Burden of Influenza in Children in the Community

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Background. Influenza vaccination of healthy children is encouraged because children are frequently hospitalized for influenza-attributable illnesses. However, most children with influenza are treated as outpatients, and scarce data are available on the burden of influenza in these children.

Methods. We performed a prospective study of respiratory infections in preenrolled cohorts of children ⩽13 years old during 2 consecutive respiratory seasons (2231 child-seasons of follow-up). At any sign of respiratory infection, we examined the children and obtained a nasal swab for the detection of influenza. The parents filled out daily symptom diaries. Of all the enrollees, 94% remained active participants in the study.

Results. The average annual rate of influenza was highest (179 cases/1000 children) among children <3 years old. Acute otitis media developed as a complication of influenza in 39.7% of children <3 years old. For every 100 influenza-infected children <3 years old, there were 195 days of parental work loss (mean duration, 3.2 days).

Conclusions. Influenza causes a substantial burden of illness on outpatient children and their families. Vaccination of children <3 years old might be beneficial for reducing the direct and indirect costs of influenza in children.

Annual morbidity due to influenza is highest in children, in whom the attack rates are often >30% [1–4]. Children are also considered to be the main disseminators of influenza in the community [4–9]. Recent studies have documented that infants and young children without underlying medical conditions are hospitalized for influenza-attributable illnesses at rates that are comparable to those of adults with high-risk conditions [10–13]. The high risk of hospitalization of children has initiated an intensive discussion about the universal vaccination of children against influenza [10–14]. In 2002, the US Advisory Committee on Immunization Practices decided to encourage the vaccination of all children 6–23 months old, when feasible [15], and, in October 2003, the Committee voted to recommend that all children in this age group be vaccinated annually against influenza, unless contraindications are present [16].

The cocirculation of other viruses, particularly respiratory syncytial virus, during influenza epidemics is a serious obstacle to reliable estimations of the burden of influenza in children. Accordingly, there are doubts about whether influenza is responsible for all of the excess morbidity that is attributed to it [14]. Moreover, hospitalized children represent only a small proportion of the overall incidence of pediatric influenza. Most children with influenza are treated as outpatients, and it is probable that these cases account for the greater part of the total disease burden in children. The widespread vaccination of healthy children against influenza will likely require an assessment of the cost-effectiveness of the intervention, and an estimation of the direct and indirect costs of influenza and its complications in children treated as outpatients is of crucial importance in that context.

The present prospective study was specifically designed to determine the total burden of influenza in

Received 9 March 2004; accepted 30 April 2004; electronically published 15 September 2004.

Presented in part: Options for the Control of Influenza V, Okinawa, Japan, 7–11 October 2003 (abstract W03-5).

Financial support: Wyeth; GlaxoSmithKline; European Scientific Working Group on Influenza; Academy of Finland; Foundation for Pediatric Research in Finland; Jenny and Antti Wihuri Foundation, Finland.

None of the sponsors played any role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation or review of the manuscript. The decision to publish the data was made solely by the authors, who did not seek or obtain any sort of authorization for publication from the sponsors.

Potential conflict of interest: T.H. has served as a consultant to Wyeth and has received honoraria for lectures at academic meetings organized by Wyeth and GlaxoSmithKline.

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The Journal of Infectious Diseases 2004;190:1369–73

0022-1899/2004/19008-0001$15.00

children in the community. To enable a reliable estimation of the impact of influenza, we obtained samples for viral detection during every episode of respiratory illness in the children.

SUBJECTS AND METHODS

Participants. We recruited the participants through day care centers, family day care, and schools in our area. All children <13 years old were eligible for participation. Of 1458 children initially recruited, 1338 were monitored during the respiratory season of 2000–2001. For the 2001–2002 season, the study group consisted of 907 children, of whom 893 were eventually monitored. Overall, the study comprised 2231 child-seasons of follow-up. The baseline demographics of the children are presented in table 1.

The study protocol was approved by the Ethics Committee of Turku University Hospital. Written, informed consent was obtained from the parents of all participating children.

