Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 30 (2012) 3009–3014

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Respiratory viruses transmission from children to adults within a household

Chandini Raina MacIntyre[a,c], Iman Ridda[a,c,*], Holly Seale[a], Zhanhai Gao[a], Vigneswary Mala Ratnamohan[b], Linda Donovan[b], Frank Zeng[b], Dominic E. Dwyer[b]

[a] School of Public Health and Community Medicine, Faculty of Medicine, University of New South Wales, Australia
[b] Centre for Infectious Diseases and Microbiology Laboratory Services, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital and the University of Sydney, NSW, Australia
[c] National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases, The Children's Hospital at Westmead, Australia

ARTICLE INFO

Article history:
Received 10 August 2011
Received in revised form 8 November 2011
Accepted 11 November 2011
Available online 23 November 2011

Keywords:
Influenza
Respiratory viruses
Children
Hospital

ABSTRACT

Background: The aim of this study was to examine the rate of transmission of influenza and other respiratory viruses from children attending an Emergency Department to their family members in the household using active surveillance.
Methods: A prospective hospital-based study was conducted over three consecutive winters (2006–2008) in children aged <1–15 years presenting with influenza-like illness (ILI). 168 children with ILI and their healthy families were recruited over three winter seasons.
Results: Respiratory viruses were detected in 101 (60.8%) children with ILI; in 91/166 (54.8%) a single pathogen was detected, and in the remaining 10 children more than one virus was detected concurrently. Influenza was the most common virus detected (34/101), followed by rhinoviruses (22/101) and adenoviruses (14/101). Of influenza viruses, 21/34 were influenza A and 13/34 influenza B. Meeting the clinical definition of ILI did not differentiate between influenza and other viruses. Clinical ILI developed within one week of follow up in 12% (26/205) of the family members who were swabbed. Viral pathogens were detected in 42.3% (11/26) of the symptomatic family members. In 6/11 cases the same virus was detected in the adult and child. The lower estimate of the household risk of transmission of respiratory viruses, based on concordant proven infection in both child and adult, from a single sick child to adult household contacts is therefore 3% per week.
Conclusion: This study provides quantitative, prospective data on rates of household transmission of infection from children to adults.

1. Introduction

Acute respiratory infections (ARIs) are the leading causes of morbidity and mortality throughout the world, particularly in developing nations [1]. Respiratory syncytial virus (RSV) is the most common viral cause of lower respiratory tract infection in young children, followed by parainfluenza viruses (PIVs) types 1, 2 and 3, influenza virus A and B, and adenoviruses. However, the characteristics of viral transmission are poorly understood. Significant understanding is required about the role of household contacts, persistence and recurrence, re-infection, potentially predisposing risk factors, age-related risks, and the effect of prior exposure and past strain infection are not well defined. Insight into the aforementioned information will arm us with more potent way of tackling infectious viral epidemics and lower the burden of healthcare cost.

Household studies [2–5] and community studies [6–8] show RSV to re-infect repeatedly throughout life, which points to a potentially significant role for re-infections within the population that may be fundamental to RSV persistence within the community. Finally, RSV is typical of many viral infections with respect to inducing less than solid immunity, and being antigenically and genotypically diverse.

In addition to being the leading cause of upper and lower respiratory tract infections in infants and young children [9], RSV is the most common cause of bronchitis and pneumonia in children younger than one year of age [10]. The peak incidence of RSV infection occurs in children aged 2–8 months [11], with over half of all children being infected with RSV by their first birthday [12].

During each influenza season, it has been estimated that 30–40% of school-aged children develop symptomatic infection and that they are the main source for transmission to healthy adults and children, and to those in high-risk groups [13–18]. Of the children who develop symptomatic influenza infection, only a small

* Corresponding author at: National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead, NSW 2145, Australia. Tel.: +61 2 98451407; fax: +61 2 98451418.
E-mail address: i.ridda@unsw.edu.au (I. Ridda).

0264-410X/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2011.11.047

proportion are admitted to hospital and it is likely that hospital admissions may represent only a small part of the total influenza-associated morbidity [19,20].

