Respiratory Viruses and Treatment Failure in Children With Asthma Exacerbation

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abstract

OBJECTIVES: Respiratory pathogens commonly trigger pediatric asthma exacerbations, but their impact on severity and treatment response remains unclear.

METHODS: We performed a secondary analysis of the Determinants of Oral Corticosteroid Responsiveness in Wheezing Asthmatic Youth (DOORWAY) study, a prospective cohort study of children (aged 1–17 years) presenting to the emergency department with moderate or severe exacerbations. Nasopharyngeal specimens were analyzed by RT-PCR for 27 respiratory pathogens. We investigated the association between pathogens and both exacerbation severity (assessed with the Pediatric Respiratory Assessment Measure) and treatment failure (hospital admission, emergency department stay >8 hours, or relapse) of a standardized severity-specific treatment. Logistic multivariate regressions were used to estimate average marginal effects (absolute risks and risk differences [RD]).

RESULTS: Of 958 participants, 61.7% were positive for ≥1 pathogen (rhinovirus was the most prevalent [29.4%]) and 16.9% experienced treatment failure. The presence of any pathogen was not associated with higher baseline severity but with a higher risk of treatment failure (20.7% vs 12.5%; RD = 8.2% [95% confidence interval: 3.3% to 13.1%]) compared to the absence of a pathogen. Nonrhinovirus pathogens were associated with an increased absolute risk (RD) of treatment failure by 13.1% (95% confidence interval: 6.4% to 19.8%), specifically, by 8.8% for respiratory syncytial virus, 24.9% for influenza, and 34.1% for parainfluenza.

CONCLUSIONS: Although respiratory pathogens were not associated with higher severity on presentation, they were associated with increased treatment failure risk, particularly in the presence of respiratory syncytial virus, influenza, and parainfluenza. This supports influenza prevention in asthmatic children, consideration of pathogen identification on presentation, and exploration of treatment intensification for infected patients at higher risk of treatment failure.

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WHAT'S KNOWN ON THIS SUBJECT: Viruses trigger the majority of asthma exacerbations in children; however, there is a lack of adequately powered high-quality studies that provide conclusive evidence on pathogen-specific determinants on clinical relevant outcomes of asthma exacerbation.

WHAT THIS STUDY ADDS: In children with moderate/severe exacerbations, viral detection is not associated with greater severity on presentation; however, the presence of specific pathogens, namely respiratory syncytial virus, influenza, and parainfluenza, identified children with worse outcomes and presenting with insufficient response to standardized corticosteroids and bronchodilator treatment.

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Exacerbations constitute the largest burden of disease in children with asthma, with 60% to 80% being triggered by respiratory pathogens.[1] The use of reverse transcriptase polymerase chain reaction (RT-PCR) has facilitated our understanding of the epidemiology of respiratory pathogens in this population,[2] with a growing interest in rhinovirus, the most frequently identified virus during exacerbations.[1] Some reports have suggested an association between rhinovirus C and severe asthma exacerbations and hospitalizations.[3,4] Recently, enterovirus D68 has also been reported in outbreaks of severe respiratory complications in children with asthma.[5] However, influenza's role in exacerbation severity and health care use remains controversial.[6] In addition, respiratory syncytial virus (RSV), parainfluenza virus (PIV), and other pathogens, including atypical bacteria (such as *Mycoplasma pneumoniae*), have been associated with exacerbations,[7] but only researchers of a limited number of studies have investigated the impact of specific pathogens on severity,[4] and none have primarily addressed treatment response.

Emergency department (ED) management with inhaled bronchodilators and systemic corticosteroids[8,9] for moderate or severe asthma exacerbations has been shown to reduce the risk of hospitalization.[10] Ducharme et al[11] investigated the determinants of treatment failure in children with moderate or severe exacerbations presenting to the ED in the Determinants of Oral Corticosteroid Responsiveness in Wheezing Asthmatic Youth (DOORWAY) study, the largest cohort of its kind. The detection of a respiratory virus was associated with treatment failure. However, pathogen-specific effects were not investigated. Quantifying the impact of specific respiratory pathogens may (1) guide infection prevention interventions in children with asthma, (2) focus efforts on pathogen diagnosis at ED presentation, and (3) identify children at higher risk of treatment failure in whom treatment intensification may be considered.

In children presenting to the ED with a moderate or severe asthma exacerbation, our aims were to ascertain the association between the presence of a laboratory-confirmed specific respiratory pathogen and both the baseline exacerbation severity and the risk of ED treatment failure.

METHODS

This study is an ancillary study in which we explore specific infectious etiologies of the DOORWAY primary objective[11] and is a multicenter prospective ethics-approved cohort study of children with moderate or severe asthma exacerbation presenting to 1 of 5 EDs of the Pediatric Emergency Research Canada network between 2011 and 2013. Briefly, the original study authors' objective was to identify determinants of ED management failure after standardized therapy. Children were eligible if they were 1 to 17 years of age, had a physician diagnosis of asthma based on a previous episode with airflow obstruction with response to asthma medication, ≥3 wheezing episodes (if <2 years of age),[12,13] or previous diagnostic lung function test results and a physician diagnosis of moderate or severe exacerbation using the validated 12-point pediatric respiratory asthma measure (PRAM) score[14] on ED presentation. An independent committee adjudicated cases with diagnostic uncertainty. Patients were excluded if there was suspicion of bronchiolitis or foreign body aspiration, another chronic respiratory disorder, or a contraindication to study medication treatment. All children received a standardized dose of oral corticosteroids (2 mg/kg [1 mg/kg in 1 site] of prednisone or prednisolone, or 0.3 mg/kg of dexamethasone) and bronchodilator treatment with salbutamol, and those with severe exacerbations additionally received ipratropium bromide. All eligible DOORWAY participants with a valid respiratory specimen were included in this study.

Exposure: Respiratory Specimen Testing

A nasopharyngeal aspirate or swab (flocked swab; Copan Diagnostics, Murrieta, CA) was systematically procured within 1 hour of study inclusion, placed in 3 mL of viral transport media (Universal Transport Medium; Copan Diagnostics), and frozen at −80°C. Adenovirus (B, C, and D), coronavirus (229E, HKU1, NL63, and OC43), enterovirus (A, B, C, and D), influenza (A and B), PIV (1, 2, 3, and 4), human metapneumovirus (hMPV) (A and B), RSV (A and B), and rhinovirus (A and B) were investigated by using a validated multiplex RT-PCR microarray hybridization assay.[15] Nucleic acids from respiratory specimens were also tested by using a commercial multiplex polymerase chain reaction (PCR) assay[16] to identify the atypical bacteria *M pneumoniae*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*.