Study conduct. The study was performed from 9 October 2000 through 20 May 2001 and from 1 October 2001 through 19 May 2002. The parents were asked to bring their children to the study clinic whenever fever or signs of respiratory infection appeared. The study clinic was open every day. At each visit, the children were examined by a study physician. Chest or sinus radiographs were routinely obtained for all children who were clinically suspected of having pneumonia or sinusitis. In addition to pneumatic otoscopy, tympanometry and spectral-gradient acoustic reflectometry were used to aid in diagnosing acute otitis media (AOM). Children without any complications were routinely reexamined after 5–7 days and whenever the parents deemed it necessary. All visits were free of charge. Influenza antiviral drugs and rapid diagnostic tests were not used for any children.

Viral specimens. During each episode of respiratory infection, a nasal swab was obtained from a depth of 2–3 cm in the nostril by use of a sterile cotton swab that was then inserted into a vial that contained viral transport medium [17]. Detection of influenza viruses in the specimens was based on viral culture in Madin-Darbey canine kidney cells and subsequent immunoperoxidase staining with monoclonal antibodies, as described elsewhere [18].

Symptom diaries. During each season, the parents were provided with 2 daily symptom diaries that consisted of charts inquiring about the symptoms and absences from day care or school of the child and from work, school, or day care of other family members. The days of absenteeism included only actual days lost; days of illness occurring during free weekends or other days off were not recorded as causing absenteeism. Parental compliance with the diaries was good—at least 1 diary was returned for 97% of the active participants, and both diaries were returned for 85% of the active participants.

Definitions. AOM was diagnosed by signs of inflammation of the tympanic membrane, the presence of middle-ear effusion as detected by pneumatic otoscopy, and ⩾1 sign of acute infection. The diagnoses of pneumonia and sinusitis were based on radiological confirmation of the condition. Any complications were considered to be associated with influenza if they were diagnosed within 14 days after the clinical visit at which the influenza-positive specimen was obtained.

Table 1. Characteristics of the children at the beginning of each season of follow-up.

Characteristic	Season 2000–2001 (n = 1338)	Season 2001–2002 (n = 893)
Age		
<6 months	5 (0.4)	6 (0.7)
6 months to <3 years	469 (35.1)	262 (29.3)
3 to <7 years	458 (34.2)	388 (43.4)
7–13 years	406 (30.3)	237 (26.5)
Sex		
Male	692 (51.7)	460 (51.5)
Female	646 (48.3)	433 (48.5)
Method of child care		
Home	33 (2.5)	118 (13.2)
Family day care	228 (17.0)	132 (14.8)
Day care center	658 (49.2)	402 (45.0)
School	419 (31.3)	241 (27.0)
History of wheezing	253 (18.9)	174 (19.5)
Diagnosis of asthma	72 (5.4)	38 (4.3)
Parental smoking		
Yes	512 (38.3)	284 (31.8)
No	798 (59.6)	591 (66.2)
No information	28 (2.1)	18 (2.0)
Influenza vaccination for the season	1 (0.07)	12 (1.3)

NOTE. Data are no. (%) of children.

Statistical analysis. Comparison of proportions between the groups was done by the χ^2 test (SigmaStat version 2.0; SPSS).

RESULTS

Rates of influenza illnesses. A total of 372 episodes of influenza in the children were documented (table 2). For both seasons combined, the annual rates of influenza illness were 179 cases/1000 children <3 years old, 175 cases/1000 children 3–6 years old, and 142 cases/1000 children ⩾7 years old. Of the 372 influenza illnesses, 301 (81%) were caused by influenza A viruses and 59 (16%) by influenza B viruses; in 12 cases (3%), the viruses remained untyped.

Complications, antibiotic treatments, and hospitalizations. Two of 372 influenza-positive children were excluded from further analyses because of double viral infection. AOM was the most frequently diagnosed complication, and it occurred in 39.7% of children <3 years old (table 3). Pneumonia was diagnosed in 2.4% and sinusitis was diagnosed in 3.5% of all

Table 2. Rates of culture-confirmed influenza in children during 2 consecutive seasons of follow-up.