Universal influenza vaccinations is not (yet) recommended for children; this is partly due to lack of data regarding the burden of laboratory-confirmed influenza in children making a meaningful cost effectiveness analysis of a universal influenza vaccination program difficult. Decisions regarding the introduction of influenza vaccine in healthy children require an accurate evaluation of influenza disease burden in the inpatient and outpatient settings, as well as the socioeconomic impact of the disease. The aim of this study was to examine the transmission of influenza and other respiratory viruses from children to their family member in the household. Our results give an estimation of the extent and impact of respiratory viruses, including influenza, in a cohort of children attending the emergency department but not admitted to hospital.

2. Methods

As described before [21], an initial prospective, cluster-randomized trial of the effect of mask use on respiratory virus transmission in households was conducted during two successive winter seasons between 2006 and 2007 in Sydney, Australia. The current study was conducted prospectively as an extension of the aforementioned over three consecutive winters between 2006 and 2008 in Sydney, Australia. The setting in which suitable families were identified was a pediatric health service comprising an emergency department of a pediatric hospital. The hospital acts as a specialized tertiary referral hospital for the western metropolitan area of Sydney, Australia, which has a population of 1.5 million people, and 15 local government areas. Over 70,000 sick children and their families are cared for each year in this area [22]. The study protocol was approved by the Human Research Ethics Committee of the Children's Hospital at Westmead.

2.1. Recruitment

Children aged <1–15 years presenting with ILI (an ILI was defined as fever >38 °C and cough and/or sore throat in the absence of a known cause), but who were not subsequently admitted to hospital were identified using an electronic triage system. Inclusion criteria for the families were that all household members were healthy at the time the child was presented to the emergency department (ED), and that they agreed to follow-up for the duration of the study.

2.2. Follow-up and case definition

An investigator-administered questionnaire was used to collect information on symptoms, relevant medical history including medication, influenza vaccination status and health related visits prior to the ED visit. A combined nose and throat swab was collected from the index child for nucleic acid testing using a multiplex PCR assay. All children were discharged from ED on the same day.

Two adult family members from the child's direct household (i.e. parents/caregivers or siblings aged 16 years and older) were followed up for a week to determine if they developed an ILI. During this follow up period we also collected information regarding the course of the child's illness, requirement for medical visits, and work absenteeism.

If the two family members developed respiratory disease symptoms on follow up (fever, myalgia, arthralgia, sore throat, cough, sneezing, runny nose, nasal congestion, and headache), a home visit was conducted on the same day and swabs were collected and tested for a range of respiratory viruses.

2.3. Laboratory testing

An in-house multiplex, real-time, reverse transcriptase polymerase chain reaction (RT-PCR; primer and probe sequences available on request) for influenza A and B, parainfluenzaviruses, RSV, picornavirus (enterovirus, rhinovirus), adenoviruses, coronaviruses 229E and OC43, and human metapneumovirus (hMPV) was performed [23]. The method was evaluated against respiratory virus antigen positive (by immunofluorescence) upper respiratory tract samples (55 cases of RSV, 35 influenza B, 60 influenza A, 45 parainfluenzaviruses, 25 hMPV, 50 adenoviruses), and PCR positive (all confirmed by sequencing) upper respiratory tract samples (68 cases of rhinovirus and 20 enterovirus infections), and 150 antigen negative samples. The sensitivity of the real-time PCR for RSV, influenza A, influenza B, parainfluenza, hMPV and adenoviruses was 15% higher than antigen detection by immunofluorescence (testing both the antigen positive and negative samples) and the specificity was 100%. All coronavirus positive samples in the study were confirmed by sequencing.

2.4. Statistical analysis

Data were analyzed using Epi Info™ (CDC, USA, version 3.3.2). Descriptive statistics was used to describe age, symptoms, and vaccination rates, etc. Comparison among groups was made with the Fisher exact test for categorical variables. A paired *t* test *p* value <0.05 was considered significant.

