8 gives further information on the past history of upper respiratory tract infections of the children in the two intervention groups.

Table 3.7 *Gender distributions, median ages of the children at their start of participation and at the start of complaints, median duration of complaints and data on perinatal histories (mean birthweights and duration of breastfeeding) of the participating children (the two intervention groups, in the three age strata and in all the children)*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
total number	71	73	9	10	4	3	84	86
gender (% male)	50	53	56	60	50	67	51	55
age start trial (yrs)	3.6	3.9	7.0	6.4	1.8	1.6	3.6	4.2
age start complaints	1.0	0.9	3.1	1.5	0.8	0.5	1.0	0.9
duration compl. (yrs)	2.3	2.5	4.4	4.9	1.0	1.1	2.3	2.6
birth weight (g)	3210	3191	3479	3467	3255	3850	3242	3246
breastfed > 3mths (%)	39	49	67	30	75	67	44	48

Recurrent upper respiratory tract infections may be more or less concentrated in different sub areas. Acute otitis media had occurred in almost equal proportions of children in the x and y group, glue-ears were more frequently reported in the y-group than in the x-group (64% versus 52%), rhino-sinusitis and pharyngo-tonsillitis were more frequently reported in the x-group.

In the past history of most children infections in at least two sub areas of the upper respiratory tract were reported. In the entire group 55% of all children had suffered from problems in two sub areas and 31% had suffered from problems in three sub areas.

Nearly half of all children had undergone an adenotomy (but not in the 6 months preceding their start of participation in the trial). Most children had not undergone a tonsillectomy. Ventilation tubes had been placed in only a minority of the participating children.

We asked the parents how their children's performance had been in the Euwing test, a hearing test which is taken around the age of nine months. The majority of children had performed well, which indicates that their recurrent URTIs probably had started at a later age.

Table 3.8 *History of upper respiratory tract problems (the numbers are percentages of the two intervention groups, in the three age strata and in all the children)*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
total number	71	73	9	10	4	3	84	86
lifetime prevalence								
acute otitis	87	89	100	80	100	100	89	88
glue ear	52	63	78	70	0	67	52	64
rhinosinusitis	82	77	89	40	100	100	83	73
tonsillitus	49	42	44	50	25	0	48	42
no sub areas urt								
1	14	15	0	30	0	0	12	16
2	49	58	67	50	75	100	52	58
3	37	27	33	20	25	0	36	26
surgery								
adenotomy	49	42	67	50	25	0	50	42
tonsillectomy	10	8	2	2	0	0	11	9
tubes								
once	8	12	22	10	0	0	10	12
>once	4	7	11	20	0	0	5	8
Ewing test								
sufficient	75	60	89	70	100	100	77	63
insufficient	14	25	0	20	0	0	12	23
not available	11	15	11	10	0	0	11	14
previous year no of episodes								
2	4	0	0	0	0	0	4	0
3	39	37	67	40	25	67	42	38
4-5	46	55	33	60	50	33	45	55
6-8	4	7	0	0	0	0	4	6
9-12	6	1	0	0	25	0	6	1
no of antib courses								
0	18	15	11	20	25	0	18	15
1	20	23	44	20	0	33	21	23
2	31	30	11	30	25	67	29	31
3	21	16	22	30	25	0	21	17
4-5	7	14	11	0	0	0	7	12
6-8	1	1	0	0	0	0	1	1
9-12	1	0	0	0	25	0	2	0

The parents and the general practitioner were asked to document the episodes cof upper respiratory infections in the year prior to the start of participation. To be eligible to participate, the child had to have had at least two episodes if he also had a glue-ear on his first visit to the clinic, and at least three episodes if he had no glue-ear.

The numbers of antibiotic courses administered for URTIs in the previous year were comparable in both treatment groups.

Family history on respiratory and atopic diseases

Family factors may play a role in the vulnerability to respiratory infections in childhood.

We enquired about frequent or chronic upper respiratory infections, middle-ear problems due to infections, chronic non-specific lung disease, hayfever and eczema. The distributions of these diseases in the parents and grandparents of the trial-children were comparable (*table 3.9*).

Social and environmental circumstances

Social circumstances may influence exposure to respiratory pathogens as well as the speed of recovery from respiratory infections. We enquired about family composition at the time of entry, school attendance and housing-conditions.

Most children lived with their own father and mother, only a very low percentage of children came from 'broken homes', which might indicate that the trial-children are not 'representative' of the population of 'Dutch children with recurrent upper respiratory tract infections'.

The number of children in the family influences the risk of contamination with respiratory pathogens and the risk for toddlers increases when they have older siblings. The numbers of children in the families of participants and the rank numbers of the participating children are given in *table 3.10*.

Attendance of a school, creche or playgroup usually increases the risk of respiratory infection. School and creche attendance were comparable in both treatment groups.

Information on housing conditions was collected during the first interview at the research centre. Data on dampness and (local) pollution are difficult to obtain without a home visit, which we were unable to pay. Therefore only data on the heating-system in the child's home can be presented. The types of heating were comparable in both treatment groups (*table 3.10*)

Passive smoking is a risk-factor for respiratory infections. In 52 of the 86 (60%) households of the y-group and in 44 of the 84 (52%) households of the x-group both parents were non-smokers, the difference was 8%. Twenty seven of

the 84 (32%) mothers of children in the x group were smokers versus 23 of the 86 (27%) mothers in the y-group.

The presence of pets may increase vulnerability in atopic children.
In the x group 38% of the children had cats and 26% had dogs at home, in the y group these percentages were 21% and 12%. ($p = 0.02$ for cats and 0.03 for dogs).

Although the children who participated in our trial came from all over the Netherlands (*table 3.11*), most of them lived in or around Amsterdam. The travel distance between living place and clinic varied from 5 minutes to two hours.

The ways in which parents and children became interested in the trial are tabulised in *table 3.12*.

General well-being questionnaire on entering the trial

The mean sum-score of the general well-being questionnaire completed on entering the trial was slightly better in the y-group. In the small group of youngest children the mean sum-score was even much better in the y-group than in the x-group.

3.7 Summary

The purpose of the study was to investigate the intrinsic effect of individually prescribed homoeopathic medicines. The choice of the subject, the design and the conduct of the study were performed in such a way that the conditions for homoeopathic remedies to exert a positive effect were optimal. The study was randomised, double-blind and placebo-controlled; randomisation was stratified according to age category and balanced in time.

Study subjects were children aged between one and a half and 10 years who suffered from frequently recurring upper respiratory tract infections. The duration of follow-up was one year.

Outcome measures of general well-being and respiratory infections were mainly based on data of questionnaires and diaries.

The number of eligible children enrolled was 175 and the data of 170 children could be analysed. The comparability of most baseline variables in the two treatment groups was reasonable with only a few exceptions.

Table 3.9 *Positive family history on frequent upper respiratory infections and atopic diseases of the participating children (the numbers are percentages of the two intervention groups, in the three age strata and in all the children)*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
total number	71	73	9	10	4	3	84	86
frequent URTI (oma not included)								
one parent	17	26	11	20	25	33	17	26
both parents	3	0	0	10	0	0	2	1
otitis								
one parent	27	21	33	30	25	0	27	21
both parents	1	3	0	0	0	0	1	2
CNSLD								
one parent	35	37	22	20	25	33	33	35
both parents	10	8	0	0	0	0	8	7
hayfever								
one parent	24	32	11	30	25	0	23	30
both parents	1	1	0	0	0	0	1	1
eczema								
one parent	38	26	22	30	25	0	36	26
both parents	1	1	11	0	0	0	2	1
atopic syndrome								
one parent	48	49	33	60	50	33	46	50
both parents	21	18	22	10	0	0	20	16

Table 3.10 *Some social circumstances of the participating children (the numbers are percentages of the two intervention groups, in the three age strata and in all the children)*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
total number	71	73	9	10	4	3	84	86
parents at home								
father	97	99	100	90	100	100	98	98
mother	100	100	100	90	100	100	100	99
both parents	97	99	100	80	100	100	98	97
no of siblings								
no	24	25	11	20	50	0	24	23
one	62	56	67	40	25	67	61	55
two	11	16	22	40	25	33	13	20
three	3	3	0	0	0	0	2	2
child's rank no								
first	54	55	67	70	75	0	56	55
second	39	32	33	10	0	67	37	30
third	4	12	0	20	25	33	5	14
fourth	3	1	0	0	0	0	2	1
school/creche	83	86	100	100	0	0	81	85
smoking adults								
mother	32	26	33	30	25	33	32	27
father	37	27	56	50	50	33	39	30
both parents	23	18	33	10	25	33	24	17
pets at home	58	48	67	40	75	0	60	45
central heating	90	95	89	100	75	67	89	94

Table 3.11 *Areas of residence of the children*

	ABC	
	x	y
Amsterdam	20	17
Amstelveen + Haarlemmermeer	39	41
Zaanstreek + Purmerend	8	8
Gooi + Almere	11	8
Alkmaar area + north of it	13	14
South-Holland	2	6
Veluwe and Utrecht	1	1
Brabant	1	2
East-Netherlands	4	2

Table 3.12 *Several ways in which the participating children were attracted to the trial (the numbers are percentages of the two intervention groups, in the three age strata and in all the children)*

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
total number	71	73	9	10	4	3	84	86
GP	42	48	44	50	75	67	44	49
school	11	12	22	0	0	33	12	12
publications	35	36	33	50	25	0	35	36
partitioners	4	1	0	0	0	0	4	1
other	7	3	0	0	0	0	6	2

Table 3.13 *Mean sum-score on the general well-being questionnaire on entering the trial at baseline*

Group	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All children	43.9	44.9	1.1	(-1.2, 3.3)	1.02
n	82	86			
Age 2-5	43.2	44.0	0.8	(-1.7, 3.2)	1.02
n	69	73			
Age 6-9	47.3	49.5	2.2	(-3.5, 7.9)	1.05
n	9	10			
Age 1,5-<2	46.5	51.5	5.0	(-11.7, 21.7)	1.11
n	4	3			

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4 COMPARATIVE ANALYSIS OF OUTCOME MEASURES

4.1 Introduction

In this chapter, the five outcome measures (see *chapter 3, paragraph 3.4.3-3.4.9*) in the x and y group will be compared and some additional information on the satisfaction questionnaire, the GP consultations and reported adverse effects of trial medicines will be given.

