Rhinovirus infection in children hospitalized with acute bronchiolitis and its impact on subsequent wheezing or asthma: a comparison of etiologies

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Summary

Background: **Children who suffer a viral lower respiratory infection early in life are prone to subsequent wheezing and asthma: RSV and rhinovirus are thought to be the primary causative pathogens. Epidemiologic and long-term data on these pathogens in Thailand are limited.**

Objectives: **To detect the causative pathogens in children hospitalized with a first episode of acute wheezing and to compare the respective impact on the recurrence of wheezing and development of asthma.**

Method: **We conducted a 5-year cohort study of children under 2 hospitalized with acute bronchiolitis at two tertiary hospitals. Nasopharyngeal secretions were collected at admission to determine the causative pathogens by RT-PCR.**

Results: **145/170 samples (85%) were positive for pathogens. RSV, rhinovirus, influenza, bacteria and hMPV was found in 64.7%, 18.2%, 17.6%, 12.9% and 3.5% of children respectively. The majority (94/152; 62%) of participants reported having recurrent wheezing within the first year of follow-up (mean duration 5.5 ± 7.2 months). Only 16% still had wheezing episodes after 5 years. Asthma was diagnosed in 41 children (45%), most of whom were treated with inhaled corticosteroid. There were no statistically significant differences among the various etiologies.**

Conclusion: **Rhinovirus ranked second after RSV as the cause of hospitalizations of children with acute bronchiolitis. More than half of these children had recurrent wheezing which mostly disappeared before the age of 6. Nearly half were subsequently diagnosed with asthma at the 5th year of follow-up. The specific pathogens did not account for a statistically significant difference in subsequent wheezing or asthma development.** ***(Asian Pac J Allergy Immunol 2014;32:226-34)***

Keywords: *rhinovirus, bronchiolitis, wheezing, asthma*

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Submitted date: 24/7/2013
Accepted date: 6/12/2013

Introduction

Wheezing associated with viral respiratory infections constitutes the leading cause for hospitalization among infants and young children.[1] Respiratory syncytial virus (RSV) is the presumed most common etiology. Other pathogens—such as human metapneumovirus (hMPV), influenza virus, parainfluenza virus, adenovirus as well as *Mycoplasma pneumoniae*—also cause wheezing in children.[2-5] Recently, rhinovirus was reported as frequently as RSV among children hospitalized with wheezing illnesses [6-11] and a number of studies have shown that it is a significant risk factor for subsequent wheezing and/or development of asthma.[12-16] Epidemiologic studies on the prevalence of the causative pathogens in young children suffering from an acute wheezing episode and their impact on subsequent respiratory illnesses in Thailand are limited.

We, therefore, conducted this study to determine the causative pathogen(s) using reverse-transcriptase polymerase chain reaction (RT-PCR) testing on the nasopharyngeal secretion of young children hospitalized for a first episode of acute wheezing and to ascertain whether the type of pathogen

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influenced recurrence of wheezing and development of asthma. The study was reviewed and approved by the Ethics Committee for Human Research of Khon Kaen University and by Khon Kaen Hospital, Ministry of Public Health, Thailand.

Methods

Study design and population

This 5-year prospective cohort study (carried out at two tertiary hospitals in Khon Kaen, Northeast, Thailand) was part of a randomized, clinical trial evaluating the efficacy of dexamethasone for the treatment of acute bronchiolitis.[17] Between April 2002 and August 2004, we invited the participation of previously healthy children between 1 and 24 months of age (with informed, written, parental consent), hospitalized with a first episode of acute wheezing; associated with a viral upper respiratory infection.

The criteria for hospitalization included one of the following: (a) age < 3 months (b) < 12 months, respiratory rate > 60 breaths/minute (c) age ≥ 12 months, respiratory rate > 50 breaths/minute (d) oxygen saturation breathing ambient air < 95% and (e) apathy and/or refusal to eat. We excluded children with (a) the presence of symptoms for more than 7 days (b) an initial admission to the intensive care unit with endotracheal intubation (c) a previous history of intubation (d) a known history of asthma or a personal history of atopy with a good response to the first dose of β_2-agonist nebulization (e) a contraindication to corticosteroid treatment or (f) premature birth.

