

History of respiratory infections in the first 12 yr among children from a birth cohort

Grüber C, Keil T, Kulig M, Roll S, Wahn U, Wahn V and the MAS-90 Study Group. History of respiratory infections in the first 12 yr among children from a birth cohort.

Pediatr Allergy Immunol 2007.

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Respiratory infections are the most frequent health problem in childhood. There is little precise information on how many respiratory illness episodes can be expected in a normal child. This study was designed to create reference values for the frequency of respiratory infections as recordable by history. Respiratory illnesses were recorded in a prospective birth cohort of 1314 German children born in 1990 and tracked until age 12 yr (760 children). Parents recorded the child's illnesses in a diary and answered structured questions yearly up to age 12. Age of study subjects was categorized into infancy (0–2 yr), pre-school age (3–5 yr), and school age (6–12 yr). The mean cumulative number of respiratory infection episodes up to age 12 yr was 21.9 (s.d. 9.0) episodes. In infancy, the mean annual number was 3.4 (3.7) episodes; at pre-school age, 2.3 (2.6) episodes; and at school, age 1.1 (1.2) episodes. The mean cumulative time of episodes up to age 7 yr was 20.1 (15.2) wk. Forty-five percent of the infants in the upper episode incidence tertile continued to be in the upper tertile at school age. Based on a twofold standard deviation of the mean number, up to 11 respiratory infection episodes per year in infancy, 8 episodes per year at pre-school age, and 4 episodes per year at school age could be regarded as normal. Episodes within these reference values *per se* should not cause unwarranted concern or intervention because of suspected immunodeficiency.

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Key words: children; respiratory infectious diseases; epidemiology

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Accepted 30 October 2007

Acute respiratory tract infections are the most frequent illnesses in childhood. Intense exposure to viral respiratory infections and a not-fully-educated immune system may be causes for children being a major risk group for common colds. The average incidence of these infections in pre-school children has been estimated at five to seven episodes per year, but exact data are sparse. Still serving as a reference are epidemiological data collected more than 35 yr ago, when households were more crowded and day care was much less common than today (1, 2). As the frequency of acute respiratory tract infections is presumably influenced by lifestyle, it is questionable how precisely these data reflect today's situation.

Respiratory infections are a burden on children and their families. Although many are not

severe, they contribute to absenteeism in education and work (3). Recurrent episodes concern parents with the threat of a possible underlying immune dysfunction. Many children undergo unnecessary evaluation for immunodeficiency and therapy with remedies believed to enhance immune function. A better knowledge of the natural frequency of respiratory tract infections may help to prevent unwarranted concern or intervention and to identify children at true risk for an immunodeficiency.

In the initial screening for immunodeficiency taking, the history of infectious illnesses is a crucial step. Aside the type and the focus, the frequency of particular illness episodes is recorded in order to assess whether the child is unusually frequent afflicted. This study describes the occurrence of respiratory tract

infection episodes as they were reported by parents in an observational birth cohort up to 12 yr of life. In addition, we aimed to identify factors associated with the number of respiratory illness episodes.

Patients and methods

Study subjects

In 1990, a cohort of 1314 neonates recruited in five German cities (Berlin, Düsseldorf, Freiburg, Mainz, and Munich) were selected for a prospective observational study (MAS-90) (4). Of these, 499 neonates (38%) were selected for being at high risk for atopy (two or more first-degree atopic family members and/or cord-blood IgE values above 0.9 kU/l), and the remainder was chosen at random from the remaining newborn infants (one or no atopic family member and cord-blood IgE value <0.9 kU/l).

The cohort infants and their parents were regularly seen for follow-up visits at monthly ages 3, 6, 12, 18, 24, and then annually up to 8 yr, and then at 10 yr. At each visit, parents filled out a questionnaire and gave a structured face-to-face interview about their children's diseases and atopic symptoms. The children received a standardized physical examination by study physicians. At ages 9, 11, and 12 yr, only questionnaires were administered. During the first 7 yr, parents kept a diary in which details were recorded whenever the child became sick. The study coordinators monitored the diary at the indicated examination intervals. For the purpose of the present study, the ages of study subjects were categorized into infancy (0–2 yr), pre-school age (3–5 yr), and school age (6–12 yr).

