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Is respiratory viral infection really an important trigger of asthma exacerbations in children?

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Abstract We performed a prospective cohort study from September 2003 to December 2004 to delineate attributing the effect of different respiratory viral infections including newly discovered ones to asthma exacerbations in children in Hong Kong. One hundred and fourteen children aged 6–14 years with chronic stable asthma and on regular inhaled steroid were monitored for respiratory symptoms over a full calendar year from recruitment. They would attend the study clinic if peak expiratory flow rate decreased to below 80% of their baselines, if they met a predefined symptom score, or if parents subjectively felt them developing a cold. Virological diagnosis using virus culture, antigen detection, and polymerase chain reaction methods on nasal swab specimens would be attempted for all these visits irrespective of triggers. Physician diagnosed outcome of each

episode was documented. Three hundred and five episodes of respiratory illnesses were captured in the cohort. Nasal specimens were available in 166 episodes, 92 of which were diagnosed as asthma exacerbations, and 74 non-asthma related episodes. Respiratory viruses were detected in 61 of 166 episodes (36.7%). There was no significant difference in virus detection rate between asthma exacerbations (32 out of 97 episodes, 34.8%) and non-asthma respiratory illnesses (29 out of 79 episodes, 39.2%). Although newly discovered respiratory viruses were identified in these episodes, rhinovirus was the commonest organism associated with both asthma exacerbations and non-asthma related episodes. Plausible explanations for much lower virus detection rate than previously reported include improved personal hygiene and precautionary measures taken during respiratory tract infections in the immediate post-severe acute respiratory syndrome period together with a significant contribution of other adverse factors like environmental air pollution. We conclude that not all viral infections in children with asthma lead to an asthma exacerbation and the attributing effect of different triggers of asthma exacerbations in children vary across different time periods and across different localities.

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Keywords Viral infection · Trigger · Asthma ·
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Abbreviations

PEFR Peak expiratory flow rate
GP General practitioner
IF Immunofluorescence
RSV Respiratory syncytial virus
PCR Polymerase chain reaction
SARS Severe acute respiratory syndrome

Introduction

Viral respiratory tract infection, with rhinovirus accounted for two thirds, was found to be associated with greater than 80% of asthma exacerbations in children in studies in the 1990s [14]. However, the prevalence of respiratory viral infection varies greatly across different places; for example, influenza is associated with more hospitalization among children in Hong Kong compared with temperate region [7]. Recent observational studies have shown that influenza infection can be associated with asthma exacerbations. Nevertheless, a meta-analysis failed to support the protective effect of influenza vaccination in asthma exacerbations [3]. Newly discovered respiratory viruses such as human metapneumovirus may also play a role [20]. Triggers other than respiratory tract infection, like air pollutions may become more prevalent over time and supersede respiratory tract infections as a major trigger. Thus, we carried out a prospective study to delineate the current role of different viral respiratory tract infections including newly discovered respiratory viruses in asthma exacerbation in children in our locality.

Subjects and methods

Design and subjects

Children aged 6–14 years who attended regular follow-up at the asthma clinic were invited to participate. Children with physician-diagnosed asthma, symptoms of asthma in the preceding year, no hospital admission for exacerbation, and on regular inhaled steroid equivalent to beclomethasone ≤ 400 μg daily for at least 3 months prior to enrolment were recruited. Exclusion criteria were those with other known chronic respiratory disease and oral steroid therapy given within 4 weeks of enrolment. The participants were followed up to cover a full calendar year to reduce potential biases associated with temporal and age-related differences in respiratory tract infections.

Procedure

Patient's demographic data, treatment at enrolment, family history of atopy and asthma, and exposure to environmental tobacco smoke were recorded at the time of recruitment. Measurement of lung function using Vitalograph Model 2120 was obtained according to American Thoracic Society recommendations in children who were able to perform spirometry [1]. Skin prick test was done according to the standardized International Study of Asthma and Allergies in Childhood Phase 2 protocol [12]. Ten aeroallergens including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, *Alternaria tenuis*, mixed tree pollen, mixed grass pollen, dog,

cockroach (American and German), and mixed moulds were tested. A wheal diameter of 3 mm greater than the diameter of the negative control was defined as positive response. Children with ≥ 1 positive responses were defined as atopic.

