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Risk Factors for Invasive *Haemophilus influenzae* Disease among Children 2–16 Years of Age in the Vaccine Era, Switzerland 1991–1993

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Background. Continued surveillance, and detailed investigation of direct and indirect effects of conjugated vaccines and risk factors for invasive *H.influenzae* serotype b (Hib) disease in the vaccine era are important.

Methods. 143 cases with invasive disease between 1991 and 1993 aged 2–16 years were selected retrospectively from a large incidence trend study. Controls (n = 336) were recruited from local vital registries and matched to cases for age, gender, and residence. Hib vaccination histories among study subjects and their siblings and other sociodemographic variables were obtained by questionnaires completed by the parents of these children. Adjusted odds ratio (OR) estimates were calculated by conditional logistic regression analysis.

Results. Most vaccinated subjects had received the Polysaccharide-Diphtheria Toxoid vaccine and estimated vaccine efficacy was high (95%; 95% confidence interval [CI] 60–99%). Also, the results suggested that protection afforded by vaccination against Hib extended to the family members of vaccinated children. School attendance was found to be protective against invasive Hib disease (OR : 0.33; CI : 0.14–0.75). Cases more often than controls reported sufferring from asthma and allergies (OR : 4.8; CI : 1.2–19.4).

Conclusions. Post-licensure vaccine efficacy is high among children ≥2 years of age. The observed association between asthma and epiglottitis is novel and deserves further investigation.

Keywords: *Haemophilus influenzae*, vaccine, vaccine efficacy, risk factors, asthma

Haemophilus influenzae type b (Hib) has been a leading cause of life threatening invasive disease among children worldwide until vaccines became available in the mid to late 1980s.[1]

In the prevaccine era the epidemiology of invasive Hib disease in Switzerland was comparable to that of other Western European countries.[2] For example, meningitis occurred at an annual incidence rate of 25 cases per 100 000 children <5 years of age.[2] The average age at disease was 29 months, higher than, for instance, in the US. Epiglottitis was as frequent as meningitis (annual incidence: 25 cases per 100 000 children <5 years old).

The first conjugate vaccine Polysaccharide-Diphtheria Toxoid (PRP-D) was licensed in May 1990 and it was recommended to vaccinate all infants (at age 4, 6 and 15–18 months). As reported from several other countries, disease rates declined rapidly after the initiation of vaccination.[2–6] For example, among children <5 years of age incidence rates fell by 80% until the year 1993.[2] The average age at disease increased to 35 months.

However, cases of invasive Hib disease continue to be diagnosed in our country. Continued surveillance, detailed investigation of direct and indirect vaccine effects and risk factors for invasive Hib disease in the vaccine era are therefore important.

METHODS

We conducted a population based case-control study among Swiss children aged 2–16 years of age for the time period 1991–1993 to investigate post-licensure

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vaccine efficacy and risk factors for invasive *H.influenzae* disease. The study protocol was approved by the ethical board of the University of Berne and the 26 state physicians of Switzerland. In addition, consent was obtained from designated people for data protection upon request by the state physicians.

Cases were selected from a retrospective study[2] on the incidence of invasive *H.influenzae* disease among children 0–16 years of age and residing in Switzerland between 1980 and 1993. Data had been collected from hospital statistics and by chart review for patients, who were diagnosed in any of 39 participating Swiss paediatric clinics with culture proven meningitis, epiglottitis, arthritis, cellulitis, or bacteraemia. In addition, clinically diagnosed epiglottitis cases were included.

Eligible for the current case-control study were patients who were hospitalized between 1 January 1991 and 31 December 1993 and had survived their disease. Cases had to be ≥2 years of age in 1991, ≥3 years old in 1992 and ≥4 years old in 1993. Age restriction had the purpose of increasing the probability that a case was not vaccinated (born before 1990), but had younger siblings eligible for vaccination. Cases had to be of Swiss or Italian nationality (residing in Switzerland).

The eligibility criteria were met by 143 cases. Seventy-nine (55.2%) cases contracted the disease in 1991. The corresponding numbers for 1992 and 1993 were 44 (30.8%) and 20 (14%) cases, respectively. Forty-four (30.8%) had meningitis, 91 (63.6%) had epiglottitis, and 8 (5.9%) arthritis (n = 1), cellulitis (n = 1), bacteraemia (n = 2), or pneumonia (n = 3). Among epiglottitis cases the diagnosis was culture confirmed in 67 (73.6%) patients.