Definition of respiratory diseases

Parent-reported respiratory symptoms were coded according to an extended version of the international classification of diseases (ICD) (5). Codes were aggregated to nine complexes: rhinitis, sinusitis, pharyngitis, tonsillitis, laryngitis (including acute laryngitis and tracheitis, spasmodic croup, epiglottitis), bronchitis (including acute bronchitis, laryngo-tracheo-bronchitis), otitis (including acute otitis media, tubotympanic catarrh), pneumonia, and unspecified. As the primary aim of MAS-90 was to observe the natural course of atopic disease, obstructive bronchitis, asthma and hay fever were recorded separately. Duration of common cold episodes was calculated on the basis of diary entries which were available up to age 7 yr.

Statistical methods

The availability of data was affected by a gradually declining participation rate during the 12 yr of follow-up in this birth cohort study. To evaluate possible differences, we compared baseline characteristics between the two groups of children with complete ($n = 477$) and incomplete follow-up data ($n = 837$). Mean number of respiratory illness episodes and mean duration per episode of all children with at least 1 episode at each time point was calculated. In bivariate analyses, we compared differences using Pearson's chi-square test for categorical data and the Mann–Whitney *U*-test for continuous non-parametric data. Statistical significance was defined by a two-sided alpha-level of 0.05. Multiple Poisson regression analyses were performed to examine the association of patient characteristics with the number of respiratory illness episodes as outcome events. Effect estimates, their corresponding 95% confidence intervals (95% CI) and *p*-values were calculated in separate models for 0–2, 0–5, and 0–12 yr. Models were additionally adjusted for possible centre effects.

Ethical approval. The parents of all children involved in the study gave their informed consent. The research protocol was approved by the Charité Ethics Committee.

Results

Response rates and characteristics of study subjects

At the end of the 1st year of life, 1056 children (80.4% of the initial sample) were evaluated. During the subsequent years, there was a gradual loss of study subjects to follow up. At 12 yr of age, 760 children were evaluated, including 477 children who participated continuously. Baseline characteristics of the study subjects are given in Table 1.

Occurrence of common cold in relation to age

The mean cumulative number of common colds in the first 12 yr of life was 21.9 (s.d. 9.0) episodes (maximum 61 episodes) in the 477 children with complete follow-up. The mean annual number was highest in infancy [1st year, 3.1 (2.1) episodes; 2nd year, 3.2 (2.5) episodes], declined during pre-school age [3rd year, 2.1 (2.0) episodes; 4th year, 2.3 (2.1) episodes; 5th year, 1.8 (1.6) episodes], and stabilized at a low level during school age [6th year, 1.3 (1.3) episodes; 7th through 9th year, 1.1 (1.0) episodes; 10th year

Table 1. Baseline characteristics of study subjects

Characteristic (%)	Initial study sample (n = 1314)	Patients evaluated through 1st yr (n = 1056)	Patients evaluated 1st through 12th yr (n = 477)
Gender, male	52.1	52.7	50.3
Breast feeding <1 m	30.9	25.4	21.6
Any sib(s) at birth	41.1	40.9	42.6
Parent(s) atopic			
None	47.8	47.6	47.8
One	38.8	39.3	40.0
Both	13.4	13.6	12.2
Season of birth, October–March	47.6	46.8	44.4
Secondary education of parent(s)	52.1	54.7	57.0
Mother regular smoker	15.9	15.9	13.7

Table 2. Occurrence of different common cold episodes by age group

	Mean (2 s.d.) annual number		
	1st–2nd yr (n = 965)	3rd–5th yr (n = 956)	6th–12th yr (n = 534)
Rhinitis	2.28 (5.22)	1.27 (3.05)	0.81 (1.69)
Pharyngitis	0.02 (0.24)	0.00 (0.06)	0.00 (0.04)
Tonsillitis	0.09 (0.63)	0.11 (0.79)	0.07 (0.37)
Sinusitis	0.00 (0.04)	0.00 (0.10)	0.01 (0.07)
Otitis	0.31 (1.61)	0.31 (1.41)	0.08 (0.46)
Bronchitis	0.37 (1.85)	0.32 (1.84)	0.07 (0.45)
Pneumonia	0.02 (0.25)	0.05 (0.41)	0.02 (0.14)
Laryngitis	0.07 (0.65)	0.08 (0.66)	0.02 (0.16)
Unspecified	0.18 (0.96)	0.15 (0.83)	0.05 (0.29)
Any respiratory illness	3.35 (7.35)	2.30 (5.22)	1.12 (2.32)

