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The September epidemic of asthma exacerbations in children: A search for etiology

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Background: Predictable peaks of asthma exacerbation requiring hospital treatment, of greatest magnitude in children and of uncertain etiology, occur globally after school returns. **Objective:** We wished to determine whether asthmatic children requiring emergency department treatment for exacerbations after school return in September were more likely to have respiratory viruses present and less likely to have prescriptions for control medications than children with equally severe asthma not requiring emergent treatment.

Methods: Rates of viral detection and characteristics of asthma management in 57 (of 60) children age 5 to 15 years presenting to emergency departments with asthma in 2 communities in Canada between September 10 and 30, 2001, (cases) were compared with those in 157 age-matched volunteer children with asthma of comparable severity studied simultaneously (controls).

Results: Human picornaviruses were detected in 52% of cases and 29% of controls ($P = .002$) and viruses of any type in 62% of cases and 41% of controls ($P = .011$). Cases were less likely to have been prescribed controller medication (inhaled corticosteroid, 49% vs 85%; $P < .0001$; leukotriene receptor antagonist, 9% vs 21%; $P = .04$).

Conclusion: Respiratory viruses were detected in the majority of children presenting to emergency departments with asthma during the September epidemic of the disease and in a significant minority of children with asthma in the community. The latter were more likely to have anti-inflammatory medication prescriptions than children requiring emergent treatment. Such medication may reduce the risk of emergency department treatment for asthma during the September epidemic. (*J Allergy Clin Immunol* 2005;115:132-8.)

Key words: Asthma, children, viral infections, rhinovirus, school return, inhaled corticosteroid, leukotriene receptor antagonist

Epidemics of asthma exacerbation requiring hospitalization of children during the month of September have been reported in many northern hemisphere countries, including Canada,¹⁻⁴ the United States,⁵⁻⁷ the United Kingdom,^{8,9} Mexico,¹⁰ Israel,¹¹ Finland,¹² and Trinidad.¹³ Between 20% and 25% of all asthma exacerbations of children requiring hospitalization in Canada occur in September.¹

Viral respiratory tract infections, particularly of rhinoviruses, are associated with exacerbations of asthma in both children^{14,15} and adults.^{16,17} In the northern hemisphere, descriptive studies have identified peaks in asthma hospitalization after school return, particularly after the summer vacation, and have linked these to coincident higher rates of respiratory tract infection,¹⁸⁻²⁰ but have not established a causal relation of the 2 phenomena.

Rhinovirus infections are the predominant cause of respiratory infections in children in the early fall.²¹ Between 80% and 85% of children with acute wheezing episodes test positive for respiratory viruses, predominantly rhinovirus, in both hospital^{22,23} and community settings,¹⁴ and half of exacerbations in adults with asthma are associated with rhinovirus infections.²¹

The peak periods for rhinovirus infection are quite distinct from those for influenza virus,²⁴ occurring in the early fall and to a lesser extent in the spring.^{25,26} Rhinovirus infections have been demonstrated to increase in frequency in September a few days after school return.²⁴ In the United States,²² France,²³ and South Africa,²⁷ children presenting to hospitals with asthma exacerbations had higher rates of respiratory virus infection than children not requiring hospitalization. Two of these studies^{22,23} compared cases with controls, one²² with subjects without asthma presenting to emergency departments, and the other with subjects with asthma with no respiratory symptoms.²³ Although there were variations among the 3 studies in the rates of detection of respiratory infections, all were consistent in finding significantly higher infection rates in the children with asthma with exacerbations than in controls. We studied all children with asthma exacerbations presenting to emergency departments in a large population center in Canada at the time they occurred in the highly predictable peak period between September 10 and 30 and a control group of children with asthma of comparable severity not having an emergency department presentation during the same period. Our objectives were to determine whether respiratory viruses could be isolated with greater frequency from asthmatic children who required emergent treatment than from asthmatic children

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who did not, and whether access to asthma control medication differed between the 2 groups.

METHODS

The study was of a case-control design in which the cases were children presenting to emergency department with asthma and controls were volunteer children with asthma recruited from the same communities who did not require hospital treatment during the study period. The study setting was Hamilton and Brant counties in Southern Ontario. These form a contiguous region including a major industrial city and farming and suburban areas with a total population of approximately 550,000. The area is served by 7 emergency departments.

