Upper Airway Viruses and Bacteria and Clinical Outcomes in Children With Cough

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Summary. Background: Cough is symptomatic of a broad range of acute and chronic pediatric respiratory illnesses. No studies in children have tested for an extended panel of upper airway respiratory viruses and bacteria to identify whether they predict cough outcomes, irrespective of clinical diagnosis at the time of acute respiratory illness (ARI). We therefore determined whether upper airway microbes independently predicted hospitalization and persistent cough 28-days later in children presenting with an ARI, including cough as a symptom. Methods: A cohort study of children aged <15-years were followed for 28-days after presenting to a pediatric emergency department with an ARI where cough was also a symptom. Socio-demographic factors, presenting clinical features and a bilateral anterior nasal swab were collected at enrolment. Polymerase chain reaction assays tested for seven respiratory bacteria and 17 viruses. Predictors of hospitalization and persistent cough at day-28 were evaluated in logistic regression models. Results: Eight hundred and seventeen children were included in the analysis; median age 27.7-months. 116 (14.2%, 95%CI 11.8, 16.6) children were hospitalized and 163 (20.0%, 95% CI 17.2, 22.7) had persistent cough at day-28. Hospitalized children were more likely to have RSV A or B detected on nasal swab than those not admitted (adjusted relative risk (aRR) 1.8, 95%CI 1.0, 3.3). *M. catarrhalis* was the only microbial difference between children with and without cough persistence (aRR for those with cough at day 28: 2.1, 95%CI 1.3, 3.1). Discussion: An etiologic role for *M. catarrhalis* in the pathogenesis of persistent cough post-ARI is worth exploring, especially given the burden of chronic cough in children and its relationship with chronic lung disease. **Pediatr Pulmonol. 2017;52:373–381.** © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

The complexity of the upper airway microbiota and its association with acute respiratory infections (ARI) in children continue to present challenges worldwide, particularly determining pharmacologic strategies to prevent and treat disease.[1,2] This is further complicated by epidemiologic differences within and between populations, and temporal variations in disease patterns, especially following vaccine introduction and changing pathogen antibiotic susceptibility profiles.[3,4]

Most research seeking to identify the causative agents of ARIs and whether they predict disease severity and outcomes focuses on specific clinical entities, such as pneumonia,[3] bronchiolitis,[5,6] and acute asthma/wheezing illness.[7–9] However, diagnosing these illnesses in young children can be challenging as the symptoms and signs may overlap. Moreover, clinical presentations can be influenced by the child's age, time taken for healthcare to be sought, recent corticosteroid, antibiotic and antipyretic therapy, underlying co-morbidities and environmental and socio-economic factors.[10] In addition, clinician specific factors such as level of pediatric experience and type of healthcare service (eg., primary vs. tertiary level facilities) may also have a role.

Cough is symptomatic of a broad-spectrum of respiratory illnesses in children ranging from mild and transient upper airway infections to severe acute and chronic lower respiratory tract disease.[11] When it is wet and chronic (>4-weeks duration), it implies increased airway secretions and endobronchial infection, which if left untreated may progress in some children to chronic suppurative lung disease, including bronchiectasis.[12] Chronic cough is also associated with poor parent cough-specific quality of life scores[13] and parental stress.[14] Thus predictors of chronic cough following an ARI may inform future interventions.

No studies in children have tested for an extended panel of respiratory viruses and bacterial pathogens in upper airway specimens to identify whether these agents, singly or in combination, predict cough outcomes irrespective of the clinical ARI diagnosis. Hence, our primary objectives were to determine whether upper airway respiratory viruses and/or bacteria independently predicted: a) hospitalization, and b) the persistence of cough 28-days following presentation to a pediatric emergency department (ED) for an ARI with cough as a symptom. We hypothesized that cough illness outcomes are dependent primarily on child-specific factors rather than upper airway viruses and bacteria detected at the time children present for medical care.

METHODS

Setting

The Royal Children's Hospital (RCH), Brisbane, Australia (now the Lady Cilento Children's Hospital) is the largest tertiary pediatric hospital in the state of Queensland. Brisbane has a subtropical climate with summer its wettest season. Brisbane is a socio-economically diverse city with a median weekly household income of approximately AUD$78,000. Thirteen percent of residents were born overseas and 3.0% are of Aboriginal and/Torres Strait Islander origin. Human immunodeficiency virus and *Mycobacterium tuberculosis* infections in our setting are very rare,[15,16] and neither was found as an etiology of chronic cough in a study involving 346 children.[13]

Design

This study is a secondary analysis of data collected during a prospective cohort study of children aged <15-years presenting to the RCH ED with an ARI where cough was a symptom.[17] The primary objective of the original study was to determine the prevalence of persistent cough (>4-weeks duration) post-ARI. The full study protocol is described elsewhere[17] and was approved by the Children's Health Queensland (HREC/11/QRCH/83), and the Queensland University of Technology (2012000700). Human Research Ethics Committees.