In each age category, all children with valid answers were included.

through 12th year, 1.0 (0.9) episodes]. Age-related curves of the number of common colds are given in Fig. 1. Children above the twofold standard deviation of the mean number experienced >7 episodes in the 1st year of life, >8 episodes in year 2, >6 episodes in year 3 and year 4, >5 episodes in year 5, >4 episodes in year 6, and >3 episodes from year 7 on.

The age-related incidence of respiratory diagnoses is summarized in Table 2. When this analysis was restricted to 477 children with complete follow-up data from year 1 to year 12, results were not statistically significant and different from the full sample for each age category.

Duration of common cold episodes

The mean duration of any common cold episode in the first 7 yr was 1.8 (s.d. 1.3) wk. The shortest duration recorded was 1 day and the longest duration was 18 wk and 3 days. For unspecified respiratory illness episodes and illness episodes of the lower respiratory tract, the mean duration was longer than 2 wk. For illness episodes of the upper respiratory tract, a mean duration between

1 and 2 wk was observed. Laryngitis episodes usually lasted less than a week (Table 3).

There was little variation in the duration of illness episodes by age. For any common cold episode, the mean duration was between 1.5 (s.d. 1.6) wk and 1.8 (2.4) wk in infancy, reached its peak in year 3 with 2.1 (3.2) wk, and thereafter continuously declined to 1.3 (1.4) wk in year 7. Beyond infancy, lower respiratory illness episodes tended to last longer than upper respiratory illness episodes (Fig. 2).

Cumulative time of common cold

The mean cumulative time of common cold in the first 7 yr of life was 20.1 (s.d. 15.2) wk for the 773 afflicted children. The cumulative time of rhinitis was 13.7 (12.8) wk. The cumulative time of pneumonia episodes was 3.2 (3.2) wk for 103 affected children and of bronchitis episodes 4.7 (6.4) wk (327 children). The cumulative time of otitis was 4.2 (5.4) wk (449 children). The mean cumulative time of other respiratory illnesses was below 3 wk (data not shown). A linear regression analysis reveals a general trend toward longer time for upper respiratory illness with younger

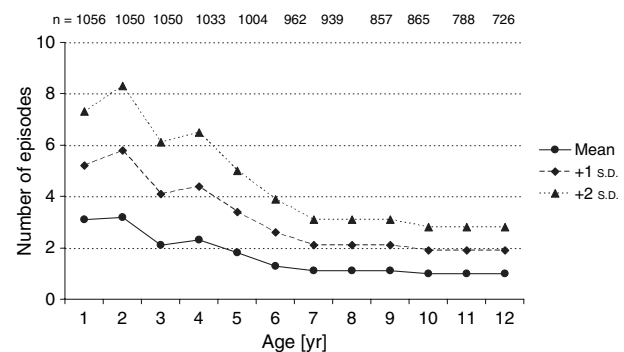


Fig. 1. Yearly number of respiratory illness episodes in relation to age.

age ($p = 0.002$), but not for lower respiratory illness ($p = 0.987$; Fig. 3).

Seasonality

Common cold episodes were clearly more frequent during the winter period through all years (data not shown). The cumulative number of common cold episodes in year 1–12 is summarized in Fig. 4.

Table 3. Average duration per common cold episode in the first 7 yr of life

Respiratory illness	Children (n)	Episodes (n)	Duration in (wk) [Mean (s.d.)]
Laryngitis	204	414	0.7 (0.7)
Pharyngitis	41	50	1.1 (0.6)
Tonsillitis	326	603	1.2 (0.8)
Otitis	616	1598	1.5 (2.7)
Rhinitis	1189	8529	1.6 (1.4)
Sinusitis	11	14	1.9 (1.3)
Bronchitis	594	1,684	2.2 (2.2)
Pneumonia	135	178	2.3 (1.5)
Unspecified	491	860	3.9 (4.6)
Any	1213	13,930	1.8 (1.3)