Season, age group	No. of of children	No. of children with influenza	Rate of influenza cases/ 1000 children (95% CI)
2000–2001			
<3 years	474	76	160 (127–193)
3–6 years	458	102	223 (185–261)
7–13 years	406	84	207 (168–246)
2001–2002			
<3 years	268	57	213 (164–262)
3–6 years	388	46	119 (87–151)
7–13 years	237	7	30 (8–52)
Both seasons combined			
<3 years	742	133	179 (151–207)
3–6 years	846	148	175 (149–201)
7–13 years	643	91	142 (115–168)

NOTE. CI, confidence interval.

children with influenza. Antibiotics were prescribed most often (42.0%) to children <3 years old.

Three (2.3%) of 131 children <3 years old were referred to the emergency department because of high fever, inspiratory stridor, and/or impaired general condition; 1 of these children was hospitalized with pneumonia. None of the older children were referred or admitted to hospital because of influenza.

Children's absences from day care or school. On average, 75.2% of children with influenza were absent from day care or school for ⩾1 day (table 4). For every 100 children with influenza, there were 274 days of absence among children <3 years old, 262 days among children 3–6 years old, and 216 days among children ⩾7 years old.

Parental work loss. A parent missed ⩾1 day of work because of the child's influenza in 61.2% of cases in children <3 years old, 53.9% of cases in children 3–6 years old, and 26.3% of cases in children ⩾7 years old (table 4). When calculated for only those cases in which the child was absent for at least 1 day, the corresponding rates of parental absence from work in the different age groups were 80.8%, 73.4%, and 33.9%, respectively. For every 100 children with influenza, there were 195 days of parental work loss for children <3 years old, 146 days for children 3–6 years old, and 54 days for children ⩾7 years old.

DISCUSSION

Our prospective cohort study has provided new and detailed evidence for the substantial burden of influenza in children. A unique feature of this study is that the estimation of the impact of influenza was not based on epidemiological surveillance data but on direct documentation of influenza virus infection on an individual level. Close clinical follow-up of large preenrolled cohorts of healthy children throughout 2 consecutive winter

Table 3. Complications, antibiotic treatments, and hospitalizations in 370 children with culture-confirmed influenza illness.

Variable	Age group <3 years (n = 131)	3–6 years (n = 148)	7–13 years (n = 91)	All children (n = 370)
Acute otitis media	52 (39.7)[a]	29 (19.6)[a]	4 (4.4)[a]	85 (23.0)
Pneumonia	4 (3.1)	4 (2.7)	1 (1.1)	9 (2.4)
Sinusitis	1 (0.8)	10 (6.8)	2 (2.2)	13 (3.5)
Antibiotic treatment	55 (42.0)[b]	41 (27.7)[b]	8 (8.8)[b]	104 (28.1)[c]
Referral to emergency department	3 (2.3)	0	0	3 (0.8)
Hospitalization	1 (0.8)	0	0	1 (0.3)

NOTE. Data are no. (%) of cases. Data for 2 children with double viral infection were excluded.

[a] $P < .001$, for all comparisons between the age groups (χ^2 test).

[b] $P \leqslant .01$, for all comparisons between the age groups (χ^2 test).

[c] The indications for antibiotic treatment were acute otitis media (81 cases), pneumonia (9), sinusitis (11), tonsillitis (1), bronchitis (1), and fever of unknown origin (1).

Table 4. Children's absenteeism from day care (0–6 years old) or school (7–13 years old) and parental absence from work because of child's influenza.

Category, age group	No. of children	Absent for ⩾1 day, no. (%)	Duration of absence,[a] mean (SE), days	Total days of absence in group	Total days of absence/100 children with influenza (95% CI)
Children's absence					
<3 years	103	78 (75.7)	3.6 (0.2)	282	274 (227–320)
3–6 years	128	94 (73.4)	3.6 (0.2)	335	262 (224–300)
7–13 years	76	59 (77.6)	2.8 (0.2)	164	216 (175–257)
Parental absence					
<3 years	103	63 (61.2)	3.2 (0.2)	201	195 (153–238)
3–6 years	128	69 (53.9)	2.7 (0.2)	187	146 (117–176)
7–13 years	76	20 (26.3)	2.1 (0.3)	41	54 (28–80)

NOTE. Data on absenteeism were available for 328 children; 21 children who were cared for at home by a parent were excluded. CI, confidence interval.

[a] Calculated for children or parents who were absent for at least 1 day.

seasons allowed us to evaluate and compare the impact of influenza between different age groups of children.

