

ORIGINAL ARTICLE

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Distinction between rhinovirus-induced acute asthma and asthma-augmented influenza infection

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Summary

Background: Rhinovirus (RV) is an established trigger of asthma attacks, whereas such a link is less consistent for influenza virus (IFV).

Objective: In the context of precision medicine, we hypothesized that IFV infection may cause a condition essentially different from RV, and we investigated this by evaluating clinical characteristics of RV/IFV-positive and -negative children with respiratory symptoms and/or fever.

Methods: One thousand two hundred and seven children, 6 months to 13 years old, hospitalized for flu-like illness were recruited in this cross-sectional study. Collected information included demographics, medical history, symptoms/physical findings/diagnosis at presentation and treatment. Nasal secretions were PCR-tested for IFV/RV. Associations were evaluated with adjusted logistic regression models.

Results: Rhinovirus positivity was associated with an asthma-like presentation, including increased wheeze/effort of breathing/diagnosis of acute asthma, and decreased fever/vomiting. Conversely, IFV⁺ children presented with less wheeze/effort of breathing/diagnosis of acute asthma, while they were more frequently febrile. In those with previous asthma history, both viruses induced wheeze; however, IFV was uniquely associated with a more generalised and severe presentation including fever, rales, intercostal muscle retractions and lymphadenopathy. These symptoms were not seen in RV⁺ asthmatics, who had fewer systemic signs and more cough.

Conclusions and Clinical relevance: In children with respiratory symptoms and/or fever, RV but not IFV is associated with wheeze and an asthma-like presentation. In those with an asthma history, IFV causes more generalised and severe disease that may be better described as “asthma-augmented influenza” rather than an “asthma attack.” Differences in the acute conditions caused by these viruses should be considered in the design of epidemiological studies.

KEYWORDS

asthma, asthma exacerbation, asthma-augmented influenza, common cold, virus

1 | INTRODUCTION

It is well documented that viral infections trigger at least 85% of asthma attacks in children and 40%–80% in adults,¹ with rhinovirus

(RV) being the most commonly identified agent.^{2–4} However, it is not clear whether this reflects the high frequency of RV infections or particular pathophysiological characteristics of the virus. Furthermore, the role of other respiratory viruses in asthma attacks is not

as well documented.⁴⁻⁶ Influenza (IFV) is one of the most common respiratory pathogens⁷ and is associated with considerable morbidity and severe outcomes in patients with asthma.⁸⁻¹¹

In this context, key questions arise as follows: Does each respiratory virus have a unique asthma-inciting capacity? Is the acute illness caused by IFV in asthmatics the same as that caused by RV? In the context of precision medicine, these questions inevitably lead to the hypothesis that RV and IFV may cause different pathophysiological and clinical conditions in predisposed individuals, not adequately described under the general terms “asthma exacerbation” or “asthma attack.” Investigating this could also ascertain whether RV is linked to asthma due to unique inherent characteristics (eg its potential for a Th₂-biased response^{12,13}) or because of its high prevalence. Finally, it could also help to establish whether the increased morbidity caused by IFV infection in asthmatics is due to asthma worsening, or to a more severe presentation of the IFV infection.¹⁴

In this context, we hypothesised that the clinical presentations of RV and IFV infections have different characteristics in relation to asthma, and opted to test this hypothesis in a population of children hospitalised for flu-like illness.¹⁵

2 | METHODS

2.1 | Study design and population

We used the data set from an IFV surveillance study conducted prospectively during 2 years and described in detail elsewhere.¹⁵ Briefly, children were recruited at the 2nd Paediatric Clinic of the University of Athens, at the “P. & A. Kyriakou” Children’s Hospital, which is one of the two largest paediatric referral centres in Athens, Greece with a catchment population of over 500 000 children. Cases were recruited 3 times per week during a 12-hour Accident & Emergency (A&E) shift. The population consisted of 1207 children aged 6 months to 13 years who were hospitalized after presenting at A&E with at least one of the following symptoms: fever (axillary temperature $\geq 37.8^{\circ}\text{C}$), cough, rhinitis, sore throat, ear ache, wheezing, hoarseness of voice, stridor, shortness of breath, apnoea and/or physical examination findings suggestive of respiratory infection such as acute otitis media, sinusitis, croup, bronchiolitis, bronchitis or pneumonia. Patients were not included if a non-respiratory cause for admission was identified. A standardised questionnaire was completed for each case including demographic data, exposures, past medical history including doctor-diagnosed asthma, symptoms, physical findings, underlying chronic disease, and diagnosis and treatment. The study protocol was approved by the Ethics Review Board of the “P. & A. Kyriakou” Children’s Hospital, and informed consent was obtained from all children’s legal guardians prior to study recruitment.