3. Results

3.1. Study population

Demographic, clinical and laboratory information on 168 children with ILI and their families were analyzed (Table 1). Sixty-three percent of the children (107/168) attended some form of childcare, leaving 61 (36%) children with no structured exposure of this type to other children outside the home. 39/168 (23%) children had a

Table 1
Characteristics of children/families with and without a child with a laboratory-confirmed infection.

Demographic characteristic	Laboratory positive *N* (%)	Laboratory negative *N* (%)
Total children	101 (60)	67 (40)
Information about the child		
Males/females	53/48	34/33
Age, mean ± S.D.	3.78 ± 3.49	3.93 ± 3.54
Previously well	93 (92.1)	66 (98.5)
Premature birth	7 (6.90)	8 (11.9)
Congenital abnormalities	1 (1.0)	3 (4.50)
History of asthma	13 (12.9)	7 (10.4)
School/day care attendance		
Daycare	67 (66.3)	40 (59.7)
School	43 (42.6)	19 (28.4)
Up to date with childhood vaccines	23 (22.8)	21 (31.3)
Vaccinated against influenza	2 (2.0)	2 (3.0)
Information about the family		
Family size, mean ± S.D.	4.3 ± 1.35	4.19 ± 1.10
Adult number, mean ± S.D.	2.4 ± 0.90	2.34 ± 0.77
Children in household, mean ± S.D.	1.9 ± 0.93	1.87 ± 0.75
Living arrangement		
House	72 (71.3)	48 (71.6)
Unit	19 (18.8)	11 (16.4)
Other	10 (9.90)	8 (11.9)
Smoking in house	17 (16.8)	14 (20.9)
Vaccinated against influenza	8 (7.90)	10 (14.9)

Table 2
Characteristics of families with and without a child with a laboratory-confirmed infection.

Demographic characteristic	Laboratory positive (%)	Laboratory negative (%)
Total	101 (60)	67 (40)
Age, mean ± S.D.	3.78 ± 3.49	3.93 ± 3.54
Males/females	53/48	34/33
Family size, mean ± S.D.	4.3 ± 1.35	4.19 ± 1.10
Adult number, mean ± S.D.	2.4 ± 0.90	2.34 ± 0.77
Children in household, mean ± S.D.	1.9 ± 0.93	1.87 ± 0.75
Living arrangement		
House	72 (71.3)	48 (71.6)
Unit	19 (18.8)	11 (16.4)
Other	10 (9.90)	8 (11.9)
Number of rooms, mean	3.1	3.1
Race[a]		
Caucasian	40 (39.6)	26 (38.8)
Asian	27 (26.7)	22 (32.8)
Indian	15 (14.9)	9 (13.4)
Middle Eastern	8 (7.90)	6 (9.0)
Other	11 (10.9)	4 (6.0)
Language other than English	39 (38.6)	24 (35.8)
Smoking in house	17 (16.8)	14 (20.9)
School/day care attendance	67 (66.3)	40 (59.7)
Daycare	43 (42.6)	19 (28.4)
School	23 (22.8)	21 (31.3)
Vaccinated against influenza		
Adults	8 (7.90)	10 (14.9)
Child	2 (2.0)	2 (3.0)
Not fully vaccinated	9 (8.90)	6 (9.0)
Previously well	93 (92.1)	66 (98.5)
Premature birth	7 (6.90)	8 (11.9)
Congenital abnormalities	1 (1.0)	3 (4.50)
History of asthma	13 (12.9)	7 (10.4)

[a] Information relates to the participating adult interviewed.

condition that put them at high risk for complications of influenza (e.g. asthma, congenital abnormalities, or premature birth).