Data collection and follow-up

Upon admission, a sample of nasopharyngeal secretion was taken from each child by inserting a disposable suction catheter connected to a mucus extractor and applying gentle suction, without inserting any solution into the nostrils. The secretion obtained was immediately put into a tube containing viral transport media which was sent to a laboratory, where the samples for pathogen detection were aliquoted and frozen at -70°C until processed.

The respective demographic characteristics, medical history, treatments and clinical course were systematically recorded for each child. After discharge, all of the children were given follow-up appointments 1 month later then every 3 to 6 months for 3 years. Children who still had a respiratory illness or were diagnosed with asthma were welcome to come for longer term, regular follow-up.

At the end of the fifth year, all of the medical records were reviewed and any child who did not come for a regular follow-up was contacted again by letter or phone to ask about any respiratory illnesses and treatments they might have had.

Definition of recurrent wheezing and asthma

Recurrent wheezing was defined as children with a history of healthcare visits with wheezing or having received β_2 agonist nebulization to relieve respiratory symptoms. Asthma diagnosis was made on the basis of one of the following: 1) the GINA guideline[18] in children with recurrent wheezing with predictive factors; 2) a doctor's diagnosis and the child's being prescribed inhaled corticosteroid for control.

Detection of pathogens

The RNA and DNA were extracted from the nasopharyngeal secretion to detect for four RNA viruses (*viz.*, RSV, hMPV, influenza A and influenza B) and atypical bacterial pathogens (*M. pneumoniae*, *C. pneumoniae* and *C. trachomatis*).[19,20] In addition, the extracted RNA from the same samples was tested for human rhinovirus using real-time RT-PCR assay and the iScript one-step RT-PCR kit for probes (Bio-Rad, Hercules, CA). One μL of the RNA extract was added to a tube of reaction mixture containing 1 μM forward and reverse primers and 0.1 μM TaqMan probe. Nucleic acid amplification was performed in a fluorescence quantitative PCR detection system (Swift™ Spectrum 48, ESCO), using previously described thermocycling conditions [21]: 10 min at 48°C for RT, 3 min at 95°C for polymerase activation, then 45 cycles of 15 s at 95°C and 1 min at 60°C. Each run included template and non-template controls.

Statistical analysis

The qualitative and quantitative variables were analyzed using the chi-squared, Student's *t* or Mann-Whitney test as appropriate (STATA software version 10). Cox regression analysis was used to estimate the hazard ratio (HR) of the risk factors of subsequent development of wheezing and asthma. *P*-values < 0.05 were considered statistically significant.

Results

During the study period, 261 children were hospitalized with acute wheezing associated with a viral upper respiratory infection; the parents of 179 gave consent, and so their children were eligible for collection of nasopharyngeal secretion. Only 170

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Table 1. Etiology of acute bronchiolitis in the study population