Controls were selected from vital statistics registries and were matched to cases by age (±0.5 years), gender, and the political community in which the case lived at disease onset. Five controls per case were recruited randomly if a community had five or more eligible children; otherwise, all eligibles were included. Out of 120 vital registries contacted, 109 (91%) participated in control selection and provided the names and addresses of 542 controls.

A self-administered questionnaire in German, French or Italian was sent to case and control families. Questionnaires were accompanied by a letter asking for participation. A second and third reminding letter and questionnaire were sent after 4 and 8 weeks, if no response was obtained. One hundred and thirty-nine (97%) of 143 case families and 539 (99%) of 542 control families for whom a current address was available, were contacted. Overall, questionnaires were returned by 121 (87.0%) cases and 399 (74.0%) controls within 12 weeks. Eight (6.7%) cases had one matched control, 20 (19.6%) cases had two controls, 24 (20%) cases had three controls, 31 (25.8%) cases had four controls, and 19 (15.8%) cases had five controls. Nineteen (15.8%) cases and 19 (15.8%) controls had no matching control or case, respectively. Therefore, 102 cases and 336 controls who had at least one matched control or case remained for further analysis.

The questionnaire asked about a) the family structure, b) the history of Hib vaccination on all children in the household as listed in the vaccine booklet, c) day care, kindergarden or school attendance and the number of children sharing a bedroom during the year of disease or reference date, d) chronic disease in any of the children, e) a history of meningitis or epiglottitis in any family member, and f) the number of smokers in the family. Only the question on chronic diseases was open ended and asked for: 'any chronic disease in a child living in the household, e.g. cancer or asthma'. Also, parents were asked for permission to contact their family physician for further completion of vaccination histories if necessary. Vaccine history was obtained from the family physician for five controls, but for none of four cases for whom data were missing in the questionnaire.

A reference date was chosen as the day when the case had been hospitalized with invasive *H.influenzae* disease. Cases and controls were considered vaccinated against Hib if they had received at least one dose of a conjugated vaccine more than 14 days before the hospitalization or reference date.

Statistical associations between categories were evaluated by the χ^2 test with Yates' correction or Fisher's exact test. Crude and adjusted odd ratios (OR) were estimated in a conditional logistic regression model using EGRET.[8] Vaccine efficacy was calculated as (1-OR) × 100%, where OR estimates the relative risk of disease comparing vaccinated to non-vaccinated children. The following variables were evaluated as confounders: family size, the number of siblings, the number of siblings sharing a bedroom with the case/control, the number of adult household members, day care, kindergarden or school attendance, the number of smokers in the family, and the presence of chronic diseases.

RESULTS

Data obtained from chart review during the incidence study of invasive *H.influenzae* disease in Switzerland[2] showed that there was little difference in the clinical and sociodemographic characteristics of the cases that were included in the analysis (n = 102) and those that were not (n = 41) (data not shown). Table 1 presents the

TABLE 1 *Sociodemographic and clinical characteristics of 102 cases and 336 matched controls, Switzerland 1991–1993*

	Cases		Controls	
	N	%	N	%
Total	102	100	336	100
Age:				
2	8	7.8	18	5.4
3–4	47	46.1	156	46.4
≥5	47	46.1	162	48.2
Gender:				
Female	43	42.1	146	43.5
Male	59	57.9	190	56.5
Family size:				
2	2	1.9	2	0.6
3	17	16.7	31	9.2
≥4	83	81.4	303	90.2
Sharing bedroom:				
No	62	60.8	196	58.3
1 sibling	31	30.4	108	32.1
≥2 siblings	7	6.9	29	8.6
Missing	2	1.9	3	1.0
Day care attendance:				
No	63	61.8	220	65.4
1–4 hours/week	27	26.5	63	18.8
>4 hours/week	11	10.7	49	14.6
Missing	1	1.0	4	1.2
Day care group size:				
0	63	61.8	220	65.6
<10	25	24.5	67	20.0
≥10	10	9.8	38	11.3
Missing	4	3.9	11	3.3
Kindergarden/school:				
No	64	62.8	169	50.3
Yes	38	37.2	167	49.7
Siblings day care attendance:				
No	85	83.3	267	79.5
1–4 hours/week	8	7.8	37	11
>4 hours/week	9	8.8	30	8.9
Missing	0	0	2	0.6
Siblings kindergarden/school:				
No	51	50	144	42.9
Yes	51	50	192	57.1
Smokers:				
0	60	58.8	207	61.6
1	26	25.5	83	24.7
≥2	14	13.7	43	12.8
Missing	2	2.0	3	0.9
Chronic disease:				
No	88	86.3	316	94
Asthma	7	6.8	16	4.8
Allergy	5	3.9	4	1.2
Other	2	2.0	0	0