Of the 168 children with an ILI, 87% (146/168) reported having four or more symptoms. 59% (99/168) had a fever of ≥39 °C. 153/168 (91%) reported having a cough, 146/158 (87%) had a congested nose, 81/168 (48%) had a sore throat and 82 (49/168) reported vomiting. Upper respiratory tract samples were collected from 166 children, with respiratory viruses detected in 101 (60%) children (Figs. 1 and 2) (Table 2). In 91/101 cases a single virus was detected. As shown in Table 3, influenza and rhinoviruses were the most common viruses detected. The remaining ten children had dual or co-infection—adenovirus and rhinovirus in 4/166 (2.4%), rhinovirus and coronavirus OC43 in 2/166, and one child with each of influenza A and enterovirus, influenza A and rhinovirus, RSV and enterovirus, and adenovirus and hMPV.

No single symptom was predictive of influenza when compared to other viral causes of ILI. However, when compared with RSV,

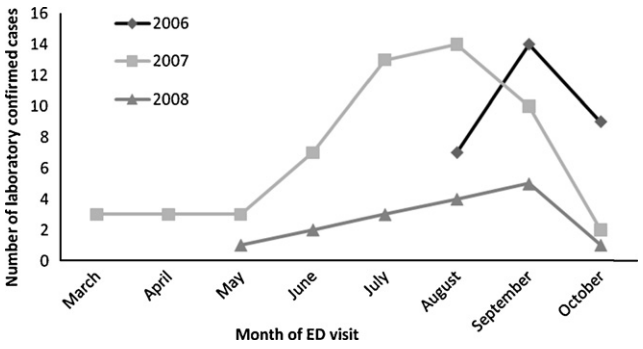

Fig. 1. Number of laboratory confirmed respiratory viruses in children participating in study, 2006–2008.

Table 3
Characteristics of children with and without a child with a laboratory-confirmed infection.

Demographic characteristic	Laboratory positive (%) N = 101	Laboratory negative (%) N = 67
Reported symptoms		
Chills	32 (31.7)	24 (35.8)
Cough	95 (94.1)	58 (86.6)
Nasal congestion	89 (88.1)	57 (85.1)
Sore throat	47 (46.5)	35 (52.2)
Ear ache	17 (16.8)	14 (20.9)
Sneezing	69 (68.3)	33 (49.3)
Lethargic	72 (71.3)	54 (80.6)
Loss of appetite	70 (69.3)	48 (71.6)
Abdominal pain	33 (32.7)	19 (28.4)
Vomiting	52 (51.5)	30 (44.8)
Diarrhea	25 (24.8)	18 (26.9)
≥4 symptoms	88 (87.1)	58 (86.6)
Previous medical visit		
GP	74 (73.3)	50 (74.6)
Emergency department	9 (8.90)	7 (10.4)
Antibiotics prescribed	42 (41.6)	24 (35.8)
Laboratory diagnosis		
Influenza A	21 (20.8)	–
Influenza B	13 (12.9)	–
RSV	7 (6.90)	–
PIV types 1–3	8 (7.90)	–
Adenoviruses	14 (13.9)	–
hMPV	8 (7.90)	–
Rhinoviruses	22 (21.8)	–
Coronaviruses	5 (5.0)	–
Picornoviruses	6 (5.9)	–
Other[a]	7 (6.9)	–
2 Viruses detected	10 (9.9)	–
Impact of virus		
Missed school	40 (39%)	23 (34%)
One family member missed work[b]	60 (36%)	18 (37%)
Both family members missed work	20 (12%)	12 (18%)
Family member who reported an ILI[c]	6 (4%)	5 (7%)

[a] Including *Enteroviruses*.
[b] Missed work to care to care for the ill child.
[c] Family members becoming ill with respiratory illness after the index patient.

the latter manifested as a lower respiratory tract infection, namely, with respiratory distress and wheezing whereas influenza cases were more likely to experience high fever (>39 °C). There was also no difference between laboratory positive and negative children in regards to the number or type of symptoms they reported. The factor significantly associated with children being diagnosed with a laboratory-confirmed infection was age ≤1 year (RR: 0.78, 95% CI: 0.62–0.98, $p = <0.05$). Being from a larger family or having more than three children in the household, or attending some form of childcare was not a significant association.