All specimens that tested positive in the enterovirus and/or rhinovirus probe on the microarray assay[15] but were negative for type-specific enterovirus or rhinovirus (n = 302) and those that tested negative in the enterovirus or rhinovirus probe but were positive for 1 of the enterovirus– or rhinovirus type–specific probes (n = 20) were further tested by using RT-PCR and sequencing[17] in which we targeted the 5′ untranslated region of rhinovirus A, B, and C and some enteroviruses, including enterovirus

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D68 (GenBank accession numbers: MF978769 to MF979073). For samples with undetermined results by additional testing (n = 16), results from the original microarray analysis were used. Results were interpreted blinded to the clinical outcome. Exposure variables were as follows: specimens that tested positive for either a virus or atypical bacteria were coded as "pathogen-positive." Coinfection was defined as the presence of ≥2 pathogens compared to a single pathogen and no pathogen.

Outcome Measures

The PRAM score on presentation was used to determine the baseline exacerbation severity and was analyzed alternatively as a continuous variable and as a binary variable; a PRAM score of 4 to 7 indicated moderate exacerbation, and 8 to 12 indicated severe exacerbation.[14] ED management failure, which was also the primary composite outcome in the DOORWAY study,[11] was defined as hospital admission for asthma, treatment in the ED lasting 8 hours or more after corticosteroid administration, or return to the ED within 72 hours of discharge leading to hospital admission or prolonged ED stay.

Data Analysis

The prevalence of each respiratory pathogen was described by using frequency counts and proportions. Pathogens with <10 positive cases were aggregated. Covariates identified in the literature were explored as potential confounders, mediators, and interaction terms. A detailed description of covariates can be found in the primary study.[11] Briefly, covariates included in the models were age in years (continuous), sex, child atopy (based on parental report of a diagnosis or symptoms of allergic rhinitis and eczema as documented by the International Study of Asthma and Allergies in Childhood questionnaire),[18] asthma phenotype (intermittent or persistent), oral corticosteroid use in the preceding 12 months as a marker of morbidity, asthma control (measured with the 6-point Asthma Quiz for Kidz),[19] asthma controller use (daily, only when sick, or none), season (based on the calendar), upper respiratory tract infection (URTI) at index visit (clinical diagnosis), fever (at ED presentation), pneumonia (physician diagnosis based on clinical signs with chest radiograph), tobacco exposure (categorical variable based on saliva cotinine levels sampled after study inclusion), average family income quantile (based on postal code census data as a proxy for socioeconomic characteristics), and study site.

Potential interactions between exposures and atopy, allergic rhinitis, income, and the possible mediators (fever, pneumonia, and URTI) were assessed on the additive scale. Linear and logistic regressions were used to investigate the association with exacerbation severity by using the baseline PRAM as a continuous or dichotomous outcome, respectively, and logistic regression for association with treatment failure. This resulted in 1 model in which the exposure was any pathogen versus no pathogen, 1 model for rhinovirus-positive versus non–rhinovirus-positive versus pathogen-negative, 8 models for each specific pathogen exposure (rhinovirus A, B, and C; RSV; influenza; hMPV; PIV; and enterovirus D68 as the categorical variable versus "any other pathogen–positive" versus pathogen-negative) in which pathogen-negative was used as the reference, and 1 final model used to compare coinfection (>1 pathogen) versus single pathogen.

Results of regression models are presented as predicted probabilities of the outcome (absolute risks [ARs] and risk differences [RDs] with their 95% confidence intervals [CIs]) and represent the average marginal effect across the total study population.[20–22] Patients with missing data for variables included in these models were excluded from the analysis. Model fit was assessed with the area under the curve for logistic (and with R-squared for linear) regression. No correction for multiple testing was applied.[23] Analyses were performed by using Stata 13 (Stata Corp, College Station, TX) and R version 3.2.1 (www.r-project.org).

RESULTS

Of 1012 participants enrolled in the DOORWAY study, 958 children were included in our assessment of association with exacerbation severity, and 924 had ED treatment failure (Fig 1).

Distribution of Respiratory Pathogens: Patient and Exacerbation Characteristics

Of the 958 respiratory specimens tested, 591 (61.7%) were positive for ≥1 pathogen, with coinfection present in 81 specimens (8.5%); RSV and coronavirus were the most frequent copathogens (n = 13). The most prevalent pathogen was rhinovirus (n = 282; 29.4%), and rhinovirus C was the most frequent species (n = 174; 18.2%), followed by RSV (n = 171; 17.9%). *M pneumoniae* was identified in only 2 patients (Table 1).

Compared to those without, children with a laboratory-confirmed pathogen were younger (median [interquartile range (IQR)] age: 2 [1–5] vs 4 [2–7] years), had higher tobacco exposure (cotinine levels ≥4 ng/mL in 6.8% vs 3.8%), and were slightly more likely to present with fever (29.4% vs 24.2%). Compared to children who were not rhinovirus-positive, children with rhinovirus were less often febrile (16.2% vs 41.2%) and less frequently diagnosed with pneumonia (5.0% vs 15.9%; Table 2). The seasonal distribution of specific respiratory viruses differed markedly (Fig 2).

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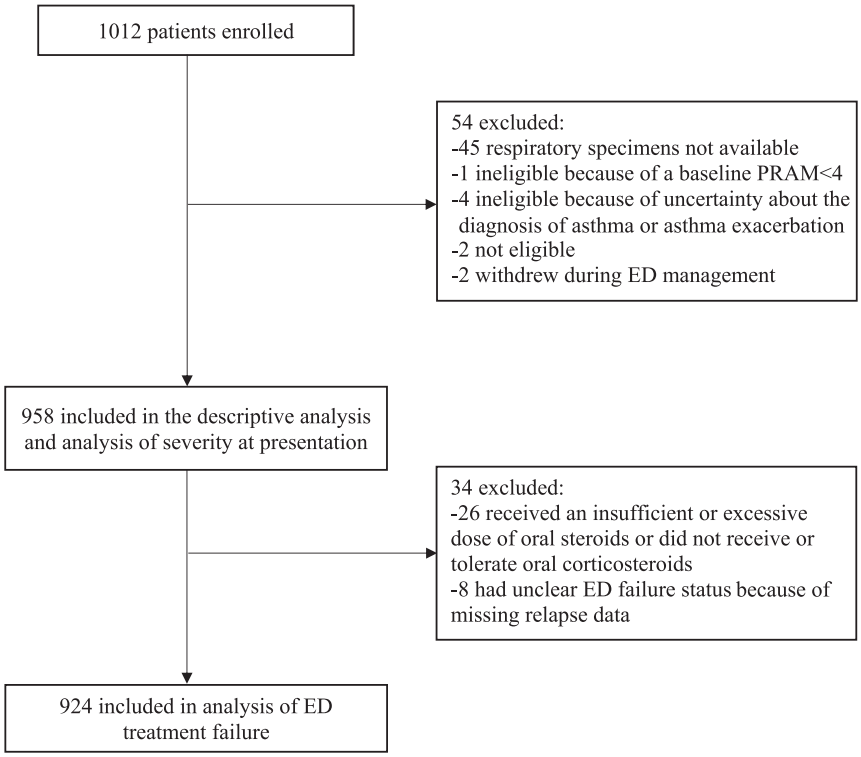

FIGURE 1
Flowchart of patient selection from the DOORWAY study.