This study was approved by the Ethics Review Board of St Joseph's Healthcare Hamilton.

Study period

To confirm that the September epidemic of asthma exacerbations occurred consistently in Ontario, data were obtained from the Canadian Institute for Health Information for all 33,825 inpatient hospitalizations for asthma (International Classification of Diseases, Version 9, 493.0-493.9) of children age 5 to 15 years that occurred in Ontario from 1990 to 2000. Inpatient hospitalization data were used for this purpose because emergency department encounter data became available only in 2001. The study period of September 10 to 30, 2001, was selected to include the timing of the asthma hospitalization peaks that occurred repeatedly in each of the 11 years before the study.

Data for all 19,384 emergency department visits in Ontario for children age 5 to 15 years with a presenting diagnosis of asthma (ICD-9, 493.0-493.9) for the period April 2001 to March 2002 were also obtained from the Canadian Institute for Health Information. We used these data to determine whether our 2001 September study period coincided with the 2001 September asthma epidemic in Ontario children as a whole.

Cases

Study cases age 5 to 15 years were recruited from September 10 to 30, 2001, at the time of presentation to 1 of the 7 emergency departments. A dedicated study nurse trained in the study protocol staffed each emergency department from 07:00 to 23:59 daily. From 00:00 to 07:00, a single nurse telephoned the 5 open emergency departments each hour to determine whether any children with asthma symptoms had presented. Once stabilized, and with the consent of the attending physician, cases presenting with a likely diagnosis of asthma were approached by the study nurse, and the parent or guardian was asked to provide written consent to participate in the study. A questionnaire was administered, chart data abstracted, and a specimen of nasal mucus obtained for virological testing. Parents were contacted again as soon as possible after the emergency department presentation to arrange a further assessment.

Controls

Volunteer subjects with asthma age 5 to 15 years were recruited from the communities by using advertisements from late June to September 30 and tested during the same 3-week period in September as the cases were seen in the emergency departments. Controls were required to have a diagnosis of asthma confirmed by a physician, to be taking short-acting β_2 -agonist medication at least once a week, and to have had at least 1 school absence or activity limitation because of asthma in the previous year. Parents provided informed consent to participate.

Assessments

Further assessments for cases and assessment of control children were conducted whenever possible during the 21-day September study period by 1 of 3 registered nurses in regular practice as asthma educators and trained in nasal specimen collection. Assessments included a detailed questionnaire, skin prick allergen testing by using 12 allergens with positive and negative controls, and collection of nasal mucus from controls.

Questionnaires

The 3 questionnaires used were based on the questionnaire developed for the International Study of Asthma and Allergies in Childhood.²⁸ The emergency department case questionnaire asked about symptoms and medication use in the week before the exacerbation. At follow-up, cases completed a comprehensive questionnaire. Controls completed a single comprehensive questionnaire. Information collected covered symptoms, medication use, disease triggers, family history of allergic disease, and the home environment.

Allergen testing

All skin testing was conducted by using a single batch of allergens (Western Allergy Services Ltd, Victoria, British Columbia, Canada). A standardized technique was ensured before the study. Subjects were asked not to take antihistamine products for 24 hours before their clinic visit. Allergens used were *Alternaria*, *Cladosporium*, *Aspergillus fumigatus*, dog epithelium, cat pelt, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, tree pollen, grass pollen, ragweed pollen, and weed mix. The positive control was histamine 10 mg/mL, and the negative control was PBS. Plastic disposable sterilized applicators were used to apply the allergens onto the volar aspect of the forearm. Pediatric lancets (Hollister-Stier, Spokane, Wash) were used for pricking the skin. Wheal sizes were measured at 15 minutes. A positive skin test was defined as a wheal size at least 2 mm greater than the negative control.

Nasal secretion collection and microbiological testing

Spontaneous nasal secretions were collected, or induced when necessary by applying a fine stream of a nebulized mist of normal saline to each of the subject's nostrils for 5 minutes. Mucus from each nostril was collected in a sterile specimen container, and 3 mL normal saline added and mixed with the mucus by using a sterile pipette. Aliquots of the secretions were placed in cryovials, immediately frozen, and kept on dry ice until transferred to a -70°C freezer, then shipped on dry ice to the analytical laboratory in London.