Etiology	Total N = 170	Age 1-6 mo N = 39	Age>6 – 12 mo N = 69	Age>12 – 24 mo N = 62
RSV, N (%)	110 (64.7)	28 (71.8)	45 (65.2)	37 (59.7)
Rhinovirus, N (%)	31 (18.2)	7 (17.9)	8 (11.6)	16 (25.8)
Influenza, N(%)	30 (17.6)	4 (10.3)	9 (13.0)	17 (27.4)
- Influenza A, N (%)	22 (12.9)	3 (7.7)	6 (8.7)	13 (21)
- Influenza B, N (%)	8 (4.7)	1 (2.6)	3 (4.3)	4 (6.5)
Atyp. Bacteria, N (%)	22 (12.9)	7 (17.9)	9 (13.0)	6 (9.7)
- *M. pneumoniae*, N (%)	15 (8.8)	3 (7.7)	6 (8.7)	6 (9.7)
- *C. trachomatis*, N (%)	4 (2.4)	3 (7.7)	1 (1.4)	0
- *C. pneumoniae*, N (%)	3 (1.8)	1 (2.6)	2 (2.9)	0
hMPV, N (%)	6 (3.5)	2 (5.1)	3 (4.3)	1 (1.6)
Mix, N (%)	49 (28.8)	12 (30.8)	15 (21.7)	22 (35.5)
- RSV + rhinovirus, N (%)	18 (10.6)	5 (12.8)	3 (4.3)	10 (16.1)
- RSV + influenza, N (%)	4 (2.4)	0	2 (2.9)	2 (3.2)
- RSV + atyp. bacteria, N (%)	10 (5.9)	3 (7.7)	5 (7.2)	2 (3.2)
- Rhino + influenza, N (%)	6 (3.5)	0	2 (2.9)	4 (6.5)
- Rhino + atyp. bacteria, N (%)	4 (2.4)	3 (7.7)	1 (1.4)	0
Others, N (%)	7 (4.1)	1 (2.6)	2 (2.9)	4 (6.5)
Not found, N (%)	25 (14.7)	6 (15.4)	12 (17.4)	7 (11.3)

samples, however, were appropriately stored for pathogen detection and of these, 145 (85.3%) were positive for causative pathogens.

Pathogen detection

Rhinovirus was detected in 31 cases (18.2%), after RSV (110, 64.7%) followed by influenza (30, 17.6%), atypical bacteria (*M. pneumoniae*, *C. pneumoniae* and *C. trachomatis*) (22, 12.9%) and hMPV (6, 3.5%). Forty-nine children (28.8%) were infected with mixed viruses (mainly RSV with other viruses). (Table 1)

A pattern of seasonal prevalence was observed: (a) RSV in the late rainy season through the cool, dry season (August–March); (b) rhinovirus and influenza virus in the early rainy and cool, dry season (May–July and February); and, (c) hMPV and atypical bacteria in the late rainy, early cool season (September–November). (Figure 1)

The baseline characteristics, clinical manifestations at enrollment and the clinical course for each of the children for any one of the various etiologies were similar. (Tables 2, 3)

Subsequent wheezing and asthma

At the end of the 1st, 2nd and 3rd year, 93 (52%), 78 (44%) and 44 (25%) of the children had a regular follow-up at one of our clinics, respectively. The remaining children were contacted by phone or letter but 18 (10%) did not respond at all. During the study period, many children who did not come for their regular visits returned to one of our hospitals because of illness. Consequently, all of the medical records of the participants from both hospitals were reviewed to ensure that we had all the data required for our analysis.

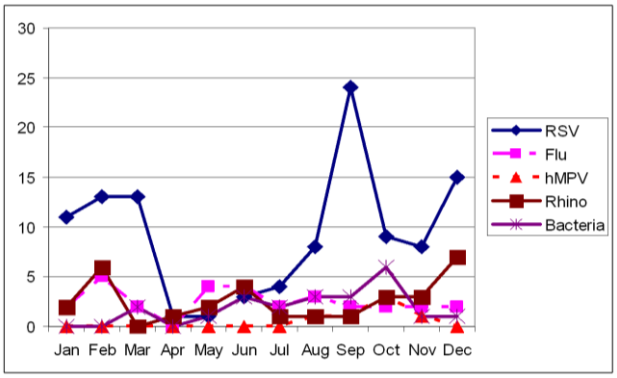

Figure 1. Distribution of the pathogens during the year

At the end of the 3rd and 5th years, we were able to contact 152 (89%) and 91 (60%) of the parents/children for medical information, respectively. In the first three years, recurrent wheezing was reported for 94 (61.8%) of the children which mostly presented within the first year

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Table 2. Baseline characteristics of the study population