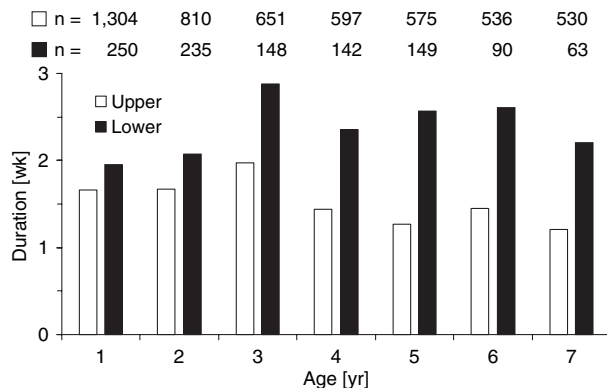


Fig. 2. Mean duration per rhinitis and lower respiratory illness episode (bronchitis, pneumonia) by age.

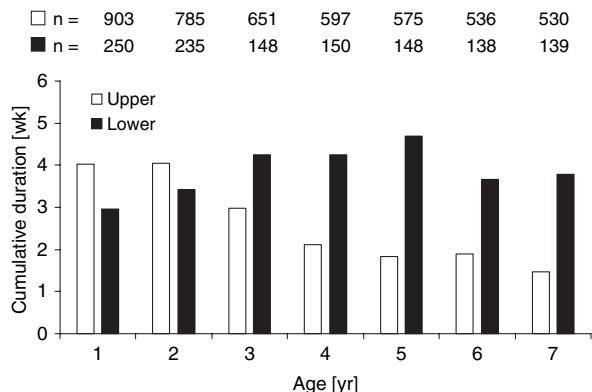


Fig. 3. Mean yearly cumulative time of upper or lower respiratory illness by age. Test for trend, upper respiratory illness, $p = 0.0016$; lower respiratory illness, $p = 0.9873$.

It is higher from October to March (peak in December, 806 episodes) and shows a trough from April to September (lowest incidence in July, 230 episodes).

More than 50% of all different respiratory disease episodes occurred during winter and spring, except pharyngitis episodes (Table 4). The season of birth had no influence on the cumulative incidence of common cold episodes in year 1 (Fig. 5) and in the years thereafter (data not shown).

Children with frequent common colds

In order to identify children with frequent common cold episodes, children were categorized in tertiles according to the frequency of respiratory illness episodes in infancy, at pre-school age and at school age. Children (41.8%) with frequent episodes in infancy (upper tertile) continued to be in the upper tertile during pre-school age (Table 5). When compared with children persisting in the lower tertile, those persisting in the upper tertile more often tended to be male (41.5% vs. 60.5%, $p = 0.005$), to have been breastfed for more than 4 wk (64.9%

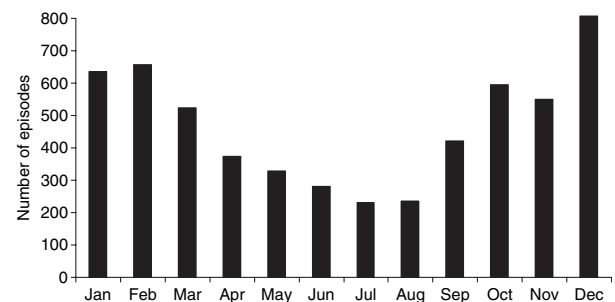


Fig. 4. Seasonality for cumulative number of common cold episodes in the first 12 yr of life (477 children with complete follow-up data).

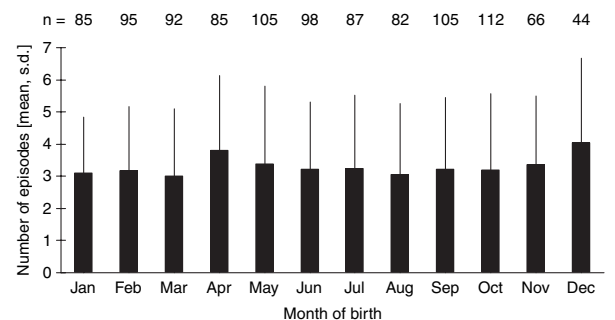


Fig. 5. Cumulative number of respiratory illness episodes at age 1 yr in relation to month of birth. In an analysis of variance, no significant difference in frequency was found among months of birth ($p = 0.373$).