2.2 | Virology

Nasopharyngeal aspirates were collected and stored at -70°C until processed for the identification of rhinovirus (RV) and influenza virus

(IFV) (serotypes A/H1N1, A/H3N2, B) via single pathogen reverse transcription-polymerase chain reaction (RT-PCR). RNA was extracted using Trizol (Invitrogen, CA), according to the manufacturer’s recommendations. Concentration and purity were determined spectrophotometrically using NanoDrop (Thermo Scientific NanoDrop 1000 Spectrophotometer, Thermo Scientific, Wilmington, DE). One hundred nanograms of RNA was reverse-transcribed using Superscript II and random hexamers (Invitrogen), according to the manufacturer’s instructions. Polymerase chain reactions were performed using conditions of reaction and primers as described before.^{16,17}

The whole population (1207 samples) was tested for IFV, while 590 randomly selected samples (~300 per year) were tested for RV. To exclude selection bias with regard to RV testing, we conducted logistic regression analysis to define whether any of the variables of interest (age, sex, ethnicity, going to the nursery, second-hand tobacco exposure, wheeze, fever, rales, cough, vomiting, intercostal muscle retractions, cervical lymphadenopathy, history of pre-existing asthma, current asthma attack diagnosis, drugs used and IFV detection) were significantly different between the subjects with or without data for RV. There were no significant differences found (data not shown).

2.3 | Statistical analysis

Multivariable logistic regression models with dependent binary variables of *wheeze, fever, rales, cough, vomiting, intercostal muscle retractions, cervical lymphadenopathy, current asthma diagnosis, systemic/inhaled corticosteroids and bronchodilators* were fitted with main predictor covariates (RV and IFV positivity) and other covariates which were controlled for confounding (age, sex, ethnicity, going to the nursery and second-hand tobacco exposure) (Table 2). Only participants with full data for RV and IFV and with full data for all the other variables used (main variables, confounders) were used for analysis ($n = 443$). In other adjusted logistic regression models, the dependent variables were the dichotomous variables “flu⁺ asthmatics vs non-asthmatics” and “RV⁺ asthmatics vs non-asthmatics,” and the predictor covariates were clinical symptoms, acute asthma diagnosis and others (Table 3).

To present the relative incidence of the viruses, we used the ratios of % positive RV and % positive IFV for each month (Figure 1).

To present differences in symptoms between IFV⁺ and RV⁺ samples, χ^2 test was used (Figure 2).

A two-sided P -value of $<.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population and viral identification

The population was balanced in terms of gender (boys: 54%) and covered the whole paediatric age range. A considerable proportion

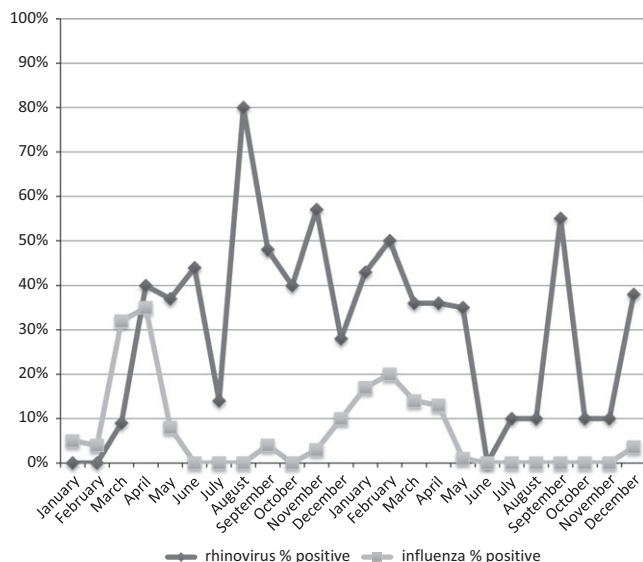


FIGURE 1 Time course of rhinovirus % positive and influenza % positive throughout the study

of children (48%) were exposed to tobacco smoke. About one-third of them had wheeze among their presenting symptoms; however, only 12% were admitted with a diagnosis of an "asthma attack." Descriptive data are shown in Table 1. The time distribution of RV

and IFV is shown in Figure 1. Flu seasons peaked in March-April on 1 year and February on the other. Fall, spring but also winter peaks were observed for RV. In both years, RV and IFV peaks overlapped.