Characteristics	Total N = 170	RSV N = 110	Rhino N = 31	Influenza N = 30	Atypical bacteria N = 22	hMPV N = 6	Mix N = 49	Not found N = 25
Age (mo), 95%CI	9.9-11.6	9.2-11.3	9.4-13.8	10.6-14.6	7.2-12.4	4.2-14.9	9.5-12.7	8.1-12.8
Median	9.65	9.23	12.17	12.72	8.85	8.40	11.43	9.23
Mean ± SD	10.74 ±5.73	10.24 ±5.71	11.62 ±5.95	12.58 ±5.36	9.80 ±5.85	9.52 ±5.08	11.08 ±5.64	10.41 ±5.74
Male, N (%)	107 (62.9)	65 (59.1)	16 (51.6)	21 (70.0)	15 (68.2)	3 (50.0)	28 (57.1)	20 (80)
Body weight (kg), Mean±SD	8.30 ±1.80	8.06 ±1.80	8.45 ±1.85	8.92 ±1.85	7.55 ±1.72	8.32 ±0.64	8.24 ±1.75	8.6 ±1.70
Breast feeding, N (%)	160 (94.1)	102 (92.7)	30 (96.8)	28 (93.3)	21 (95.5)	6 (100.0)	46 (93.9)	24 (96.0)
Duration of breast feeding (mo), Mean±SD	4.10 ±3.50	4.12 ±3.51	3.73 ±2.94	3.92 ±3.81	3.18 ±2.28	2.83 ±1.33	3.53 ±2.88	4.3 ±3.5
Self atopy, N (%)	13 (7.6)	7 (6.4)	3 (9.7)	2 (6.7)	4 (18.2)	1 (16.7)	6 (12.2)	2 (8.0)
Atopic parent, N (%)	50 (29.4)	35 (31.8)	10 (32.3)	6 (20.0)	6 (27.3)	1 (16.7)	17 (34.7)	9 (36.0)
Relative atopy, N (%)	37 (21.8)	23 (20.9)	6 (19.4)	8 (26.7)	4 (18.2)	4 (66.7)	13 (26.5)	5 (20.0)
Passive smokers, N (%)	102 (60.0)	63 (57.3)	15 (48.4)	21 (70.0)	19 (86.4)	6 (100.0)	31 (63.3)	14 (56.0)

of follow-up (mean duration 5.5±7.2 months after the first episode). Among these subsequent wheezers, two thirds (65/94, 69%) did not experience wheezing episode after 3 years of follow-up. Persistent wheezing after the age of 6 was reported for 15 children (15/94, 16%) (9 in the RSV and 4 in the rhinovirus group); all were asthmatic children. At the end the 5th year, asthma was diagnosed in 41 children (41/91 = 45%); most of whom (40/41) received inhaled corticosteroid (either by parent-reported or patient's records). Among the asthmatic children, 9 (9/41, 22%) and 17 (17/41, 41.5%) were symptom free by the third and fifth year of follow-up, respectively. There was no statistically significant difference in wheezing and asthma among the various etiologies. (Table 4)

Rhinovirus is an important risk factor for both recurrent wheezing and asthma development with an HR of 1.63 and 1.34, respectively, while bacterial pathogens had a similar result for recurrent wheezing (HR 2.07) but not for asthma. Notwithstanding, the difference was not statistically significant among the various pathogens. (Table 5, 6)

Discussion

This study demonstrated that rhinovirus was the second (after RSV) most common pathogen causing acute bronchiolitis among children in Northeast Thailand. The incidence peaked in the early rainy and cool seasons. Influenza virus, hMPV and atypical bacteria also caused wheezing among these young children. Two-thirds of the children had subsequent wheezing, mostly within a year after their first episode. Asthma was diagnosed in nearly half of these children. Rhinovirus is therefore an important risk factor for wheezing and asthma although there was no statistically significant difference among the various etiologies.