Children were excluded if they had a known underlying medical condition, including chronic pulmonary disorders (except asthma); were receiving immunomodulating drugs (except short-course (<2-weeks) oral and ongoing maintenance inhaled corticosteroids) in the 30-days prior to presentation; or insufficient English to understand the requirements of the study. Parents/guardians gave written, informed consent, while participants aged >12-years also provided their assent.

Sociodemographic and presenting clinical features were recorded on enrolment and a bilateral anterior nasal swab was collected using the Virocult® Specimen Collection system (Medical Wire and Equipment, Wiltshire, England). Children were followed weekly for 28-days to ascertain cough persistence. Previously

validated, parent-completed, daily cough diary cards, and weekly telephone/email contacts were implemented to record cough type (wet/dry), severity and duration.[18] Loss to follow-up was defined as two consecutive weeks where weekly contacts were unsuccessful. If it was known a child had stopped coughing prior to loss-to-follow, cough persistence at day-28 was classified as "no." The decision to hospitalize a child and the assessment of persistent cough at day-28 were undertaken by physicians blinded to the PCR results. Laboratory testing occurred upon completion of the study and the laboratory blinded to the clinical data.

Nasal swabs were stored at−80°C within 24-hr of collection before being batch tested at the Queensland Paediatric Infectious Diseases Laboratory, RCH, for respiratory viruses and bacterial pathogens using previously validated polymerase chain reaction (PCR) assays.[17] Virus testing included adenovirus, respiratory syncytial virus (RSV) types A and B, influenza virus types A and B, parainfluenza virus types 1–3, human metapneumovirus, rhinoviruses, human coronaviruses (OC43, 229E, NL63 + HKU1), human bocavirus, and human polyomaviruses KI and WU. Bacterial testing included *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

Analyses

Descriptive analyses were performed with data expressed as proportions and/or means of the selected characteristics with the corresponding 95% confidence intervals (CI). Where continuous data were not normally distributed, medians with accompanying interquartile ranges (IQR) are presented.

Univariable analyses were performed to assess potential associations between child-specific characteristics (Suppl 1), detection of virus and bacteria and the primary endpoints of hospitalization, and persistence of cough at day-28 post-ED presentation. Factors identified in univariable analyses with a P-value < 0.1 were entered into a backwards selection binomial regression model to identify characteristics independently associated with hospitalization and multinomial regression for cough persistence; adjusted relative risks (aRR) and adjusted odds ratio (aOR), and their corresponding 95%CI were calculated and a P-value < 0.05 was considered statistically significant. Model goodness of fit was assessed using the Homer-Lemeshow χ^2 statistic. All analyses were performed in Stata V12SE (StataCorp, College Station, TX).

RESULTS

Between December 11, 2011 and August 31, 2014, 876 children were enrolled. Nasal swabs were collected from 827 (94.4%) enrolled children; median age 27.7-months (IQR 13.9–60.3) and 498 (60.2%) were male. Ten swabs were excluded due to inhibition during laboratory processing leaving 817 children providing nasal swabs for analysis. Of these, 116 (14.2%, 95%CI 11.8, 16.6) children were hospitalized for their illness and 163 (20.0%, 95%CI 17.2, 22.7) had persistent cough at day-28 following enrolment. Cough status at day-28 was unknown for 233 children (28.5%); 107 (45.9%) of these children were lost to follow-up within the first 14-days. Univariate analyses of differences in characteristics between children followed and not followed-up are presented in Table 1. In regression analyses having a household income of <AUD\$26, 000 (aOR 3.53 95%CI 1.37, 9.10), being enrolled in autumn (aOR 1.77, 95%CI 1.06, 2.96) or spring (aOR 2.70, 95%CI 1.46, 4.99), and having a cough duration of 14–<21-days at time of enrolment (aOR 2.84, 95%CI 1.33, 6.07) were independently associated with loss to follow-up.