Analysis was performed for the group as a whole as well as for the three age strata separately. For differences in means and proportions 95% confidence intervals were computed, means were compared with Student's t-test and proportions with a chi-square test or a chi-square test for trend, where appropriate. The level of significance was 0.05 (two-sided). For comparing means, not only differences but also ratios were calculated to facilitate interpretation.

Differences in means of scores between the two treatment groups and their 95% confidence intervals were adjusted for small differences in prognostic factors at the baseline by means of multiple regression analysis. This analysis was done on the scores of the day sum-scale, the chronicity scale, the overall scale and the overall respiratory scale.

The independent variables that were considered for inclusion in the model were: the numbers of episodes and the numbers of antibiotic courses in the preceding year, the performance of adenotomy or tonsillectomy in the past, the score on the first questionnaire on general well-being, the occurrence of recurrent respiratory infections in parents and grandparents (from father's side, mother's of both parents's), the presence of older siblings in the family, smoking habits of the parents (whether the mother or both the parents smoked at home), the presence of cats or dogs in the home, and the season in which trial participation started (in the months September, October, November or December, or in the months January, February, March or in the months April, May, June, July or August). The age stratum to which the child belonged (A, B or C) was unconditionally put into the model as independent variable.

4.2 Symptoms of respiratory tract infections

4.2.1 Episodes

Episodes of respiratory tract infections were defined by combinations of general and respiratory symptoms (see *chapter 3 paragraph 3.4.4*). For each child the total number of the so defined episodes and the total number of episode days over the year of follow up were counted.

No statistically significant difference in the number of recorded episodes in both treatment groups was found *(table 4.1)*. Over the whole year, children in the y group were nearly 6 days less in an episode than children in the x group; this difference was not statistically significant *(table 4.2)*.

For each child the mean day sum-score for each episode and the means of the mean day sum-scores of all episodes during the year of follow-up were computed, the last served as a combined measure of severity of the episodes. The means of this combined measure of severity in the x and y group were compared. There was a small difference in severity of the episodes between the x and the y group which was not statistically significant, this difference was in the same direction as the duration and numbers of episodes *(table 4.3)*.

4.2.2 Day sum-scores

For all children, a day sum-score for respiratory infections was computed for each day of follow-up, based on the ear, nose, throat and general symptoms (presence and degree) reported by the parents and for each child the mean day sum-score for the entire follow-up period was computed (see *chapter 3, paragraph 3.4.5*). The range of the day sum-score is 0-56, a score of zero indicates no complaints and a high score indicates numerous and outspoken complaints.

Figure 4.1 shows the distributions of mean day sum-scores of all the 84 children in the x group and the 86 children in the y group. The means of the mean day sum-score of the two treatment groups were compared for the whole year of participation and also for the last nine months, leaving the first three months out, for homoeopathic remedies are believed to need time to develop their positive action and symptoms are even expected to grow worse when starting homoeopathy.

Table 4.1 *Numbers of episodes of respiratory infections during the year of follow-up*

	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All (170)	8.4	7.9	0.5	(-0.8, 1.8)	0.94
A (144)	8.8	8.3	0.4	(-1.0, 1.8)	0.95
B (19)	5.2	4.1	1.1	(-2.6, 4.8)	0.79
C (7)	9.0	9.3	-0.3	(-7.4, 6.8)	1.04

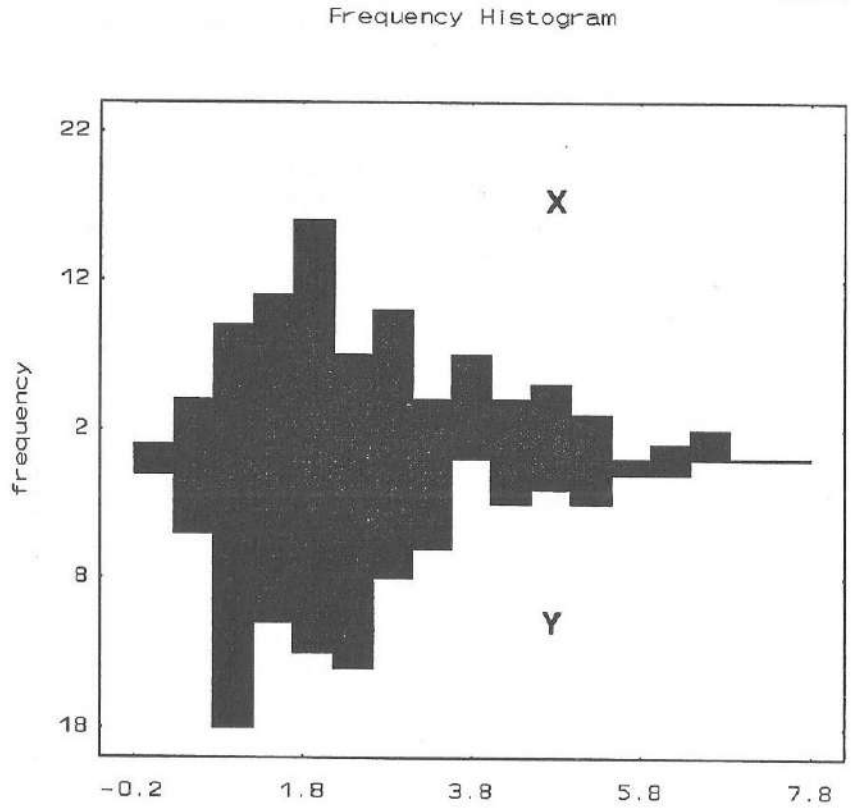
Table 4.2 *Sums of durations of all episodes in days*

	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All (170)	47.1	41.3	5.9	(- 6.4, 18.1)	0.88
A (144)	50.2	45.2	5.0	(- 8.9, 18.9)	0.90
B (19)	21.9	16.7	5.2	(-13.0, 23.4)	0.76
C (7)	49.5	27.7	21.8	(-15.1, 58.8)	0.56

Table 4.3 *Combined measures of severity of episodes (weighted mean day sum-scores)*

	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All (170)	14.1	13.6	0.5	(-0.4, 1.5)	0.96
A (144)	14.3	13.6	0.8	(-0.2, 1.7)	0.95
B (19)	11.6	13.3	-1.7	(-5.7, 2.3)	1.15
C (7)	15.1	14.7	0.4	(-6.0, 6.7)	0.97

Figure 4.1 *Histograms of mean day sum-scores of all children in the x group and all children in the y group*



During the year of follow-up, 61 children had days on which data was missing, but the total numbers of days with missing data were small (*table 4.4*): 53 children missed less than 8 days and only 4 children missed more than a whole month. The mean number of days with missing data was 2.7 for all children, 2.6 for x children and 2.8 for y children. The mean day sum-scores were calculated for all days with available data.

The mean day sum-score was higher in the x group than in the y group. Over the whole year, a difference in the means of the mean day sum-scores of 0.41 was found ($p = 0.06$) and over the last nine months the difference was 0.37 ($p = 0.09$). The results are presented in the *tables 4.5 and 4.6.*

Table 4.4 *Distribution of days with missing data over both treatment groups*

	A		B		C		ABC	
days	x	y	x	y	x	y	x	y
1-7	19	26	3	2	1	2	23	30
8-14	1	1	0	0	0	0	1	1
15-28	1	1	0	0	0	0	1	1
29-56	1	0	0	1	0	0	1	1
57-112	1	0	0	1	0	0	1	1
total	23	28	3	4	1	2	27	34

Table 4.5 *Day sum-scores for the whole year*

	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All (170)	2.61	2.21	0.41	(-0.02, 0.83)	0.85
A (144)	2.69	2.31	0.38	(-0.09, 0.85)	0.86
B (19)	1.93	1.52	0.41	(-0.92, 1.73)	0.79
C (7)	2.77	2.02	0.75	(-0.67, 2.18)	0.73

Table 4.6 *Day sum-scores for the last nine months*

	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All (170)	2.48	2.11	0.37	(-0.06, 0.81)	0.85
A (144)	2.56	2.20	0.37	(-0.11, 0.85)	0.86
B (19)	1.77	1.49	0.28	(-1.09, 1.66)	0.84
C (7)	2.58	2.02	0.56	(-1.31, 2.43)	0.78

In each child the proportion of follow-up days on which the day sum-score was zero (indicating symptom free days) was computed and the means of these proportions in the x and y group were compared. The mean percentage of days with a day sum-score of zero was 49 in the x group and 53 in the y group *(table 4.7)*.