3.2 | Associations between viral presence and clinical parameters

Multivariable controlled logistic regression was used for all associations. We evaluated associations between virus positivity and the presence of symptoms related or not to asthma (wheeze, rales, cough, fever, vomiting), physical findings (intercostal muscle retractions, cervical lymphadenopathy), diagnosis of asthma attack at presentation, as well as medication used at admission. Odds ratios, 95% confidence intervals and *P*-values are presented in Table 2.

We found a positive association of wheeze with RV positivity as compared to RV negativity (OR = 2.21, CI = 1.30-3.76) after adjustment for IFV, age, sex, ethnicity, going to the nursery and second-hand tobacco exposure. Conversely, a negative association was observed between wheeze and IFV positivity as compared to IFV negativity (OR = 0.23, CI = 0.10-0.54) after adjustment for the same confounders and RV, indicating that patients who were later found to be IFV⁺ had significantly less wheezing at presentation than those who were IFV⁻.

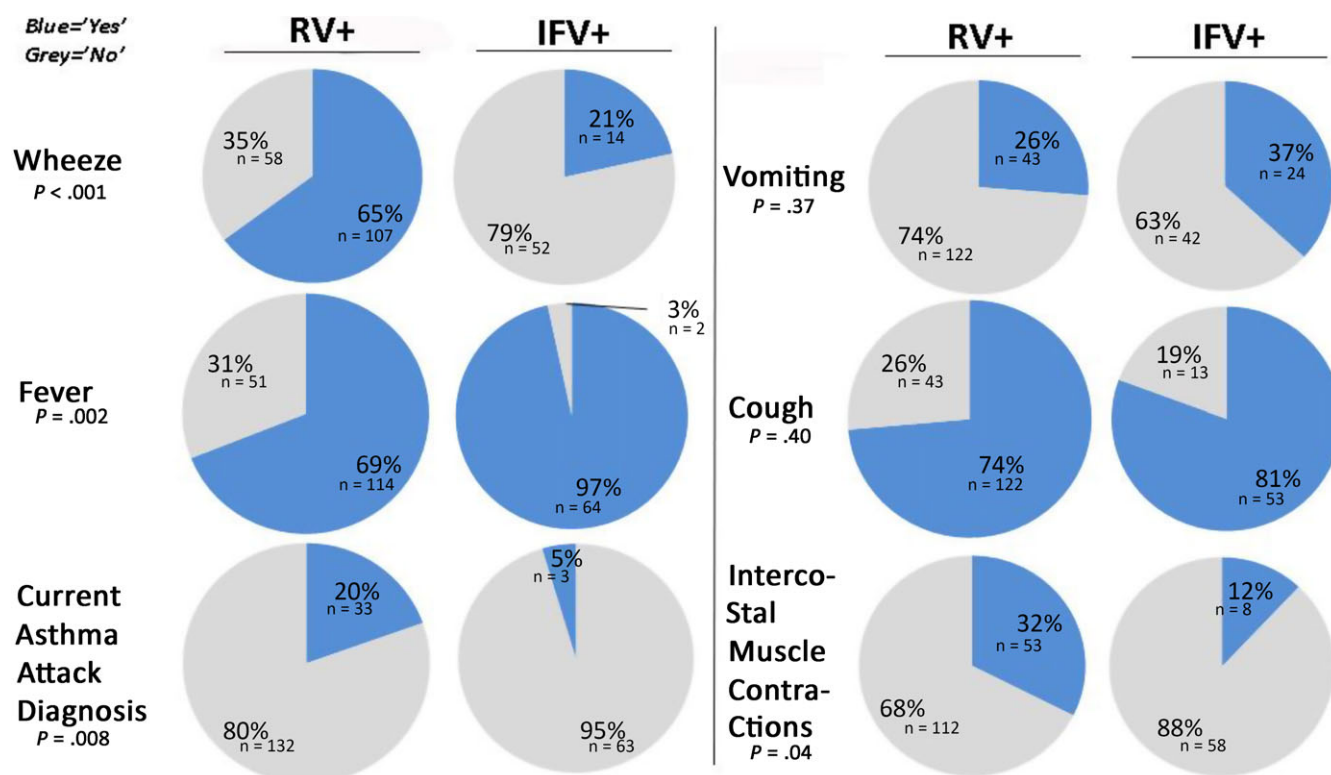


FIGURE 2 Graphical depiction of proportions of children who presented with wheeze, fever, vomiting, cough, intercostal muscle retractions or had an asthma attack diagnosis on admission, between RV-positive and IFV-positive samples (Total *n* = 443, *n*(RV⁺) = 181, *n*(IFV⁺) = 82). Double positives (both IFN⁺ & RV⁺) (*n* = 16) were excluded from this analysis. χ^2 was conducted between a dichotomous "RV⁺ vs IFN⁺" variable and the other binary variables (wheeze, fever etc.)

TABLE 1 Descriptive data for the whole population (n = 1207)

Descriptive variables (Whole population n=1207)					
	n	%	Symptoms	n	%
Age in years					
<2	511	(42%)	Wheeze	433	(36%)
2-5	371	(30.5%)	Fever	1047	(86%)
5-10	206	(17%)	Rales	443	(37%)
>10	119	(9.5)	Cough	701	(58%)
			Vomiting	183	(15%)
Male gender	652	(54%)			
Diagnosis on admission					
Gestational age			Asthma attack	144	(12%)
<30	15	(1.5%)	Otitis media	178	(13.5%)
30-37	122	(11.5%)	Croup	61	(5%)
>37	906	(87%)	Bronchiolitis	75	(6%)
			Pneumonia	89	(7%)