Overall, 740/817 (90.6%) nasal specimens were positive for any organism. There were 508 (62.2%) specimens positive for at least one virus, 73 (8.9%) had only viruses detected, while 93 (11.4%) had >2 viruses present. The most common viruses were rhinoviruses (n = 252; 30.8%) and RSV (n = 157; 19.2%). Similarly, 622 (76.1%) swabs had at least one bacterial pathogen identified, 232 (28.4%) were positive for bacteria only, while in 386 (47.2%) >2 bacteria were detected. The most common bacteria detected were *M. catarrhalis* (n = 467; 57.2%), *S. pneumoniae* (n = 401; 49.1%) and *H. influenzae* (n = 259; 31.7%). Both viruses and bacteria were identified in 423 (51.8%) swabs and, of these, at least two bacteria and two viruses were detected in 67 (15.8%).

The univariate analyses of predictors for hospitalization, including child characteristics, clinical characteristics, and upper airway viruses and bacteria are presented in Supplement Tables S1–S3. For the multivariable regression analyses of factors identified as being associated with hospitalization in the univariate analyses, complete data were available for 654 (88.0%) children. The final model identified five independent predictors after controlling for age in months and gender. These included: having ≥3 other children in the house (aRR 4.0, 95%CI 1.6, 9.8); age-adjusted tachypnea in the ED (aRR 1.8, 95%CI 1.1, 2.9); a peripheral oxygen saturation <95% in room air in the ED (aRR 5.1 95%CI 2.9, 9.0); requiring oxygen therapy in the ED (aRR 6.7, 95%CI 3.2, 14.1); and having RSV A or B detected on nasal swab specimens (aRR 1.8, 95%CI 1.0, 3.3).

The univariate analyses of predictors for persistent cough at day-28, including child characteristics, clinical characteristics, and upper airway viruses and bacteria are presented in Supplement Tables S4–S6. For the multivariable regression analyses of factors identified as being associated with persistent cough at day-28 post-ARI

TABLE 1—Characteristics of 817 Children Presenting With Cough to a Pediatric Emergency Department by Completion of Study

	Known cough status day-28	Unknown cough status at day-28	
	n (%)	n (%)	*P*-value
Gender			
Male	355 (71.3)	251 (50.4)	0.877
Female	229 (71.8)	167 (52.4)	
Age group (months)			
0–<12	119 (72.1)	46 (27.9)	0.654
12–<24	146 (73.4)	53 (26.6)	
24–<60	178 (72.4)	68 (27.6)	
60+	141 (68.1)	66 (31.9)	
Aboriginal and/or Torres Strait Islander (n = 815)			
Yes	16 (55.2)	13 (44.8)	0.045
No	568 (72.3)	218 (27.7)	
Total annual household income (AUD) (n = 722)			
≥$200,000	62 (78.5)	17 (21.5)	0.303
$156,000–<$200,000	77 (74.0)	27 (26.0)	
$104,000–<$156,000	147 (72.1)	57 (27.9)	
$78,000–<$104,000	102 (75.0)	34 (25.0)	
$52,000–<$78,000	65 (70.7)	27 (29.4)	
$26,000–<$52,000	57 (72.2)	22 (27.9)	
<$26,000	15 (53.6)	13 (46.4)	
Season of enrolment (n = 817)			
Summer	134 (80.7)	32 (19.3)	0.003
Autumn	200 (70.4)	84 (29.6)	
Winter	182 (71.7)	72 (28.4)	
Spring	68 (60.2)	45 (39.8)	
Gestational age (n = 806)			
<37-weeks	64 (68.8)	29 (31.2)	0.491
≥37-weeks	515 (72.3)	198 (27.8)	
Birth weight (n = 768)			
<2500 grams	49 (68.1)	23 (31.9)	0.402
≥2500 grams	506 (72.7)	190 (27.3)	
Breastfeeding history (n = 716)			
Ever breastfed	460 (72.7)	172 (27.2)	0.104
Never breastfed	54 (64.3)	30 (35.7)	
School/child care attendance (n = 802)			
Yes	285 (71.3)	115 (28.8)	0.662
No	292 (72.6)	110 (27.4)	
Number of other children in house (n = 817)			
0	179 (69.7)	78 (30.4)	0.590
1	246 (73.7)	88 (26.4)	
2	101 (72.1)	39 (27.9)	
≥3	58 (67.4)	28 (32.6)	
Allergies (n = 817)			
Yes	132 (72.1)	51 (27.9)	0.858
No	448 (71.5)	179 (28.6)	
Parent reported wheeze in past 12-months (n = 798)			
Yes	281 (70.8)	112 (27.9)	0.687
No	289 (72.1)	116 (29.2)	
Parent reported wheeze in past 7-days (n = 734)			
Yes	266 (73.5)	96 (26.5)	0.549
No	266 (71.5)	106 (28.5)	
Ever had eczema (n = 793)			
Yes	168 (72.4)	159 (28.3)	0.829
No	402 (72.4)	64 (27.6)	
Pets in household (n = 814)			
Yes	311 (72.2)	120 (27.8)	0.719
No	272 (71.0)	111 (29.0)	
Exposure to household tobacco smoke (n = 807)			
Yes	103 (65.2)	55 (34.8)	0.045
No	475 (73.2)	174 (26.8)	

