

ORIGINAL ARTICLES

Respiratory sequelae and lung function after whooping cough in infancy

I Krantz, J Bjure, I Claesson, B Eriksson, R Sixt, B Trollfors

Abstract

The lung function of 31 children, aged 6-13 years, who had whooping cough as infants and 32 control children matched for age, sex, and residence area were compared in a community based cohort study. Family history of obstructive airway disease, smoking habits in the family, atopy, and other background factors examined were similar in the two groups. The ratios of recalled repeated acute respiratory infections did not differ among the groups. Children in the control group were slightly more involved in physical activities. History of obstructive airway disease, findings on chest radiography, and distribution of immunoglobulin concentrations, including IgE, did not differ significantly. Lung function before and after exercise and after inhalation of salbutamol were not different. No impairment of small airways was detected. Our data do not support the hypothesis that whooping cough in itself is a causal factor for later obstructive respiratory disease.

Vaccination against whooping cough was stopped altogether in Sweden 1979. An increased incidence of whooping cough had been observed even before the discontinuation of general immunisation. Judged by reported figures of complications and mortality the disease has not had as serious immediate consequences during the 1970s and 1980s as before the vaccination era.¹

On the other hand respiratory diseases during childhood have been claimed to cause abnormal pulmonary function later in life.²⁻³ Lung disease, when the airways are most vulnerable, can leave scars detectable only many years later.⁴

Children with a history of lower respiratory tract infections in infancy are said to be at a greater risk of developing symptoms of respiratory disease later in life.⁵⁻⁷ The same statement has been made for whooping cough alone or complicated by bronchopneumonia.⁸⁻¹⁰ Whooping cough is said to be most severe in infancy.¹¹⁻¹²

Chest radiography and spirometry will detect gross abnormalities like hyperinflation, bronchiectasis, and atelectasis. Whooping cough during infancy might result in minor degrees of residual damage to the lung, detectable only when measurements of small airways function are made.

Preliminary data based on more refined methods reported pulmonary abnormalities in seven out of 10 Swedish adolescents who were

symptom free more than 12 years after infant whooping cough with pneumonia.¹³

A British comparative study found no impairment of lung function nine years after infant whooping cough as judged by conventional tests of lung function and histamine challenge testing of bronchial reactivity.¹⁴ Respiratory symptoms, however, were more common in children who had had whooping cough and who were also more likely to have a family history of wheezing illness.

The aim of this study was to investigate if infant whooping cough could be considered as a predisposing factor for small airways disease later in life because of the implications for childhood prevention even though the disease and its immediate sequelae are basically under control in Sweden.

Methods**SUBJECTS**

To be included children had to have had whooping cough at <13 months of age. Controls had to have had no overt signs of whooping cough or longer coughing periods and to have had no contact with suspected cases as recalled by the parents and/or recorded in available medical and welfare records.

For children without records of a positive culture of *Bordetella pertussis* whooping cough was defined as an acute respiratory infection lasting four to eight weeks, with a catarrhal stage followed by paroxysmal coughing with or without whoops and vomiting.

Children with whooping cough were recruited from two sources. (1) Twenty eight children with whooping cough reported by their parents during infancy were taken from a 10% random sample of four birth cohorts in Göteborg from 1972, 1977, 1978, and 1980. They had earlier participated in a study on incidence and vaccination coverage.¹⁵ Twelve (43%) came for an interview and had a venous blood sample taken (table 1). Two of these had been in hospital during the course of their whooping cough. (2) In the same age cohorts 32 other children from the same town had been treated in the two existing hospitals with infant whooping cough. These were invited as well and 21 (66%) participated after the same invitation procedure as above with one letter and a telephone call (table 1). Of the total number of 60 children, eight had moved from town and could not be reached.

Four control subjects for each case were initially chosen from the random sample, matched for age, sex, and area of residence. Thirty six of the 116 that could be reached participated (31%).

East Hospital, Göteborg,
Sweden,
Department of
Infectious Diseases
I Krantz

Department of
Paediatric Clinical
Physiology
J Bjure
R Sixt

Department of
Paediatric Radiology
I Claesson

The Nordic School
of Public Health,
Göteborg
B Eriksson

Department of
Paediatrics,
University of Göteborg
B Trollfors

Correspondence to:
Dr I Krantz,
The Nordic School
of Public Health,
PO Box 12 133,
S-402 42 Göteborg,
Sweden.