After Papadopoulos et al. [22] demonstrated that rhinovirus can directly infect the lower airway (i.e., it is not limited to the upper airway as once thought), many epidemiologic studies have shown that rhinovirus is an important causative pathogen of lower respiratory infection in children.[4-15] This virus can indeed cause all sorts of lower respiratory illnesses; such as bronchiolitis, pneumonia and asthma exacerbation.[23]

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Table 3. Clinical manifestations at enrollment and clinical course of acute bronchiolitis

Characteristics	Total N = 170	RSV N = 110	Rhino N = 31	Influenza N = 30	Atyp.bact N = 22	hMPV N = 6	Mix N = 49	Not found N = 25
History of fever, N (%)	155 (91.2)	99 (90)	24 (77.4)	29 (96.7)	20 (90.9)	6 (100)	43 (87.8)	24 (96)
SpO_2 <95%, N (%)	105 (61.8)	68 (61.8)	18 (58.1)	20 (66.7)	15 (68.2)	3 (50)	32 (65.3)	15 (60)
SpO_2, %								
Min-max	63-100	70-99	72-99	88-99	89-99	84-97	72-99	63-100
Mean±SD	93.7±4.9	93.8±4.8	94.0±4.9	94.1±3.1	94.2±2.8	93.0±4.8	93.9±4.2	93.2±7.3
95%CI	93.0-94.5	92.9-94.7	92.2-95.8	92.9-95.3	93.0-95.5	88.0-98.0	92.7-95.1	90.3-96.3
Clinical score*,								
Min–max	5-11	5-11	5-11	5-10	5-9	6-10	5-11	5-11
Mean±SD	7.0±1.4	7.0±1.3	7.1±1.5	7.2±1.4	7.2±1.1	7.5±1.6	7.1±1.3	6.9±1.6
95%CI	6.8-7.3	6.7-7.2	6.6-7.7	6.7-7.7	6.7-7.7	5.8-9.2	6.8-7.5	6.3-7.6
Temperature, °C								
Mean±SD	38.9±0.9	38.1±0.9	37.8±0.7	38.3±0.9	38.2±0.8	38.1±0.6	38.0±0.8	38.0±0.9
95%CI	37.9-38.2	37.9-38.3	37.6-38.1	38.0-38.7	37.9-38.6	37.5-38.8	37.8-38.3	37.6-38.3
Duration of fever, days								
Mean±SD	4.4±3.0	4.3±2.8	2.2±2.6	4.4±3.4	3.5±2.3	4.3±1.9	3.2±2.6	5.5±3.3
95%CI	3.9-4.8	3.7-4.8	1.2-3.2	3.1-5.7	2.4-4.5	2.4-6.3	2.5-4.0	4.1-6.9
Duration of O_2 treatment, hour								
Mean±SD	32.6±34.6	34.7±36.3	23.0±17.8	27.2±24.5	37.7±30.9	64.7±55.5	33.1±27.5	27.7±26.5
95%CI	27.4-37.8	27.8-41.5	16.4-29.5	17.9-36.5	24.0-51.4	6.5-12.9	25.2-41.0	16.7-38.6
Length of stay, hour								
Mean±SD	63.5±38.1	64.6±40.4	50.3±24.3	60.0±29.4	65.5±34.9	76.0±63.4	59.3±32.5	64.3±32.3
95%CI	57.8-69.3	56.9-72.2	41.4-59.2	49.0-71.0	50.0-80.9	9.5-142.5	49.9-68.6	61-77.7
Duration of respiratory distress, day								
Mean±SD	5.1±4.4	4.9±3.9	3.7±3.7	4.6±3.1	5.6±5.1	9.2±9.8	4.5±3.9	5.6±5.5
95%CI	4.4-5.7	4.2-5.6	2.3-5.1	3.5-5.7	3.3-7.8	1.2-19.5	3.3-5.6	3.4-7.9
Duration of cough, days								
Mean±SD	11.1±6.9	11.2±6.6	8.7±5.4	10.1±6.4	11.7±8.5	16.2±12.4	10.4±7.1	11.7±6.6
95%CI	10.1-12.1	9.9-12.4	6.7-10.7	7.8-12.5	8.0-15.5	3.2-29.2	8.4-12.4	9.0-14.5