Of the children with ILI, 124/168 (73.8%) visited their local family doctor prior to the hospital visit and a further 9.5% (16/168) had previously visited ED for the same illness. Of note, 39.8% (66/168) of the children had been prescribed antibiotics prior to the hospital visit. The identity of the antibiotics and the reason for their prescription was not pursued. Of the children with a laboratory-confirmed virus infection, 74/101 (73.2%) had previously visited their local family doctor prior to the hospital visit. For the children PCR positive for influenza A or B, 70.6% (24/34) visited a family doctor. 41.6% (44/101) of the PCR positive children and 35.8% (24/67) of the PCR negative children had received antibiotics prior to the ED visit. Of the children diagnosed with influenza, none had received the influenza vaccine.

3.2. Transmission rate to adults family members

ILI developed within one week of follow-up in 12% (26/205) of the adult family members of the 101 children with a viral

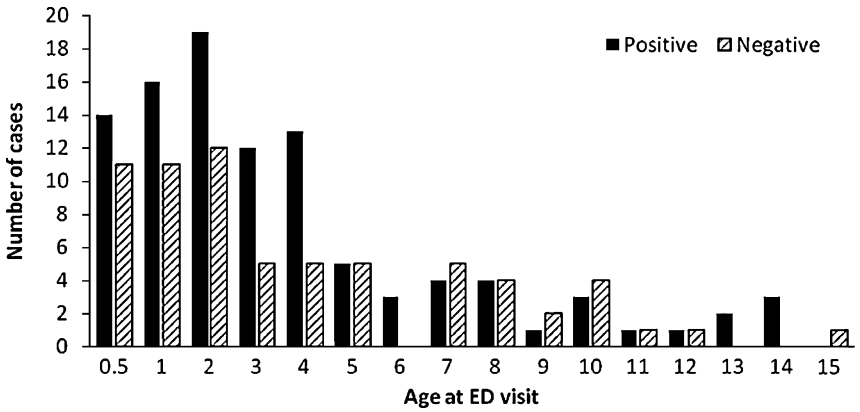

Fig. 2. Age distribution of laboratory positive and negative children.

pathogen detected. Viral pathogens were detected in 42.3% (11/26) of the symptomatic family members. In all 11 cases only a single pathogen was isolated: two cases each of RSV and adenovirus, and one case each of PIV-3 and coronavirus OC43. Other viruses detected included picornaviruses (4/11 rhinoviruses, 1/11 uncharacterized non-sequenced picornavirus). In 6/11 cases, the virus detected for the adult family members was the same as what was detected in their child. Only one case was detected where the parent had a laboratory-confirmed infection and the child did not. The lower estimate of the household risk of transmission of respiratory viruses, based on concordant, proven infection in both child and adult, from a single sick child to adult household contacts is therefore 3% per week. It is known that adults have a lower rate of laboratory detection of viral infections compared to children, and this was confirmed in our study, with only 42% of symptomatic family members compared to 60% of symptomatic children, being PCR positive for a respiratory virus. Based on symptoms, the rate of transmission could be as high as 12% per week. Of the adult family members interviewed, 38% (128/336) took time off work to care for their child. In some cases, two adults took time off (26/128, 25%).

We found that among the healthy children $\leq$15 years of age meeting a clinical case definition of ILI, 60% were found to have a laboratory-confirmed respiratory virus. The results of this study demonstrated that influenza A, rhinoviruses and picornaviruses were the most commonly detected viruses from pediatric outpatients using an ILI definition that included a fever $\geq$38 °C.

In a previous study based on epidemiology surveillance data it was estimated that influenza accounted for 24–35% of excess outpatient visits observed in children less than 3 years of age during the winter [24]. In response to this finding was the assumption by Tsolia et al. that even if other viruses are co-circulating in the community it appears that influenza predominates and is the main cause of respiratory morbidity in outpatients [25]. This may be true in other settings but in our cohort, influenza A and B only accounted for 37% of the laboratory-confirmed illnesses. A range of different viruses were detected.