Table 4.7 *Percentage of days with a day sum-score of zero*

		Means		Differences in means		
		x	y	x-y	(95% c.i.)	y/x
All	(170)	49.3	53.0	3.7	(-3.6, 11.0)	1.08
A	(144)	48.4	51.4	3.0	(-4.7, 10.7)	1.06
B	(19)	56.4	60.2	3.8	(-26.8, 34.5)	1.07
C	(7)	49.7	68.4	18.6	(-26.3, 63.6)	1.38

In the separate analysis of the mean day sum-scores for the four quarters of the follow-up year separately the same trend was seen: the y group had lower day sum-scores during all 4 quarters of the year *(table 4.8)*. Children in both treatment groups who started participation in the months September, October, November or December had the greatest difference of the mean day sum-score in the last quarter of participation and the first quarter of participation. This indicates the influence of the season on the symptoms.

Apart from analyzing day sum-scores, we looked at the constituent symptoms: the number of days with ear symptoms, nose symptoms, throat symptoms and general symptoms. Children in the y group had fewer days with cough and pain in the throat (difference between mean number of days 16, 95% c.i. 2.7, 29.8, p=0.02), fewer days with nose symptoms (difference 15, 95% c.i. -5.6, 36.3, p=0.15), fewer days with ear symptoms (difference 2.7, 95% c.i. -1.2, 6.6, p=0.17) and fewer days with listlessness or fever (difference 3.8, 95% c.i. -13.2, 20.8, p=0.66), see *table 4.9*. The mean severity of ear symptoms was greater in the y group.

Table 4.8 *Differences in mean day sum-scores between the x and y group, during the first, second, third and fourth quarter of the follow-up year*

	I x-y (95% c.i.)	II x-y (95% c.i.)
All children	0.54 (-0.007, 1.08)	0.22 (-0.28, 0.72)
Age 2-5	0.42 (-0.18, 1.01)	0.20 (-0.34, 0.74)
Age 6-9	1.19 (-0.30, 2.68)	-0.05 (-1.73, 1.63)
Age 1,5-<2	1.34 (-3.09, 5.77)	1.21 (-2.14, 4.55)
	III x-y (95% c.i.)	**IV** x-y (95% c.i.)
All children	0.38 (-0.15, 0.91)	0.53 (-0.05, 1.10)
Age 2-5	0.48 (-0.12, 1.08)	0.53 (-0.10, 1.16)
Age 6-9	0.01 (-1.08, 1.10)	0.42 (-1.70, 2.54)
Age 1,5-<2	-0.26 (-1.80, 1.28)	0.75 (-1.53, 3.02)

Table 4.9 *Duration and severity (on days with the symptom) of separate dimensions of the day sum-score for all children in group x (n=84) and y (n=86), ranges of severity for throat, nose and ear symptoms and malaise are 0-14*

	Means		Differences in means		Ratio
	x	y	y-x	(95% c.i.)	y/x
throat dur	72.1	55.9	16.2	(2.7, 29.8)	0.78
throat sev	3.1	3.1	0.0	(-0.2, 0.07)	1.00
nose dur	104.0	88.7	15.4	(-5.6, 36.3)	0.85
nose sev	3.6	3.5	0.1	(-0.2, 0.4)	0.97
ear dur	10.3	7.5	2.7	(-1.2, 6.6)	0.73
ear sev	2.6	3.0	-0.4	(-0.9, 0.03)	1.15
malaise dur	71.0	67.1	3.8	(-13.2, 20.8)	0.95
malaise sev	3.9	4.1	-0.2	(-0.4, 0.06)	1.05

4.2.3 Chronicity scores

As a measure for long lasting complaints, the chronicity scores were computed as described in *chapter 3, paragraph 4.6.* The chronicity score indicates the proportion of time during which a child was not particularly ill, but was not entirely well either.

The scores were slightly higher in the x group *(table 4.10)*, for the total group the difference was statistically significant (p=0.03).

Apart from the chronicity scores, in *table 4.11* the mean number of days on which all children in the x and y group had a day sum-score in the three defined categories (ranging from 0 to and including 6, 7 to and including 13, 14 to and including 28, the highest day sum-score measured) are presented. By looking at this table, the reader gleans more information on the meaning of the chronicity score, although this score is computed for each child separately.

The mean number of days on which the day sum-score is in the medium and high category is larger in the x group than in the y group, and the opposite applies to the mean number of days on which the day sum-score is in the lowest category.

Table 4.10 *Chronicity scores*

	Means		Differences in means		Ratio
	x	y	x-y	(95% c.i.)	y/x
All	0.14	0.11	0.04	(0.002, 0.07)	0.79
A	0.15	0.11	0.03	(-0.004, 0.07)	0.73
B	0.10	0.07	0.04	(-0.04, 0.11)	0.70
C	0.16	0.09	0.07	(-0.07, 0.21)	0.56

Table 4.11 *Number of days in all x children and all y children on which the day sum-score was low (0, 1, 2, 3, 4, 5 or 6), medium (7, 8, 9, 10, 11, 12, 13 or 14) and high (15, 16, 17, 18, 19, 20, 21 or 22, 23, 24, 25, 26, 27 or 28)*

	Means		Differences in means	
	x	y	x-y	(95% c.i.)
low	302.6	314.4	-11.9	(-26.2, 2.5)
medium	51.0	37.9	13.2	(1.3, 25.1)
high	6.3	5.6	0.7	(-1.6, 3.0)

4.3 Courses of systemic antibiotics

Apart from trial-medication, antibiotics could be prescribed by general practitioners and specialists. On the one hand, prescriptions of antibiotics may indicate the degree of seriousness of the infection, but on the other, the use of antibiotics may alter the clinical course in both the short and the long run.

As expounded in *chapter 3 paragraph 3.5.6*, four categories of antibiotic courses were distinguished: for existing respiratory problems, to prevent respiratory problems, for existing other problems and to prevent other problems.

We compared the number of courses in each category in both treatment groups *(table 4.12)*. The total percentage of children who did not have any antibiotic courses was 62 in the y group and 49 in the x group (χ^2 = 2.82, p 0.09) and the difference was 13% (95% c.i. -2, 28). In the x group 67 antibiotic courses were received for the treatment of respiratory infections, and in the y group 52.

Most courses of antibiotics were broad spectrum penicillins of 7 days. However, a proportion of children in both treatment groups were given a longer course of antibiotics because of a respiratory infection. Long courses probably indicate a more serious or persistent infection and may also have had a greater impact on the long term clinical course. Fourteen of the 84 children in the x group (17%) and 10 of the 86 children in the y group (12%) received one or two courses of 10 days or longer, the difference was 5% (95% c.i. -5%, 15%), see *table 4.13*. More information about the antibiotic courses of these children can be found in the *appendix*.

In de verum groep kregen 62% van de kinderen geen antibioticum tijdens deelname en in de placebogroep 49%, het verschil bedroeg 13% (95% betrouwbaarheidsinterval -2% tot 28%).

Bij 21% van de placebokinderen die nog nooit een adenotomie hadden ondergaan werd in het jaar van deelname een adenotomie verricht. In de verum groep bedroeg dit percentage 16%. Het verschil was 5% (95% betrouwbaarheidsinterval -11% tot 21%)

Zowel in de verum als in de placebo groep werd bij 5% van de kinderen die nog nooit een tonsillectomie hadden ondergaan gedurende het jaar van deelname een tonsillectomie verricht.

In beide groepen verbeterde de score van de vragenlijst algemeen welbevinden. De score op deze vragenlijst kon variëren tussen 13 en 61 punten en een hoge score representeerde een goed algemeen welbevinden. De verbetering bedroeg 4,81 punten in de verum groep en 4,17 punten in de placebo groep, het verschil was 0,64 punten (95% betrouwbaarheidsinterval -1,73 tot 3,02 punten).

De overall score kon variëren van 0 tot 20 punten en een hoge score representeerde veel problemen met de gezondheid. De gemiddelde overall score was in de verum groep lager dan in de placebo groep. Het verschil, gecorrigeerd voor kleine verschillen in baseline variabelen (met name van de percentages kinderen die reeds een adenotomie hadden ondergaan), bedroeg 1,15 punten (95% betrouwbaarheidsinterval -0,06 punten tot 2,35 punten).

In beide groepen werden bijwerkingen toegeschreven aan trial middelen, in de verum groep bij 14% van de kinderen en in de placebogroep bij 15%.

Na beëindigen van de deelname vonden de ouders van de meeste kinderen uit beide groepen dat hun kind baat gehad had bij de gegeven behandeling.

Andere onderzoekingen

Voor zover ons bekend, zijn er tot nu toe geen vergelijkende onderzoekingen met lange follow-up duur naar het effect van individueel voorgeschreven homeopathisch middelen bij kinderen met recidiverende luchtweginfekties verricht.

Conclusie

In deze trial werden kleine verschillen in uitkomsten gevonden tussen de placebo en de verum groep ten gunste van de verum homeopathische middelen. De meeste verschillen waren statistisch niet significant.

ADDENDUM

ADDENDUM 1

INGANGSCRITERIA

Kinderen moeten aan één van de volgende combinaties van ingangscriteria voldoen om tot het onderzoek te kunnen worden toegelaten:

Combinatie I:
- Bij aanvang van deelname aan het onderzoek moet de leeftijd tussen minimaal 2 en maximaal 9 jaar liggen.
- In het jaar voorafgaand aan deelname moet het kind tenminste 3 maal een duidelijke infectie hebben doorgemaakt in het gebied van de bovenste luchtweg.