Each child was given an asthma diary chart and a peak flow meter (Mini-Wright AFS Low range peak flow meter) during the run-in period. Parents and children were taught on data entry, use of peak flow meter, and record twice daily peak expiratory flow rate (PEFR) and any upper and lower respiratory symptoms for 2 weeks as baseline. [14] (Appendix). The diary chart was then reviewed and the child's calculated 80% baseline PEFR was recorded on a new log sheet. Parents were instructed to start to record PEFR twice daily and respiratory symptoms in a new log sheet when the symptoms scored >3 . They were to call the research nurse if PEFR fell to below 80% of the child's baseline, if total upper or lower respiratory symptom score totalled ≥ 4 , or if parents subjectively felt the child was developing a cold even though PEFR fell by $<20\%$ of baseline. An unscheduled clinic visit would be arranged within 48 h. During the unscheduled visit, upper and lower respiratory symptoms and physical signs were recorded. An asthma exacerbation was defined as a fall in morning PEFR to below 80% of baseline in the absence of expiratory wheeze for ≥ 2 consecutive days. The presence of wheeze detected by the attending paediatrician at the time of visit (Lee SL/Chiu SS), or an increase in the use of short-acting beta 2 agonists on at least two occasions per day for ≥ 2 consecutive days. Diagnoses other than asthma exacerbation were also captured. Chest radiograph were ordered if clinically indicated. Respiratory secretions from children were obtained using nasal swabs. The cotton-tipped swab was inserted into the nostril for 2 to 3 cm and rotated three times against the respiratory epithelial surface of the nasal cavity. Once collected, the specimen was put in a virus transport medium and immediately transported to the microbiology laboratory for processing. The child was treated as appropriate. The parents and child continued to record daily PEFR and symptoms in the subsequent 2 weeks or longer until symptoms subsided completely. Follow-up visits would be arranged. All participants also attended scheduled clinic visit every 3 months. At each scheduled visit, all respiratory symptoms at follow-up or any respiratory problems in between visits that were not reported would be recorded.

Detection of respiratory viruses

Part of the aliquot was used for routine detection of viral antigen using immunofluorescence (IF) detection of viral antigens for five respiratory viruses, viz. influenza viruses types A & B, respiratory syncytial virus (RSV), parainfluenza virus, and adenovirus. It was also cultured for virus isolation. The remaining aliquot was used for polymerase chain reaction (PCR) detection of rhinovirus,

human metapneumovirus, human coronavirus NL 63, OC43, 229E, HKU1, and bocavirus. [6, 8, 19, 21]

Ethical approval

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The study was conducted in accordance with the Declaration of Helsinki. Verbal consent was obtained from the participants and written consent was obtained from their parents or legal guardians.

Statistical analysis

Previous studies showed virus identification rate ranged from 32% to 85% of asthma exacerbation in children [14, 19]. The conservative estimation of virus detection rate of 50% would give the largest sample size estimate of 96 exacerbations with level of confidence at 95% and precision of detection rate of 10%. As the number of urgent visits due to asthma was 1.2 per person-year in children on regular inhaled steroids in another study, the number of subjects required would be around 80 [22]. We performed simple descriptive analyses of demographic data. The frequencies of presenting symptoms and physician diagnoses of unscheduled visits, virus detection rate and the distribution of different types of viruses were described. Student *T* test (+– Mann–Whitney *U* test) was used to compare continuous variables; for example, age and Pearson's chi-square test (with Yates' correction/Fisher's exact test) was used to compare categorical variables; for example, sex (female or male), atopic status (yes or no) between children with and without unscheduled visits. A *p* value less than 0.05 was considered to be statistically significant. All statistical analyses were carried out by the SPSS 11.0 software (SPSS Inc., Chicago, IL).