4. Discussion

This study provides quantitative, prospective data on rates of household transmission of infection from children to adults, and shows that defined ILI symptoms may not differentiate between infection with influenza or other respiratory viruses. The results confirm that during winter, influenza viruses are not the only respiratory pathogens which are responsible for a febrile illness and hospital visits in this cohort of children. While these viruses were not serious enough to require the child to be admitted to hospital, taking into account lost days from work and school, hospital admissions and mortality rates in infants and the elderly, the health and economic costs are considerable. Children often carry these viruses to their homes and spread infection to younger siblings or to their parents, whereas those admitted to hospital tend to shed the virus abundantly for prolonged periods, thus potentiating spread [10].

In Australia, timely community-level information about respiratory tract infection is scarce. Lambert et al. [26] examined the burden of respiratory illness during winter in a cohort of urban children. They reported that the risk factors for ILI included younger age, fewer people residing in the household, structured exposure to other children outside the home, and a higher household income. While we cannot comment on risk factors for ILI, we found that being $\leq$1 year of age was significant for being diagnosed with a respiratory illness. As documented in this study, the rate of laboratory-confirmed illness was not related to the number of people living in the house. This is in comparison to many other studies in developed settings, which have found that the rate of infections within the household decreases with increasing household incomes, thought to be a reflection of household crowding [27]. Our findings are however, in line with the results from the previous Australian study *ref*, who also reported that there was no significant relationship between crowding and reported illness.

These results have global relevance to respiratory disease control planning. Blocking transmission of respiratory viruses is an important part of halting spread of disease and epidemics. Using barriers such as face masks and gloves, isolating people known to be infected as well as introducing hygiene measures (e.g. hand washing) are effective ways of containing respiratory virus epidemics. This is particularly important for children because it will help to protect them as well as reduce the chance of transmission to other household members.

While the children in our study were not admitted to hospital with respiratory illness, these events consumed considerable resources, both in social and family terms. 73% of the cohort had visited their local GP, 40% had received antibiotics and in 38% of cases, a family member had missed work to care for the sick child. In Australia, the minimum cost of a visit to a GP's office is estimated as AU$33.20 (standard consultation rebate from Medicare). For this cohort of children, the cost of these visits would amount to AU$4070. The costs calculated here do not capture the full cost attributable to the illness. The direct out-of-pocket costs to individuals can be substantial and includes costs for pharmaceuticals (both over-the counter and prescribed), travel related costs for GP visits and hospital visits, and gap payments for GP's consultation. In addition, there are the costs associated with lost economic production. Of the family members interviewed, 38% took time to care for the child. Previous studies have shown that parental work loss for the

care of sick children forms a substantial proportion of the total cost of influenza in children [28,29]. Cohen and Nettleman [28] found that the mean duration of work loss (3.2 days) due to influenza in these children would translate into US $300 in lost wages (assuming US $93 for a day's salary for a parent in the United States).

In our study, we found a high proportion of probably inappropriate antibiotic use in the community, since about 42% of the patients, most of whom had a viral infection identified as the cause of their febrile illness, received antibiotics prior to presenting to hospital. This is similar to the results from Tsolia et al. [30] who also found an excess of antibiotic use in their cohort of outpatient children (≥6 months to <14 years) with influenza. They found that the most common reason for justified antibiotic administration was acute otitis media. In our study, 37% of the children who were PCR positive for influenza received antibiotics. In the comparator study, influenza accounted for 37% of all antibiotic courses given to outpatients with febrile respiratory infection during the period studied. The study by Neuzil et al. [31] also analyzed excess antibiotic use attributable to influenza. They found an average of 0.072 excess courses of antibiotics per preschool-aged child. The inappropriate or excess use of antibiotics could theoretically by reduced and perhaps avoided by inclusion of rapid influenza testing for evaluation of febrile infants on assessment during the influenza season as early antiviral treatment has been shown to reduce both the use of antibiotic treatment and the length of hospital stay [32]. As only 31% of the children recruited were under one year of age, the use and role of antivirals in these children could be considered. A recent study indicated that antiviral use in hospitalised children under 12 months of age is safe [33].