Microbiological testing was conducted by using PCR techniques.¹⁴ Samples were tested for picornaviruses with specific identification of human rhinoviruses, as well as adenoviruses, influenza A and B, parainfluenza viruses 1 to 3, coronaviruses 229E and OC43, respiratory syncytial viruses A and B, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

Provincial prescription data

Data for all prescriptions for inhaled corticosteroid products reimbursed by Assure Health, a major provider of prescription insurance in Ontario, were obtained for the period from January 1998 to October 2000. Of the total of 466,239 claims reimbursed for inhaled corticosteroids, 257,845 were for children age 2 to 15 years. We used these data to examine monthly patterns of reimbursement of children's inhaled corticosteroid prescriptions.

Statistical analyses

Questionnaire data were entered into computer systems by 1 person and verified by a second person against the original

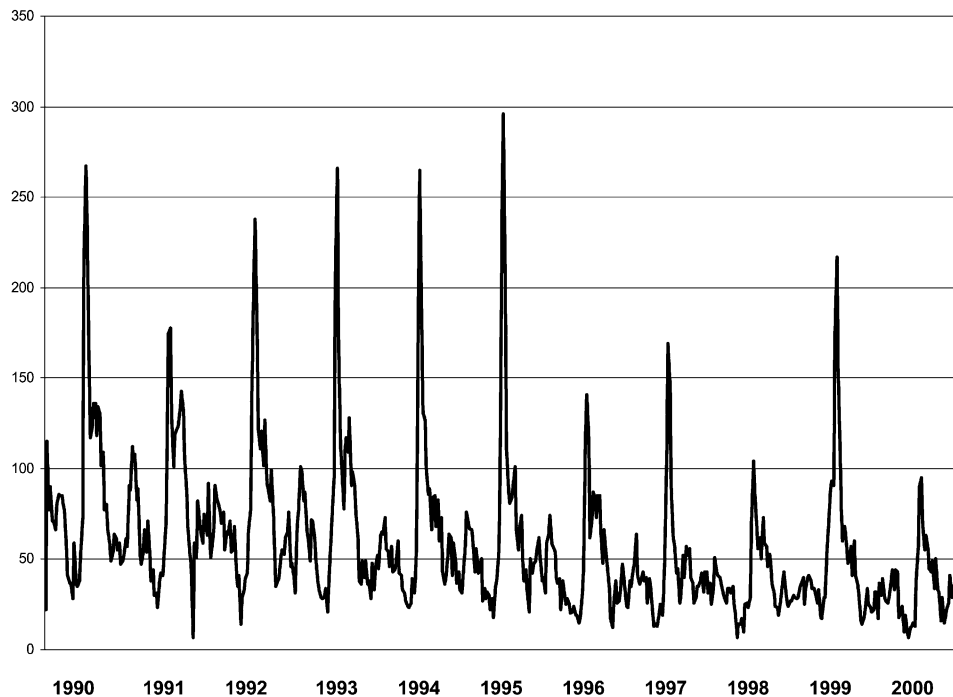


FIG 1. Number of hospitalizations of children age 5 to 15 years by week of the year in Ontario from 1990 to 2000.

questionnaire. Data were transferred to SAS (Statistical Analysis Systems, Cary, NC) for analyses. Probabilities of the observed differences between cases and controls occurring by chance were calculated by using the χ^2 statistic.

RESULTS

Repeated timing of the fall peak in asthma hospitalizations

The frequency of inpatient asthma hospitalization of children age 5 to 15 years by week of the year from 1990 to 2000 in Ontario is shown in Fig 1. In every year, the fall peak of asthma hospitalization of children occurred in week 38 (September 17-23), except in 1997, when it was in week 37, and in 1992, when it was in week 39. The consistency of timing and magnitude of the peak in children age 5 to 15 years supported our decision to study children with asthma during the last 3 weeks of September.