The severity of influenza epidemics varies between different seasons and viral strains [19, 20]; therefore, results obtained during 1 epidemic may not be directly generalizable to other outbreaks. The value of our 2-year follow-up is demonstrated by the noticeable differences in influenza attack rates between the different age groups of children during the 2 seasons. In 2000–2001, the outbreak was caused primarily by type A/H1N1 influenza viruses that had not been circulating at epidemic levels in Finland since 1996 [21], and the incidence of influenza was fairly similar in all age groups, although the highest attack rates were seen in children 3–6 years old. In contrast, during the 2001–2002 season, when the circulating viruses were mainly of type A/H3N2, which had been prevalent for several years before 2000 [22], the incidence of influenza was 7 times higher in children <3 years old than in those ⩾7 years old. It should be emphasized, however, that both of these influenza epidemics in Finland were considered to be mild [21, 22]; therefore, it is unlikely that our study would have overestimated the impact of influenza during an average outbreak.

To increase children's compliance with repeated sampling, we chose to obtain nasal swabs instead of nasopharyngeal aspirates. The sensitivity of nasal swabs for the detection of influenza in children is ~90%, compared with nasopharyngeal aspirates [17], and it is thus probable that the true incidence of influenza in our cohort may have been at least 10% higher than was actually diagnosed. Moreover, although our virus culture method, which used immunoperoxidase staining with monoclonal antibodies, is more sensitive than conventional virus culture [18], the use of polymerase chain reaction (PCR) for the detection of influenza might have further increased the rates of influenza in our cohorts [23]. Therefore, our results on the incidence of influenza should be regarded as conservative estimates, and the total burden of influenza in children may be even substantially higher than we observed. It is most unlikely, however, that the use of PCR would have affected our findings regarding the relative rates of complications or average durations of absenteeism for influenza-infected children.

AOM was the most frequent complication of influenza and accounted for ~80% of antibiotic prescriptions in influenza-infected children. The high incidence of AOM in our cohort corroborates earlier findings in other settings [12, 24–27]. Considering that the total cost of a single episode of AOM has been estimated to be US $228–$262 [28–30], it is obvious that the frequency of this complication makes it one of the key factors in calculations of the cost-effectiveness of influenza vaccination in children.

Only 1 child in our cohort was hospitalized for an influenza-associated condition. This finding clearly supports the concept that the greatest part of the total disease burden of influenza, including its complications, occurs in the outpatient setting. However, this finding does not challenge the results of previous studies that have demonstrated the increased risk of hospitalization of children for influenza-attributable illnesses [10–13]. Extrapolation of our data suggests that the annual rate of influenza-associated hospitalization among children <3 years old in our study would be 135 cases/100,000 children, which is comparable to previous estimates from the United States [10–12]. Larger sample sizes and longer follow-up than in the present study would be needed to determine the rates of rarely occurring severe manifestations of influenza.

Parental work loss for the care of sick children forms a substantial proportion of the total cost of influenza in children [31–33]. In our study, both the highest rate and the longest duration of parental absence from work were observed for children <3 years old. By use of a conservative assumption of US $93 for a day's salary for a parent in the United States [31], the mean duration of work loss (3.2 days) due to influenza in these children would translate into US ~$300 in lost wages.

Our data can be used to help determine the direct and indirect costs of influenza, which are necessary for assessment of the cost-effectiveness of influenza vaccination in children. The results demonstrate that influenza causes a substantial burden of illness on children and their families in terms of morbidity, complications, treatment, and absenteeism. For each of these aspects, the burden of illness is greatest in children <3 years old. The findings imply that the vaccination of children <3 years old might be beneficial in reducing the total burden of pediatric influenza on society.

Acknowledgments

We are indebted to the other members of the study group: study physicians Minna Aaltonen, Matti Ahonen, Janne Kataja, Riku Kiviranta, Mikko Lintu, Jussi Niemelä, Esa Partanen, Jaakko Pulkkinen, and Otto Rahkonen; study nurses Satu Heikkinen, Susanna Lehtonen, Jaana Marku, Maria Marttila, Anne Riihimäki, and Kirsi-Maija Suomela; virological researchers Eeva Broberg, Katja Rannikko, and Aimo A. Salmi; and data manager Tanja Reunanen.

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