Association Between Pathogen and Exacerbation Severity on Presentation

The proportion of children presenting with a severe exacerbation was 33.3% (95% CI: 30.3% to 36.3%). By using the initial triage PRAM score as a binary outcome (moderate versus severe exacerbation), no positive association was found between the presence of any pathogen and severe versus moderate exacerbation. The adjusted AR of a severe exacerbation was 32.4% (95% CI: 29.0% to 35.8%) in the presence of a pathogen and 38.3% (95% CI: 33.6% to 43.0%) in the absence of a pathogen, representing an RD of −5.8% (95% CI: −11.8 to 0.01; Fig 3A, Supplemental Table 3, Supplemental Fig 5). Although the risk of severe exacerbation in rhinovirus-positive children was similar to that in those with no pathogen, the presence of a nonrhinovirus pathogen was associated with a 12.9 percentage point–lower (95% CI: −19.5% to −6.3%) adjusted risk of severe exacerbation compared with no pathogen. The presence of hMPV and PIV were associated with a lower risk of severe asthma with adjusted RDs (95% CI) of −13.6% (−23.0% to −4.3%) and −31.7% (−44.5% to −18.9%), respectively. No statistically significant association was found between severity and RSV, influenza, enterovirus D68, adenovirus, and coronavirus (Fig 3B, Supplemental Table 3, Supplemental Fig 5). The pathogen-specific risk did not change when stratifying for coinfection. The association between exposure and severity was also investigated by using the PRAM score as a continuous outcome and repeating the exposure models; they confirmed the conclusion of all results using PRAM as a dichotomous outcome.

Association Between Pathogen and Treatment Failure

Overall, 156 of 924 participants (16.9%; 95% CI: 14.5% to 19.3%) experienced treatment failure. The presence of any respiratory pathogen (AR = 20.7%; 95% CI: 17.4% to 24.1%) compared to no pathogen (AR = 12.5%; 95% CI: 9.0% to 16.0%) was associated with an increased risk of treatment failure (RD = 8.2%; 95% CI: 3.3% to 13.1%; Fig 4A, Supplemental Table 3, Supplemental Fig 6). Although the presence of rhinovirus and its species was not associated with treatment failure, there was a higher risk of failure in children with a nonrhinovirus infection (AR = 25.4%; 95% CI: 19.8% to 31.0%) compared to those with no pathogen present, resulting in an adjusted RD of 13.1% (95% CI: 6.4% to 19.8%).

More specifically, RSV, influenza, and PIV were associated with a higher risk of treatment failure: 21.4% (95% CI: 14.1% to 28.7%), 37.5% (95% CI: 17.8% to 57.2%), and 46.7% (95% CI: 20.4% to 73.0%), respectively. This resulted in AR increases of 8.8% (95% CI: 0.4% to 17.2%), 24.9% (95% CI: 4.7% to 45.1%), and 34.1% (95% CI: 7.5% to 60.7%; Fig 4B), respectively. hMPV had an RD of 8.0% (95% CI: −1.6% to 17.6%). Coronavirus, adenovirus, enterovirus D68, and the presence of a coinfection were not associated with an increased risk of failure (Fig 4B, Supplemental Table 3, Supplemental Fig 6). Pathogen-specific risk did not change when stratifying for the presence of a coinfection.

DISCUSSION

In this large cohort, approximately two-thirds of children presenting to the ED with moderate or severe asthma exacerbation had a positive respiratory specimen result for 1 or more respiratory viruses or, rarely, atypical bacteria. No positive association was found between the presence of any pathogen and exacerbation severity on presentation. In fact, some viruses were associated with a significantly lower severity. Despite standardized

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TABLE 1 Results of Multiplex PCR Testing of Nasopharyngeal Aspirate Specimens

Respiratory Pathogen Identified	*N* = 958, *n* (%)
Respiratory pathogen[a]	591 (61.7)
Virus	590 (61.6)
Atypical bacteria[b]	2 (0.2)
No. pathogens[c]	
0	367 (38.3)
1	510 (53.3)
2	68 (7.1)
3	13 (1.4)
Specific pathogens	
Rhinovirus (any)	282 (29.4)
A	97 (10.1)
B	11 (1.2)
C	174 (18.2)
Enterovirus (any)	31 (3.2)
A	1 (0.1)
B	2 (0.2)
C	3 (0.3)
D68	25 (2.6)
Nontyped enterovirus and/or rhinovirus	14 (1.5)
Other (nonenterovirus or rhinovirus)	
RSV (any)	171 (17.9)
A	126 (13.2)
B	46 (4.8)
hMPV (any)	96 (10.0)
A	46 (4.8)
B	53 (5.5)
Influenza virus (any)	24 (2.5)
A	17 (1.8)
B	7 (0.7)
Adenovirus (any)	12 (1.3)
A	2 (0.2)
B	0 (0)
C	10 (1.0)
E	0 (0)
PIV (any)	14 (1.5)
1	0
2	0
3	10 (1.0)
4	4 (0.4)
Coronavirus (any)	33 (3.4)
OC43	16 (1.7)
HKU1	6 (0.6)
229E	3 (0.3)
NL63	10 (1.0)

[a] Viral pathogen or atypical bacteria.
[b] Total of 952 specimens.
[c] Viral and atypical bacteria.

therapy with corticosteroids and severity-specific inhaled bronchodilators, the presence of any respiratory pathogen (and more specifically, of a nonrhinovirus pathogen) was associated with more treatment failure compared with noninfected counterparts. Severity on presentation and response to treatment thus appear as 2 distinct dimensions of the impact of viral infections in children with acute asthma.

The high prevalence of rhinovirus C in children presenting with asthma exacerbation, its presumed association with asthma-related hospitalization, and its peak in the fall have brought this virus to the forefront as a potential cause for more severe disease.[4] We confirmed its high prevalence but were unable to confirm an increased severity or greater treatment failure in rhinovirus- or rhinovirus C–infected children. Perhaps rhinovirus plays a role in the initiation of exacerbations that are severe enough to warrant health care contact, but once infected, response to treatment appears favorable. This is in line with a subgroup analysis of a randomized controlled trial of children treated with corticosteroids in which those with rhinovirus responded better to steroid treatment than those who tested negative for entero/rhinovirus.[24]

In contrast, the presence of nonrhinovirus pathogens as a group, and particularly hMPV and PIV, was associated with a larger proportion of children presenting with a moderate, rather than severe, exacerbation; however, nonrhinovirus pathogens were significantly linked to higher treatment failure, particularly with RSV, influenza, and PIV, even after adjustment for patient and exacerbation characteristics. Indeed, in this group of children aged at least 1 year in whom bronchiolitis was specifically excluded, we observed a significant association between RSV and increased treatment failure by an absolute 8%. This observation is in line with a small study in which researchers documented a lower response to steroids in children with asthma who were infected with RSV compared to those who were not infected.[25] It is also congruent with substantive literature on the lack of response to corticosteroids and bronchodilators in children with RSV bronchiolitis,[26,27] which raises the possibility that RSV per se confers treatment resistance irrespective of disease and not only in infants aged <1 year with wheezing.[28] The third most frequent organism, hMPV, was associated with a risk of treatment failure similar to that of RSV, but its RD