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Table 1 Selection of study groups, their age, and sex. The children were taken from a 10% random sample of the 1972, 1977, 1978, and 1980 birth cohorts in Göteborg. All children having been in hospital during infancy in Göteborg with whooping cough and belonging to the same age cohorts were also invited

| | Infant whooping cough | | Control group | |
|----------------------------|-----------------------|-------------|---------------|-------|
| | From hospital | From sample | | |
| Study population | 32 | 28 | | 116 |
| Interviewed | 21 | 12 | | 36 |
| Included in the study | 21 | 10 | | 32 |
| Children included by year: | Boys | Girls | Boys | Girls |
| | (n=31) | | (n=32) | |
| 1972 | 3 | 3 | 11 | 10 |
| 1977 | 11 | 3 | 10 | 5 |
| 1978 | 0 | 3 | 1 | 2 |
| 1980 | 4 | 4 | 3 | 1 |
| Total | 18 | 13 | 19 | 13 |

The sample size of the children who had had whooping cough was fixed by the number of children available. The larger number of control subjects was selected because a substantial non-response was anticipated.

The most common cause for non-attendance both for cases and controls was fear of venepuncture. Among children who had had whooping cough who dropped out there was no difference in distribution of age and sex. They did not have any severe respiratory disease as judged by available hospital and outpatient department records, and their median age for infection with whooping cough was 5 months (range 1–11).

After the interview it was found that two children who had had whooping cough did not come for lung function tests and four controls did not meet the inclusion criteria (table 1).

The median age for the 31 cases at the time of their disease was 7 months (range 1–11).

Nineteen cases (61%) had a positive pernasal swab for *B pertussis* during their disease and 10 (32%) had clinical features and contact histories according to hospital or outpatient department records. Two (6%) cases had not been in contact with health services at the time of their disease, but they were included on account of a correct description of the symptoms by the parents in conjunction with circumstantial evidence. The first child born 1977 had detectable serum IgG antibodies against pertussis toxin and filamentous haemagglutinin as measured by enzyme linked immunoadsorbent assay (ELISA).^{16 17} The other one born in 1980 had a sibling with whooping cough verified on culture.

PROTOCOL

One of the parents (the mother in 88% of cases) came with the child for a semistructured interview by one of the authors (IK). During the interview the history of the child from pregnancy up to date was recapitulated. History of atopy for subjects, parents, and siblings in terms of eczema and asthma or respiratory diseases was asked for. Circumstantial evidence was sought as much as possible. History of illnesses was checked in welfare and medical records from hospitals and outpatient clinics.

Vaccination state of the subjects was ascertained by notifications in the cards from child welfare centres, where all newborns are registered and virtually all childhood vaccinations take place.

Frequent acute respiratory infections were considered present when the parent judged the child having had much absence from day care, preparatory school, or school or they themselves had to stay home much from work to care for the child. Acute respiratory symptoms were defined for practical purposes as symptoms from an infection somewhere in the respiratory tract and related structures (sinus, middle ear, and pleura). Previous and current treatment with antibiotics, remedies for obstructive symptoms, nose drops, etc was noted.

Physical ability was estimated during the same interview from answers by the parents and children to questions of the child's activities inside and outside school—for example, whether the child played with friends, took part in training sessions, had sports as a hobby, and whether he or she had any achievements in athletics.

If the child had been in a household for more than a year with one or more habitual smokers (smoking daily in the household) this was considered as a background factor.

At the same time a blood sample was taken for determination of erythrocyte sedimentation rate, white cell count, haemoglobin concentration, and concentrations of IgA, IgE, IgG, and IgM, and with IgG subclasses 1, 2, and 3. The child then got an appointment for radiography and lung function tests, which were done without the laboratory staff knowing to which group the child belonged. Bicycle ergometry was done by the same person throughout the study (JB). Height and weight development was assessed by a growth nomogram.¹⁸

Lung function tests were performed when the subjects had been free from any intercurrent respiratory symptoms for at least three weeks before testing and if chest radiography by anteroposterior and lateral position was normal. The films were re-examined after the initial examination by one of the authors (IC). Three cases and one control refused to have the radiographic examination but were allowed to participate because there were no suspicions of ongoing respiratory disease.