Overall frequency of emergency department visits for asthma during the study period

Fig 2 shows the weekly numbers of emergency department presentations for asthma of children aged 5 to 15 years in Ontario from April 2001 to March 2002. As expected, there was a peak in visits in the 3 weeks of our study (752, 862, and 646 respectively) compared with a weekly average of 373 for the period from April 2001 to March 2002.

Study subjects

In the study region, 60 children age 5 to 15 years meeting inclusion criteria presented to the study emergency departments from September 10 to September 30. The parents of 57 provided informed consent for study participation. Of 157 control subjects recruited, 2 were found during analysis to have been age 4 years and 10 months at recruitment. Both were included in the study population.

Nasal secretions were obtained from 52 of 57 cases during their emergency department presentation and from 150 of 157 controls at their study encounter. Three cases did not return for follow-up. Skin allergen testing was performed on 48 of the 54 cases presenting for follow-up and on 155 of 157 controls.

Comparability of cases and controls

There were no significant differences between cases and controls in age, sex distribution, and birth weight (Table I). Controls had asthma of similar or possibly greater severity than cases (Table II). They reported more breathing problems, limitation of activity, and exercise-induced wheezing than cases, but no differences in the frequency of waking at night or time lost from school because of asthma. Both groups had similar frequencies of family histories of asthma. The majority were atopic, and there were no differences between cases and controls in the frequency of positive skin allergen tests overall or the responses to individual allergens.

Notwithstanding the apparent comparability of asthma severity, cases appeared to have had more frequent or

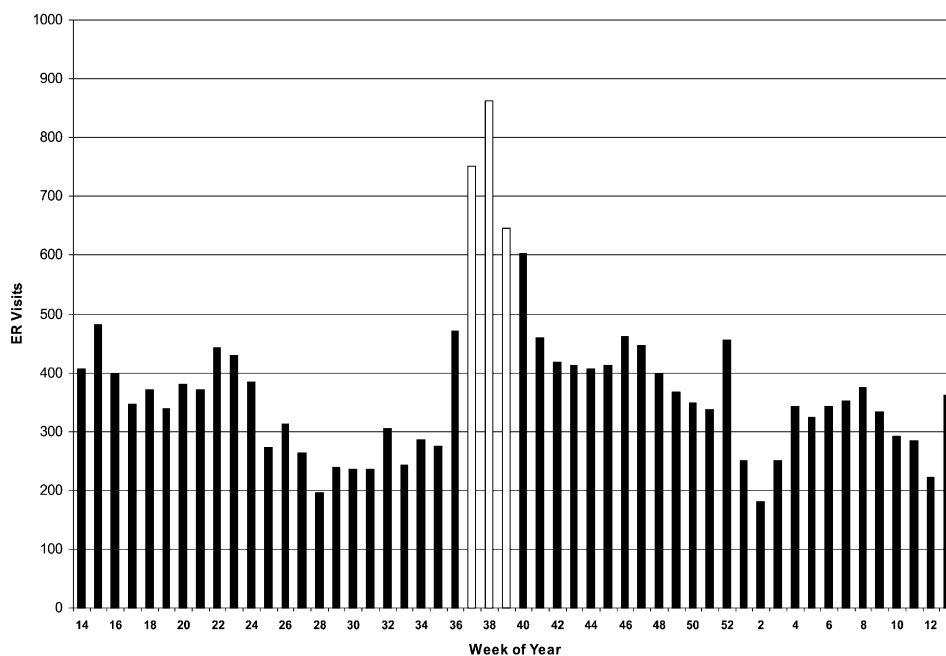


FIG 2. Emergency department visits in Ontario, April 2000 to March 2001 (study period, weeks 37-39, highlighted).

TABLE I. Demographic characteristics of cases and controls*

	Cases		Controls	
	Males	Females	Males	Females
Number (%)	33 (58)	24 (42)	90 (57)	67 (43)
Mean age, y	9.2	10.3	9.5	10.1
SD	3.5	3.4	2.9	2.9
Mean birth weight, (kg)	3.5	3.3	3.5	3.3
SD	0.6	0.5	0.5	0.7
Birth weight under 2.5 kg, n (%)	2 (6)	2 (8)	3 (3)	6 (9)

*None of these differences was statistically significant.

severe exacerbations than controls. Only 5 (9%) of 57 cases reported no previous emergency department visits for asthma in the last year, compared with 63 (40%) of 157 controls. In contrast, more than 3 emergency department visits in the previous year were reported by 47% of cases compared with 22% of controls ($P < .0001$ for overall emergency department use differences). Paradoxically, a high percentage of both cases (66.7%) and controls (74.2%) reported that their asthma was well controlled (NS).