Ethnicity			Febrile seizure	163	(12.5%)
Greek	857	(71%)	Non-classifiable febrile condition	549	(44%)
Albanian	206	(17%)			
Roma	42	(3.5%)	Intensive care admission ever	4	(0.3%)
Tobacco smoke exposure	579	(48%)			
Virus PCR					
Attending day care	777	(64%)	RV ⁺	251 (of 590)	(42.5%)
			IFV ⁺	160 (of 1207)	(13%)
Pre-existing asthma history	245	(20%)	Double positivity	30	12% of the RV ⁺ 19% of the IFV ⁺

Only participants with full data for all used variables were included in the analyses (n = 443). This subgroup included 181 RV⁺ participants and 82 IFV⁺ participants, of which 16 participants were double RV/IFV positives.

In contrast, there was a positive association between IFV positivity and the presence of fever (OR = 5.02, CI = 1.18-21.34), but a borderline significant negative association between RV positivity and fever (OR = 0.58, CI = 0.34-1.00). A negative association was also seen between RV infection and vomiting (OR = 0.32, CI = 0.16-0.66), while IFV had no effect on vomiting ($P = .19$). Intercostal muscle retractions were increased in RV⁺ children as compared to RV⁻ (OR = 1.98, CI = 1.7-3.65), but decreased in IFV⁺ as compared to IFV⁻ ones (OR = 0.45, CI = 0.23-0.86).

Asthma attack was diagnosed significantly more often at presentation in subjects that turned out to be RV⁺ as compared to RV⁻ (OR = 1.89, CI = 1.07-3.65). In contrast, IFV positivity was associated with a reduced chance of diagnosis of an asthma attack at presentation, as compared to IFV⁻ participants (OR = 0.29, CI = 0.08-0.96). Also, fewer bronchodilators were used for IFV⁺ subjects as opposed to IFV⁻ ones (OR = 0.41, CI = 0.21-0.82) (Table 2).

3.3 | Comparison between RV⁺ and IFV⁺ participants

From a different perspective, children who were uniquely positive for RV, when compared to those who were uniquely positive for

IFV, were found to wheeze more frequently and were more likely to be diagnosed with an asthma attack (χ^2 , $P < .001$ and $P = .008$, respectively). This was not the case with fever which was more frequent in IFV⁺ rather than RV⁺ children (χ^2 , $P = .002$) (Figure 2).