Lung function studies were performed before noon. Each subject produced at least three visually acceptable flow-volume curves (Jaeger Pneumoscreen). Forced expiratory volume in one second (FEV₁), maximum expiratory flows when 50 and 25% of forced vital capacity remained to be expired (MEF₅₀, MEF₂₅) were read from the curve with the largest forced vital capacity. Static lung volumes—that is, total lung capacity, vital capacity, functional residual capacity, and residual volume were measured by means of a pressure compensated volume displacement body plethysmograph.¹⁹ Airway closure expressed in percent of vital capacity and the slope of the alveolar plateau (ΔN_2) were assessed by the single breath nitrogen washout test.²⁰

After establishment of basal lung function exercise capacity was assessed by bicycle ergo-

metry to exhaustion. Exercise induced bronchial constriction was looked for by flow-volume curve recordings 2 and 4 minutes after stopping exercise. Salbutamol (0.15 mg/kg, maximum dosage 5.0 mg) by means of a Pari-Boy nebuliser (Siemens Elema) was then given and flow-volume curves were again registered 20 minutes after salbutamol.

All lung function equipment was calibrated daily. All results were corrected to body temperature, pressure, and saturation conditions.

Table 2 Comparison of background characteristics. Results are number (%) of children unless otherwise stated

| Characteristics | Cases (n=31) | Controls (n=32) | p Value |
|--|-------------------|-------------------|---------|
| Mean age (years) | 8.4 | 9.2 | |
| Mean (range) birth weight (g) | 3471* (1800-4795) | 3397† (2000-4500) | 0.53 |
| Mean (range) time breast fed (months) | 4* (0-11) | 4‡ (0-9) | 0.52 |
| Family history of obstructive disease | 8 (26) | 8 (26)† | ≤0.61 |
| Mother having normal pregnancy | 25 (81) | 25 (81)† | 0.74 |
| Presence of smoker in the household | 14 (45) | 8 (25) | 0.15 |
| Case or control who smoked | 0 | 0 | |
| History of atopic symptoms | 4 (13) | 4 (13) | 0.63 |
| History of frequent acute respiratory infections | 0 | 3 (9) | 0.13 |
| History of pneumonia | 3 (10) | 2 (6) | 0.49 |
| Additional physical training | 16 (52) | 25 (78) | 0.05 |

Data available for only *28 children, †31 children, and ‡24 children.

Table 3 Mean (SD) values for erythrocyte sedimentation rate, white cell count, and concentrations of haemoglobin and immunoglobulins

| | Cases (n=30) | Controls (n=31) | p Value* |
|---|--------------|-----------------|----------|
| Erythrocyte sedimentation rate (mm in first hour) | 5.0 (3.0)† | 7.0 (5.7)‡ | 0.17 |
| White cell count ($\times 10^9/l$) | 7.1 (1.4)§ | 6.6 (1.6) | 0.21 |
| Haemoglobin (g/l) | 133.0 (8.8)§ | 132.0 (9.3) | 0.72 |
| IgA (g/l) | 1.65 | 1.86 | 0.11 |
| IgE (kU/l) | 24.5 | 20.0 | 0.82 |
| IgG (g/l) | 12.37 | 11.94 | 0.66 |
| IgG ₁ | 8.07 | 8.15 | 0.65 |
| IgG ₂ | 2.45 | 2.65 | 0.55 |
| IgG ₃ | 0.65 | 0.78 | 0.65 |
| IgM (g/l) | 1.64 | 1.72 | 0.59 |

*p Values by either *t* test or Wilcoxon's rank sum test. Data available for only †27 children, ‡25 children, and §31 children.