TABLE 1— (*Continued*)

	Known cough status day-28	Unknown cough status at day-28	
	n (%)	n (%)	*P*-value
Hospitalization for ARI in past 12-months (n = 814)			
Yes	118 (67.8)	56 (32.2)	0.209
No	465 (72.7)	175 (27.3)	
Doctor diagnosis of asthma in past 12-months (n = 817)			
Yes	146 (69.2)	65 (30.8)	0.393
No	438 (72.3)	168 (27.7)	
Flu vaccine in past 12-months (age ≥6-months only) (n = 779)			
Yes	48 (75.0)	16 (25.0)	0.474
No	506 (70.8)	209 (29.2)	
Hospitalized for this illness (n = 817)			
Yes	77 (66.4)	39 (33.6)	0.189
No	507 (72.3)	194 (27.7)	
Duration of cough in days at time of ED presentation (n = 807)			
<3	253 (73.8)	90 (26.2)	0.032
3–<7	203 (74.9)	68 (25.1)	
7–<14	48 (66.7)	24 (33.3)	
14–<21	19 (55.9)	15 (44.1)	
21–<28	16 (53.3)	14 (46.7)	
>28	41 (71.9)	16 (28.1)	
Antibiotics prior to ED presentation (n = 817)			
Yes	95 (74.8)	32 (25.2)	0.367
No	489 (70.9)	201 (29.1)	
Antibiotics given in ED (n = 817)			
Yes	27 (67.5)	13 (32.5)	0.567
No	557 (71.7)	220 (28.3)	
Antibiotics post ED discharge (n = 815)			
Yes	51 (64.6)	28 (35.4)	0.148
No	532 (72.3)	204 (27.7)	
Any organism positive on nasal swab			
Yes	530 (71.6)	210 (28.4)	0.783
No	54 (70.1)	23 (29.9)	
Any bacteria positive on nasal swab			
Yes	474 (71.6)	188 (28.4)	0.875
No	110 (71.0)	45 (29.0)	
Any virus positive on nasal swab			
Yes	364 (71.7)	144 (28.3)	0.889
No	220 (71.2)	89 (28.8)	
Both virus and bacteria positive on nasal swab			
Yes	304 (71.9)	119 (28.1)	0.800
No	280 (71.1)	114 (28.9)	

presentation in the univariate analyses, complete data were available for 778 (95.2%) children. The aRR for factors associated with both persistent cough at day-28 and unknown cough status at day-28 are presented in Table 2. The inclusion of "any virus positive" in the model did not affect the final results.

DISCUSSION

This study of 817 children presenting with an ARI, including cough, to the ED of an Australian tertiary pediatric center shows that after controlling for age and gender, RSV was weakly associated with hospitalization, whereas reduced peripheral oxygen saturation, supplemental oxygen treatment, and having at least three other children in the house were associated with an increased likelihood of admission. In contrast, cough duration at the time of enrolment of greater than 14-days and being *M. catarrhalis* positive on nasal swab were the only factors associated with an increased risk of cough persistence at day-28. Enrolment during the spring months and, although the actual number of children was small, having received oxygen therapy whilst in the ED were associated with a reduced risk of persistent cough.