TABLE 2 *Conditional logistic regression analysis for risk factors of invasive* H.influenzae *disease among children 2–16 years of age, Switzerland, 1991–1993*

	OR[a] crude	OR[a] adjusted	95% CI[b]
Vaccination	0.06	0.05	0–0.40
Day care attendance:			
(≤4[c], >4 hours/week)	0.69	0.61	0.24–1.52
School attendance (no[c], yes)	0.27	0.33	0.14–0.75
Adults:			
2[c]	1.0	1.0	–
1	3.15	3.52	1.0–15.37
≥3	0.78	0.83	0.30–2.27
Siblings <4 years old (0, 1, 2,≥3)	0.94	1.00	0.62–1.64
Siblings day care attendance:			
(≤4[c], >4 hours/week)	0.95	1.01	0.37–2.95
Siblings school attendance:			
(no[c], yes)	0.74	0.55	0.32–0.99
Sharing bedrooms (n)	0.93	1.03	0.57–1.89
Smokers (n)	1.05	1.10	0.76–1.57

[a] Odds ratio crude or adjusted for all other variables in the model. Analysis on 93 of 102 matched sets; 19 patients had missing values.
[b] 95% confidence interval.
[c] Reference group.

distribution of the matching variables and selected sociodemographic characteristics of cases and controls. During the 3 years after the introduction of conjugated vaccine the average age at disease rose among children older than one year by 2 months. However, the skewed age distribution of cases and controls reflects the age restriction during sampling.

Only one of 102 cases had been vaccinated compared to 44 (13.1%) control children. Adjusted vaccine efficacy was therefore calculated to be 95% (95% confidence interval [CI] 59.7–99.4; Table 2). The vaccinated case had received one dose of a PRP-D vaccine at the age of 19 months; 8 months before contracting purulent arthritis. All except two of the controls were vaccinated with one dose of PRP-D vaccine at age 15 months or older; two controls got two doses of PRP-D vaccine. For all three study years (1991–1993) diphtheria toxoid conjugated vaccine PRP-D (ProHibit®) was the most frequently used vaccine brand for case or control siblings. It had been given to 120 (75.5%) of 159 case or control families with at least one vaccinated child. The PRP-meningococcal outer membrane protein complex conjugate (PedvaxHIB®), the diphtheria protein

TABLE 3 *The influence of asthma and allergies on the risk of invasive* H.influenzae *disease in non-vaccinated children 2–16 years of age, Switzerland, 1991–1993*

	Cases N	Controls N	OR[a] crude	OR[a] restricted	95% CI[b]
Epiglottitis:					
Asthma/Allergies					
No[a]	56 (37)	214 (186)	1.0	1.0	
Yes	9 (7)	10 (6)	3.30	4.80	1.18–19.44
Meningitis:					
Asthma/Allergies					
No[c]	26 (25)	81 (72)	1.0	1.0	
Yes	2 (2)	8 (7)	1.15	0.87	0.16–4.72

[a] Odds ratio crude or restricted to non-vaccinated cases and controls and to culture proven epiglottitis cases. The figures in parentheses indicate the number of cases and controls after restriction.
[b] 95% confidence interval.
[c] Reference group; cases and controls with a chronic disease other than asthma or allergies are excluded.

TABLE 4 *The influence of vaccination of siblings on the risk of invasive* H.influenzae *disease in non-vaccinated children 2–16 years of age, Switzerland 1991–1993*

	Cases N	Controls N	OR[a] crude	OR[a] adjusted	95% CI[b]
Siblings vaccinated:					
0	23	48			
1	6	11	0.30	0.16	0.01–1.56
2	0	4			

[a] Odds ratio restricted to non-vaccinated cases and controls with at least 1 sibling <4 years of age and not attending day care >4 hours/week, kindergarden or school. Adjusted for the number of siblings and day care, kindergarden or school attendance of siblings.
[b] 95% confidence interval. Test for trend: $P = 0.16$.