Combinatie II:
- Bij aanvang van deelname aan het onderzoek moet de leeftijd tussen minimaal 2 en maximaal 9 jaar liggen.
- In het jaar voorafgaand aan deelname moet het kind tenminste 2 maal een duidelijke infectie hebben doorgemaakt in het gebied van de bovenste luchtweg.
- Bovendien moet het kind ten tijde van het eerste polikliniekbezoek een duidelijk otitis media serosa hebben.

Combinatie III:
- Bij aanvang van deelname moet het kind ouder zijn dan 18 maanden en jonger dan 2 jaar.
- In het half jaar voorafgaand aan deelname moet het kind minstens 3 maal een duidelijke infectie hebben doorgemaakt in het gebied van de bovenste luchtweg.

Onder een duidelijke infectie in het gebied van de bovenste luchtweg wordt hier verstaan:
a. een ziek kind met oorpijn, koorts en een afwijkend trommelvliesbeeld (otitis media acuta);
b. een ziek of kwakkelend kind met periodieke temperatuurverhoging, purulente rhinitis, neusverstopping en pijn in hoofd en/of kaken (sinusitis, adenoiditis);
c. een ziek kind met koorts, rode gezwollen tonsillen, eventueel bedekt met witte of geelgroene punten, al dan niet met gezwollen klieren aan de hals (tonsillitis, eventueel met lymfadenitis);
d. een ziek kind met laryngotracheïtis met koorts die duidelijk het gevolg is van, dan wel samenhangt met een nasopharyngitis.

UITSLUITINGSCRITERIA

- Het kind mag in de 6 maanden voorafgaande aan het onderzoek niet met homeopathische constitutiemiddelen zijn behandeld op voorschrift van een homeopathisch arts;
- Het kind mag in de 6 maanden voorafgaande aan het onderzoek geen adenotomie en/of tonsillectomie hebben ondergaan;
- Het kind mag niet wegens een andere chronische aandoening onder behandeling staan van huisarts of specialist;
- Het kind mag geen congenitale aandoening van de tractus respiratorius of het hart hebben. Een neurologische aandoening, mentale retardatie, abnormale lengtegroei (buiten de derde percentiel) en acuut reuma, endocarditis, myocarditis of nefritis in de voorgeschiedenis vormen eveneens een reden tot uitsluiting;
- Het gebit van het kind mag niet duidelijk carieus zijn;
- De ouders of verzorgers van het kind moeten de Nederlandse taal machtig zijn;
- Wanneer er minder dan 3 voor een homeopathisch geneesmiddel karakteristieke symptomen uit de categorieën 'generals' en 'mentals' duidelijk aanwezig zijn kan het kind niet deelnemen aan de studie.

ADDENDUM 2

1. Ligt de leeftijd van dit kind op dit moment tussen 2 en 9 jaar (inclusief 2 en 9 jaar)?
   - ja ☐ ga naar 2
   - nee ☐ stop
2. Heeft dit kind het afgelopen jaar (van nu tot 1 jaar geleden) drie of meer keren een infectie in het K.N.O.-gebied doorgemaakt? (otitis media acuta, purulente rhinitis met periodieke temperatuurverhoging, tonsillitis. Zie ingangscriteria voor omschrijvingen)
   - ja ☐ ga naar 3
   - nee ☐ stop
3. Heeft het kind (een) ernstige of uitgebreide congenitale aandoening(en)? (bijvoorbeeld een vitium cordis, een stofwisselingsstoornis, een cheilognathopalatoschisis).
   - ja ☐ stop
   - nee ☐ ga naar 4
4. Is dit kind onder behandeling van een huisarts of specialist wegens een andere dan in 3 bedoelde chronische aandoening?
   - ja ☐ stop
   - nee ☐ ga naar 5
5. Is dit kind in de afgelopen 6 maanden met homeopathische constitutiemiddelen behandeld?
   - ja ☐ stop
   - nee ☐ ga naar 6
6. Heeft dit kind in de afgelopen 6 maanden een adenotomie en/of tonsillectomie ondergaan?
   - ja ☐ stop
   - nee ☐ ga naar 7
7. Beheersen de ouders of de verzorgers van het kind de Nederlandse taal?
   - ja ☐ verzoek hen om het kind deel te laten nemen
   - nee ☐ stop

ADDENDUM 3

Aan:
Elly de Lange, homeopathisch arts
Polikliniek Kindergeneeskunde VU
Postbus 7057
1007 MB AMSTERDAM

Betreft: verwijzing

Datum:.....

Voor het onderzoek homeopatische preventie van bovenste-luchtweginfecties komt mijn patiëntje

Naam:.....

Geboortedatum:.....

Adres:.....

Postcode en Woonplaats:.....

Telefoonnummer:.....

Afgelopen jaar had dit patiëntje de volgende bovenste-luchtweginfekties (minstens 4):

Datum	Localisatie van de infectie	Behandeling

De volgende bijzonderheden uit de voorgeschiedenis en/of de gezinssituatie en/of de familie-anamneses zijn m.i. belangrijk:.....

.....

Handtekening:

Naamstempel:

ADDENDUM 4

Geneesmiddelen bij interventie

Bij therapeutische interventie kunnen uitsluitend de volgende geneesmiddelen voorgeschreven worden:

Als antibiotica:
- amoxicilline oraal gedurende 6,5 dagen in een dosering van 25 mg per kg lichaamsgewicht per 24 uur
- erythromycine oraal gedurende 6,5 dagen in een dosering van 40 mg per kg lichaamsgewicht per 24 uur

Als neusdruppels:
- rhinoguttae xylometazolini 0,5%, maximaal 7 dagen
- fysiologisch zout

Als pijnstiller en/of koortsdemper:
- paracetamol

Als hoestsiroop:
- sir. thymi FNA
- sir. promethazini FNA

Als vloeistof om te spoelen of te gorgelen:
- fysiologisch zout

Om te stomen:
- kamille of kamillosan

Sterk aromatische stoffen zoals menthol, eucalyptus en kamfer (b.v. in Vicks, dampo, poho olie) mogen beslist niet gebruikt worden daar deze de homeopathische geneesmiddelen onwerkzaam maken. De werking van homeopathische geneesmiddelen wordt ook teniet gedaan door corticosteroïden. Bij interventie is het voorschrijven van homeopathische geneesmiddelen niet toegestaan. Het kan uiteraard voorkomen dat tijdens weekeinde of vakantie een onbekende arts voor het kind geraadpleegd wordt. Daarom krijgt het kind bij het afspraakkaartje een kaartje voor deze arts met het verzoek om in verband met het deelnemen aan het onderzoek het geneesmiddelvoorschrift af te stemmen op deze lijst.

ADDENDUM 5

Geachte mevrouw, mijnheer,

Uw kind heeft last van steeds weer terugkerende ontstekingen van de oren en/of keel en/of neus. Homeopathische artsen menen dat zij deze ontstekingen kunnen voorkomen door het geven van onschadelijke geneesmiddelen die de weerstand van uw kind verhogen. Dit wordt wetenschappelijk onderzocht in het VU-Ziekenhuis. In het onderzoek worden twee verschillende soorten kindvriendelijke middelen met elkaar vergeleken. Een groep kinderen krijgt homeopathische geneesmiddelen, de andere groep kinderen krijgt zogenaamde placebo's. De dokter noch u weten vooraf of tijdens het onderzoek welk soort middelen uw kind krijgt.

Spreekuurbezoeken en begeleiding

Als u en uw kind willen deelnemen aan het onderzoek, wordt uw kind gedurende een jaar begeleid door een homeopathisch arts. Deze schrijft geneesmiddelen voor op grond van de verzamelde gegevens van uw kind. U en uw kind worden in dat jaar zes maal verwacht op het spreekuur van de homeopathisch arts op de polikliniek kindergeneeskunde van het VU-Ziekenhuis. Bij het eerste en laatste bezoek zal ook een keel-, neus-, en oorarts (KNO-arts) uw kind onderzoeken. Wanneer dat nodig is, wordt dan het gehoor van uw kind getest. Bij het eerste bezoek wordt ook een beetje bloed afgenomen voor bloedonderzoek. Als het kind deelneemt kunt u zonodig bij acute problemen altijd telefonisch met de homeopathisch arts overleggen.

Geneesmiddelen en kosten

De voorgeschreven geneesmiddelen worden verstrekt door de apotheek van het VU-Ziekenhuis. U krijgt hierover nog aparte informatie. U hoeft deze geneesmiddelen niet te betalen. Deelname aan het onderzoek is kosteloos. Buiten het project om mag u geen homeopathische middelen gebruiken. Als het echt nodig is wel niet-homeopathische geneesmiddelen.

Samenwerking

We hopen dat het onderzoek een bijdrage levert aan de vermindering van de klachten van uw kind en vele andere kinderen. We vragen ook medewerking van u. We vragen u om tijdens het jaar de klachten van uw kind bij te houden op een kalender. Deze krijgt u tijdens het eerste spreekuurbezoek. Verder wordt u om de twee weken opgebeld door een medewerkster die u een aantal vragen stelt over de gezondheid van uw kind in de afgelopen tijd.