3.4 | Impact of IFV and RV infections on patients with a history of asthma

Twenty per cent of the children reported a previous history of doctor-diagnosed asthma. These patients were far more likely to have fever, rales and intercostal muscle retractions than those with no history of asthma, when infected with IFV (OR = 1.7, 15.68 and 19.3, respectively) (Table 3). They were also more likely to have non-respiratory symptoms such as lymphadenopathy (OR = 7.3, CI = 2.23-24.37), whereas there was no difference in relation to cough ($P = .71$) (Table 3). Conversely, rales, intercostal muscle retractions and cervical lymphadenopathy did not differ between asthmatics and non-asthmatics with RV infection. Actually, among RV⁺ subjects, asthmatics had less fever (OR = 0.22, CI = 0.07-0.68) and more cough (OR = 20.76, CI = 2.12-203.27) than non-asthmatics, hinting towards a more typical “asthma-like” presentation. As expected, when presented at the ED, participants with pre-existing

TABLE 2 Associations in multivariable logistic regression models with the main variables (first horizontal row—wheeze, fever etc.) as depended variables, and positivity or not for rhinovirus and influenza as independent covariates (both inserted in the same model, and therefore mutually adjusted)

	Wheeze	Fever	Rales	Cough	Vomiting	Intercostal muscle retractions	Cervical lymphadenopathy	Diagnosis of asthma attack	Systemic steroids	Inhaled steroids	Bronchodilators
Total n = 443	Odds Ratio, 95% confidence interval and P-value										
Rhinovirus											
RV ⁻ (n = 262)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
RV ⁺ (n = 181)	OR = 2.21 CI = 1.30-3.76 P = .003	OR = 0.58 CI = 0.34-1.00 P = .05	OR = 1.20 CI = 0.66-2.18 P = .53	OR = 1.26 CI = 0.69-2.28 P = .44	OR = 0.32 CI = 0.16-0.66 P = .002	OR = 1.98 CI = 1.07-3.65 P = .029	OR = 0.83 CI = 0.45-1.55 P = .57	OR = 1.89 CI = 1.10-3.26 P = .021	OR = 0.79 CI = 0.44-1.41 P = .43	OR = 0.94 CI = 0.60-1.48 P = .81	OR = 1.11 CI = 0.72-1.71 P = .64
FLU											
IFV ⁻ (n = 361)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
IFV ⁺ (n = 82)	OR = 0.23 CI = 0.10-0.54 P = .001	OR = 5.02 CI = 1.18-21.34 P = .029	OR = 0.23 CI = 0.08-0.67 P = .007	OR = 1.10 CI = 0.47-2.60 P = .81	OR = 0.53 CI = 0.21-1.36 P = .19	OR = 0.45 CI = 0.23-0.86 P = .016	OR = 2.01 CI = 0.94-4.29 P = .07	OR = 0.29 CI = 0.08-0.96 P = .044	OR = 1.86 CI = 0.69-4.99 P = .21	OR = 1.63 CI = 0.81-3.26 P = .16	OR = 0.41 CI = 0.21-0.82 P = .012

Models were further adjusted for age, sex, ethnicity, going to the nursery and second-hand tobacco exposure. Total n = 443, n(RV⁺) = 181, n(IFV⁺) = 82. Bold indicates statistical significance (P < .05).

TABLE 3 Associations in multivariable logistic regression models with main dichotomous depended variables of IFV⁺ asthmatics vs non-asthmatics and RV⁺ asthmatics vs non-asthmatics, and with the variables in the first horizontal row (wheeze, fever etc.) as independent covariates