Usual treatment of cases and controls

Short-acting β_2 -agonists, inhaled corticosteroids, and leukotriene receptor antagonists were prescribed more frequently for controls than cases (Table III). There was no significant difference between the proportions of cases and controls whose prescription costs were covered by insurance. Protective mattress covers impervious to house dust mite were in use by only 1 case (2%), compared with 32 (20%) controls ($P = .004$).

TABLE II. Clinical characteristics of cases and controls

	Cases		Controls		P
	n	%	n	%	
Reported breathing trouble					
Continuous or repeated	32/54 (59.3)	123/157 (78.3)	} .007		
Only with colds or rarely	22/54 (40.7)	34/157 (21.7)			
Exercise-induced wheezing	34/52 (65.4)	121/152 (77.6)			.038
Emergency department visit history					
No emergency department visits previous year	5/55 (9.1)	63/156 (40.4)	} <.001		
1-3 Emergency department visits previous year	25/55 (43.6)	59/156 (37.8)			
>3 Emergency department visits previous year	26/55 (47.3)	34/156 (21.8)			
Currently has cold	22/54 (40.7)	26/150 (17.3)			<.001
Parental history of asthma	25/54 (46.3)	71/157 (45.2)			NS
Wakes at night	34/57 (59.6)	112/157 (71.3)			NS
Activity limited	21/57 (36.8)	98/157 (62.4)			<.001
Time lost from school	28/57 (49.1)	87/157 (55.4)			NS
Asthma reported well-controlled	38/57 (66.7)	115/155 (74.2)			NS

Virologic testing of cases and controls

Viruses were detected in nasal secretions of 32 of 52 cases (62%) and 62 of 150 controls (41%; $P = .011$; Table IV). Picornaviruses (more than 80% of which were rhinoviruses) were detected in 27 (52%) cases and 43 (29%) controls ($P = .002$). The number of cases with negative skin tests was too low to permit evaluation of potential differences between cases and controls within this category. Likewise, the numbers of control children

TABLE III. Treatments prescribed for cases and controls

	Cases		Controls		P
	n	(%)	n	(%)	
Prescribed β_2 agonist	43/57	(75.4)	148/157	(94.3)	<.001
Prescribed inhaled corticosteroids	28/57	(49.1)	133/157	(84.7)	<.001
Prescribed leukotriene receptor antagonist	5/57	(8.8)	32/157	(20.4)	.04
Prescription coverage	46/57	(80.7)	133/157	(84.7)	NS
Mite-impervious mattress cover	1/54	(1.9)	32/157	(20.4)	.004

TABLE IV. Microbiological detections in cases and controls

	Cases, n = 52		Controls, n = 150		P
	n (%)	n (%)	n (%)	n (%)	
Influenza	0 (0)	2 (1)	2 (1)	0 (0)	NS
Parainfluenza	1 (2)	0 (0)	0 (0)	0 (0)	NS
Respiratory syncytial virus	4 (8)	16 (11)	16 (11)	16 (11)	NS
Human picornaviruses (>80% rhinovirus)	27 (52)	43 (29)	43 (29)	43 (29)	.002
Any viral detection	32 (62)	62 (41)	62 (41)	62 (41)	.011
<i>C pneumoniae</i>	2 (4)	6 (4)	6 (4)	6 (4)	NS
<i>M pneumoniae</i>	0	0	0	0	

TABLE V. Viral detection in cases and controls with and without inhaled corticosteroid prescriptions and any or no positive skin test

	Picornavirus detection			Any virus detection		
	Cases n (%)	Controls n (%)	P	Cases n (%)	Controls n (%)	P
Any positive skin test	21/40 (53)	35/127 (28)	.004	25/40 (63)	50/127 (39)	.01
No positive skin test	0/4 (0)	6/21 (29)	.22	1/4 (25)	10/21 (48)	.40
Inhaled corticosteroid prescription	15/27 (56)	37/130 (28)	.007	20/27 (74)	56/130 (43)	.003
No inhaled corticosteroid prescription	12/25 (48)	6/20 (30)	.22	12/25 (48)	6/20 (30)	.22

without prescriptions for asthma control medication did not permit the examination of differences between cases and controls with and without prescriptions in numbers of viral detections (Table V).