Aanmelding

Wanneer u uw kind deel wilt laten nemen verzoeken we u bijgevoegd formulier in te vullen en portvrij te retourneren in de bijgesloten envelop.

Met vriendelijke groet,
Elly de Lange, homeopathisch arts

ADDENDUM 6

PROJECT BOVENSTE LUCHTWEGINFECTIES EN HOMEOPATHIE

Aanmeldingsformulier

- Datum:
- Naam ouder/verzorger:
- Naam kind:
- Geboortedatum kind:
- Begin klachten (jaar):
- Heeft u de KNO-arts ooit bezocht? ja/nee
- Zo ja, wanneer?
- Eventuele verrichte of geplande KNO-ingrepen met datum of jaar:

Ziekteperiodes in het afgelopen jaar:

datum	welke ziekte?/welke klachten?	behandeling/geneesmiddel?

- Heeft het kind gaatjes in tanden of kiezen? ja/nee/onbekend
- Is het kind onder behandeling van huisarts of specialist wegens een andere aandoening? ja/nee
- Zo ja, welke ?
- Wilt u nog verdere bijzonderheden vermelden ?
- Heeft uw kind het laatste jaar homeopatische middelen gebruikt?
- Zo ja, welke ?

Adres:
Plaats:
Telefoonnummer:
Dit formulier s.v.p. zenden aan: E. de Lange, arts, kinderpoli, Postbus 7057, 1007 MB Amsterdam

ADDENDUM 7

Ik vind het goed dat mijn kind,

....., geboren .....

meedoet aan het

effectiviteitsonderzoek van homeopathische therapie bij kinderen met recidiverende bovenste

luchtweginfecties.

Plaats:.....

Datum:.....

Handtekening:.....

ADDENDUM 8

Geneesmiddelen
U heeft van uw homeopathische arts medicijnen voorgeschreven gekregen. U kunt deze geneesmiddelen twee dagen na het spreekuur afhalen bij de apotheek van het VU ziekenhuis. U kunt hiervoor terecht bij de uitgifte balie. Deze is geopend op werkdagen van 8.00-12.00 uur en van 12.45-17.30.

U hoeft deze geneesmiddelen niet te betalen. Deelname aan het onderzoek is kosteloos.

We willen u vragen uw kind alleen de geneesmiddelen te geven die u bij de ziekenhuisapotheek heeft gekregen. Soms gaat er met de medicijnen iets mis, bijvoorbeeld het flesje valt stuk. U kunt dan altijd de ziekenhuisapotheek bellen. Het telefoonnummer staat onder aan deze brief vermeld.
Middelen die menthol bevatten zoals vicks en dampo en andere sterk geurende stoffen mag u niet gebruiken voor uw kind. Dit omdat ze de werking van de geneesmiddelen verminderen. De geneesmiddelen mogen niet uit hun oorspronkelijke verpakking worden gehaald.

Wilt u bij elk spreekuurbezoek de overgebleven medicijnen meebrengen?

Telefoonnummers apotheek:
op werkdagen (020) 548 6530
in het weekeinde (020) 548 9111

ADDENDUM 9

PROJECT BOVENSTE LUCHTWEGINFECTIES EN HOMEOPATHIE

RICHTLIJNEN VOOR VOEDING VAN KINDEREN MET FREKWENTE INFECTIES

* Zo weinig mogelijk suiker (koek, snoep, roosvicee, limonade)
* Dagelijks vers fruit
* Dagelijks verse groente
* Bruin brood of volkoren brood
* Melk en melkprodukten (yoghurt, karnemelk) tot 0,5 l per dag beperken
* Geen varkensvlees

ADDENDUM 10

DAG	Week van tot	Week van tot	Week van tot	Week van tot	Week van tot	Week van tot	Week van tot
Zondag							
Maandag							
Dinsdag							
Woensdag							
Donderdag							
Vrijdag							
Zaterdag							

ADDENDUM 11

Mw. E.S.M. de Lange-de Klerk,
homeopathisch arts
Polikliniek Kindergeneeskunde (receptie L)
VU-Ziekenhuis
De Boelelaan 1117
1081 HV AMSTERDAM
tel. (020) 431456

DAGKALENDER

Geachte Ouders,

We willen graag een goed beeld krijgen van de gezondheidstoestand van uw kind. Zou u daarom per dag willen invullen hoe u de gezondheidstoestand van uw kind vond?

1. Ten eerste willen we weten of u uw kind
   fit (1)
   hangerig (2)
   ziek (3)
   of erg ziek (4) vond.
   U kunt dit aangeven door het betreffende nummer op de betreffende datum in te vullen.

2. Indien uw kind klachten had, wilt u dan kort opschrijven welke? (Bijvoorbeeld oorpijn, verstopte neus, neusafscheiding).

3. Indien u uw kind ziek of erg ziek vond, wilt u dan de lichaamstemperatuur noteren (rectaal gemeten tussen 17.00 en 21.00 uur)?

We verzoeken u de kalender elke eerste week van de maand op te sturen in de u verstrekte, reeds geadresseerde en gefrankeerde envelop.

Bij voorbaat dank,

ADDENDUM 12.1

TWEEWEKELIJKS TELEFONISCH INTERVIEW PROJECT BOVENSTE LUCHTWEGINFECTIES EN HOMEOPATHIE

Naam kind: ..... Interviewer: .....
Datum interview: ..... Periode: .....

1. Had uw kind de afgelopen 2 weken koorts?
   Zo ja, hoe hoog was de temperatuur?

2. Was uw kind de afgelopen 2 weken één of meer dagen hangerig?
   Zo ja, welke dagen?

3. Heeft u de afgelopen 2 weken een arts voor uw kind geraadpleegd?
   Zo ja, wat was de aanleiding?
   Wat was de behandeling van die arts?

4. Heeft uw kind de afgelopen 2 weken de school, crèche of peuterspeelzaal verzuimd?
   Zo ja, welke dagen?

5. Heeft uw kind de afgelopen 2 weken één of meerdere van de volgende klachten gehad?

- neusafscheiding	veel/matig/weinig kleurloos/wit/geel/groen gedurende ..... dagen
- oorpijn	hevig/matig/gering ..... uren ..... dagen
- loopoor	gedurende ..... dagen
- gehoorvermindering	sterk/matig/enigszins ..... dagen
- hoesten	sterk/matig/weinig gedurende ..... dagen
- keelpijn	hevig/matig/gering gedurende ..... dagen
- hoofdpijn	hevig/matig/gering gedurende ..... dagen
- buikpijn	hevig/matig/gering gedurende ..... dagen

6. Heeft uw kind de afgelopen 2 weken geneesmiddelen gebruikt?
   Zo ja, welke middelen,
   welke doses,
   op welke dagen,

7. Is in de afgelopen 2 weken iemand van het gezin ziek geweest?
   Zo ja, wat was de aard van de ziekte?

   De duur?
   De ernst?

ADDENDUM 12.2

BI-WEEKLY TELEPHONE INTERVIEW PROJECT UPPER RESPIRATORY INFECTIONS AND HOMOEOPATHY

Name child: ..... Interviewer: .....
Date interview: ..... Period: .....

1. Has your child been feverish in the past two weeks?
   If so, how high was the temperature ?

2. Has your child been listless on any day in the past two weeks?
   If so, which day(s)?

3. Was the child seen by a doctor in the past two weeks?
   If so, for what reason?
   Which treatment was given?

4. Has the child been absent from school or day nursery in the past two weeks?
   If so, on which days?

5. Did your child in the past two weeks have one or more of the following complaints?

- nasal discharge	much / moderate amount / little transparent / white / yellow / green during ..... days
- earache	severe / moderate / light ..... hours ..... days
- ear-discharge	during ..... days
- deafness	severe / moderate / light during ..... days
- cough	severe / moderate / light during ..... days
- sore throat	severe / moderate / light during ..... days
- headache	severe / moderate / light during ..... days
- tommy-ache	severe / moderate / light during ..... days

6. Did your child take any medicines in the past two weeks?
   If so, which medicines?
   which doses?
   on which days?

7. Were there any illnesses in the family in the past two weeks?
   If so, what was the nature of this illnesses?

   the duration?
   the severity?

VRAGENLIJST ALGEMEEN WELBEVINDEN VAN HET KIND

Deze vragenlijst werd samengesteld ten behoeve van onderzoek naar de algemene gezondheid van kinderen.
De auteurs van de vragenlijst zijn:

J. Blommers
E.S.M. de Lange-de Klerk
P.D. Bezemer
D.J. Kuik
L. Feenstra

Vrije Universiteit
Faculteit der Geneeskunde
Amsterdam
1987

ADDENDUM 13: VRAGENLIJST ALGEMEEN WELBEVINDEN VAN HET KIND

Instructies

U vindt u hier vijf pagina's met vragen die betrekking hebben op de gezondheidstoestand en/of het gedrag van uw kind.