The high prevalence of any organism overall detected in our study is consistent with other studies of pediatric ARI that have utilized molecular methods reflecting the higher sensitivity of PCR compared to traditional culture methods.[19] Further, we tested for an extensive range of organisms, some of which are infrequently assessed in

TABLE 2— Adjusted Relative Risks (aRR) for Cough Persistence at Day-28 Following Presentation to a Pediatric Emergency Department With Acute Respiratory Illness With Cough as a Symptom (n = 778 Children)[1]

	Cough persistence at day 28			Unknown cough persistence at day 28		
	aRR	95%CI	*P*-value	aRR	95%CI	*P*-value
Age group (months)						
60+	Ref					
24–<60	1.05	0.58–1.90	0.868	0.81	0.51–1.30	0.384
12–<24	1.33	0.71–2.48	0.370	0.73	0.43–1.23	0.434
<12	1.75	0.93–3.29	0.082	1.03	0.60–1.77	0.596
Season						
Summer	Ref					
Autumn	1.08	0.64–1.82	0.784	1.78	1.07–2.96	0.026
Winter	1.03	0.59–1.79	0.912	1.57	0.92–2.68	0.100
Spring	0.47	0.21–1.05	0.067	2.31	1.27–4.24	0.006
Cough duration at enrolment (days)						
<3						
3–<7	1.04	0.66–1.64	0.865	0.93	0.63–1.38	0.714
7–<14	1.45	0.69–3.04	0.322	1.60	0.87–2.96	0.134
14–<21	7.29	2.56–20.79	<0.001	5.13	1.88–14.04	0.001
21–<28	4.11	1.43–11.81	0.009	3.61	1.34–9.71	0.011
≥28	5.20	2.43–11.11	<0.001	2.01	0.92–4.39	0.082
Oxygen therapy in ED	0.26	0.07–0.89	0.033	1.50	0.79–2.85	0.210
Nose swab positive for *M. catarrhalis*	2.05	1.34–3.12	0.001	1.32	0.92–1.90	0.133
Nose swab positive for Bocavirus	0.78	0.22–2.73	0.702	3.05	1.27–7.36	0.013
Any virus positive	1.01	0.65–1.55	0.976	0.96	0.66–1.40	0.852

aRR, adjusted relative risk.
[1]Model baseline is children with no cough persistence at day-28.

combination with other organisms in clinical or research settings that focus on ARI (for example, the coronaviruses, bocavirus, and polyomaviruses). Similarly, the high prevalence of *S. pneumoniae* in the pneumococcal conjugate vaccine era reflects our use of PCR, the diversity of serotypes that continue to circulate in the pediatric population and that overall carriage of any *S. pneumoniae* is not affected by vaccination.[20]

The relationship between RSV detection and hospitalization is consistent with other studies where it is associated with disease severity,[21,22] particularly with high virus loads.[5] However, the association in our study was relatively weak and this may reflect the small sample of young infants in our study population in whom RSV is generally associated with more severe disease. The clinical signs of tachypnea and hypoxemia triggering oxygen administration are also established markers of severe lower airway disease in children,[23] particularly if cough is present.

The number of other children in the house as an independent predictor of hospitalization is less readily explained. It may suggest different caring patterns leading to delayed presentation of the unwell child at an ED, social issues associated with a physician's decision to admit the child from ED, or the intensity of transmission and increased microbial load possibly associated with household crowding.[24,25] Overcrowding is a recognized

risk factor for pediatric ARI hospitalization in several settings.[26,27] While child numbers in the house was a determinant of hospitalization in our study, the total number of people living in the house and the number of people per bedroom were not. A US study[28] found having older siblings was associated with an increased risk of respiratory symptoms, ED visits and hospitalizations, although this contrasted with their previous study of wheeze and allergic rhinitis in a similar population.[29] Finally, a chance finding cannot be discounted given the large number of variables and analyses performed on our dataset.

Our study is the first to report predictors of persistent cough (>4-weeks as defined in the American and Australian pediatric chronic cough guidelines[30,31]) in children post-acute presentation that included comprehensive microbiologic data together with clinical and epidemiologic factors, and modeled for unknown cough status at day-28. Hence, our finding with respect to *M. catarrhalis* is novel. *M. catarrhalis* carriage in healthy children varies worldwide and estimates range from 20% to 80%, depending on geographic location, socio-economic status, age, and method of identification.[32–35] Hence, associating *M. catarrhalis* in the upper airways with respiratory disease is complex and its individual association with symptoms in ARI is not well studied. A Finnish study of 426 children with acute respiratory

symptoms found cough was positively associated with *M. catarrhalis* (OR 1.9, 95%CI 1.2, 3.2) as well as RSV (OR 7.2, 95%CI 1.6, 32.7) and parainfluenza viruses (OR 2.8, 95%CI 1.0, 7.7). [36] Nevertheless, caution is required in interpreting these findings as 86% of children with *M. catarrhalis* had respiratory virus co-detections. [36]