Table 4 Mean height and weight with means for static, dynamic lung function and maximum working capacity with heart rate and respiratory rate at maximum work

| Test | Cases (n=31) | | Controls (n=32) | | p Value (t test) |
|-----------------------------------|---------------|----------------|-----------------|----------------|------------------|
| | Mean (SD) | No of children | Mean (SD) | No of children | |
| Height (cm) | 142.0 (14.6) | 31 | 145.9 (16.8) | 32 | 0.33 |
| Weight (kg) | 36.7 (11.9) | 31 | 39.0 (13.3) | 32 | 0.47 |
| Total lung capacity (l) | 3.43 (1.01) | 27 | 3.48 (1.14) | 30 | 0.64 |
| Vital capacity (l) | 2.60 (0.85) | 27 | 2.79 (0.92) | 30 | 0.44 |
| Residual volume (l) | 0.74 (0.26) | 27 | 0.72 (0.28) | 30 | 0.85 |
| FEV ₁ (l) | 2.19 (0.68) | 31 | 2.37 (0.86) | 32 | 0.38 |
| MEF ₅₀ (l/sec) | 2.97 (1.02) | 31 | 3.15 (1.24) | 32 | 0.53 |
| MEF ₂₅ (l/sec) | 1.39 (0.51) | 31 | 1.53 (0.81) | 32 | 0.39 |
| Closing volume (% vital capacity) | 2.56 (0.82) | 31 | 2.82 (0.93) | 31 | 0.24 |
| ΔN_2 (% nitrogen/l) | 1.274 (0.510) | 31 | 1.245 (0.497) | 31 | 0.82 |
| Maximum work load (watts) | 126.5 (41.7) | 31 | 140.6 (43.3) | 32 | 0.20 |
| Heart rate/min at max work | 191.3 (11.3) | 31 | 191.3 (7.01) | 32 | 0.97 |
| Respiratory rate/min at max work | 41.1 (9.2) | 31 | 41.2 (5.6) | 32 | 0.98 |

In the comparison between cases and controls Fisher's exact test was used for dichotomous variables. Quantitative variables were analysed using Student's *t* test and Wilcoxon's rank sum test. Later statements about significance refer to a level of 5%.

The study was approved by the ethical committee of the medical faculty, University of Göteborg and written parental consent was obtained.

Results

There was no statistically significant difference in age and sex distribution between the groups (table 1). Records and cards could be checked for all children.

Birth weight, history of atopy, pneumonia, and frequent respiratory infections before the child started school, and whether the mother had had a normal pregnancy were similar in both groups (table 2). Fourteen cases (45%) and 13 controls (41%) had attended day care centres.

Sixteen of the cases (52%) and 25 of the controls (78%) had been vaccinated against pertussis.

The present mean weight and height did not differ among groups. Their height and weight development did not show any deviance with mean height for cases at +0.4 SD, for controls 0 SD and median weight for cases +0.6 SD, for controls +0.5 SD.

Values for erythrocyte sedimentation rate, white cell count, haemoglobin, IgA, IgM, IgG with subclasses 1, 2, and 3 did not differ (table 3).

More controls than cases were engaged in additional physical activities outside school, 25/32 (78%) compared with 16/31 (52%). The difference was significant.

Radiography detected two girls with pulmonary infiltrates, one in each group. In both cases it was connected with acute respiratory infections and examination after two months showed complete regression. Five of 29 children who had had whooping cough showed signs of hyperinflation (17%) and four in the control group (13%). One of the five in the former and two of the four in the latter group were considered to have pronounced signs of hyperinflation.

Lung function tests did not show any difference (table 4). The control group had a 10%

better working capacity, which did not reach statistical significance, with a maximum work load of 140.6 watts as compared with 120.5 for children who had had whooping cough ($p=0.2$). Both groups declined in MEF_{50} after maximum work by 5%. Five cases (16%) and two controls (6%) reduced their MEF_{50} to less than 80% after exercise with a minimum of 73% in both groups. Values after salbutamol increased with 17% and 15% respectively.

Power calculations were carried out using the data of table 4. To illustrate consider the MEF_{25} : the difference between the means of cases and controls was 0.15, which is 10% of the general level of the two groups. Given this as the true difference, the actual sample size and the observed SDs the power according to tables was below 50%.²¹

Discussion

The present study could not show any difference between the children who had had whooping cough during the first year of life and control children with respect to retrospective data on airway diseases. Furthermore differences in indices of present lung function, including small airways function, were not seen.