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TABLE 2 Baseline Patient Characteristics

Variable	Total Patients (n = 958),[a] N (%)	Respiratory Pathogen–Positive (n = 591),[b] N (%)	Respiratory Pathogen–Negative (n = 367), N (%)	Rhinovirus-Positive (n = 282)				Non–Rhinovirus-Positive (n = 309)						Coinfection	
				Total, N (%)	Rhinovirus A (n = 97), N (%)	Rhinovirus B (n = 11), N (%)	Rhinovirus C (n = 174), N (%)	Total, N (%)	Enterovirus D68 (n = 25), N (%)	RSV (n = 171), N (%)	hMPV (n = 96), N (%)	Influenza (n = 24), N (%)	PIV (n = 14), N (%)	Single Pathogen (n = 510), N (%)	Coinfection (n = 81), N (%)
Age (n = 957; 0.1% missing)															
Median (IQR)	3 (2–6)	2 (1–5)	4 (2–7)	3 (1–5)	3 (2–5)	8 (2–12)	2 (1–5)	2 (1–4)	3 (1–5)	2 (1–3)	2.5 (1–5)	3.5 (2–7)	2 (1–2)	2 (1–5)	2 (1–4)
Male sex	635 (66.3)	393 (66.5)	242 (65.9)	197 (69.9)	73 (75.3)	5 (45.5)	119 (68.4)	196 (63.4)	15 (60)	111 (64.91)	61 (63.5)	14 (58.3)	9 (64.3)	331 (64.9)	62 (76.54)
Risk factors for exacerbation															
Atopy	666/957 (69.6) (0.1% missing)	413 (69.9)	253 (69.1)	189 (67.0)	64 (66.0)	7 (63.6)	118 (67.8)	224 (72.5)	19 (76.0)	123 (71.9)	68 (70.8)	13 (54.2)	9 (64.3)	366 (71.8)	47 (58.0)
Tobacco exposure	(0.3% missing)														
Cotinine level ≥4 ng/mL	54/955 (5.7)	40 (6.8)	14 (3.8)	20 (7.1)	4 (4.2)	1 (9.1)	15 (8.7)	20 (6.5)	0 (0)	18 (10.53)	4 (4.2)	2 (8.3)	0 (0)	35 (6.9)	5 (6.2)
Cotinine level 1–4 ng/mL	252/955 (26.4)	156 (26.5)	96 (26.2)	67 (23.9)	29 (30.2)	1 (9.1)	37 (21.4)	89 (28.9)	8 (33.3)	38 (22.22)	27 (28.1)	9 (37.5)	2 (14.3)	137 (27.0)	19 (23.5)
Cotinine level <1 ng/mL per d	649/955 (68.0)	392 (66.7)	257 (70.0)	193 (68.9)	63 (65.6)	9 (81.8)	121 (69.9)	199 (64.6)	16 (66.7)	115 (67.25)	65 (67.7)	13 (54.2)	12 (85.7)	335 (66)	57 (70.4)
Asthma phenotype (n = 957; 0.1% missing)															
Intermittent asthma	731 (76.4)	450 (76.4)	281 (76.8)	221 (78.14)	71 (73.2)	7 (63.6)	143 (82.2)	229 (74.1)	19 (76.0)	130 (76.0)	69 (71.9)	18 (75.0)	10 (71.4)	393 (77.1)	57 (70.4)
Persistent asthma	226 (23.6)	141 (23.9)	85 (23.2)	61 (21.6)	26 (26.8)	4 (36.4)	31 (17.8)	80 (25.9)	6 (24.0)	41 (24.0)	27 (28.1)	6 (25.0)	4 (28.6)	117 (22.9)	24 (29.6)
Morbidity before enrollment															
Patients with ≥1 course of oral corticosteroids in previous y	475/952 (46.9) (0.6% missing)	275 (46.9)	192 (52.6)	140 (49.7)	49 (50.5)	3 (27.3)	88 (50.6)	135 (44.3)	9 (36.0)	73 (43.2)	41 (43.1)	9 (37.5)	10 (71.4)	243 (48.0)	32 (39.5)
Patient with ≥1 hospital admission in previous y	146/957 (15.3) (0.1% missing)	96 (16.2)	50 (13.7)	48 (17.0)	16 (16.5)	0 (0)	32 (18.4)	48 (15.5)	4 (16.0)	24 (14.04)	8 (8.3)	5 (20.8)	4 (28.6)	87 (17.1)	9 (11.1)
Asthma quiz for kids score, median (IQR)	3 (2–4) (n = 938, 2.1% missing)	3 (2–4)	3 (2–4.5)	3 (2–4)	4 (2–5)	3 (2–5)	3 (1–4)	4 (2–5)	3 (1.5–3.5)	4 (2–4)	4 (3–5)	4 (2–5)	4 (2–5)	3 (2–5)	3.5 (2–4)
Prescribed asthma controller															
None	403 (42.1)	254 (43.0)	149 (40.6)	122 (43.7)	40 (41.2)	6 (54.6)	76 (43.7)	132 (40.6)	14 (56.0)	85 (49.7)	36 (37.5)	8 (33.3)	4 (28.6)	215 (42.2)	39 (48.1)
Daily maintenance	279 (29.1)	175 (29.6)	104 (28.3)	84 (29.8)	29 (30.0)	0 (0)	55 (31.6)	91 (29.5)	5 (20.0)	44 (25.7)	30 (31.3)	11 (45.8)	6 (42.9)	151 (29.6)	24 (29.6)
Episodic intake (when sick)	276 (28.8)	162 (27.4)	114 (31.1)	76 (27.0)	28 (28.9)	5 (45.5)	43 (24.7)	86 (27.8)	6 (24.0)	42 (24.6)	30 (31.3)	5 (20.8)	4 (28.6)	144 (28.2)	18 (22.2)
Season															
Spring	225 (23.5)	128 (21.7)	97 (26.4)	79 (28.0)	47 (48.5)	1 (9.1)	31 (17.8)	49 (15.9)	0 (0)	25 (14.6)	23 (24.0)	5 (20.8)	3 (21.4)	108 (21.2)	20 (24.7)
Summer	85 (8.9)	61 (10.3)	24 (6.5)	39 (13.8)	12 (12.4)	1 (9.1)	26 (14.9)	22 (7.1)	8 (32.0)	11 (6.4)	13 (5)	0 (0)	1 (7.1)	50 (9.8)	11 (13.6)
Fall	369 (38.5)	201 (34.0)	168 (45.8)	124 (44.0)	28 (28.9)	9 (81.8)	87 (50.0)	77 (24.9)	17 (68.0)	33 (19.3)	18 (18.8)	3 (12.5)	5 (35.7)	186 (36.5)	15 (18.5)
Winter	279 (29.1)	201 (34.0)	78 (21.3)	40 (14.2)	10 (10.31)	0 (0)	30 (17.2)	161 (52.1)	0 (0)	102 (59.7)	42 (43.8)	16 (66.7)	5 (35.7)	166 (32.6)	35 (43.2)
Symptoms of infection															
Fever present	260/949 (27.4) (0.9% missing)	172 (29.4)	88 (24.2)	45 (16.2)	15 (15.6)	1 (9.1)	29 (17.0)	127 (41.2)	4 (16.7)	76 (44.7)	41 (43.1)	13 (54.2)	1 (7.1)	141 (27.9)	31 (38.8)