	Wheeze	Fever	Rales	Cough	Vomiting	Intercostal muscle retraction	Cervical lymphadenopathy	Diagnosis of asthma attack	Systemic steroids	Inhaled steroids	Bronchodilators
IFV⁺ Non-asthmatics (n = 64)	Odds Ratio, 95% confidence interval and P-value										
IFV ⁺ asthmatics (n = 18)	OR = 36.54 CI = 5.87-227.48 P < .001	OR = 1.7 CI = 1.00-3.2 P = .05	OR = 15.68 CI = 3.71-66.26 P < .001	OR = 1.26 CI = 0.35-4.56 P = .71	OR = 3.09 CI = 0.23-40.28 P = .39	OR = 19.3 CI = 3.61-103.88 P = .001	OR = 7.3 CI = 2.23-24.37 P = .001	OR = 1.70 CI = 0.99-2.93 P = .055	OR = 10.53 CI = 1.75-63.39 P = .01	OR = 17.48 CI = 3.74-81.64 P < .001	OR = 28.99 CI = 6.40-131.18 P < .001
RV⁺ Non-asthmatics (n = 80)	Odds Ratio, 95% confidence interval and P-value										
RV ⁺ asthmatics (n = 101)	OR = 30.41 CI = 5.06-182.6 P < .001	OR = 0.22 CI = 0.07-0.68 P = .009	OR = 2.28 CI = 0.64-8.16 P = .20	OR = 20.76 CI = 2.12-203.27 P = .009	OR = 0.78 CI = 0.19-3.22 P = .73	OR = 0.87 CI = 0.43-3.31 P = .62	OR = 0.66 CI = 0.17-2.56 P = .55	OR = 28.21 CI = 5.90-134.50 P < .001	OR = 13.73 CI = 3.13-60.18 P = .01	OR = 28.41 CI = 6.17-130.68 P < .001	OR = 83.9 CI = 12.88-246.65 P < .001

Model was further adjusted for age, sex, ethnicity, going to the nursery and second-hand tobacco exposure. n(RV⁺) = 181, n(IFV⁺) = 82. Bold indicates statistical significance (P < .05).

asthma were more likely than non-asthmatics to have wheeze and to be given asthma medication, both when infected with RV and IFV (Table 3).

4 | DISCUSSION

We show that among children who were hospitalised after presenting at the A&E with a flu-like illness, those who tested positive for RV had a higher risk to have had wheeze and to have received a diagnosis of “asthma attack” at presentation, but had a lower risk of non-respiratory symptomatology (eg fever, vomiting), after adjustment for confounders (including IFV). Conversely, IFV⁺ children had a lower risk to have had wheeze and to have received an asthma attack diagnosis at presentation but had an increased risk of fever, after adjustment for confounders (including RV). Furthermore, children with a history of asthma had a more severe clinical presentation than non-asthmatics when infected by either virus; however, when IFV was the culprit, the clinical presentation was more generalised (fever, lymphadenopathy) and possibly more severe (intercostal muscle retractions), whereas RV infection was associated with a more typical “asthma-like” presentation (including cough and no fever). Altogether, these findings suggest that the acute illness caused by IFV should be distinguished from the one caused by RV—both in terms of severity and “asthma-like” clinical characteristics—in children who present with flu-like illness, and also in the subgroup with a history of asthma.

Several studies have established that RV is the most commonly identified virus in patients experiencing an asthma attack.⁴ We add here that in children with flu-like illness, RV positivity predisposes to wheeze, whereas IFV positivity is—conversely—negatively associated with wheeze. These findings suggest that IFV and RV activate distinct clinical-pathophysiological pathways.

Several studies have shown that during IFV epidemics, pre-existing asthma predisposes to hospitalisation.^{8–11,18,19} These IFV-triggered events are frequently considered to be “asthma exacerbations,” but there is little evidence to suggest that this is indeed the case. Although there is no doubt that IFV infection can cause acute respiratory episodes in children with asthma (as also evidenced by a protective effect of IFV vaccination^{6,20–22} and anti-IFV drugs²³), in the absence of a unique term such episodes could be described either as part of the influenza clinical condition, or as an “extension” of pre-existing asthma (ie an “asthma exacerbation”). This impreciseness, however, may explain some of the discrepancies in the literature. For instance, in the last update of a series of Cochrane reviews, the authors concluded that there is uncertainty about the degree of protection from IFV vaccination against IFV-induced asthma attacks.²⁴

Although several studies have assessed IFV-induced “asthma attacks” from an epidemiological perspective,^{7–11,18} few studies have directly focused on the actual clinical presentation of these episodes (and, therefore, whether they could actually be defined as “asthma attacks”).^{25,26} A recent study in children showed a link between

asthma attacks and RV, but not IFV.²⁵ In this study, RV infection was associated with increased wheeze and the absence of fever, whereas IFV was associated with malaise and post-natal drip.²⁵ In other paediatric studies, IFV caused significantly less wheeze and asthma attacks than RSV and metapneumovirus²⁷; also, although children with a history of pre-existing asthma did have increased susceptibility to infection,^{14,28} IFV was not associated with wheeze/current asthma attack diagnosis.²⁸