In 2008 the American Advisory Committee on Immunization Practices (ACIP) recommended routine influenza immunization in all children aged 6 months to 18 years [18]. The recommendation of childhood influenza vaccination by the ACIP was justified along several grounds. Major factors included the burden of childhood disease, healthcare utilization, and caregiver absenteeism. While this vaccine may not have protected all the children in our cohort, it may have prevented 32 cases of influenza in the cohort. Vaccines to protect against RSV and parainfluenzaviruses may also be available in the future. For family members, aside from recommending the use of the influenza vaccine, masks and hand washing may be other methods of preventing the spread in these households.

There are some considerations when interpreting the findings of this study. While this study was conducted over three consecutive winters, the study recruited from only one site, and was limited to examining children whose family members had agreed to participate in the study. Although we may have missed children with a potential respiratory illness, we were able to prospectively examine the impact of the child's illness on the family members as in order to be recruited, the family members had to have been symptom-free prior to the date of recruitment.

5. Conclusion

Our results demonstrate that during winter influenza viruses are not the only respiratory pathogens which are responsible for illness and hospital visits in children. While these viruses were not serious enough to require the child to be admitted to hospital, they were responsible for excess GP, ED visit and antibiotic use. This study has provided solid estimates of transmission rates of respiratory viruses between children and family members.

Acknowledgements

We thank the staff of the National Centre for Immunization Research, the Institute of Clinical Pathology and Medical Research (ICPMR), Emergency Department at the Children's Hospital Westmead and of the primary care practice of Dr. Michael Fasher.*Conflict of interest statement:* Professor Raina MacIntyre receives funding from influenza vaccine manufacturers GSK and CSL Biotherapies for investigator-driven research. The remaining author(s) declare that they have no competing interests. *Funding:* There is no funding received for this study. *Ethical approval:* Ethics approval was obtained from the Human Research Ethics Committee of the Children's Hospital at Westmead.

References

[1] Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. Coordinated data group of BOSTID researchers. Rev Infect Dis 1990;12(Suppl. 8): S870–88.
[2] Glezen W, Taber L, Frank A, Kasel J. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140:543–6.
[3] Hall CB, Geiman JM, Biggar R, Kotok DI, Hogan PM, Douglas Jr GR. Respiratory syncytial virus infections within families. N Engl J Med 1976;294(8): 414–9.
[4] Monto A, Sook K. The Tecumesh study of respiratory ilness. III. Incidence and periodicity of respiratory syncytial virus and Mycoplasma pneumoniae infections. Am J Epidemiol 1971;94:290–301.
[5] Hall CE, Brandt CD, Frothingham TE, Spigland I, Cooney MK, Fox JP. The virus watch program: a continuing surveillance of viral infections in metropolitan New York families. IX. A comparison of infections with several respiratory pathogens in New York and New Orleans families. Am J Epidemiol 1971;94:436–54.
[6] Beem M. Repeated infections with respiratory syncytial virus. J Immunol 1967;98:1115–22.
[7] Henderson F, Collier A, Clyde WJ, Denny F. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. N Engl J Med 1979;300:530–4.
[8] Wilson S, Roberts K, Hammond K, Ayres J, Cane P. Estimation of incidence of respiratory syncytial virus infections in school children using salivary antibodies. J Med Virol 2000;61:81–4.
[9] Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Respir Care 2003;48(March (3)):209–31 [discussion 31–3].
[10] Centres for Disease Control and Prevention. Respiratory syncytial virus. Available from: www.cdc.gov/ncidod/dvrd/revb/respiratory/rsvfeat.htm; 2008 [cited 6.02.08].
[11] Krilov LR. Respiratory syncytial virus (RSV) infection. Available from: www.emedicine.com/ped/TOPIC2706.HTM [cited 16.02.09].
[12] Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140(June (6)):543–6.
[13] Frank AL, Taber LH, Glezen WP, Geyer EA, McIlwain S, Paredes A, et al. Virus infections in the community and the family. The epidemics of 1976–1977 and 1979–1980 in Houston, Texas. Am J Epidemiol 1983;118(September (3)):313–25.
[14] Glezen WP, Taber LH, Frank AL, Gruber WC, Piedra PA. Influenza virus infections in infants. Pediatr Infect Dis J 1997;16(November (11)):1065–8.
[15] Hurwitz ES, Haber M, Chang A, Shope T, Teo S, Ginsberg M, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. JAMA 2000;284(October (13)): 1677–82.
[16] Hurwitz ES, Haber M, Chang A, Shope T, Teo ST, Giesick JS, et al. Studies of the 1996–1997 inactivated influenza vaccine among children attending day care: immunologic response, protection against infection, and clinical effectiveness. J Infect Dis 2000;182(October (4)):1218–21.
[17] Longini Jr IM, Koopman JS, Monto AS, Fox JP. Estimating household and community transmission parameters for influenza. Am J Epidemiol 1982;115(May (5)):736–51.
[18] Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med 2001;344(March (12)):889–96.
[19] Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpaa R, Vuorinen T, et al. Burden of influenza in children in the community. J Infect Dis 2004;190(October (8)):1369–73.
[20] Principi N, Esposito S, Gasparini R, Marchisio P, Crovari P, Flu-Flu Study G. Burden of influenza in healthy children and their households [retraction in Arch Dis Child 2006;91(September (9)):797; PMID: 16969914]. Arch Dis Child 2004;89(November (11)):1002–7.
[21] MacIntyre C, Cauchemez S, Dwyer DE, Seale H, Cheung P, Browne G, et al. Face mask use and control of respiratory virus transmission in households. Emerg Infect Dis 2009;15:233–41.
[22] Westmead TCsHa. Annual review report. Accessed on http://www.chw.edu.au/about/corporate/chw_annual_report_2010_web_version.pdf; 2010.
[23] Druce J, Tran T, Kelly H, Kaye M, Chibo D, Kostecki R, et al. Laboratory diagnosis and surveillance of human respiratory viruses by PCR in Victoria, Australia, 2002–2003. J Med Virol 2005;75:122–9.