*Modified from Tal et al (Pediatrics. 1983;71:13–18) as described in Teeratakulpisarn et al.[17]

As assessed by molecular methods, the prevalence of rhinovirus causing acute lower respiratory infection among young children <3 years of age varies between 17 and 35%.[4,5,7,9,10,24,25] The variation may be due to the age range and diagnoses of the study populations. Acute bronchiolitis is a disease of children under 2 years. Jartti et al.[4] showed that RSV occurred mostly among children under 12 months while rhinovirus predominated amongst older children. We found that RSV was highest among children 1-6 months of age and less so among older children, while rhinovirus ranked second in all age groups (overall prevalence 18%). This figure was slightly lower than some previous studies for the same age group;[7,9] most of which indicated that rhinovirus was the second most

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Table 4. Recurrent wheezing/asthma

Characteristics	Total N = 152	RSV N = 101	Rhino N = 29	Influenza N = 27	Atypical bacteria N = 20	hMPV N = 6	Mix N = 45	Not found N = 19
Recurrent wheezing, N (%)	94 (61.8)	62 (61.4)	20 (69.0)	15 (55.6)	13 (65.0)	4 (66.7)	30 (66.7)	14 (73.7)
Duration after1st episode, (month), mean±SD	5.4±7.2	6.1±8.3	7.7±12.8	5.0±4.3	5.9±4.3	3.0±2.8	6.4±10.6	3.1±3.1
Recurrent wheezing	**Total *Nw = 94**	**RSV Nw = 62**	**Rhino Nw = 20**	**Influenza Nw = 15**	**Atypical bacteria Nw = 13**	**hMPV Nw = 4**	**Mix Nw = 30**	**Not found Nw = 14**
Wheeze disappear within 1 yr, Nw (%)	7 (7.4)	5 (8.1)	1 (5)	3 (20)	1 (7.7)	0	3 (10)	0
Wheeze disappear within 2 yr, Nw (%)	29 (30.9)	23 (37.1)	7 (35)	3 (20)	6 (46.2)	1 (25)	10 (33.3)	2 (14.3)
Wheeze disappear within 3 yr, Nw (%)	29 (30.9)	17 (27.4)	6 (30)	7 (46.7)	3 (23.1)	0	9 (30)	5 (35.7)
Wheeze disappear within 4 yr, Nw (%)	11 (11.7)	7 (11.3)	1 (5)	2 (13.3)	2 (15.4)	1 (25)	3 (10)	2 (14.3)
Wheeze disappear within 5 yr, Nw (%)	3 (3.2)	1 (1.6)	1 (5)	0	1 (7.7)	2 (50)	1 (3.3)	0
Persist wheeze > 60 mo, Nw (%)	15 (16)	9 (14.5)	4 (20)	0	1 (7.7)	0	4 (13.3)	5 (35.7)
At 5th year of follow-up, **N_{5th} = 91								
Dx Asthma, N_{5th} (%)	41 (45)	27 (29.7)	8 (8.8)	4 (4.4)	5 (5.5)	3 (3.3)	11 (12.1)	7 (7.7)

*Nw = number of children who had recurrent wheezing

**N_{5th} = number of children at the 5th year of follow up

common causative pathogen among young children hospitalized with wheezing.[5,9,10,26]

The seasonal prevalence of respiratory pathogens varies among countries in different climate zones. An epidemiologic study of these respiratory viruses causing hospitalization in young children should help in the selection of treatment (antiviral vs. bacterial), awareness of potential long-term co-morbidities (such as wheezing and asthma) and in encouraging disease prevention (vaccination).[26] In temperate vs. tropical climates, the respective prevalence peak for RSV is during the winter vs. the rainy season. Our study confirmed that in Thailand RSV peaks during the rainy season.[27] We also found that rhinovirus (the second most common pathogen encountered) and influenza (the only vaccine-preventable disease) had two peaks; the first in the early rainy season (May–July) and the second during the cool, dry season (December–February).