Table 4. Seasonal distribution of common cold episodes in the first 7 yr of 477 children with complete follow-up

Season (%)	Rhinitis (n = 3292)	Pharyngitis (n = 25)	Tonsillitis (n = 250)	Otitis (n = 714)	Laryngitis (n = 188)	Bronchitis (n = 672)	Pneumonia (n = 102)	Unspecified (n = 391)
Winter	35.5	16.0	32.0	33.1	42.0	31.5	43.1	32.5
Spring	30.8	20.0	32.4	37.0	25.0	35.7	37.3	32.2
Summer	17.1	24.0	22.2	16.8	17.6	17.7	10.8	18.9
Fall	16.6	40.0	13.2	13.2	15.4	15.0	8.8	16.4

Percentages of episodes are rounded to the nearest 10th and may not add to 100.

Table 5. Tracking of children with frequent common colds by age

	Preschool age (3–5 yr)			School age (6–12 yr)		
	Lower tertile (0–4 episodes) n (%)	Middle tertile (5–7 episodes) n (%)	Upper tertile (≥8 episodes) n (%)	Lower tertile (0–5 episodes) n (%)	Middle tertile (6–8 episodes) n (%)	Upper tertile (≥9 episodes) n (%)
Infancy (0–2 yr)						
Lower tertile (0–4 episodes)	118 (44.2)	79 (29.6)	70 (26.2)	51 (35.9)	50 (35.2)	41 (28.9)
Middle tertile (5–7 episodes)	98 (32.8)	83 (27.8)	118 (39.5)	51 (30.9)	51 (30.9)	63 (38.2)
Upper tertile (≥8 episodes)	73 (24.6)	100 (33.7)	124 (41.8)	39 (21.0)	63 (38.9)	84 (45.2)

Distribution of 863 children followed from birth to preschool age and of 493 children followed from birth to school age on tertiles of cumulative common cold episodes in the respective age window. Percentage of the respective preschool age or school age tertiles' population is rounded to the nearest 10th and may not add to 100.

vs. 81.5%, $p = 0.008$), and to have wheezing at age 5 yr (3.4% vs. 17.7%, $p < 0.001$). No significant differences were seen with regard to siblings, maternal smoking habits, educational or atopic status of the parents, season of birth or other allergic phenotypes of the child (data not shown). At school age, 45.2% of the children in the upper tertile of common cold episodes also had been in the upper tertile during infancy (Table 5). No significant difference in the characteristics mentioned earlier was found between children persisting in the lower tertile and those persisting in the upper tertile, except borderline significance of breastfeeding for more than 4 wk (62.7% vs. 88.6%, $p = 0.050$).

Influencing factors of frequent common colds

Poisson regression models were used to identify further influencing factors on the number of common colds. During infancy, day care and wheezing were factors significantly associated with an increase of common colds (both +0.3 episodes). Furthermore, older siblings (+0.2 episodes), eczema (+0.1 episodes) and breastfeeding (+0.003 episodes per week breastfeeding) also showed significant associations with an increased number of common colds. Foreign family background nationality (vs. German) and having a dog at home (vs. no dog) were associated with a significant reduction of 0.2 common cold episodes. Atopic family history or

allergic sensitization of the child had no significant effect (Table 6). Up to pre-school age, the effects of wheezing in infancy (+0.2 common cold episodes, $p < 0.0001$) and at pre-school age (+0.4 episodes, $p < 0.0001$), day care (+0.3 episodes; $p = 0.0036$), foreign family background (−0.2 episodes, $p = 0.0218$) and breastfeeding (+0.003 episodes per week breastfeeding, $p = 0.0012$) were identified as significant. Up to age 12 yr, only wheezing for at least 2 yr was significantly associated with an increase of 0.2 common cold episodes ($p = 0.0312$). When all bronchitis and pharyngitis episodes were removed as outcome events from the Poisson regression models, only a weak association between wheezing and common cold episodes was observed at school age (effect estimate 0.16; 95% CI 0.002, 0.32; $p = 0.047$), and significant associations between wheezing and common cold episodes were not observed neither at pre-school age (effect estimate −0.08; 95% CI −0.27, 0.12; $p = 0.437$) nor in infancy (effect estimate 0.10; 95% CI −0.01, 0.20; $p = 0.065$). Relevant regional effect was not found when adjusting the Poisson regression models for the five centres that recruited children for the MAS study.