[24] Neuzil KM, Mellen BG, Wright PF, Mitchel Jr EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. NEJM 2000;342:225–31.
[25] Tsolia MN, Logotheti I, Papadopoulos NG, Mavrikou M, Spyridis NP, Drossatou P, et al. Impact of influenza infection in healthy children examined as outpatients and their families. Vaccine 2006;24:5970–6.
[26] Lambert SB, O'Grady KF, Gabriel SH, Nolan TM. Respiratory illness during winter: a cohort study of urban children from temperate Australia. J Paediatr Child Health 2005;41(March (3)):125–9.
[27] Monto AS. Epidemiology of viral respiratory infections. Am J Med 2002;112(April (Suppl. 6A)):4S–12S.
[28] Cohen GM, Nettleman MD. Economic impact of influenza vaccination in preschool children. Pediatrics 2000;106(November (5)):973–6.
[29] Nichol KL. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines. Vaccine 2003;21(May (16)):1769–75.
[30] Tsolia MN, Logotheti I, Papadopoulos NG, Mavrikou M, Spyridis NP, Drossatou P, et al. Impact of influenza infection in healthy children examined as outpatients and their families. Vaccine 2006;24(33–34):5970–6.
[31] Neuzil KM, Mellen BG, Wright PF, Mitchel Jr EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342(January (4)):225–31.
[32] Benito-Fernandez J, Vazquez-Ronco MA, Morteruel-Aizkuren E, Mintegui-Raso S, Sanchez-Etxaniz J, Fernandez-Landaluce A. Impact of rapid viral testing for influenza A and B viruses on management of febrile infants without signs of focal infection. Pediatr Infect Dis J 2006;25(December (12)):1153–7.
[33] Khandaker G, Zurynski Y, Lester-Smith D, Kesson A, Heron L, Dwyer DE, et al. Clinical features, oseltamivir treatment and outcome in infants aged <12 months with laboratory-confirmed influenza A in 2009. Antivir Ther 2011;16(7):1005–10.