There are limited data on the role of *M. catarrhalis* in symptom persistence. A small study of 82 children[37] with ARI reported cough lasted significantly longer in children harboring *M. catarrhalis* in their anterior nares at study entry than those who were not, but the actual duration was unreported. *M. catarrhalis* in the nasopharynx was also associated with persistent cough >9-days in Swedish preschool children,[38] although respiratory viruses were not included in that study. Similarly, a double-blind randomized, placebo-controlled trial of amoxicillin-clavulanate in 52 children with cough >10-days[39] reported *M. catarrhalis* as the dominant nasopharyngeal organism (71% of children) and the group allocated antibiotics had significantly better treatment response than those receiving placebo. Recovery was also more rapid in an open label trial of erythromycin in 40 children with prolonged cough[40] that evaluated the nasopharyngeal prevalence of *M. catarrhalis* in the untreated group: 20% of those colonized recovered within 1-week compared to 75% of those who were not colonized ($P = 0.01$).

M. catarrhalis is commonly detected in the lower airways of children with chronic suppurative lung disease, including bronchiectasis,[41,42] and in those with protracted bacterial bronchitis.[43–45] However, as with ARI, its individual role in the pathogenesis of disease is unknown. Our data, the limited existing studies of *M. catarrhalis* and cough duration in children, and the increasing data on its prevalence in the lower airways of children with chronic lung disease suggest it may have an important role in chronic cough development in children, warranting further study. Importantly, data on whether the association between *M.catarrhalis* and chronic cough is related to its presence as a single pathogen or due to co-infection with other viruses and/or bacteria are not available. Our analyses controlled for co-infection, but evaluating the role of *M. catarrhalis* as a single pathogen was not feasible given it was found in isolation in only 4.4% of episodes.

We found enrolment in the spring months was associated with a lower risk of persistent cough, and this potentially reflects the seasonality of respiratory viruses and bacteria identified in the overall study on which this paper is based.[46] The data associated with the protective effect of oxygen supplementation in the ED are interesting, although not immediately plausible, and difficult to interpret given the small numbers of children involved. It might reflect the more aggressive and supervised management of severe acute disease received in hospital and subsequent reduced risk of adverse sequelae.

Children for whom cough status was unknown at day-28 were more likely to be enrolled during the autumn or spring months, have a longer duration of cough at presentation and be Bocavirus positive on nasal swab at enrolment. The seasonal findings are consistent with a reduced risk of cough at day-28 in those for whom the outcome was known, suggesting an illness with a more acute duration. This may also explain both the rate of loss to follow-up prior in the 2-weeks following ED presentation and the increased risk of cough status being unknown if the cough duration at ED presentation was greater than 14-days. Data from systematic reviews suggest only 10% of children attending primary care with a cough have this symptom 21-days later.[47] Hence, it is plausible that many children lost to follow-up had stopped coughing and parents chose not to continue in the study, particularly given the study incentive of providing children with rapid access (within 2-weeks of day 28) to a pediatric pulmonologist if persistent cough was present.[17] The association with Bocavirus and cough status being unknown is difficult to explain and may be either an anomaly of the data or related to milder illness given the severity of Bocavirus respiratory infections in children may be more dependent on viral load and/or co-detection.[48]

Our study is not without limitations. The microbiologic data are point prevalence only and do not account for carriage duration and/or infection prior to the acute illness, nor new infections in the 28-days post-presentation, while data from asymptomatic healthy controls are also lacking. The single-center study population may also not be representative of all children with cough presenting to EDs, particularly given our lower recruitment rates in young infants. Further, those whose parents consented to participate in the study may have had different characteristics and outcomes to those who did not, particularly children who were not approached in the ED given their critical illness or alternatively rapid assessment and discharge.

In summary, we evaluated the predictors of outcomes in children presenting to a pediatric ED with an ARI that included cough. Hospitalization was more likely in those from a crowded household, having decreased peripheral oxygen saturation, receiving supplemental oxygen and with RSV infection. In contrast, we found a possible role for *M. catarrhalis* in developing a persistent cough post-ARI. Our microbiological findings are likely to have little immediate application in the clinical setting, however they provide important epidemiological data to better understand the etiology of the development of chronic cough in children. Further studies collecting prospective clinical specimens in the weeks following an ARI are

warranted, particularly given the burden of chronic cough in children and its relationship with chronic lung disease.

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