Result

There were totally 122 participants recruited from the end of September to the end of December 2003 and were followed up until the end of December 2004. Eight of these participants withdrew early as their parents found it inconvenient to attend unscheduled visit. One hundred and fourteen children aged 6 to 13 years completed the study. They were followed up for 12 to 15 months. Their baseline characteristics were tabulated in Table 1. Among these 114 children, 16 children (14.0 %) did not report any exacerbations or respiratory illnesses. Children with respiratory illnesses were younger than children without respiratory illnesses ($p < 0.05$) and there was greater proportion with normal pulmonary lung function test at the time of recruitment ($p = 0.02$). Fifteen children had reported 20 episodes of mild respiratory illness with symptoms with

scores ≤ 3 that did not warrant unscheduled visits. The remaining 83 children had experienced ≥ 1 episode of respiratory illnesses with symptoms score > 3 and the maximum number of episodes per children was seven in two children. There were a total of 211 episodes with a symptom score > 3 . Nasal swab specimens were obtained in 166 and the interval between onset of respiratory symptoms and nasal swab collection ranged from 0.5 to 6 days. Nasal swab specimens were not available in the remaining 45 episodes as the children attended general practitioner (GP) instead. There were 74 episodes of mild respiratory illnesses with symptom score ≤ 3 reported in these 83 children that were also managed by GP. The distribution of these episodes of respiratory illnesses among the children was illustrated in Fig. 1. Thus, there were a total of 305 episodes of respiratory illnesses including asthma and non-asthma related episodes in our study cohort over the 14-month study period. The mean number of asthma exacerbations, other respiratory illnesses, and all episodes as diagnosed at unscheduled visits were 0.69, 1.6, and 2.29 per person-year, respectively.

The presenting symptoms of 166 episodes of unscheduled visits with nasal swab specimens obtained are tabulated in Table 2. Ninety-two episodes were diagnosed as asthma exacerbations and 74 non-asthma related. Among 92 episodes of asthma exacerbations, physician also made a diagnosis of concomitant respiratory tract infection in 69 (59 with upper respiratory tract infection, 5 with lower respiratory tract infection, and 5 with sinusitis) of these episodes based on history and physical findings.

Respiratory viruses were detected in 61 of these 166 episodes (36.7 %) (Table 3). There was no significant difference in virus detection rate between asthma (32 out of 97 episodes, 34.8 %) and non-asthma related episodes (29 out of 74 episodes, 39.2 %). Rhinovirus was detected in 41 episodes, influenza in 7, coronavirus in 6, parainfluenza virus in 2, RSV in 1, and mixed viruses in the remaining 4. The patterns of distribution of respiratory viruses were quite similar in asthma exacerbations and non-asthma related episodes. (Table 4)

Discussion

A community study carried out in Southampton, UK over a decade ago found viral infections in $> 80\%$ of asthma exacerbations in 9–11-year-old children [14]. Our virus detection rate was only 36.7 % of all unscheduled sick visit in children aged 6 to 14 years old and the rate was not significantly different between asthma exacerbations (34.8 %) and that of other diagnoses (39.2 %). This low detection rate was not due to inadequate power based on a priori sample size calculation. Neither was it due to virus detection method as we included PCR detection of more

Table 1 Characteristics of the participants at baseline

Characteristics	All children (N=114)	Children with sick visits (N=98)	Children with no sick visits (N=16)	<i>p</i> value ^c
Age, year (range)	6.0–13.0	6.0–13.0	6.1–12.7	<0.05
Sex, number				0.09
Male	79	71	8	
Female	35	27	8	
Level of asthma control ^a				0.347
Controlled	63	56	7	
Partly controlled	47	38	9	
Uncontrolled	4	4		
Treatment at enrollment (number of participants)				0.66
Budesonide	60	50	10	
Beclomethasone	53	47	6	
Fluticasone	1	1	–	
Atopy ⁺				0.76
Yes	99	84	15	
No	13	12	1	
Not done	2	2	–	
Pulmonary function test				0.02
Normal	78	72	6	
Abnormal ^d	33	24	9	
Not done	3	2	1	
Exposure to environmental tobacco smoke ^b				0.89
Yes	34	29	5	
No	80	69		