Our results showed that vis-à-vis the various etiologies, the differences in clinical manifestations and severities were not statistically significant. Children infected with rhinovirus had a higher mean age and less fever than those infected with RSV or other pathogens. These findings are similar to a study from Finland [8] but contrast with one from France [5] which showed that children infected with RSV had significantly more cough, feeding difficulty and needed more oxygen administration than rhinovirus.

Aeroallergen sensitization and virus-induced wheezing in early life are known to be important risk factors for subsequent development of asthma and children with both risk factors are at particularly high risk of having asthma at school age.[11,14] Before the discovery of rhinovirus, RSV was reported to be the most important pathogen causing wheezing illness and related to subsequent asthma.[28,29]

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Table 5. Risk of subsequent wheezing

Risks	Subsequent wheeze = 94 N_w (%)	HR	95%CI
Self atopy (N_t = 12)	11 (11.7)	1.16	0.57-2.36
Family atopy			
- Parent asthma			
(father/mother/both) (N_t = 44)	32 (34.0)	1.09	0.67-1.76
Relative atopy (N_t = 35)	24 (25.5)	1.05	0.63-1.75
Male (N_t = 95)	60 (63.8)	1.15	0.72-1.85
Early cow milk (N_t = 86)	52 (55.3)	0.8	0.49-1.30
Wheeze 6 mo (N_t = 31)	20 (21.3)	0.98	0.53-1.79
Pet (N_t = 78)	42 (44.7)	0.55	0.33-0.91
Passive smoking (N_t = 87)	53 (56.4)	0.89	0.55-1.45
Family size > 5 (N_t = 58)	40 (42.6)	1.37	0.86-2.19
RSV infection (N_t = 101)	62 (66.0)	1.04	0.55-1.97
Rhinovirus (N_t = 29)	20 (21.3)	1.63	0.57-4.63
hMPV (N_t = 6)	4 (4.3)	0.67	0.17-2.69
Influenza (N_t = 27)	15 (16.0)	0.95	0.43-2.08
Atypical bacteria (N_t = 20)	13 (13.8)	2.07	0.74-5.75
Mixed (N_t = 45)	30 (31.9)	1.01	0.34-3.01

N_w = the number of children who had the risk among subsequent wheezing children

N_t = the number of children who had the risk among total children

Table 6. Risk of asthma development

Risks	Asthma = 41 N_a (%)	HR	95%CI
Self atopy (N_t = 12)	5 (12.2)	1.72	0.59-5.02
Family atopy			
- Parent asthma			
(father/mother/both) (N_t = 44)	15 (36.6)	0.84	0.39-1.79
Relative atopy (N_t = 35)	14 (34.1)	1.37	0.64-2.95
Male (N_t = 95)	28 (68.3)	1.21	0.53-2.77
Early cow milk (N_t = 86)	26 (63.4)	0.99	0.47-2.11
Wheeze 6 mo (N_t = 31)	9 (22.0)	0.88	0.38-2.04
Pet (N_t = 78)	18 (43.9)	0.54	0.25-1.14
Passive smoking (N_t = 87)	17 (41.5)	0.73	0.33-1.62
Family size > 5 (N_t = 58)	20 (48.8)	1.92	0.89-4.14
RSV infection (N_t = 101)	27 (65.9)	0.94	0.36-2.43
Rhinovirus (N_t = 29)	8 (19.5)	1.34	0.26-6.95
hMPV (N_t = 6)	3 (7.3)	0.44	0.05-4.01
Influenza (N_t = 27)	4 (9.8)	0.67	0.17-2.65
Atypical bacteria (N_t = 20)	5 (12.2)	0.76	0.14-4.06
Mixed (N_t = 45)	11 (26.8)	0.96	0.17-5.51

