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Short Communication

Influenza-like illness surveillance may underestimate the incidence of respiratory syncytial virus in adult outpatients

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ABSTRACT

Objectives: Although respiratory syncytial virus (RSV) is a leading cause of acute respiratory infections (ARIs), it is unclear which of the case definitions that prompt swab collection predicts RSV best. We aimed to profile RSV-positive adults and to identify possible RSV case definitions.

Methods: This individual-based pooled analysis was based on influenza-like illness (ILI) surveillance conducted among Italian outpatient adults. All samples were tested for influenza, RSV and other respiratory viruses.

Results: RSV was detected in 5.2% of the 1240 ILI adults tested. The prevalence of fever/feverishness was significantly lower (83.3%) in individuals positive for RSV and those negative for both viruses (79.4%) than in influenza-positive subjects (96.2%). Conversely, 98.3% of RSV-positive adults reported cough. Compared with subjects who tested negative, the adjusted relative risk ratio of cough in RSV-positive subjects was much higher than in influenza-positive subjects (6.89 vs 2.79). Using ARI with cough as the RSV case definition increased specificity.

Conclusion: As fever/feverishness is more common among influenza than RSV cases, ILI-based surveillance may underestimate RSV incidence in adult outpatients. While broad ARI definitions are useful for routine RSV surveillance, their low specificity may hamper vaccine effectiveness studies. The use of further ARI qualifiers like cough increases specificity.

Introduction

In adults, respiratory syncytial virus (RSV) is a common cause of acute respiratory infections (ARIs) and is associated with a significant burden [1]. Two adult RSV vaccines have recently been authorized [2].

Enrollment of subjects in both surveillance and vaccine effectiveness (VE) studies is based on a prespecified case definition that triggers sample collection. An accurate case definition is crucial to obtain consistent estimates of the burden of disease and VE [3]. A recent review [4] has shown that lack of consistency in case definitions is a main limitation of the available RSV-related studies.

As in several other countries, the Italian RSV surveillance program is based on the existing influenza surveillance network, and thus relies on the ILI case definition [5]. Unlike influenza studies, in which swab collection is typically triggered by the onset of ILI [3], it is currently less clear which clinical definition should be used for RSV surveillance and future VE studies. The main goal of the present study was to describe the symptom profile of RSV-positive adult outpatients and compare this with those of influenza and test-negative controls, to identify possible case definitions that better predict RSV infection.

Methods

In this analysis, adults (≥18 years) were enrolled in an influenza VE study conducted in a primary care setting during the 2018/19 and 2019/20 winter seasons in Genoa (Italy). The full study protocol is available elsewhere [6]. Briefly, subjects with ILI were enrolled by sentinel general practitioners (GPs). ILI was defined according to the European criteria, i.e., the sudden onset of ≥1 systemic (fever [≥38 °C] or feverishness/subfebrility [37-38 °C],

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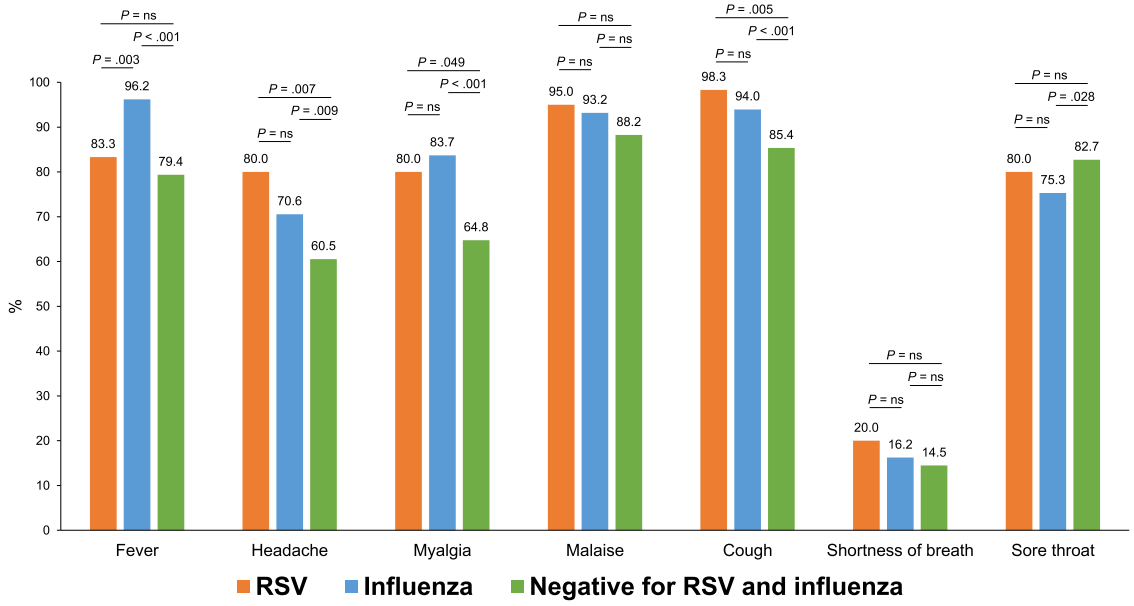