^a Classified based on GINA guideline [2]

^b Defined by presence of current smoking history in any household member

^c Comparison between children with any sick visits and children with no sick visit during the study period

^d Abnormal pulmonary function test refers to obstructive (FEV1 \leq 80% and FEV1/FVC ratio <80%) or restrictive pattern (FVC <80% and FEV1/FVC ratio >80%); FEV1 forced expiratory volume in 1 s; FVC forced vital capacity

⁺ Defined by \geq 1 positive response to skin prick test

recently discovered respiratory viruses including human metapneumovirus, human coronavirus NL 63, OC43, 229E, HKU1, and bocavirus in addition to the virus detection method adopted in the Southampton study, i.e., using IF detection of viral antigens and culture for five respiratory viruses, viz. influenza viruses types A & B, RSV, parainfluenza virus, and adenovirus and PCR for detection of rhinovirus. Our previous study using PCR method in detecting rhinovirus was shown to be comparable to the global literature [5]. Our result was comparable to a clinic-based prospective study [19] and more closely matched to the Canadian case-control study conducted in September 2001 before the epidemics of severe acute respiratory syndrome (SARS) in which 62% of asthma children attending emergency department for exacerbations had respiratory viruses isolated [13].

We offered several explanations for our findings. Firstly, our study was carried out in the immediate post-SARS

period when the population was still highly cautious about infection control and practising good personal hygiene [15]. This could greatly reduce common viral infection. The low average number of unscheduled sick visits per person-year compared to previous epidemiology studies [18] inferred excellent general health status in our children population over the study period. The beneficial effect of improved community hygienic measures was also supported by a local study which showed significantly lower respiratory virus circulation in the community in the immediate post-SARS period [17].

Secondly, we used three criteria so as to capture as many as possible asthma exacerbations. The use of a symptom score that included both upper and lower airway symptoms and that parents could attend the study clinic if they subjectively felt that the child develop a cold were less stringent than the first criteria of a fall of 80% of baseline PEFr. Thus, 74 of 166 unscheduled visits were not asthma exacerbations. We might have overdiagnosed respiratory tract infection as a trigger in

