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SUPPLEMENT ARTICLE

World Health Organization Influenza-Like Illness Underestimates the Burden of Respiratory Syncytial Virus Infection in Community-Dwelling Older Adults

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Background. Respiratory syncytial virus (RSV) surveillance is heavily dependent on the influenza-like illness (ILI) case definition from the World Health Organization (WHO). Because ILI includes fever in its syndromic case definition, its ability to accurately identify acute respiratory tract infections (ARTI) caused by RSV in older adults is uncertain.

Methods. The accuracy of the WHO ILI and a modified ILI (requiring only self-reported fever) case definitions in identifying patients with PCR-confirmed RSV-ARTI was evaluated in community-dwelling older adults (≥60 years) from the prospective European RESCEU cohort study.

Results. Among 1040 participants, 750 ARTI episodes were analyzed including 36 confirmed RSV-ARTI. Due to a general lack of fever, sensitivity for RSV-ARTI was 33% for modified ILI and 11% for ILI. The area under the curve for both ILI definitions was 0.52 indicating poor discrimination for RSV. RSV-ARTI could not be distinguished from all other ARTI based on clinical symptoms.

Conclusions. The use of ILI underestimated the occurrence of RSV-ARTI in community-dwelling older adults up to 9-fold (11% sensitivity). Because worldwide RSV surveillance depends largely on ILI, there is an urgent need for a better approach to measure the occurrence of RSV disease and the impact of future RSV vaccine introduction.

Clinical Trials Registration. NCT03621930.

Keywords. case definition; ILI; older adults; RESCEU; respiratory syncytial virus; RSV.

Acute respiratory tract infections (ARTI) are the leading cause of disease worldwide with an estimated incidence of 17.2 billion upper ARTI annually [1]. Lower respiratory tract infections are estimated to be responsible for 4.4% of all deaths worldwide in people of all ages, with higher rates in both ends of the age spectrum [2]. Amongst others, respiratory syncytial virus (RSV) is responsible for part of this worldwide burden [3, 4]. Respiratory surveillance programs provide information for public health authorities, which is used to minimize the impact of the disease by planning appropriate control and intervention measures and allocate health resources. The World Health Organization (WHO) collects worldwide data about ARTI epidemiology by using standardized case definitions [5, 6]. Influenza-like illness (ILI) includes acute respiratory infection (ARI) with measured fever (≥38°C) and cough and is commonly used as a case definition for respiratory infection. Case definitions that include fever such as ILI and severe ARI show a wide range of sensitivities (24%–86%) in identifying confirmed RSV ARTI [7–11]. This wide range in sensitivity displays the high dependency on the studied population (children, adults, older adults) and clinical setting (community, outpatient, inpatient). Unfortunately, older adults living in the community were not well represented in these studies. Increasing age can alter symptomatology, which can result in a more atypical disease presentation in older adults compared to younger adults or children [12, 13]. Because RSV is known to cause an appreciable disease burden in the elderly population [14], we aimed to validate the performance of the WHO ILI case definition in identifying confirmed RSV ARTI in a population of community-dwelling older adults.

METHODS

Study Design

Participants from the RESCEU older adult study were studied. The design and data collection of the RESCEU older adult study

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has been described previously [14]. In summary, the RESCEU older adult study is a European multicentre, prospective, observational cohort study in community-dwelling adults aged 60 years or older. Before the start of the 2017–2018 and 2018–2019 RSV season (1 October–1 May), 1040 participants were recruited at 17 general practices in the Netherlands (Utrecht), Belgium (Antwerp), and the United Kingdom (Oxford). Participants with comorbidity were included as long as this was not life-threatening, caused immunodeficiency, or would hinder in completing the study procedures. More detailed information about the RESCEU older adult study and the complete inclusion and exclusion criteria can be found at Clinicaltrials.gov, identifier: NCT03621930.

This study was approved by the Ethical Review Authority in Belgium (reference No. B300201732907), The Netherlands (reference No. NL60910.041.17), and United Kingdom (Ethics reference 17/LO/1210, IRAS Ref: 224156). Participants gave informed consent before taking part in this study. The study was conducted according to the Declaration of Helsinki, as revised in 2013.