Discussion

In this study, we found a mean annual number of 3.4 common cold episodes in infancy, 2.3 episodes at pre-school age, and 1.1 episodes at

Table 6. Factors influencing the number of common cold episodes from 0 to 2, 3 to 5, and 6 to 12 years of life

Variable	At age 0–2 yr			At age 3–5 yr			At age 6–12 years		
	Effect estimate	95% CI	p	Effect estimate	95% CI	p	Effect estimate	95% CI	p
Gender, male vs. female	0.05	−0.03; 0.14	0.226	0.001	−0.08; 0.08	0.984	−0.01	−0.11; 0.09	0.864
Breastfeeding (wk)	0.003	0.001; 0.005	0.008	0.003	0.001; 0.005	0.004	0.001	−0.001; 0.004	0.303
Wheezing (yr)									
1–2 vs. no	0.29	0.19; 0.38	<0.001	0.24	0.14; 0.34	<0.001	0.03	−0.08; 0.15	0.575
≥3 vs. no	–	–	–	0.56	0.41; 0.70	<0.001	0.32	0.16; 0.47	<0.001
Eczema (yr)									
1–2 vs. no	0.13	0.03; 0.23	0.012	−0.03	−0.13; 0.08	0.632	0.02	−0.10; 0.14	0.775
≥3 vs. no	–	–	–	−0.10	−0.26; 0.06	0.203	0.03	−0.13; 0.18	0.745
Day care, yes vs. no	0.30	0.09; 0.51	0.005	0.22	−0.03; 0.47	0.086	−0.01	−0.28; 0.25	0.916
Older siblings, yes vs. no	0.16	0.07; 0.25	<0.001	−0.10	−0.19; −0.01	0.025	−0.09	−0.19; 0.01	0.093
Nationality, foreign vs. German	−0.24	−0.47; −0.01	0.041	−0.15	−0.39; 0.08	0.194	−0.16	−0.46; 0.14	0.289
Cats at home, yes vs. no	0.03	0.10; 0.16	0.627	−0.09	−0.22; 0.04	0.158	−0.04	−0.16; 0.08	0.487
Dogs at home, yes vs. no	−0.16	−0.32; −0.004	0.044	−0.04	−0.20; 0.11	0.606	−0.10	−0.24; 0.03	0.137
Season of birth, Apr.–Sep. vs. Oct.–Mar.	0.05	0.03; 0.14	0.213	−0.14	−0.23; −0.06	0.001	0.01	−0.09; 0.11	0.856
IgE to indoor allergens, yes vs. no	−0.05	−0.27; 0.17	0.667	−0.06	−0.20; 0.09	0.441	−0.10	−0.23; 0.04	0.154
IgE to outdoor allergens, yes vs. no	−0.12	−0.36; 0.13	0.357	0.01	−0.12; 0.13	0.922	−0.04	−0.16; 0.09	0.575
Atopic parent, yes vs. no	0.06	−0.03; 0.14	0.192	−0.01	−0.10; 0.08	0.818	0.01	−0.10; 0.11	0.913
Mother regular smoker vs. no smoker	0.07	−0.05; 0.19	0.245	0.01	−0.10; 0.13	0.857	−0.08	−0.23; 0.07	0.284
Parental schooling ≥12 yr, yes vs. no	0.02	−0.07; 0.11	0.649	0.001	−0.09; 0.09	0.989	0.04	−0.67; 0.14	0.472

Effect estimates from Poisson regression analysis are given for the number of common colds as the outcome variable among 671 children (0–2 yr), 762 children (3–5 yr), and 450 children (6–12 yr) with complete data, adjusted for study centre.

school age. Respiratory infections occurred predominantly during the winter months, but the season of birth was not influential. About 45% of infants with frequent common colds continued to have frequent colds at school age. We recorded just a few episodes of sinusitis, but because of the fact that sphenoid and frontal sinuses are not fully developed until about age 12 yr, no high rates of sinusitis would be expected in the investigated age groups.