Figure 1. Frequency of systemic and respiratory symptoms, by virus positivity pattern, Genoa (Italy), 2018/19 and 2019/20 winter seasons ($N = 1236$).
ns, nonsignificant ($P > .05$); RSV, respiratory syncytial virus. Four subjects, positive for both influenza and respiratory syncytial viruses, were excluded. All *P*-values are adjusted by means of the Bonferroni method.

Table 1
Bias-reduced multinomial logistic regression to predict positivity for influenza and respiratory syncytial viruses from systemic and respiratory symptoms, Genoa (Italy), 2018/19 and 2019/20 winter seasons ($N = 1236$).

Symptom	Respiratory syncytial virus [a]		Influenza [a]	
	RRR (95% CI)[b]	*P*-value	RRR (95% CI)[b]	*P*-value
Fever	1.50 (0.75-2.99)	.25	6.82 (3.45-13.48)	<.001
Headache	2.08 (1.10-3.96)	.025	1.43 (1.03-1.99)	.033
Myalgia	1.56 (0.81-2.99)	.18	2.15 (1.46-3.17)	<.001
Malaise	1.60 (0.53-4.78)	.40	1.50 (0.86-2.62)	.15
Cough	6.89 (1.40-33.76)	.017	2.79 (1.60-4.87)	<.001
Shortness of breath	1.20 (0.62-2.33)	.60	1.02 (0.67-1.56)	.92
Sore throat	1.00 (0.52-1.92)	.99	0.68 (0.49-0.99)	.034

CI, confidence interval; RRR, relative risk ratio.
[a] Reference category is that of subjects negative for both influenza and respiratory syncytial viruses.
[b] Adjusted for sex, age, season, swab delay, presence of comorbidities and other symptoms.

malaise, headache, myalgia) and ≥1 respiratory (any dry or wet cough, sore throat, shortness of breath) symptom [7]. The principal exclusion criteria were: (i) institutionalized individuals; (ii) onset of ILI symptoms >7 days before the current examination; (iii) positivity for influenza before the current episode.

GPs collected demographic and clinical data and performed a nasopharyngeal swab. This latter was tested in real-time polymerase chain reaction (RT-PCR) by means of the Allplex (Seegene Inc.; Seoul, Korea) Respiratory Panels for RSV, influenza and other respiratory viruses.

The study endpoint was RT-PCR positivity to either RSV or influenza viruses. Independent variables of interest were the previously described ILI symptoms. Sex, age, season, swab delay, presence of comorbidities were regarded as potential confounders.

The chi-square test with Bonferroni's correction was used to compare the frequency of symptoms. Bias-reduced multinomial logistic regression was applied to estimate the relative risk ratios (RRRs) of testing positive for RSV and influenza (compared with subjects testing negative for both RSV and influenza) when presenting with a given symptom. The predictive performance of the alternative RSV case definitions was quantified by means of sensitivity, specificity and area under the curve (AUC) parameters. All analyses were conducted in R stat packages v. 4.1.0 (R Foundation for Statistical Computing; Vienna, Austria).

Results

A total of 1240 adults (mean age 51.5 ± 17.9 years, 54.8% women) were enrolled and their characteristics are reported in Table S1. A total of 269 (21.7%) and 64 (5.2%) swabs tested positive for influenza and RSV, respectively, and their detection curves overlapped (Figure S1). Four (0.3%) samples tested positive for both influenza and RSV and were excluded from the subsequent analyses. Full RT-PCR results are reported in Table S2.

Compared with negative individuals, subjects positive for RSV and influenza reported headache, myalgia, and cough more frequently. Additionally, subjects positive for influenza showed a higher frequency of fever, while sore throat was reported less frequently. Compared with adults positive for influenza, RSV-positive individuals were less likely to report fever (Figure 1).