Fig 3 shows the numbers of inhaled corticosteroid prescriptions reimbursed by 1 large insurer each month between January 1998 and October 2000 for children age 2 to 15 years. In each year, the number of prescriptions reimbursed reached its lowest point in August and then rose rapidly, starting in September, to a high level during the winter months.

DISCUSSION

We were able to assess 95% of all children age 5 to 15 years who presented to emergency departments with asthma exacerbations in a large population center in Southern Ontario between September 10 and 30, 2001. Our own research staff in each emergency department stayed in contact with the triage staff 24 hours a day for the 3-week period. Only 3 parents declined participation in the study, and we are confident that the cases we recruited typify those presenting to emergency departments throughout the September peak period in Ontario. Controls were evaluated during the same 3-week study period.

We detected respiratory viruses in 62% of the cases, of which 84% were picornaviruses. In the control group, we detected respiratory viruses in 41%, of which 69% were picornaviruses.

We have previously shown that in Canada, more than 20% of all hospital admissions of school-age children for asthma occur in September.¹ Respiratory viruses have been detected in 80% of children with asthma exacerbations

in a study in the United Kingdom.¹⁴ Our finding that 62% of children attending emergency departments for asthma have viral infections is consistent with this figure. There are biases that could influence the rates of viral detection we have observed in cases and controls. The approved method of nasal mucus specimen collection for cases may have been less successful than methods used in other studies.¹⁴ In our study, cases were sampled in an emergency department setting, where conditions of the encounter and the lesser experience of our specimen collectors may have diminished our chances of getting a good sample. In contrast, samples from controls were taken in a clinic setting by more experienced nurses with ample time. Cases were seen at a time when their likelihood of infection was greatest. Controls may have been positive at another time during the study period, which may have been undetected by us. Despite these issues, our results confirm that respiratory viral infections, particularly rhinoviruses, occur in a significant majority of children with asthma presenting to emergency departments with asthma, and show that they are present in a substantial minority of asthmatic children not requiring emergency treatment in the same period.

The relatively high virus detection rate among controls (41%) is interesting and invites further study. Our interpretation of this finding is that it is likely that the vast majority of children returning to school encounter respiratory viruses, principally rhinoviruses, extremely frequently during this period. It is therefore not surprising that a substantial minority have detectable virus in clinical samples taken during this time. The comparable or possibly greater asthma severity in the controls suggests that disease severity per se is not a primary factor in the use of emergency departments for asthma exacerbations.