CRM197 conjugate (Hib TITER®) and the tetanus toxoid conjugate PRP-T (ActHIB®) had been administered in 18 (11.3%), 9 (5.7%) and 1 (0.6%) families. Among control siblings up to 2 years of age at the reference date 76.3% (58 of 76) had received at least one dose of a conjugated vaccine. This percentage vaccinated increased slightly from 71.4% in 1991, to 84.0% and 77.8% in 1992 and 1993, respectively.

Adjusting for vaccination history, day care, kindergarden or school attendance, and smoking there was no increased risk associated with the number of children in a family (OR : 0.86; 95% CI : 0.61–1.20; test for trend: $P = 0.36$), the number of siblings <4 years of age (OR : 1.0, 95% CI : 0.62–1.61), or having siblings 4–16 years of age (OR : 1.11, 95% CI : 0.59–2.08). Also, sharing a bedroom with siblings was not a risk factor (OR : 1.03; 95% CI : 0.57–1.89). In six case and six control families the mother was the only adult (Table 1). Having only one adult household member seemed to be associated with an increased risk of invasive *H.influenzae* disease (OR : 3.57, 95% CI : 1.0–12.86) (Table 2).

Only 11% of cases and 15% of controls attended day care for more than 4 hours a week (Table 2). Children with regular day care attendance seemed to have a relatively lower risk of invasive *H.influenzae* disease (adjusted OR : 0.61, 95% CI : 0.24–1.52) (Table 3). Also, a smaller proportion of cases attended school than their matched controls (OR : 0.33, 95% CI : 0.14–0.75) and they less often had siblings who attended school (OR : 0.65, 95% CI : 0.44–0.97) (Table 3). Restricting the analysis to cases and controls <6 years of age did not appreciably influence the OR estimate (data not presented).

The presence of smokers in a family did not increase the risk of invasive *H.influenzae* disease in this study population (OR : 1.05, 95% CI : 0.76–1.57).

Seven cases and 16 controls had a history of asthma and four cases and four controls had an 'allergy'. Only three cases and three controls specified their disease as allergic asthma or allergic rhinitis. The proportion of case and control families who mentioned a sibling with a chronic disease were similar, namely 4% and 6% (Table 1). One case had epilepsy and another case suffered from Crohn's disease. Asthma and allergies taken together were associated with an increased risk of culture proven epiglottitis among non-vaccinated cases and controls (OR : 4.8, CI : 1.2–19.4) (Table 3). Analysed separately, the OR estimate associated with asthma was 5.5 (95% CI : 1.0–29.7) and for allergies the OR was 3.3 (95% CI : 0.2–40.0). However, a history of asthma and allergies did not increase the risk for *H.influenzae* meningitis (Table 3).

In order to evaluate if Hib vaccination of siblings conferred indirect protection on other family members, the study population was restricted to 29 cases and 63 controls who were not vaccinated, had at least one sibling 4 years of age or younger and did not attend day care (more than 4 hours a week), kindergarden or school. Fifteen controls (25.6%) had at least one vaccinated sibling in contrast to six (20.7%) cases. The relative risk associated with having vaccinated siblings was 0.16 (95% CI : 0.01–1.56, test for trend: $P = 0.12$) (Table 4).

DISCUSSION

This case-control study evaluated risk factors of invasive *H.influenzae* disease among children 2–16 years of age during a 3-year period after the licensure of conjugate vaccines in Switzerland. Vaccination was found to be highly protective against invasive Hib disease in this study population where the PRP-D was the most frequently administered vaccine brand. This observation agrees also with the rapid decline of invasive Hib disease in Switzerland soon after the initiation of the vaccine programme.[2] However, the PRP-D vaccine has been found to be less immunogenic[9] and it may be less protective.[9,10]

Some limitations may be considered when interpreting our study results. While the possibility of confounding is present in every non-randomized study of treatment efficacy, we feel that confounding is unlikely to have been responsible for the whole of the observed association. Within the Swiss population there is no reason to suggest that the decision to give/receive the vaccine is related to the disease,[11] and in any event the association with vaccination *per se* was adjusted for a variety of characteristics. Also, in Switzerland socioeconomic standard is uniformly high and school attendance is obligatory. The incidence study from which cases were recruited also included disease caused by non-serotype b strains. This should not have had an important influence on the study result, since over 98% of disease events were due to serotype b strains.

Recently, Barbour *et al.*[12] observed a reduced rate of nasopharyngeal colonization with Hib among older, non-vaccinated siblings of vaccinated children. Our study suggests that vaccination of children also confers indirect protection from invasive *H.influenzae* disease to their older siblings.