From an epidemiological standpoint, whether acute episodes caused by IFV can be classified as “asthma attacks” may depend on several factors, including atopy and age: an IFV/asthma attack association was shown only in atopic and not in non-atopic asthmatics.²⁹ Also, IFV infection may trigger events identified as “asthma attacks” more frequently in adults rather than in children,^{30,31} as we have previously suggested in a GA²LEN systematic review.⁴ Seasonality may also be important and, therefore, it is optimal that all months are studied, as is the case with our study. All these factors hamper our efforts to better define the acute events triggered by IFV infection.

The discrepancies in epidemiological findings (including conflicting evidence on the efficiency of IFV vaccination on asthma attacks²⁴) may well be because of differences in the clinical definition of the IFV-induced events, as our findings suggest. In the era of precision medicine, it is important to set apart conditions with different aetiology, response to treatment and clinical outcome; therefore, we propose to differentially classify “asthma-augmented influenza” or, “augmented flu” for short, from a typical asthma attack. This characterisation will likely allow us to investigate into additional management regimens for each separate entity in the future; indeed, from our findings, we can see that both proposed conditions were treated by the attending physicians with inhaled bronchodilators. Future trials could clarify whether these distinct conditions have a different response to this type of treatment, and could identify more effective management approaches.

Further study is required to understand the mechanisms underpinning the propensity of RV to induce wheeze and “typical” asthma attacks, as opposed to the IFV infection which—although more severe—appears to be lacking in this respect. Although both RV^{32,33} and IFV are able to infect the bronchi and induce local inflammation, the increased bronchial cytotoxicity of IFV as compared to RV could play some part in these differences.^{34,35}

This study has certain limitations. We lack measures of atopy (which may affect susceptibility to infection) and data on the children’s flu vaccination status. However, IFV vaccination is not recommended in Greece for children who do not suffer with significant medical conditions and, therefore, coverage is very low³⁶ and could not have significantly affected our conclusions. Diagnosis of an asthma attack at presentation is dependent on physician assessment, which was performed in a real-life setting by clinicians who were on-call when the children attended A&ED. Only part of the samples were analysed for RV positivity, albeit our analysis found no difference in the investigated variables between participants who underwent RV screening and those who did not, indicating that there was

no selection bias. Also, viral detection was performed by PCR which cannot discriminate between active infection and mere presence of innocuous viral genetic material. However, IFV is a virus of high pathogenicity, unlikely to be found outside an infection; we therefore surmise that the reported symptoms were indeed due to IFV infection. RV, however, is frequently found in the healthy state. Finally, coinfection with other viruses was not assessed; however, apart from the effect of RSV in children <2 y.o, the risk attributed to viruses other than RV and IFV is small; furthermore, there is no evidence in the literature that coinfection itself affects clinical presentation, and we believe that analysis of other viruses would just add unnecessary "noise" to our findings.

Important strengths should also be mentioned as follows: our cohort covers the entire age span of childhood and has been sampled throughout the year, for 2 years. The sample size is large and the observed associations withstood control for several relevant confounders.

In conclusion, wheeze and typical asthma attacks are associated with the presence of RV proportionally much more than IFV. In children with asthma, IFV infection results in a clinical condition which can be differentiated from a typical asthma attack; we suggest defining this condition as "asthma-augmented influenza." This new classification may help to clarify discrepancies relating to the effect of IFV on asthma. Future research in the distinct pathophysiological mechanisms that potentially underpin these different conditions can bring us closer to utilising precision medicine for their diagnosis and management.

CONFLICT OF INTEREST

NGP has received research support for his institution by Nestle, MSD and GSK; has acted as a consultant for Abbvie, Novartis, Menarini, Meda, ALK-Abello, GSK; has received honoraria from Novartis, Uriach, GSK, Allergopharma, Stallergenes, MSD; and has been on the scientific advisory board for Abbvie, Sanofi, Menarini, Meda. The other authors have no relevant conflict of interest to disclose.

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