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TABLE 2 Continued

Variable	Total Patients (n = 958),[a] N (%)	Respiratory Pathogen–Positive (n = 591),[b] N (%)	Respiratory Pathogen–Negative (n = 367), N (%)	Rhinovirus-Positive (n = 282)					Non–Rhinovirus-Positive (n = 309)						Coinfection	
				Total, N (%)	Rhinovirus A (n = 97), N (%)	Rhinovirus B (n = 11), N (%)	Rhinovirus C (n = 174), N (%)	Total, N (%)	Enterovirus D68 (n = 25), N (%)	RSV (n = 171), N (%)	hMPV (n = 96), N (%)	Influenza (n = 24), N (%)	PIV (n = 14), N (%)	Single Pathogen (n = 510), N (%)	Coinfection (n = 81), N (%)
Pneumonia	87/957 (9.1) (0.1% missing)	63 (10.7)	24 (6.5)	14 (5.0)	3 (3.1)	2 (18.2)	9 (5.2)	49 (15.9)	2 (8.0)	33 (19.3)	16 (16.7)	3 (12.5)	0 (0)	53 (10.4)	10 (12.4)
URTI symptoms	178/957 (18.6) (0.1% missing)	116 (19.7)	62 (16.9)	61 (21.7)	19 (19.8)	3 (27.3)	39 (22.4)	55 (17.8)	3 (12.0)	35 (20.5)	15 (15.6)	5 (20.8)	5 (35.7)	102 (20.0)	14 (17.3)
Study site															
1	281 (29.3)	182 (30.8)	99 (27.0)	104 (36.9	32 (32.9)	1 (9.1)	71 (40.8)	78 (25.2)	9 (36.0)	45 (26.3)	17 (17.7)	7 (29.2)	3 (21.4)	162 (31.8)	20 (24.7)
2	174 (18.2)	77 (13.0)	97 (26.4)	41 (14.5)	8 (8.3)	1 (9.1)	32 (18.4)	36 (11.7)	3 (12.0)	16 (9.4)	7 (7.3)	3 (12.5)	3 (21.4)	74 (14.5)	3 (3.7)
3	77 (8.0)	41 (6.9)	36 (9.8)	21 (7.5)	9 (9.3)	3 (27.3)	9 (5.2)	20 (6.5)	2 (8.0)	11 (6.4)	6 (6.3)	0 (0)	0 (0)	38 (7.5)	3 (3.7)
4	426 (44.5)	291 (49.2)	135 (36.8)	116 (41.1)	48 (49.5)	6 (54.6)	62 (35.6)	175 (56.6)	11 (44.0)	99 (57.9)	66 (68.8)	14 (58.3)	8 (57.1)	236 (46.3)	55 (67.9)
PRAM score on presentation															
PRAM score 4–8 (moderate)	639 (66.7)	387 (65.5)	252 (68.7)	178 (63.1)	53 (54.6)	7 (63.6)	118 (67.8)	209 (67.6)	16 (64.0)	108 (63.2)	64 (66.7)	14 (58.3)	13 (92.9)	339 (66.5)	48 (59.3)
PRAM score 8–12 (severe)	319 (33.3)	204 (34.5)	115 (31.3)	104 (36.9)	44 (45.4)	4 (36.4)	56 (32.2)	100 (32.4)	9 (36.0)	63 (36.8)	32 (33.3)	10 (41.7)	1 (7.1)	171 (33.5)	33 (40.7)

Shown are overall and by pathogen.
[a] Unless otherwise stated.
[b] Positive for at least 1 of the RT-PCR–investigated viral pathogens or *M pneumoniae*–positive.

did not reach statistical significance. Although involved in recent outbreaks of severe respiratory infections,[5] enterovirus D68 was not associated with more severe exacerbations or excess treatment failure in our cohort perhaps because of differences in subtypes related to the more recent outbreaks. Although previously associated with severe infection and lower respiratory tract symptoms in patients with asthma,[29] our few cases of PIV 3 specifically and PIV in general were insufficient to firmly conclude on the effect on severity. Finally, the few children who tested positive for influenza or PIV (n = 24 and n =14, respectively) had a striking ≥20% AR of treatment failure than pathogen-negative patients. Although this may explain the reported excess hospitalizations for cardiopulmonary disease in children with asthma that is associated with influenza,[30] asthma was not identified as a risk factor for influenza-related hospitalization in a large meta-analysis.[6] Nevertheless, response to therapy is significantly reduced with RSV, influenza, and PIV.

Only a limited number of patients were found positive for atypical bacteria, compared to previous studies.[7] The use of nasopharyngeal or nasal swabs instead of throat swabs might have accounted for the lower sensitivity of our tests.[31] Moreover, there was no association between coinfection and less favorable outcomes perhaps because the species is more important than the number of pathogens.

What are the implications of these findings? Perhaps treatment intensification with inhaled anticholinergics or magnesium sulfate, both of which reduce acetylcholine release at the myoneural junction, could block the vagal-mediated reflex bronchoconstriction observed in viral-induced exacerbation.[32] These therapies that are currently reserved for severe exacerbations may be tested for their efficacy in exacerbations of any severity triggered

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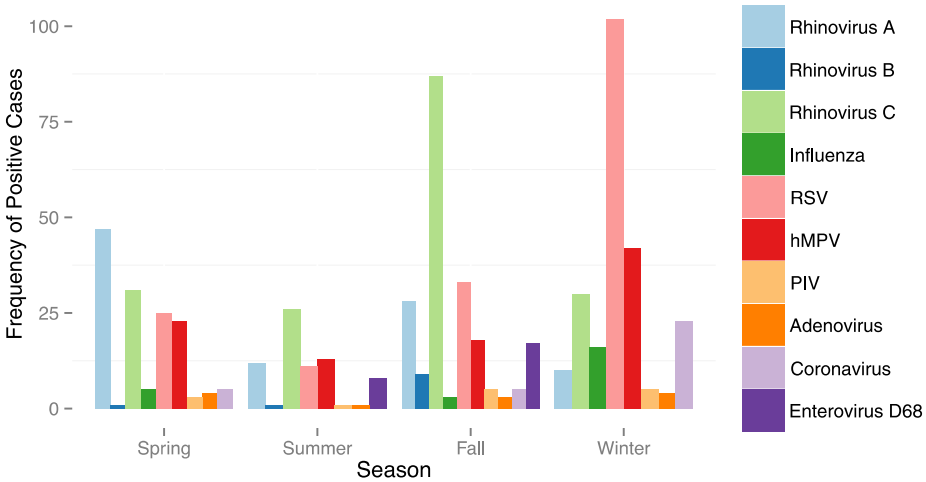