This is in accordance with the findings of Johnston *et al*, who measured lung function after infant whooping cough in a controlled study, taking presumed functional silence of the peripheral airways into account.¹⁴

Sveger *et al* in their report of 10 subjects found evidence of changes in minor airways. The study was uncontrolled, based on children hospitalised with whooping cough and bronchopneumonia verified by chest radiography.¹³ Likewise an Australian study using measurements of small airways function came to the same conclusion based on 30 children treated in hospital with whooping cough when they were less than 6 months old.¹⁰

Currently available epidemiological data relevant for testing the hypothesis that infant whooping cough is a risk factor for subsequent small airways disease are inconclusive. A direct test of this by a prospective longitudinal study is very difficult.

As the hypothesis is of great interest for the discussion about risks and benefits of pertussis vaccination, indirect evidence has to be collected from different studies using either historical cohorts or case-control methodology. To our knowledge only three other studies have used the former approach with a control group.^{9 14 22}

Misclassification reduces the strength of association—for example, if controls have had the disease this would diminish an existing difference. The cases in our study were ascertained as far as possible with a positive cultures (found in 61%). According to various sources the children in the control group had not had overt disease with long standing cough.

Whooping cough may occur more frequently or be more easily recognised in children with constitutional factors that predispose to respiratory morbidity. This would cause a bias in the exposed group.²³ Our groups did not differ in

distributions of immunoglobulins and IgG subclasses; this has not been investigated before.

Earlier studies have examined children in hospital for whooping cough during infancy. The applicability of the hospital population based studies for inferences and comparisons is unknown and unreliable, depending on different criteria for hospitalisation. If most children with whooping cough are not hospitalised the results apply only to those episodes sufficiently severe on clinical grounds—for example, with secondary complications—to require admission. Around 10% of the infants from our community based sample were treated in hospital.

Recall bias of the preferential type can mask a real difference between the groups by parents denying previous problems with frequent respiratory infections. This is unlikely in view of the corroborative evidence looked for in each case.

Johnston *et al* found that respiratory symptoms were more common in children with previous episode of infant whooping cough, although the difference was not significant.¹⁴ Their cases were more likely to be atopic or have a family history of wheezing illness. In our study current respiratory symptoms among children who had had whooping cough were not more common. Clinical features of atopy were equally prevalent in the case and the control group and in their first degree relatives. Serum IgE concentration was similar, which should rule out a difference in atopic constitution among the groups. Neither group included children with evidence of immunoglobulin deficiency.

The observed association in children between whooping cough and impaired lung function may not be a direct consequence of the infection. Martinez *et al* studied 214 newborns. They found that the differences in lung function after lower respiratory tract illness in infancy could in part be due to differences in lung function that were present before the illness occurred.²³ Endogenous susceptibility together with whooping cough during infancy when the lung is still developing might give minor airways disease later in life. An atopic constitution would be one such host factor.

The difference found in physical ability is difficult to assess as the interview was not blinded. It could also be explained by the control group being somewhat older.

Our study addresses the question of whether *B pertussis* in itself, by its damage to the ciliary epithelium, could cause subclinical pulmonary abnormalities, which in turn could predispose for airway disease in adulthood. Histopathology studies on the damage by *B pertussis* to human respiratory epithelium are old.²⁴ Animal models using guinea pig and rabbit tracheal epithelium indicate that the bacterium restricts its damage to the epithelium of the airways.^{25 26}

Direct structural alteration seems unlikely, although definite data are not available. Even if whooping cough involves the bronchiolar wall, respiratory epithelium regenerates rapidly given that there is no destruction of elastic fibres and smooth muscles.²⁷ One could therefore assume that bronchopneumonia with lung tissue infil-

trates visible on radiography in a patient with whooping cough is due to secondary invasion of other potential airway pathogens.

Because of the limited sample size there is a possibility that a real difference has been overlooked. The demonstration of statistical significance of differences as large as the observed, however, would require sample sizes far beyond practical feasibility.²¹

The possible mechanisms by which whooping cough might permanently affect pulmonary function are still speculative in terms of biological coherence. The association in adolescents between infant whooping cough and impaired lung function observed earlier is probably non-causal and not a direct consequence of the specific infection. Studies with longer follow up of a larger sample might show minor differences in lung function, which together with other predisposing factors could provoke chronic airway symptoms.

CONCLUSION

In a country like Sweden, where secondary complications usually are treated adequately, it is highly unlikely that whooping cough in itself would result in long term sequelae in the airways. The available data do not support the hypothesis that whooping cough in infancy is a risk factor for chronic airflow obstruction in adolescence in Swedish children.

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