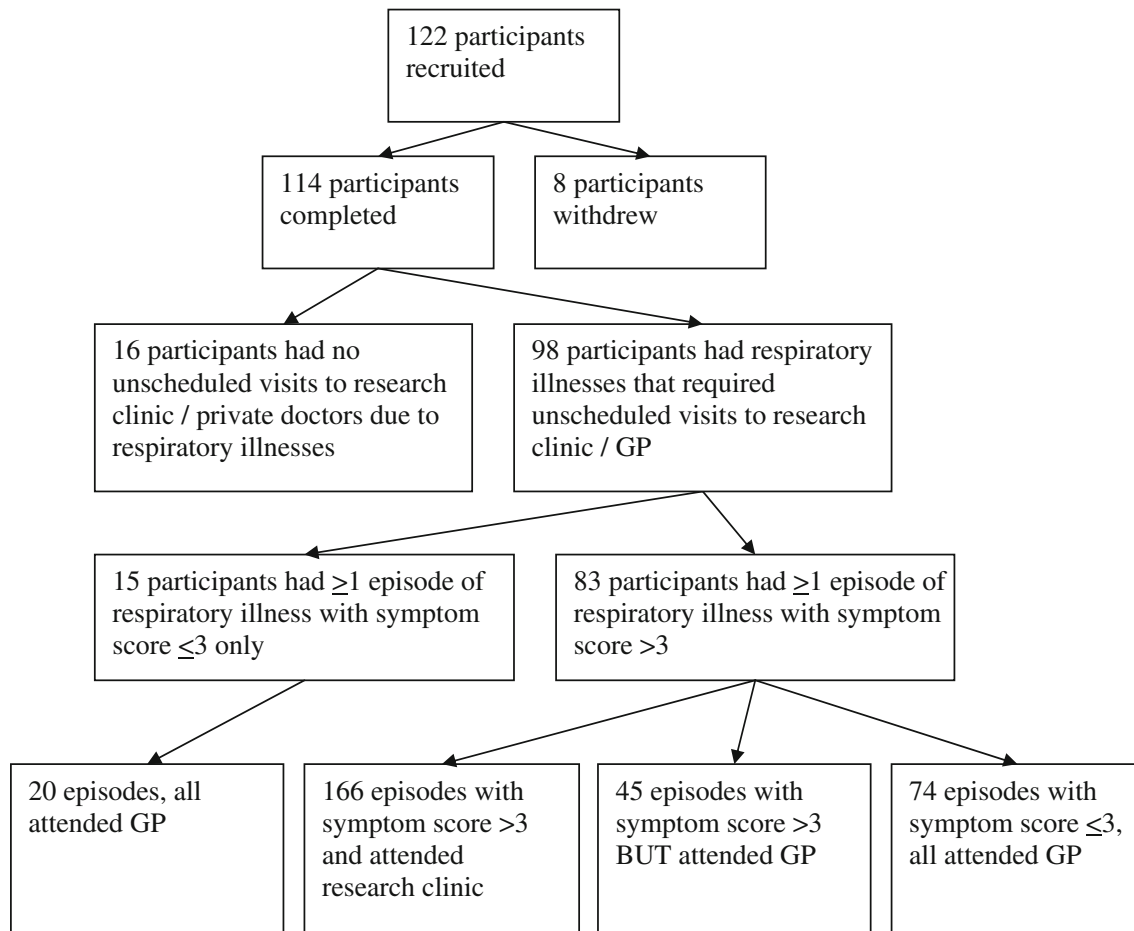


Fig. 1 Flow chart to show episodes of respiratory illnesses of all participants

Table 2 The presenting symptoms of 166 unscheduled sick visits

	Episodes		
	Present	Absent	NA
Upper respiratory symptoms			
Runny nose	140	20	6
Sneezing	109	42	15
Blocked or stuffy nose	104	47	15
Itchy, sore, or watery eyes	37	101	28
Sore throat	65	85	16
Hoarse voice	40	102	24
Fever or shivering	48	110	8
Headaches or facial pain	21	122	23
Generalized muscle ache	16	125	25
Lethargy	7	0	159
Lower respiratory symptoms			
Cough during the day	121	28	17
Cough during the night	84	51	31
Wheeze during the day	33	122	11
Wheeze during the night	28	111	27
Difficulty breathing or shortness of breath	63	86	17
Limitation of activity because of chest tightness	18	125	23

NA data not available

Table 3 Viruses detection of 166 episodes of unscheduled visits

Types of unscheduled visits	Number of episodes	Number of episodes with virus detected
Asthma exacerbations alone	23	6
Asthma exacerbations with respiratory tract infection	69	26
Non-asthma related episodes	74	29
Total	166	61

our cohort with asthma exacerbations who in fact had concomitant symptoms of allergic rhinitis that mimic upper respiratory tract infection as it can be difficult to differentiate these two conditions clinically. While other unknown viruses might account for those exacerbations without viral aetiology, factors other than respiratory viral infection, for example, air pollution could also be an alternative explanation. This was substantiated by our earlier study which showed that ambient air pollutants level was associated with hospital admission for asthma in children in Hong Kong from 1997 to 2002 [16].

One other possibility is that all of our participants had better control of asthma symptoms that was reflected in the lower overall number of episodes of unscheduled sick visits per person time year compared to the Southampton cohort. We speculated that the use of regular inhaled steroids might also have some effect. While most clinical or experimental studies failed to document the efficacy of inhaled steroids in preventing intermittent virus-induced asthma exacerbations [9, 10], the aforementioned Canadian case-control study [5] showed that children attending emergency department for asthma exacerbations were more likely to have respiratory viruses isolated but less likely to have prescription of anti-inflammatory medications.

As in previous studies, rhinovirus was also the most frequent organism detected, accounting for followed by influenza among those asthma exacerbations with virus isolated in our cohort.