De vragen zijn als volgt in vijf groepen ingedeeld:

- slapen
- behoefte aan rust
- eten
- spelen
- stemming

Achter elke vraag ziet u een aantal mogelijkheden staan. Het is de bedoeling dat u een cirkeltje zet om het antwoord dat het meest overeenkomt met de gedragingen of eigenschappen van uw kind. Alle vragen gaan over het gedrag van uw kind zoals dat in de afgelopen maand is geweest met uitzondering van de periode(n) dat uw kind last had van een acute koortsende aandoening. Sommige vragen gaan over het aantal keren dat een bepaald gedrag de afgelopen maand is voorgekomen. Deze vragen hebben betrekking op een periode van 30 dagen dat uw kind min of meer gezond was. Indien uw kind in de afgelopen 30 dagen een acute koortsende aandoening heeft doorgemaakt, dan moet u het gedrag tijdens deze ziekteperiode(n) niet mee tellen. In plaats van het aantal dagen dat uw kind ziek was, telt u dan eenzelfde aantal gezonde dagen voorafgaande aan de afgelopen maand mee.

VOORBEELD

U ziet de volgende vraag staan:
Hoe vaak is uw kind de afgelopen maand verkouden geweest?

de hele tijd verkouden	1
drie keer	2
twee keer	3
één keer	4
geen enkele keer	5

Veronderstel dat u de vragenlijst invult op 1 mei. De lijst heeft dan betrekking op de 30 dagen die aan 1 mei voorafgingen, dit zijn de dagen 1 t/m 30 april. Indien uw kind in april geen acute koortsende aandoening heeft doorgemaakt en twee keer verkouden is geweest, zet u een cirkeltje om de 3.
Heeft uw kind echter in april wel een acute koortsende aandoening doorgemaakt, bijvoorbeeld van 7 t/m 13 april (dus 7 dagen), dan laat u deze 7 dagen van 7 t/m 13 april buiten beschouwing. In plaats daarvan telt u de laatste 7 dagen van maart mee. Was uw kind in de laatste week van maart en in de laatste week van april verkouden, dus in totaal twee maal, dan zet u een cirkeltje om de 3 (twee maal).

Een ander voorbeeld. U ziet de volgende vraag staan:

Houdt uw kind van snoepen?

zeer veel	1
veel	2
matig	3
weinig	4
zeer weinig	5

Wanneer uw kind dol is op snoep zet u een cirkeltje om de 1. Wanneer uw kind wel graag snoept, maar niet overdreven veel, dan zet u een cirkeltje om de 3. Bij vragen over gedragingen die soms wel en soms niet voorkomen, omcirkelt u het antwoord met het gedrag dat de afgelopen maand het meest is voorgekomen.

code:

naam van het kind:
Datum van invullen: dag maand jaar
Dit formulier werd ingevuld door: ☐ Moeder ☐ Vader ☐ Beide ouders

Betreft periode:

Begindatum:

Einddatum:

De volgende vragen hebben betrekking op het slapen van uw kind.
Er wordt gevraagd naar het aantal nachten dat uw kind een bepaald gedrag vertoont, niet naar het aantal keren per nacht.

1 Hoe vaak is uw kind de afgelopen maand 's nachts meer dan een kwartier wakker geweest?

tien of meer keer	1
zes tot en met negen keer	2
drie, vier of vijf keer	3
één of twee keer	4
geen enkele keer	5

2 Hoe vaak heeft u de afgelopen maand gemerkt dat uw kind 's nachts angstig was?

tien of meer keer	1
zes tot en met negen keer	2
drie, vier of vijf keer	3
één of twee keer	4
geen enkele keer	5

3 Hoe vaak wilde uw kind de afgelopen maand 's nachts niet alleen slapen?

tien of meer keer	1
zes tot en met negen keer	2
drie, vier of vijf keer	3
één of twee keer	4
geen enkele keer	5

De volgende vragen hebben betrekking op de behoefte aan rust van uw kind.

4 Op hoeveel dagen kwam het de afgelopen maand voor dat uw kind langer dan een uur hangerig was?

tien of meer dagen	1
zes tot en met negen dagen	2
drie, vier of vijf dagen	3
één of twee dagen	4
geen enkele dag	5

5 Op hoeveel dagen had uw kind de afgelopen maand overdag extra rust nodig?

tien of meer dagen	1
zes tot en met negen dagen	2
drie, vier of vijf dagen	3
één of twee dagen	4
geen enkele dag	5

6 Op hoeveel dagen ging uw kind de afgelopen maand vroeger naar bed dan andere kinderen van dezelfde leeftijd?

tien of meer keer	1
zes tot en met negen keer	2
drie, vier of vijf keer	3
één of twee keer	4
geen enkele keer	5

De volgende vragen hebben betrekking op <u>het eetgedrag</u> van uw kind.

7 Hoe vaak kwam het de afgelopen maand voor dat uw kind een maaltijd weigerde of met tegenzin at?
(Het maakt niet uit of dit een warme danwel een broodmaaltijd of pap is.)

tien of meer keer	1
zes tot en met negen keer	2
drie, vier of vijf keer	3
één of twee keer	4
geen enkele keer	5

8 Weigert uw kind zijn/haar lievelingseten wel eens?

zeer vaak	1
vrij vaak	2
regelmatig	3
soms	4
zelden	5

ADDENDUM 13: VRAGENLIJST ALGEMEEN WELBEVINDEN VAN HET KIND

De volgende vragen gaan over <u>het spelen</u> van uw kind

9 Speelt uw kind graag met andere kinderen?

helemaal niet graag	1
niet graag	2
niet zo graag	3
graag	4
zeer graag	5

10 Gaat uw kind met plezier naar crèche, peuterklas of basisschool toe?

gaat er niet heen	0
met erg weinig plezier	1
met weinig plezier	2
met matig plezier	3
met veel plezier	4
met zeer veel plezier	5

11 Hoe is het contact met de andere kinderen op de crèche, peuterklas of school?

gaat er niet heen	0
zeer slecht	1
slecht	2
redelijk	3
goed	4
zeer goed	5

De volgende vragen hebben betrekking op de stemming van uw kind.

12 Vindt u uw kind onrustig?

zeer onrustig	1
onrustig	2
een beetje onrustig	3
niet onrustig	4

13 Vindt u uw kind druk?

zeer druk	1
druk	2
een beetje druk	3
niet druk	4

14 Huilt uw kind veel?

zeer veel	1
veel	2
matig	3
weinig	4

15 Wordt uw kind gauw boos?

zeer gauw boos	1
gauw boos	2
niet zo gauw boos	3
niet gauw boos	4

PROJECT BOVENSTE LUCHTWEGINFECTIES

EN

HOMEOPATHIE

Elly de Lange, homeopathisch arts,
tel. 020-5487836 of 02206-5247 (privé)

Postadres:
Poliklinick Kindergeneeskunde
Postbus 7057
1007 MB AMSTERDAM

Spreekuur:
Poliklinick Kindergeneeskunde
Receptie L
De Boelelaan 1118
Amsterdam

Telefonische afspraken (020) 5488003

Geachte collega,

naam:_____ geboren:_____

doet mee aan een onderzoek naar het effect van homeopathie bij recidiverende bovenste luchtweginfecties.

Daarom verzoeken wij u om, indien u antibiotica voor wilt schrijven, u te beperken tot een van de volgende voorschriften:

- Amoxicilline oraal gedurende 6,5 dagen;
  in een dosering van 25 mg. per kg. lichaamsgewicht
  per 24 uur.

Of bij allergie voor amoxicilline:

- Erythromycine oraal gedurende 6,5 dagen;
  in een dosering van 40 mg. per kg. lichaamsgewicht per 24 uur.

Bij uw interventie is het voorschrijven van homeopathische middelen niet toegestaan. Indien u homeopathische therapie prefereert kunt u contact op nemen met Elly de Lange.

Tevens verzoeken wij u om van elk consult enkele notities in dit boekje te maken.

Bij voorbaat dank,

ADDENDUM 14: 'GELE BOEKJE'

Datum	Probleem en/of diagnose	Ingestelde therapie	Handtekening

Homeopathische geneesmiddelen.

De homeopathische geneesmiddelen worden gratis verstrekt via de apotheek van het VU-Ziekenhuis. De uitgiftebalie is maandag t/m vrijdag geopend van 8.00-12.00 en van 12.00-17.30.

We verzoeken u om uw kind uitsluitend de geneesmiddelen die u via de Ziekenhuisapotheek (tel. uitgiftebalie: 5486530, - 's avonds en in het weekend via de portier).

De homeopathische geneesmiddelen mogen niet uit de oorspronkelijke verpakking worden overgepakt in een andere verpakking.

Mentholpreparaten als Vicks en Dampo en andere sterk geurende stoffen mogen niet worden gebruikt, omdat ze de werking van de geneesmiddelen aantasten. Bepaalde sterk werkende cremes tegen eczeem kunnen dat ook doen. Overleg eventueel met Elly de Lange.

ADDENDUM 15.1

Geachte collega,

Uw patiëntje
participeerde van:
tot:
in ons onderzoeksproject.

Zou u voor ons willen nagaan of u of uw waarnemer hem/haar in deze periode gezien heeft en zou u ons daarover gegevens willen verstrekken?
U kunt hiertoe gebruik maken van bijgevoegd formulier.
NB: We zijn geïnteresseerd in alle consulten, dus niet alleen die t.b.v. luchtwegklachten.
Bij voorbaat dank namens het onderzoeksteam.

Met vriendelijke groet,

Elly de Lange, homeopathisch arts.

ADDENDUM 15.2

Geachte collega,

Uw patiëntje:

geboren:

wonende:

participeerde in onze trial "Bovenste luchtweginfecties en homeopathie"

van:

tot:

Helaas is de deelname aan de trial voortijdig beëindigd.