FIGURE 2
Seasonal distribution of all 25 respiratory viruses identified in 958 specimens, representing species for rhinovirus (A, B, and C) and enterovirus (D68) and aggregated groups for the remainder (a total of 10 exposures); 80 specimens were positive for >1 respiratory virus.

by RSV, influenza, and PIV, which have been associated with poor treatment response. Although the mechanism of action remains to be clarified, azithromycin,[33] which has been shown effective in preschoolers with previously severe exacerbations, could be explored as an alternative pathogen-nonspecific therapy to target antineutrophilic inflammation. Clearly, any pathogen-specific antiviral and/or treatment intensification first requires an identification of pathogens associated with each exacerbation; this would imply real-time diagnostic test in the ED by using RT-PCR or a wider introduction of point-of-care testing. Until then, preventive measures should be prioritized. This is particularly important in light of the growing knowledge that early-life RSV and rhinovirus infections are also associated with an increased risk of inception of asthma[34] and, for the former, poorer ED treatment response. Children with asthma should remain a priority group for influenza immunization because of the newly established association between influenza and ED management failure combined with well-recognized influenza-related complications. Although this recommendation has been challenged by a 2013 Cochrane review, in which researchers failed to find clear evidence that immunization reduced the occurrence and severity of influenza-associated asthma, Cates et al[35] underlined the paucity of efficacy trials contributing data to their meta-analysis. Given the documented safety of influenza immunization in children with asthma and its expected protective effect, it appears reasonable to pursue strategies to improve immunization coverage for influenza and invest in efforts for the development of vaccines for RSV and rhinovirus.

We acknowledge the following limitations. Although our study is the largest cohort of its kind, with a richness of data that made it possible to adjust for important patient characteristics, children presenting with a mild exacerbation were excluded, thus limiting our ability to identify a potential differential impact of pathogens on the full range of asthma exacerbation severity. Although we tested for

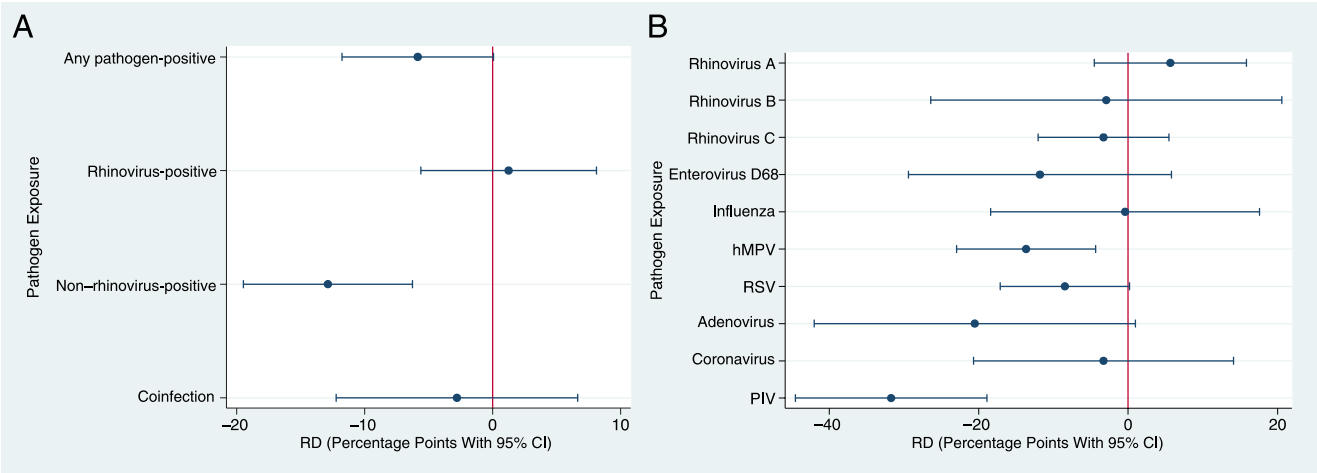

FIGURE 3
Association between respiratory pathogens and the severity of exacerbation at presentation. Average marginal effects are presented with adjusted RDs of severe exacerbation from multivariate logistic regressions. The reference used for RDs was the pathogen-negative category for each given model except for coinfection, for which the reference used was pathogen-positive for a single pathogen. A, Average RDs of severe exacerbation by pathogen. B, Average RDs of severe exacerbation by pathogen.

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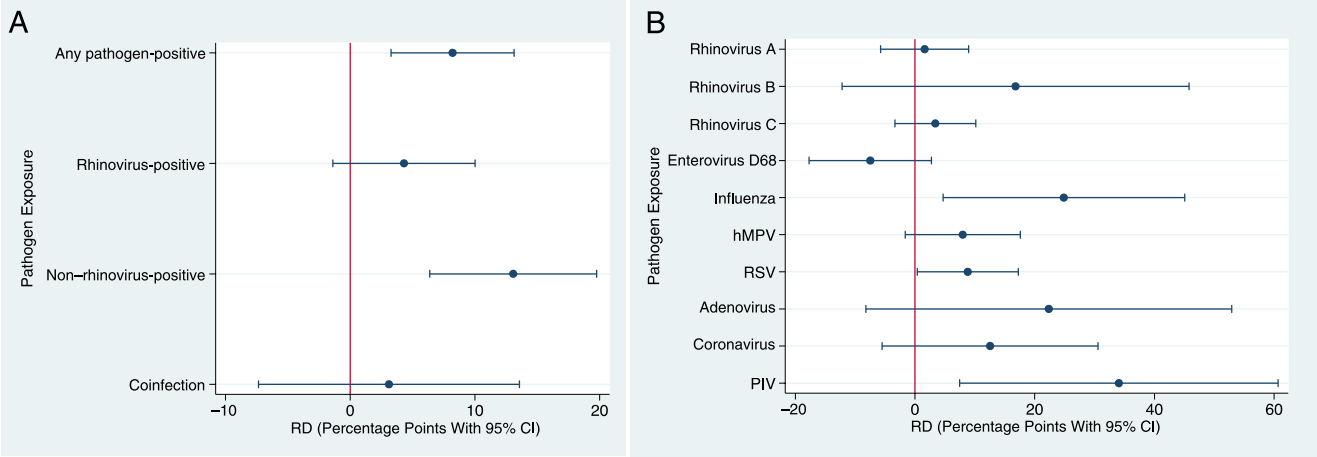

FIGURE 4

Association between respiratory pathogens and ED treatment failure. Average marginal effects are presented with adjusted RDs of ED treatment failure from multivariate logistic regressions. [a] The reference used for RDs was the pathogen-negative category for each given model except for coinfection, for which the reference used was "pathogen-positive for a single pathogen." Rhinovirus-positive and non–rhinovirus-positive test for interaction had a *P* value result of .0499. A, Average RDs of failure of ED treatment by pathogen. B, Average RDs of failure of ED treatment by specific pathogen.