In the fully adjusted bias-reduced multinomial logistic regression (Table 1), compared with RSV- and influenza-negative individuals, those positive for RSV had a higher risk of headache and cough. Although the point estimate was imprecise and the corresponding 95% CIs overlapped with those of influenza, the RRR of cough in RSV-positive subjects was very high (RRR 6.89; $P = .017$). The analogous RRR in influenza-positive subjects was much lower (RRR 2.79; $P < .001$). Notably, the presence of fever predicted influenza ($P < .001$), but not RSV ($P = .25$).

A sensitivity analysis in which only influenza ($n = 259$) and RSV ($n = 55$) mono-detections were considered, while the reference group retained only subjects negative for all respiratory viruses investigated ($n = 581$), yielded similar results (Table S3).

Setting ARI (i.e., ≥1 presence of respiratory symptom) with cough as an RSV case definition yielded sensitivity and specificity values of 98.3% and 12.7%, respectively; the AUC was 0.56. On considering ARI patients with cough but without fever (to distinguish between RSV and influenza), sensitivity substantially decreased (16.7%) and specificity increased (84.3%), while the AUC was 0.50. Adding the presence of headache to the case definition of ARI with cough slightly increased the AUC value to 0.61 (Table S4).

Discussion

The results of this study showed that the frequency of fever was lower in RSV-positive community-dwelling adults than in those positive for influenza, being similar to that seen in individuals testing negative for both viruses. RSV detection may be therefore underestimated within ILI-based and fever-based surveillance systems.

Utilizing ARI with cough as a symptom (independently of the presence of fever and other systemic symptoms) proved to be simple and sufficiently sensitive. Indeed, a comprehensive review [8] reported that 90%-97% of RSV-positive older adults had a cough. Adding headache to this case definition slightly improved its overall predictive accuracy, but this could potentially place an additional burden on sentinel GPs. ARI with cough and without fever was the most specific case definition. However, given its low sensitivity, this definition appears to be too restrictive for VE studies. These results are aligned with a study on community-dwelling older adults conducted in the United Kingdom, the Netherlands and Belgium [9]. It found that fever and feeling feverish were less common among RSV cases than influenza cases. Analogously, 97% of RSV patients had a cough. The case definition proposed by these authors, i.e., ARI with cough and the production of sputum/phlegm (and irrespective of the presence of fever), identified 94% of RSV cases, while specificity was 30%. When this case definition specifically excluded cases with fever, in order to distinguish RSV from influenza, specificity increased to 55% and sensitivity was 61%. It should be, however, stressed that the available evidence, including our study, reported AUC values <0.7, suggesting poor or no discrimination.

The present study has two major limitations. Firstly, our retrospective assessment was based on data from an influenza VE study and the set of respiratory and systemic symptoms was composed of only those listed among the European ILI criteria. Therefore, other signs and symptoms potentially attributable to RSV infection, such as wheezing, rales or nasal congestion [8], were not collected. Secondly, a larger number of positive samples would produce more precise RRRs, especially regarding the association between cough and RSV positivity.

In conclusion, ILI- and fever-based case definitions may underestimate the attack rate of RSV, since a significant proportion of adult outpatients with mild-to-moderate RSV infection have no fever or feverishness. While the use of ARI case definitions has been recommended for RSV surveillance programs [10], its application to future RSV VE studies may potentially require the enrollment of larger samples. The use of cough as an ARI qualifier may increase specificity.

Declaration of competing interest

A.D. provided consultancies and received speaker fees from CSL Seqirus and SD Biosensor. A.O. provided consultancies and/or received speaker fees from CSL Seqirus, Moderna, Novavax and SD Biosensor. D.P. provided consultancies for Pfizer and CSL Seqirus and received grants for conducting observational studies from Sanofi, Pfizer, GSK and Viatris. G.I. provided consultancies and/or received grants for conducting experimental and/or observational studies for GSK, Sanofi, MSD, CSL Seqirus and Pfizer. Other authors declare no conflicts of interest.

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Ethical approval

The study was approved by the Ethics Committee of the Liguria Region (protocols 315/2018 and 246/2019). Written informed consent was obtained from all participants.

Author contributions

A. D. and G. I. conceptualized the study. A. O. and D. P. contributed methodology, data acquisition and interpretation. M. O. and A. F. contributed methodology, data cleaning and interpretation. B. B. performed laboratory analyses. A. D. and M. O. performed data analysis and wrote the original draft. D. P. and G. I. acquired funding, performed project administration and supervision. All authors contributed to reviewing and editing manuscript drafts.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.02.011.

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