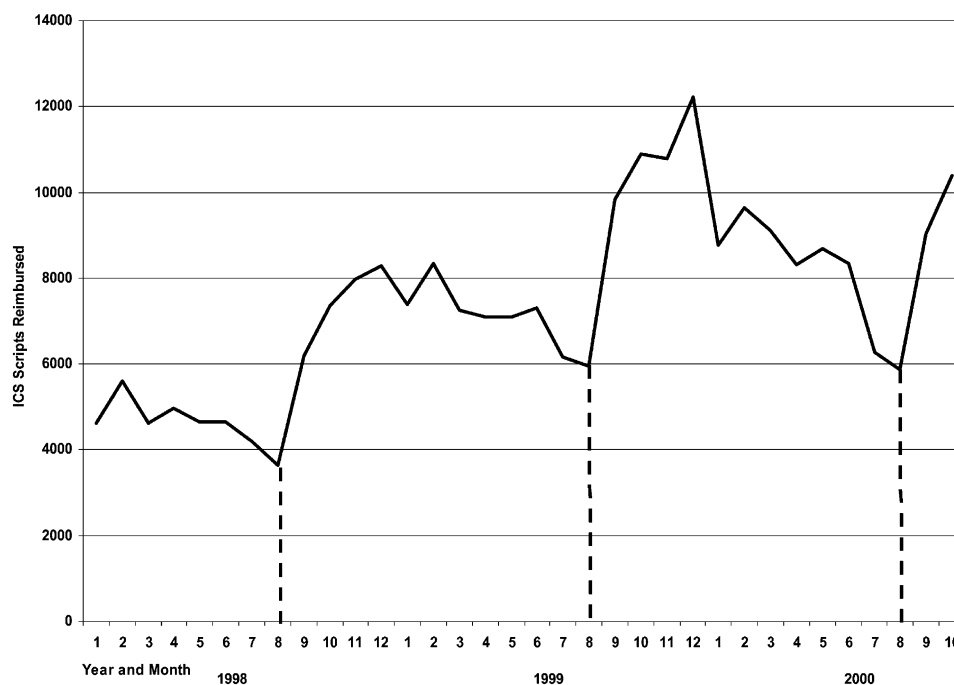


FIG 3. Number of prescriptions for children age 2 to 15 years for inhaled corticosteroids reimbursed by 1 major insurer in Ontario from January 1998 to October 2000.

However, fewer cases had asthma control medications (inhaled corticosteroids or leukotriene receptor antagonists) prescribed, and hardly any used environmental control measures. The much greater reported previous rate of emergency department visits for asthma in the cases may be attributable to undertreatment as well. The controls had much less morbidity than cases, suggesting that their host response to viruses and/or their increased level of asthma control was preventing clinical illness. Similar studies investigating host responses and duration of viral carriage as well as viral loads in this context would yield further important information.

Our finding that insurance claims for children's prescriptions for inhaled corticosteroids may be lowest in August immediately before school return raises the possibility that the September peak may in part relate to children using less controller medication immediately before the period when they may be at greatest risk of a viral-induced asthma exacerbation.

Factors other than viral infections and lower use of control medications may also contribute to asthma exacerbations after school return. Children may face increased allergen exposure on return to school. Cat allergen is transported to school by children on their clothing,^{29,30} and fungal and pollen allergens may be more prevalent and at higher levels in the school than in the home.^{31,32} Children with asthma may be more susceptible to rhinovirus infections than children without asthma,¹⁶ and exposure to an allergen to which one is sensitized has been shown to act in synergy with viral infection in increasing the risk of asthma exacerbation.³³ The nature of the possible interaction of

allergen exposure and rhinovirus infection in increasing the likelihood of asthma exacerbations has not yet been fully articulated,³⁴⁻³⁶ but children are re-exposed to both insults on return to school. Because we included only school-age children in our study and there were no differences in the age distribution of the groups, both cases and controls would have been equally exposed to typical school environments.

An examination of seasonal patterns of children's asthma in the National Cooperative Inner-City Asthma Study⁵ found no significant relation of the observed September increase in hospitalizations, emergency department visits, and symptoms to atopy, air pollutants, or tobacco smoke. The authors concluded that respiratory viral infections were "a likely cause" of the increase. It is possible that this risk may be compounded by concurrent re-exposure to allergens, and quite probable that diminished asthma control medication use may make children more vulnerable at that time.

In summary, we identified virtually all of the children with asthma presenting to emergency departments in a large community with disease exacerbations during the September asthma epidemic. We have confirmed that respiratory viral infections, especially rhinoviruses, are associated with this seasonal epidemic in children. We have also shown that a substantial but smaller proportion of children with asthma not experiencing exacerbations requiring emergency department treatment had viruses present at the same time.

A limitation of this study is that all cases had samples taken during an asthma exacerbation, and controls were sampled irrespective of symptoms. Accordingly, the rate

of infection found in controls may be underestimated. This may diminish or even eliminate the difference in the rate of infection between cases and controls but emphasizes the very high risk to children with asthma of viral infection in the September period after school return.

We conclude that rhinovirus infections occur with high frequency in children with asthma who present to emergency departments with exacerbations during the September epidemic and in children who do not, and that children with asthma prescribed anti-inflammatory medications are less likely to require emergency department treatment during this period of high risk of exacerbation.

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