Day care attendance has been found to increase the risk of invasive *H.influenzae* disease.[13–17] However, in our study control children attended day care more often than cases. In Switzerland, vaccination is not required for day care or school attendance. The reason for the observed association may have been that we studied children over 2 years of age. Three previous investigations had shown that the risk associated with day care was highest under the age of 2 years and waned thereafter.[13,15,16] Redmond and Picchichero[13] hypothesized that longer duration of day care may lead to greater isoimmunization (i.e. exposure to cross reactive antigens carried by other bacteria) and protection from disease. This may also explain why in our study school attendance among the study subjects and their siblings was found to be protective.

Recently, Jafari *et al.*[17] reported that having a single mother was a risk factor for invasive Hib disease and delay of vaccination in a post-licensure case-control study among children 2–18 months of age. Our results suggested a similar association. However, small numbers did not allow us to explore this relationship further.

An interesting observation was that a higher proportion of epiglottitis cases reported a history of asthma or allergies than did control children. We did not have more detailed information on the nature of reported allergies or documentation of asthma. Also, we cannot exclude that case families were more aware of allergies or asthma and reported them more often. To our knowledge no other study has investigated asthma as a risk factor for invasive *H.influenzae* disease. In fact most of the earlier studies on risk factors have been conducted in the US where epiglottitis is a rare manifestation of invasive Hib disease which is itself uncommon in children of the age group addressed in this study. However, several observations indicate that damage to the respiratory mucosa e.g. through other infections or exposure to smoke may increase the risk of invasive *H.influenzae* disease.[18–21] Similarly, chronic inflammation of the respiratory mucosa in asthma patients may help the bacterium to invade its host. *H.influenzae* is able to synthesize histamine and it has been suggested that the increase in bronchial permeability induced by histamine may be used by the bacterium to acquire necessary growth factors from the circulation.[22–24] Histamine is also present in high concentrations in respiratory secretions of asthma patients and may favour colonization or invasion by *H.influenzae*. In this study, asthma was only a risk factor for epiglottitis but not for meningitis. This may be a consequence of the relatively high average age of the study population or it may indicate the role of a local event in the respiratory tract. The rapidly decreasing incidence of invasive Hib disease in the vaccine period will make it difficult to study this question further. However, mucosal damage through viral infections or smoking has also been found to increase the risk of invasive infection with *Neisseria meningitidis*[25] and *Streptococcus pneumoniae*,[26] and the prevalence of asthma is believed to have been increasing in the last decades.[27,28] Therefore, the role of asthma for the pathogenesis of invasive *H.influenzae* disease and other bacterial infections deserves further study.

REFERENCES

[1] Mäkelä H P, Takala A K, Peltola H, Eskola J. Epidemiology of invasive *Haemophilus influenzae* Type b disease. *J Infect Dis* 1992; **165 (Suppl. 1)**: 2–6.

[2] Mühlemann K, Alexander E R, Pepe M, Schopfer K. Invasive *Haemophilus influenza* disease among Swiss children 1980–1993: Evidence for herd immunity among older age groups? *Scand J Infect Dis* (In press), 1996.

[3] Adams W, Deaver K A, Cochi S L *et al.* Decline of childhood *Haemophilus influenzae* Type b (Hib) disease in the Hib vaccine era. *JAMA* 1993; **269:** 221–26.

[4] Broadhurst L E, Erickson R L, Kelley P W. Decreases in invasive *Haemophilus influenzae* diseases in US Army children, 1984 through 1991. *JAMA* 1993; **269:** 227–31.

[5] Murphy T V, White K E, Pastor P *et al.* Declining incidence of *Haemophilus influenzae* Type b disease since introduction of vaccination. *JAMA* 1993; **269:** 246–48.

[6] Peltola H, Kilpi T, Anttila M. Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunisation with conjugate vaccines. *Lancet* 1992; **340:** 592–94.

[7] Van Alphen L, Spanjaard L, van der Erde A, Dankert J. Predicted disappearance of *Haemophilus influenzae* type b meningitis in Netherlands. *Lancet* 1994; **344:** 195.

[8] Breslow N E, Day N E. *Statistical Methods in Cancer Research. Volume 1: The analysis of case-control studies.* Lyon: IARC Scientific Publications, 1980.

[9] Zangwill K, Wenger J D, Sutter R W, Hadler S C. Recommendations for use of *Haemophilus* b conjugate vaccines and a combined diphtheria, tetanus, pertussis, and *Haemophilus* b vaccine. *Morb Mortal Wkly Rep* 1993; **42 (RR-13):** 1–15.