27 respiratory (including new) pathogens, microorganisms identified by PCR could have included both nonreplicating viruses and colonizing microorganisms. Thus, we cannot rule out that some episodes may not have been triggered by the identified respiratory pathogen. Such misclassification may lead to some inaccuracies; however, it should be nondifferential and would have biased our results toward the null. Yet, because most parents reported that the index episode was triggered by a URTI, it is more likely than not that the identified microorganism was associated with symptoms. Because atopy was assessed by parental report and their recall of allergy testing, with no systematic testing with serum-specific immunoglobulin E or allergy testing, our ability to investigate the interaction between pathogen and atopy as observed in some studies[36] was suboptimal. Moreover, recent exposure to allergens[37] was not documented. Finally, the use of anticholinergics was severity-specific, and because it differed between children with moderate and severe exacerbations, it may have interacted with some viruses to improve treatment response and reduce our ability to identify poor responders.

CONCLUSIONS

In children presenting to the ED with a moderate or severe asthma exacerbation, no virus, including the most prevalent organism (rhinovirus C), was associated with higher exacerbation severity. In fact, nonrhinovirus pathogens were associated with less severe exacerbations but with more ED treatment failure; RSV, influenza, and PIV increased by 8% to 34% the AR of treatment failure. Interventions for RSV prevention and influenza immunization thus need to be revisited. The efficacy of both pathogen-specific and nonspecific therapies should be further explored to decrease the risk of treatment failure in children with acute asthma by using advanced and rapid pathogen identification in the ED to enable their implementation.

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ABBREVIATIONS

AR: absolute risk
CI: confidence interval
DOORWAY: Determinants of Oral Corticosteroid Responsiveness in Wheezing Asthmatic Youth
ED: emergency department
hMPV: human metapneumovirus
IQR: interquartile range
PCR: polymerase chain reaction
PIV: parainfluenza virus
PRAM: pediatric respiratory asthma measure
RD: risk difference
RSV: respiratory syncytial virus
RT-PCR: reverse transcriptase polymerase chain reaction
URTI: upper respiratory tract infection

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Dr Merckx conceptualized the data analysis, conducted the analysis and presentation of results, and wrote the manuscript; Dr Ducharme provided the primary study data, protocol, and statistical analysis from the primary study, provided feedback on the analysis protocol, interpretation of results, and feedback on manuscript revisions, and revised the final version; Dr Quach led the laboratory analysis of the respiratory specimens, supervised the data analysis plan, statistical analysis, and manuscript writing, provided feedback on the interpretation of results and manuscript revisions and funding for the substudy, and revised the final version; Drs Martineau, Zemek, Gravel, Chalut, and Poonai provided feedback on manuscript revisions and revised the final version; and all authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02013076).

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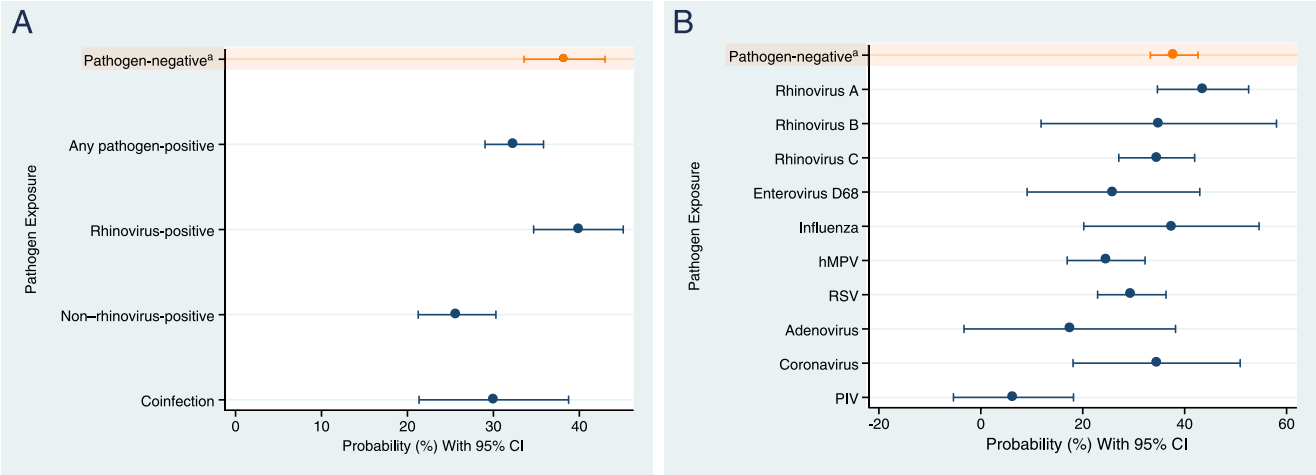
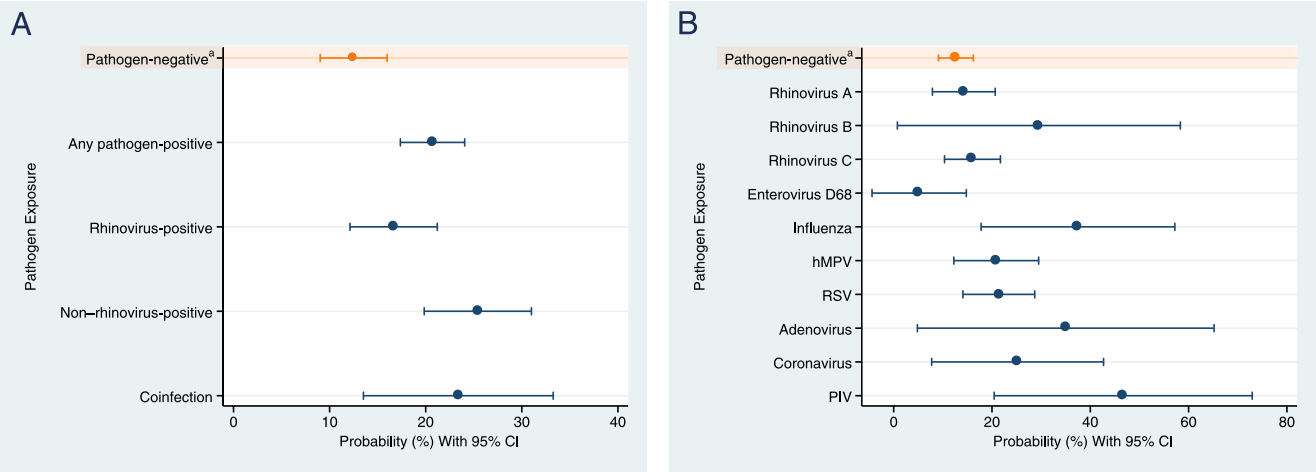


SUPPLEMENTAL FIGURE 5
Association between respiratory pathogens and the severity of exacerbation at presentation. Average marginal effects are presented with adjusted ARs of severe exacerbation from multivariate logistic regressions. [a] The reference used for RDs was the pathogen-negative category for each given model except for coinfection, for which the reference used was pathogen-positive for a single pathogen. A, ARs of severe exacerbation by pathogen. B, ARs of severe exacerbation by specific pathogen.