The source of information regarding common cold episodes was a parental report. A misinterpretation of allergic symptoms, a recall bias of episode duration and under-reporting of episodes can not be fully ruled out. The information is, however, similar to what could be expected from parents in consultations. We sought to keep the imprecision of reports low through the use of parental diaries and by careful clinical screening for symptoms of respiratory allergy in a cohort, which was originally designed to describe the natural course of atopic disorders in childhood. The results obtained here were robust regarding independent tests in atopic and non-atopic strata, thus indicating that the cohort data can be applied to a normal population in a developed region with moderate climate. It remains to be elucidated whether our data can be applied to children in developing countries who live under quite different conditions.

Comparison with previous research

In previous studies initiated more than 40 yr ago, the reported frequency of common colds was about twice as high as in our study (1, 2). Aside from differences in study design, differing life circumstances of children may have contributed to less common colds today.

A strong seasonality of common colds in childhood has been discussed earlier (6–8). In our study, episodes occurred predominantly during the winter months, when the incidence was threefold as high as in summer months. The season of birth, however, had no influence on the cumulative number of respiratory illness episodes in infants, indicating that the immune system requires a time window larger than a season for effective maturation.

Some children seem to be at particular risk of respiratory infections. Day care was associated with a modest increase of 0.3 episodes, both in infancy and at pre-school age, a finding which is well in line with other study results (9). Of note is that about half of the school children with a high number of episodes (upper tertile) were also in the upper tertile during infancy. We could not identify socio-demographic factors to explain for persistence in the upper tertile into school age. A deficiency of defence factors has been discussed as contributory in non-immune-compromised children,

including mannose-binding lectin and interferon- γ (10–12).

Some findings of our study may be surprising. We found no association of exposure to tobacco smoke and respiratory infection. There is sufficient evidence that exposure to tobacco smoke promotes wheezing, cough, and phlegm (13, 14). Tobacco smoke is an airway irritant and may contribute to the severity of respiratory infections, but it is less likely to enhance susceptibility to infections *per se*. Breastfeeding has been reported to be associated with protection from lower respiratory illness in developing countries, but the effect in more developed countries is less clear. Previous studies suggested a mild effect of longer breastfeeding on the incidence of lower respiratory infection (15) or of respiratory infection in the first few months of life (16). In our study, breastfeeding was associated with a mildly elevated risk of respiratory infection and may be due to over-reporting of episodes in participating families with a higher social status, longer breastfeeding, and less smoking (17).

Implication for clinical practice

The twofold standard deviation of acute respiratory illness episodes per year included up to 11 episodes in infancy, up to 8 episodes at pre-school age, and up to 4 episodes at school age. Episodes of this frequency could be regarded as normal and should not give rise to suspicion of an underlying immunodeficiency *per se*, unless the course is unusual or episodes affecting particular target organs accumulate. Further indicators of immunodeficiency are early growth failure and a positive family history of immunodeficiency. These children should be considered seriously for an immunologic work-up (18). Children with recurrent monotypic infections beyond normal limits should be considered for an evaluation of possible local pre-disposing factors.

In conclusion, the normal extent of annual respiratory illness in infants and children provided by this study may prevent unwarranted concern or intervention for suspected immune weakness and may help to identify children at true risk for immunodeficiency. It should be kept in mind that aside from the number of respiratory illness episodes, further well-defined criteria are elsewhere available to discriminate normal susceptibility to respiratory illness from what is pathologic. Future longitudinal studies, designed to monitor the occurrence of respiratory infections in childhood and set in different climatic and geographical regions, may help to validate these data.

Acknowledgments

We thank all the participating children, parents, and the nurses of the MAS-90 Study Group for their involvement in recruitment and follow-up of the children. We also thank the collaborators of the MAS-90 Study Group: Marketa Groeger (Düsseldorf, Germany); Fred Zepp, Imke Bieber (Mainz, Germany); Johannes Forster, Uta Tacke (Freiburg, Germany); Carl-Peter Bauer (Gaissach, Germany); Renate Bergmann, Susanne Lau, Bodo Niggemann (Berlin, Germany). We appreciate the data management assistance of Andreas Reich.

Competing interests

None declared.

Funding

This study was supported by the German Ministry of Research and Education grant number 01EE9405/5.

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