We zouden toch heel graag willen weten hoe het verder met patiëntje gegaan is en verzoeken u daarom vriendelijk maar dringend om ons informatie te verstrekken over het beloop vanaf het begin van deelname aan onze trial tot heden.

Met dank en vriendelijke groet,

Elly de Lange, homeopathisch arts

ADDENDUM 15.3

PROJECT BOVENSTE LUCHTWEGINFECTIES EN HOMEOPATHIE

Betreft:
Naam:
geboren:
wonende:

Dit patiëntje zag ik/mijn waarnemer op de volgende data:

datum	diagnose	therapie

Naam van de huisarts:

ADDENDUM 16

PROJECT "BOVENSTE LUCHTWEGINFECTIES EN HOMEOPATHIE".
Vragenlijst voor de ouders over de deelname in het afgelopen jaar.

INFORMATIE

1. Vindt u dat u van te voren voldoende informatie over het onderzoek heeft gekregen?
   - ☐ voldoende
   - ☐ matig
   - ☐ onvoldoende
2. Vindt u de informatie die u van te voren over het onderzoek heeft gekregen duidelijk?
   - ☐ ja, duidelijk
   - ☐ nee, onduidelijk
3. Welke informatie vooraf heeft u gemist?
4. Welke informatie vooraf vindt u overbodig?
5. Van wie heeft u informatie over het onderzoek gekregen? (meerdere antwoorden zijn mogelijk)
   - ☐ huisarts
   - ☐ de homeopathisch arts van het project
   - ☐ anders, nl.
6. Vindt u dat u voldoende informatie over de praktische gang van zaken tijdens het onderzoek heeft gekregen?
   - ☐ voldoende
   - ☐ matig
   - ☐ onvoldoende
7. Vindt u de informatie, die u over de praktische gang van zaken tijdens het onderzoek heeft gekregen duidelijk?
   - ☐ ja, duidelijk
   - ☐ nee, onduidelijk
8. Welke praktische informatie heeft u tijdens deelname gemist?

BEZOEKEN AAN DE ARTS

9. Wat vindt u van het aantal controlebezoeken aan de homeopathisch arts?
   - ☐ te veel
   - ☐ voldoende
   - ☐ te weinig
10. Hoe heeft u de begeleiding door de homeopathisch arts ervaren?
    - ☐ voldoende
    - ☐ matig
    - ☐ onvoldoende
11. Welke aspecten in de begeleiding door de homeopathisch arts heeft u als negatief ervaren?
12. Welke aspecten in de begeleiding door de homeopathisch arts heeft u als positief ervaren?
13. Heeft u buiten de te voren afgesproken bezoeken nog onverwachte bezoeken aan de homeopathisch arts gebracht?
    - ☐ zo ja, hoeveel? waarom:
    - ☐ nee
14. Hoe belastend waren voor u de controlebezoeken?
    - ☐ niet belastend
    - ☐ een beetje belastend
    - ☐ behoorlijk belastend
15. Indien de controlebezoeken belastend waren, wat was hiervan de oorzaak?
    - ☐ afstand tot de VU / bereikbaarheid van de VU
    - ☐ moeilijke opvang voor de kinderen thuis
    - ☐ lange wachttijden in de VU
    - ☐ anders, nl.
16. Hoe belastend waren de controlebezoeken voor uw kind?
    - ☐ niet belastend
    - ☐ een beetje belastend
    - ☐ behoorlijk belastend
17. Waarom waren de controlebezoeken belastend voor uw kind?

BEREIKBAARHEID

18. Hoe vaak heeft u tijdens deelname getracht contact op te nemen met de homeopathisch arts i.v.m. een vraag of een probleem?

19. Hoe vaak is het u gelukt om contact te krijgen met de homeopathisch arts?

20. Indien u de homeopathisch arts vaak niet kon bereiken, kunt u dan aangeven waaraan dat volgens u lag?

21. Vindt u dat er voldoende mogelijkheid was om afspraken te maken?
    - ☐ voldoende
    - ☐ matig
    - ☐ onvoldoende

22. Welke problemen heeft u ondervonden bij het maken van afspraken?

GENEESMIDDELVERSTREKKING

23. Vindt u dat de geneesmiddelverstrekking voldoende is geweest?
    - ☐ voldoende
    - ☐ matig
    - ☐ onvoldoende

24. Welke problemen m.b.t. de geneesmiddelverstrekking heeft u ondervonden?
    - ☐ geneesmiddelen arriveren niet snel genoeg
    - ☐ er is een verkeerd medicijn verstrekt
    - ☐ anders, nl.

DAGKALENDERS EN INTERVIEWS

25. Heeft u het invullen van de dagkalenders als belastend ervaren?
    - ☐ niet belastend
    - ☐ een beetje belastend
    - ☐ behoorlijk belastend

26. Welke problemen heeft u ondervonden bij het invullen van de dagkalenders?
    - ☐ ik vergeet het vaak
    - ☐ ik weet niet goed wat ik op moet schrijven
    - ☐ anders, nl.

27. Heeft u de tweewekelijkse telefonische interviews als belastend ervaren?
    - ☐ niet belastend
    - ☐ een beetje belastend
    - ☐ behoorlijk belastend

28. Welke problemen m.b.t. de telefonische interviews heeft u ondervonden?
    - ☐ er wordt vaak op een ongelegen tijdstip gebeld
    - ☐ de vragen zijn te moeilijk
    - ☐ anders, nl.

BAAT

29. Vindt u dat uw kind baat heeft gehad bij deelname aan het onderzoek?
    - ☐ ja, mijn kind heeft baat gehad
    - ☐ mijn kind heeft een beetje baat gehad
    - ☐ nee, mijn kind heeft geen baat gehad

SUGGESTIES

30. Indien u nog opmerkingen of suggesties heeft m.b.t. het onderzoek, zou u deze dan hieronder willen noteren?

ADDENDUM 17.1

Overzicht van alle voorgeschreven homeopathische middelen in de gehele a + b + c-groep

Frequency Tabulation

REMEDY	comp.	oer	D3	D4	D6	D12	D30	D60	D200	D1000	TOTAAL
ABROT.		-	1	-	-	-	-	-	-	-	1
ACON.		-	-	-	3	-	-	-	-	-	3
AGRA.		-	1	-	2	-	-	-	-	-	3
ALL-C.		-	-	-	6	-	-	-	-	-	6
ALOE		-	-	-	3	-	-	-	-	-	3
ANT-C.		-	-	-	3	-	-	-	-	-	3
ANT-T.		-	-	-	2	-	-	-	-	-	2
APIS		-	-	-	10	-	-	-	-	-	10
ARN.		2	-	-	1	1	1	-	-	-	5
ARS.		-	-	-	-	4	4	1	-	-	9
ARS-I.		-	-	-	6	4	-	-	-	-	10
BAF	3	-	-	-	-	-	-	-	-	-	3
BAR-C.		-	-	-	2	1	-	-	-	-	3
BAR-I.		-	-	-	2	-	-	-	-	-	2
BELL.		-	-	-	108	1	-	-	-	-	109
BIOFORC		2	-	-	-	-	-	-	-	-	2
BRY.		-	-	-	6	-	-	-	-	-	6
CALC-I.		-	-	-	-	-	1	-	-	-	1
CALC-P.		-	-	-	20	10	5	2	1	-	38
CALC-S.		-	-	-	1	-	-	-	-	-	1
CALC.		-	1	-	47	29	19	7	4	-	107
CALEN.		3	-	-	-	-	-	-	-	-	3
CAPS.		-	-	-	2	-	-	-	-	-	2
CAUST.		-	-	-	-	6	-	-	-	-	6
CHAM.		-	-	-	10	3	3	-	-	-	16
CHIN.		-	-	-	1	-	-	-	-	-	1
CHLOR.		-	-	1	-	1	-	-	-	-	2
CINNB.		-	-	-	1	-	-	-	-	-	1
COCC.		-	-	-	6	-	-	-	-	-	6
COFF.		-	-	-	1	-	-	-	-	-	1
COR-R.		-	-	-	2	-	-	-	-	-	2
CYPR.		-	-	-	4	-	-	-	-	-	4
DROS.		-	-	2	4	-	-	-	-	-	6
DULC.		-	-	-	1	-	-	-	-	-	1
ECHI-P.		5	-	-	-	-	-	-	-	-	5
ELAPS		-	-	-	-	1	-	-	-	-	1

Overzicht van alle voorgeschreven homeopathische middelen in de gehele a + b + c-groep (vervolg)