N_a = the number of children who had the risk among asthmatic children

N_t = the number of children who had the risk among total children

The long prospective cohort study by Sigurs et al.[29] demonstrated that children infected with severe RSV bronchiolitis in early life had an increased risk of asthma, airway hyper-responsiveness and allergic sensitization which can last into adulthood. Later evidence is contradictory. Data on long-term outcomes after viral bronchiolitis show that the rate of recurrent wheezing is significantly higher among non-RSV than RSV infections.[30] Kneyber et al.[31] also found that RSV bronchiolitis had no significant effect on recurrent wheezing after 5 years compared to a control group in their quantitative review.

Recent advances in virological detection of non-RSV induced bronchiolitis have changed the focus to the emerging rhinovirus as an important risk factor for future asthma. Some recent cohort studies found an association between allergic sensitization and rhinovirus wheezing and subsequent asthma.[11,14,32] Two birth cohorts from Europe and Australia confirmed that human rhinovirus causing wheezing illness in early life is a significant predictor of asthma at the age of 5 or more.[11,14] The COAST study showed that the risk of subsequent asthma increases when the child is infected at an older age. Children wheezing from rhinovirus during the first year had (a) a 3-fold higher risk of asthma at the age of 6 (b) a 7-fold risk if the wheezing developed in the second year of life, or (c) a 32-fold risk if rhinovirus wheezing developed in the third year of life.[14] A recent review article also confirmed that rhinovirus-induced wheezing in infancy played an important role in both asthma development and asthma exacerbation and could lead to airway remodeling.[33] On the other hand, Tantilipikorn et al. showed that airway allergy might increase the risk of rhinovirus infection by up-regulation of viral receptors on airway epithelium.[34]

The sequence of the causal relationship between allergic sensitization and virus-induced wheezing in the development of asthma remains unclear until recently, when Jackson et al.[35] demonstrated that sensitization to aeroallergens in the first year of life consistently predisposes children to viral wheezing, while the converse is not true. This novel recent work may lead to a preventive strategy for asthma in the future.

The Early Life study showed that 92% of children with viral bronchiolitis experienced at least 1 or more additional episodes of wheezing before 3 years of age and 48% received a physician diagnosis of asthma by the age of seven.[36] Our study found a lower prevalence of subsequent wheezing, in only

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62%, and showed similar results for asthma development (45%). However, the wheezing disappeared in most before the age of 6. The reason for the lower prevalence in our study was that some children were diagnosed or treated elsewhere. As the prevalence of asthma in our study (although similar to the previous study) was quite high, it might not reflect the real asthma prevalence after bronchiolitis in our country because of high dropout rate.

Although there were no statistically significant differences among the pathogens, we found that children infected with rhinovirus had the highest risk for asthma. We also found that personal history of atopy was an important risk factor for asthma in our study but we did not study in depth of its correlation with the various etiologies.

Limitations

Our results may have been skewed: 1) the sample size at the beginning of the study was not large enough for a long-term cohort; 2) some of the data relied on parental reports of recurrent wheezing; 3) some data were missing, as some children were diagnosed or treated elsewhere; and, 4) we had not planned to demonstrate the association between allergic sensitization and viral pathogens.

In summary, rhinovirus was the second most common cause of hospitalization of children under 2 years of age with acute bronchiolitis. More than half of these children had recurrent wheezing but these symptoms mostly disappeared before the age of 6. Nearly half of these patients subsequently had asthma. The specific pathogens did not account for a statistically significant difference in subsequent wheezing or asthma development.

Acknowledgement

The authors thank (a) the Faculty of Medicine, Khon Kaen University for grant support (Number I 51216) (b) Miss Jitjira Chaiyarit, Biostatistician, Clinical Epidemiology Unit, Faculty of Medicine, Khon Kaen University for statistical analysis and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

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