SUPPLEMENTAL FIGURE 6
Association between respiratory pathogens and ED treatment failure. Average marginal effects are presented with adjusted ARs of ED treatment failure from multivariate logistic regressions. [a] The reference used for RDs was the pathogen-negative category for each given model except for coinfection, for which the reference used was "pathogen-positive for a single pathogen." A, ARs of failure of ED treatment by pathogen. B, ARs of failure of ED treatment by specific pathogen.

SUPPLEMENTAL TABLE 3 Adjusted ARs and RDs of Severe Exacerbation and Treatment Failure

Exposure	Exacerbation Severity			ED Treatment Failure		
	No. Patients Included	AR % (95% CI)	RD % (95% CI)	No. Patients Included	AR % (95% CI)	RD % (95% CI)
Total population (crude)	958	33.3 (30.3 to 36.3)	—	924	16.9 (14.5 to 19.3)	—
Respiratory pathogen in general[a]						
Pathogen-negative	840	38.3 (33.6 to 43.0)	Reference	803	12.5 (9.0 to 16.0)	Reference
Pathogen-positive	840	32.4 (29.0 to 35.8)	−5.8 (−11.8 to 0.01)	803	20.7 (17.4 to 24.1)	8.2 (3.3 to 13.1)
Rhinovirus-positive versus non–Rhinovirus-positive versus pathogen-negative[b]						
Pathogen-negative	840	38.6 (34.1 to 43.2)	Reference	803	12.4 (8.9 to 15.8)	Reference
Non–Rhinovirus-positive	840	25.8 (21.3 to 30.3)	−12.9 (−19.5 to −6.3)	803	25.4 (19.8 to 31.0)	13.1 (6.4 to 19.8)
Rhinovirus-positive	840	39.9 (34.7 to 45.1)	1.3 (−5.6 to 8.1)	803	16.7 (12.1 to 21.2)	4.3 (−1.4 to 10.0)
Pathogen specific[c]						
Pathogen-negative	840	37.9 (33.3 to 42.6)	Reference	808	12.7 (9.1 to 16.2)	Reference
Rhinovirus A	840	43.6 (34.6 to 52.6)	5.7 (−4.5 to 15.8)	808	14.3 (7.9 to 20.7)	1.6 (−5.7 to 9.0)
Rhinovirus B	840	34.9 (11.8 to 58.0)	−2.9 (−26.4 to 20.6)	808	29.5 (0.7 to 58.3)	16.8 (−12.2 to 45.8)
Rhinovirus C	834	34.5 (27.1 to 42.0)	−3.3 (−12.0 to 5.5)	808	16.0 (10.3 to 21.7)	3.4 (−3.4 to 10.1)
Enterovirus D68	840	26.0 (9.1 to 43.0)	−11.8 (−29.4 to 5.8)	808	5.2 (−4.4 to 14.8)	−7.5 (−17.7 to 2.8)
Influenza	840	37.4 (20.2 to 54.6)	−0.4 (−18.4 to 17.6)	808	37.5 (17.8 to 57.2)	24.9 (4.7 to 45.1)
hMPV	840	24.6 (16.9 to 32.2)	−13.6 (−23.0 to −4.3)	808	20.9 (12.2 to 29.5)	8.0 (−1.6 to 17.6)
RSV	840	29.6 (22.9 to 36.3)	−8.5 (−17.1 to 0.2)	803	21.4 (14.1 to 28.7)	8.8 (0.4 to 17.2)
Adenovirus	840	17.5 (−3.3 to 38.2)	−20.5 (−42.0 to 1.0)	808	35.0 (4.8 to 65.2)	22.4 (−8.2 to 52.9)
Coronavirus	840	34.5 (18.1 to 50.9)	−3.3 (−20.7 to 14.1)	808	25.2 (7.7 to 42.7)	12.5 (−5.5 to 30.6)
PIV	840	6.4 (−5.3 to 18.2)	−31.7 (−44.5 to −18.9)	808	46.7 (20.4 to 73.0)	34.1 (7.5 to 60.7)
Coinfection[d]						
Single pathogen–positive	840	32.8 (29.1 to 36.6)	Reference	803	20.3 (16.7 to 23.8)	Reference
Coinfection	840	30.0 (21.3 to 38.7)	−2.8 (−12.2 to 6.7)	803	23.4 (13.5 to 33.3)	3.1 (−7.4 to 13.6)

—, not applicable.

[a] Presence of a viral pathogen or *M pneumoniae*; model for severity: interaction of exposure with asthma phenotype and income group, adjusted for age, sex, atopy, previous steroid use, asthma control, control medication, season, tobacco exposure, and site; model for treatment failure: interaction of exposure with fever, adjusted for age, sex, PRAM score, asthma phenotype, previous steroid use, asthma control, control medication, season, tobacco exposure, atopy, income group, and site.

[b] Model for severity: adjusted for age, sex, asthma phenotype, previous steroid use, asthma control, control medication, season, tobacco exposure, atopy, income group, and site; model for treatment failure: interaction exposure with fever, adjusted for age, sex, asthma phenotype, PRAM score, previous steroid use, asthma control, control medication, season, tobacco exposure, atopy, income group, and site.

[c] Separate models for specific pathogen exposure; reference from the rhinovirus A model is presented; model for severity: interaction of rhinovirus C with fever, adjusted for coinfection, age, sex, asthma phenotype, previous steroid use, asthma control, control medication, season, tobacco exposure, atopy, income group, and site; model for treatment failure: interaction of influenza with asthma phenotype, interaction of hMPV with atopy and with asthma phenotype, and interaction of RSV with fever; adjusted for age, sex, PRAM score, previous steroid use, asthma control, control medication, season, tobacco exposure, income group, and site.

[d] AR in the presence of ≥2 pathogens and RD comparing the presence of ≥2 pathogens to a single pathogen; model for severity adjusted for age, sex, atopy, asthma phenotype, previous steroid use, asthma control, control medication, season, tobacco exposure, income group, and site; model for treatment failure: interaction of coinfection with fever, adjusted for age, sex, PRAM score, asthma phenotype, previous steroid use, asthma control, control medication, season, tobacco exposure, atopy, income group, and site.