Frequency Tabulation

REMEDY	comp.	oer	D3	D4	D6	D12	D30	D60	D200	D1000	TOTAAL
FERR-P.		-	15	3	13	1	-	-	-	-	32
GRAPH.		-	-	-	-	2	-	-	-	-	2
HEP.		-	-	-	-	30	3	3	-	-	36
HYDR.		-	-	-	1	-	-	-	-	-	1
HYOS.		-	-	-	1	-	-	-	-	-	1
IGN.		-	-	-	2	-	-	-	-	-	2
IP.		-	-	-	42	1	-	-	-	-	43
KALI-BI.		-	-	-	13	1	-	-	-	-	14
KALI-C.		-	-	-	-	1	-	-	-	-	1
KALI-CHL.		-	-	-	1	-	-	-	-	-	1
KALI-M.		-	-	-	15	2	-	-	-	-	17
KALI-S.		-	-	-	14	1	-	-	-	-	15
LACH.		-	-	-	-	2	3	-	-	-	5
LYC.		-	-	-	1	9	8	1	-	-	19
MED.		-	-	-	-	-	-	-	1	-	1
MERC.		-	-	-	23	4	2	1	1	-	31
MERC-C.		-	-	-	-	1	-	-	-	-	1
NAT-M.		-	-	-	-	-	1	-	2	-	3
NAT-S.		-	-	-	-	3	-	-	-	-	3
NUX-V.		-	-	-	3	1	2	-	-	-	6
NYSIKIN	1	-	-	-	-	-	-	-	-	-	1
PASSI.		2	-	-	-	-	-	-	-	-	2
PHOS.		-	-	-	-	3	22	5	3	-	33
PULS.		-	-	-	44	17	18	5	2	-	86
RUMX.		-	-	-	1	-	-	-	-	-	1
SABIN.		-	-	-	1	-	-	-	-	-	1
SIL.		-	-	-	32	24	15	4	3	-	78
SPONG.		-	-	-	15	-	-	-	-	-	15
STRAM.		-	-	-	4	-	-	-	4	-	8
SUL-I.		-	-	-	7	-	-	-	-	-	7
SULPH.		-	-	-	-	5	86	37	24	1	153
TARAX.		-	1	-	-	-	-	-	-	-	1
THUJ.		-	-	-	-	-	13	2	1	-	16
TUB.		-	-	-	-	-	-	-	20	-	20
TUSSIST	1	-	-	-	-	-	-	-	-	-	1
VARIO.		-	-	-	-	-	-	-	1	-	1
TOTAAL	5	14	19	6	487	169	206	68	67	1	1042

ADDENDUM 17.2

First prescriptions (all children)

REMEDY	tot.	x	y	REMEDY	tot.	x	y	REMEDY	tot.	x	y
ACON.	1	0	1	CHAM.	4	1	3	MERC.	13	7	6
ANT-C.	2	1	1	COCC.	3	3	0	NUX-V.	1	0	1
ANT-T.	1	0	1	DROS.	1	0	1	PHOS.	10	5	5
ARS-I.	2	1	1	FERR-P.	8	3	5	PULS.	30	16	14
ARS	1	1	0	HEP.	10	5	5	SIL.	26	14	12
BAF	1	1	0	IP.	13	5	8	SPONG.	2	1	1
BAR-C.	2	1	1	KALI-BI.	3	3	0	SUL-I.	1	1	0
BELL.	73	40	33	KALI-M.	4	2	2	SULPH.	60	30	30
CALC-P.	13	8	5	KALI-S.	4	3	1	TUB.	10	7	3
CALC.	34	17	17	LYC.	2	0	2				
CAPS.	1	0	1	MERC-C.	1	0	1				

First prescriptions (A group)

REMEDY	tot.	x	y	REMEDY	tot	x	y	REMEDY	tot	x	y
ACON.	1	0	1	CAPS	1	0	1	LYC	1	0	1
ANT-C.	2	1	1	CHAM.	3	1	2	MERC-C	1	0	1
ANT-T.	1	0	1	COCC.	3	3	0	MERC.	9	4	5
ARS-I.	2	1	1	DROS.	1	0	1	PHOS.	9	5	4
ARS	1	1	0	FERR-P.	8	3	5	PULS.	28	15	13
BAF	1	1	0	HEP.	7	4	3	SIL.	22	12	10
BAR-C.	2	1	1	IP.	11	4	7	SPONG.	2	1	1
BELL.	65	36	29	KALI-BI.	3	3	0	SUL-I.	1	1	0
CALC-P.	10	7	3	KALI-M.	4	2	2	SULPH.	53	26	27
CALC.	28	13	15	KALI-S.	3	2	1	TUB.	7	5	2

First prescriptions (B group)

REMEDY	tot.	x	y	REMEDY	tot	x	y	REMEDY	tot	x	y
BELL.	3	1	2	IP.	1	0	1	PHOS.	1	0	1
CALC-P.	3	1	2	KALI-S.	1	1	0	PULS.	2	1	1
CALC.	3	2	1	LYC.	1	0	1	SIL.	3	2	1
CHAM.	1	0	1	MERC.	4	3	1	SULPH.	4	2	2
HEP.	2	0	2	NUX-V	1	0	1	TUB.	3	2	1

First prescriptions (C group)

REMEDY	tot.	x	y
BELL.	5	3	2
CALC.	3	2	1
HEP.	1	1	0
IP.	1	1	0
SIL.	1	0	1
SULPH.	3	2	1

ADDENDUM 18

List of reported adverse effects of trial medicines in the placebo group

childcode	medicine	symptom
A018	Cham D6	irritable
	Sulph D30	irritable
		a convulsion
A027	Spong D6	cough aggravates
A042	Sil D6	a rash
A047	Ars-i D6	restlessness
A059	Sulph D30	fever after first dose, later no problems
A084	Sulph D30	epistaxis increased
A086	Nux-v D6	agressive behaviour
A090	Calc-c D6	agressive behaviour, tantrum tempers
A098	Kali-bi D6	nausea
A131	Kali-c D 12	fever, tummy ache
A131	Merc sol D6	albuminuria
A132	Hep sulf D30	hyperactivity
A139	Bell D6	constipation
A145	Phos D30	headache

List of reported adverse effects of trial medicines in the verum group

childcode	medicine	symptom
A020	Calc-s D6	rash
A034	Sulph D30	headache aggravates
A038	Puls D30	vomiting after first dose, later doses gave no problems
A040	Ars-i D6	eczema if taken in a certain frequency
A060	Puls D12	agressive behaviour
A074	Calc D6	perspiration increased and irritability
A099	Sulph D30	agressive behaviour
A111	Puls 12	tummy ache
A142	Caps D6	rash
A146	Calc D12	hyperactivity, increased perspiration
A146	Merc D200	ear discharge
B020	Calc D6	cross mood
C006	Calc D6	obstinate behaviour

ADDENDUM 19

Area of residence

	A		B		C		ABC	
	x	y	x	y	x	y	x	y
Amsterdam	15	11	2	2	0	2	17	15
Amstelveen e.o.	21	21	2	1	0	0	23	22
Uithoorn + Aalsmeer	3	11	2	0	2	1	7	12
Waterland + Purmerend	4	3	0	1	0	0	4	4
Gooi	5	4	0	0	1	0	6	4
Almere	3	1	0	2	0	0	3	3
Zaanstreek	3	3	0	0	0	0	3	3
West-Friesland	3	7	0	0	0	0	3	7
Noord-Holland Noord	3	2	0	0	0	0	3	2
Alkmaar e.o.	5	2	0	1	0	0	5	3
Haarlem	2	1	1	0	0	0	3	1
Zuid-Holland Noord	2	1	0	0	0	0	2	1
Zuid-Holland Zuid	0	4	0	0	0	0	0	4
Veluwe	1	0	0	0	0	0	1	0
Utrecht	0	0	0	1	0	0	0	1
Brabant	1	0	0	2	0	0	1	2
Oost-Nederland	0	2	2	0	1	0	3	2

Dankwoord

Nu dit proefschrift voltooid is, wil ik allen die er hun bijdrage aan hebben geleverd hartelijk bedanken.
In de eerste plaats dank ik de kinderen die aan het onderzoek deelnamen en hun ouders. De vele huisartsen die ons geholpen hebben en die gegevens voor ons hebben verzameld, zeg ik hartelijk dank.
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Elly de Lange

stellingen

bij het proefschrift
'effects of homoeopathic medicines
on children with
recurrent upper respiratory tract infections'

E.S.M. de Lange-de Klerk

stellingen bij 'effects of homoeopathic medicines on children with recurrent upper respiratory tract infections'

1 Ook homeopathische geneesmiddelen dienen lege artis op effectiviteit en schadelijkheid te worden onderzocht.

2 Een cross-over trial is ongeschikt om het effect van homeopathische geneesmiddelen te meten.

3 Kinderen met frequente luchtweginfecties en hun ouders zijn gebaat bij een zorgvuldige begeleiding door hun huisarts.

4 Bij het besluit om antibiotica voor te schrijven voor een luchtweginfectie, spelen gewoonten en omstandigheden vaak een grotere rol dan de geschatte ernst van de infectie.

5 Door een behandeling met homeopathische geneesmiddelen kunnen de klachten van kinderen met recidiverende bovenste luchtweginfecties in geringe mate worden gereduceerd.

6 Het toekennen van een symbolische betekenis aan de klachten van anderen dient met de nodige terughoudendheid te gebeuren.

7 Een arts loopt het risico om bij patiënten die hem of haar vaak raadplegen met allerlei klachten een ernstige aandoening niet tijdig te onderkennen door een ongunstige signaal-ruis verhouding.

8 De stelligheid waarmee sommige alternatieve genezers hun cliënten allerlei inwendige kwalen aanpraten is omgekeerd evenredig met de validiteit van hun diagnostische methoden.

9 De sleutel tot de verlichting van langdurige klachten ligt vaak in de leefwijze. Een dagboek kan de patiënt en de arts inzicht geven in de samenhang tussen onbegrepen klachten en het alledaagse leven.

10 Het lijkt logisch dat een destructieve aandoening als reumatoïde artritis al in een vroeg stadium agressief behandeld wordt en niet pas als de gewrichten reeds onherstelbaar zijn beschadigd.

11 Het geneesmiddel mag uiteindelijk niet erger zijn dan de kwaal.