We must address our limitations. Firstly, nasal swab were not collected in 45 out of 211 of episodes that met the criteria for unscheduled visits. For the extreme case scenario whereby all these 45 episodes were asthma exacerbations with viruses isolated, the virus detection rate would have been 56.2 % but this is still much lower than Southampton study. For the remaining 94 episodes of mild respiratory illnesses that did not meet the criteria for unscheduled visit, it was difficult to ascertain whether the subjects actually had very mild asthma exacerbations, leading to a possible underestimation. The second limitation was that nasal swab instead of nasopharyngeal aspirate was used for infection control reasons as the study was carried out in the immediate post-SARS period. A recent study also showed that the sensitivity of nasal swabs was comparable to that of nasopharyngeal aspirates for the detection of all major respiratory viruses except RSV [11]. Yet, RSV virus is not a common trigger of asthma exacerbations in school-aged children. The use of a flocked nasopharyngeal swab, which was not available at time of the study, can certainly lead to a better yield should similar study to be conducted in the future [4].

We found that viral infections accounted for about 35% of asthma exacerbations and 39% of non-asthma associated respiratory illnesses in children with stable asthma control during the immediate post-SARS period. We did not negate the well-established causal relationship between respiratory viral infections and asthma exacerbations. Rather, our study sug-

Table 4 Pattern of virus distribution in asthma exacerbation versus non-asthma related episodes

Viruses	Asthma	Non-asthma related episodes
Influenza A	4	1
Influenza A, coronavirus HKU1	1	0
Influenza B	1	1
Respiratory syncytial virus	1	0
Parainfluenza 1, 2, 3	1	1
Rhinovirus	19	22
Rhinovirus, coronavirus 229E	2	0
Rhinovirus, coronavirus NL63	0	1
Coronavirus (type HKU1/NL63/OC43/229E)	3	3
Metapneumonvirus	0	0
Bocavirus	0	0
Total	32	29

gested that the improved personal hygiene and precautionary measures taken during respiratory tract infections may help to reduce the potential adverse effect at high risk groups, like children with asthma. In addition, factors like environmental air pollution may also contribute significantly to morbidity of children with asthma in locality where the problem is particularly adverse.

We conclude that not all viral infections in children with asthma lead to an asthma exacerbation and the attributing effect of different triggers of asthma exacerbations in children varies across different time periods and across different localities. Updated local data whenever available are preferred when planning for health care policies.

Acknowledgment Lee SL and Chiu SS participated in study design, conduct study, data analysis, and report writing. Peiris JS provided advice on identification of viruses in addition to study design and report writing. Chan KH provided laboratory support in identification of viruses and report writing. Wong WHS provided statistical support. Lau YL participated in study design, data analysis, and report writing. We thank our research assistants Miss Winnie Lau and Miss Eunice Chan, and we are also grateful to our study subjects and their parents for their support.

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Conflict of interests All authors declare that they have no conflicts to declare.

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Appendix

Table 5 Upper and lower respiratory symptoms score—each item score 1 mark

Upper respiratory symptoms	Lower respiratory symptoms
Runny nose	Cough during the day
Sneezing	Cough during the night
Blocked nose or stuff nose	Wheeze during the day
Itchy, sore, or watery eyes	
Sore throat	Wheeze during the night
Hoarse voice	Difficulty breathing or shortness of breath
Fever or shivery	Limitation of activity because of chest tightness
Headaches or facial pain	
Generalized muscle ache	
Lethargy	

Modified from Johnston SL et al. *BMJ* 1995)

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What is already known on this topic

Viral respiratory tract infection is an important trigger of asthma exacerbations in children.

Rhinovirus is the most common identified virus associated with asthma exacerbations.

What this paper adds

Prevalence of triggers of asthma exacerbations in children varies with geographic locations and time period.

With improved vigilance in personal hygiene after the SARS period, viral respiratory tract infection became less prevalent as a trigger of asthma exacerbation in children in a polluted city like Hong Kong.

Yet, rhinovirus is still the most common identified virus associated with asthma exacerbations despite the emergence of different newly discovered respiratory viruses.