[10] Ward J, Brenneman G, Letson G W, Heyward W L. Limited efficacy of *Haemophilus influenzae* Type b conjugate vaccine in Alaska Native infants. *N Engl J Med* 1990; **323:** 1393–1401.

[11] Schorr D M, Von Känel S, Kürsteiner W, Schwemmer C. Durchimpfung bei 210 zufällig ausgelesenen Kindern im dritten Lebensjahr im Sommer 1992 im Kanton Basel-Landschaft. *Bull BAG/OFSP* 1993; **34:** 616–20.

[12] Barbour M L, Booy R, Crook D W M *et al. Haemophilus influenzae* type b carriage and immunity four years after receiving the *Haemophilus influenzae* oligosaccharides-CRM 197 (HbOC) conjugate vaccine. *Pediatr Infect Dis J* 1993; **12:** 478–84.

[13] Redmond S R, Pichichero M E. *Haemophilus influenzae* Type b Disease. *JAMA* 1986; **252:** 2581–84.

[14] Istre G R, Conner J S, Broome C V, Hightower A, Hopkins R S. Risk factors for primary invasive *Haemophilus influenzae* disease: Increased risk from day care attendance and school-aged household members. *J Pediatr* 1985; **106:** 190–95.

[15] Cochi S L, Fleming D W, Hightower A W *et al.* Primary invasive *Haemophilus influenzae* Type b disease: A population-based assessment of risk factors. *J Pediatr* 1986; **108:** 887–96.

[16] Takala A K, Eskola J, Palmgren J *et al.* Risk factors of invasive *Haemophilus influenzae* type b disease among children in Finland. *J Pediatr* 1989; **115:** 694–701.

[17] Jafari H, Adams W, Deaver K, Plikaytis B, Wenger J. Efficacy of *Haemophilus influenzae* type b (Hib) conjugate vaccines, risk factors for invasive Hib disease and under-vaccination in the United States. In: *Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Francisco, CA: American Society for Microbiology. 1995, pp. 160.

[18] Takala A K, Muerman O, Kleemola M *et al.* Preceding respiratory infection predisposing for primary and secondary invasive *Haemophilus influenzae* type b disease. *Pediat Infect Dis J* 1993; **12:** 189–95.

[19] Kaplan S, Taber L H, Frank A L, Feigin R D. Nasopharyngeal viral isolates in children with *Haemophilus influenzae* type B meningitis. *J Pediatr* 1981; **99:** 591–93.

[20] Vadheim C M, Greenberg D P, Bordenave N *et al.* Risk factors for invasive *Haemophilus influenzae* Type b in Los Angeles County children 18–60 months of age. *Am J Epidemiol* 1992; **136:** 221–35.

[21] Wilson R, Read R, Cole P. Interaction of *Haemophilus influenzae* with Mucus, Cilia and Respiratory Epithelium. *J Infect Dis* 1992; **165 (Suppl. 1):** 100–2.

[22] Read R C, Wilson R, Rutman A *et al.* Interaction of nontypable *Haemophilus influenzae* with human respiratory mucosa in vitro. *J Infect Dis* 1991; **163:** 549–58.

[23] Sheinman B D, Devalia J L, Davies R J, Crook S J, Tabaquali S. Synthesis of histamine by *Haemophilus influenzae. Br Med J* 1986; **292:** 857–8.

[24] Moxon, Wilson R. The Role of *Haemophilus influenzae* in the Pathogenesis of Pneumonia. *Rev Infect Dis* 1991; **13 (Suppl. 6):** 518–27.

[25] Harrison L H, Armstrong C W, Jenkins S R *et al.* A cluster of meningococcal disease on a school bus following epidemic influenza. *Arch Intern Med* 1991; **151:** 1005–09.

[26] Hakansson A, Kidd A, Wadell G, Sabharwal H, Svanborg C. Adenovirus infection enhances in vitro adherenence of *Streptococcus pneumoniae. Infect Immun* 1994; **62:** 2707–14.

[27] CDC. Asthma—United States, 1982–1992. *Morb Mortal Wkly Rep* 1995; **43:** 952–55.

[28] Anderson H R, Butland B K, Strachan D P. Trends in the prevalence and severity of childhood asthma. *Br Med J* 1994; **308:** 1600–01.

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APPENDIX

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