Study Procedures

During the RSV season, participants were followed up weekly by email or telephone by the local study teams. Home visits for viral testing were scheduled within 72 hours if 1 or more of the following ARTI symptoms were present for at least 1 day: nasal congestion or discharge, cough, wheezing, or shortness of breath. Nasopharyngeal flocked swabs collected during the home visit were tested for RSV and influenza with a molecular point-of-care test (POCT; Xpert Xpress Flu/RSV assay, Cepheid, Sunnyvale, CA, USA) [15]. All respiratory samples were validated for RSV after the study by in-house quantitative polymerase chain reaction (qPCR). During the home visit, vital signs, including temperature, saturation, heart rate, and respiratory rate, were measured by the local study teams. All participants were instructed to complete a daily log to score the presence and severity of various symptoms for as long as symptoms were present, for a maximum of 28 days (Supplementary Material). Participants had to indicate daily whether they measured their temperature or felt feverish, but they were not obliged to measure temperature daily. Participants from the RESCEU older adult study with an ARTI that was tested for RSV with POCT and/or qPCR and who completed a symptom diary during their illness were included in the current study.

Definitions

We tested the official ILI case definition from the WHO [5]. We also used a less stringent ILI-definition (modified ILI) based on the feeling of being feverish because participants were not obliged to measured temperature in our study (Box 1). Fever was defined as a recorded body temperature of ≥ 38°C during the home visit or as measured by patients during the respiratory episode. Measurement of temperature was either auricular, axillary, by infrared, or oral. Feeling feverish was defined as the feeling of being warm/feverish as reported in the daily diary. Symptoms were considered present if a symptom was reported for at least 1 day during the infectious episode. RSV-ARTI was defined as an ARTI with a positive RSV test result (POCT and/or qPCR positive for RSV). Those with a POCT-confirmed influenza infection were classified as influenza-ARTI, while all other PCR-negative ARTI were classified as other-ARTI.

Box 1. Influenza-Like Illness (ILI) Case Definitions

World Health Organization ILI [5]	An acute respiratory infection with: • measured fever ≥ 38C° • and cough • with onset within the last 10 d
Modified ILI	An acute respiratory infection with: • feeling of being warm/feverish • and cough • with onset within the last 10 d

Statistical Analysis

The presence of signs and symptoms was compared between those with RSV-ARTI, influenza-ARTI, or other-ARTI. We calculated the sensitivity, specificity, positive and negative predictive values, and likelihood ratios of the ILI and modified ILI case definitions for RSV-ARTI. The discriminative accuracy of these case definitions for RSV-ARTI was assessed as a point on the area under the receiver operating characteristic curve (AUC). The case definitions were subsequently tested in a subcohort of participants with medically attended (outpatient) RSV-ARTI. No imputation of missing values was performed.

Post hoc analyses were performed to explore 2 alternative case definitions. First, differences in symptomatology between RSV-ARTI, influenza-ARTI, and other-ARTI were used to develop a case definition with a high sensitivity for RSV that could distinguish RSV from all other infections. The second aim was to increase specificity to distinguish RSV from influenza. Alternative case definitions had to be concise and easy to use in order to make them applicable for community surveillance. These alterative case definitions were again tested in patients with RSV-ARTI and medically attended RSV-ARTI. Internal validation of these alternative case definitions was performed using bootstrapping (1000 random samples of 750 episodes with replacement). Last, we explored the performance of all tested case definitions to detect RSV using targeted sampling. From the proportion of RSV ARTI within a case definition we calculated the number patients that needed to be tested to identify 1 RSV case. By dividing this number of tested patients by the proportion of the case definition within all ARTI episodes we calculated the number of patients with ARTI that needed to be screened using a certain case

definition to identify 1 RSV case. All analyses were performed in R version 4.0.1.

RESULTS

Patients and Infections

From the 1040 older adults that participated in the RESCEU study, 616 (59%) experienced at least 1 ARTI episode during study follow-up (median 1, range 1–5 ARTI). In total, 844 ARTI episodes occurred, of which 805 (95%) were sampled during a home visit. Diary information was available in 750/805 (93%) ARTI episodes from 583 patients. These 750 tested ARTI episodes with diary information were included for analysis (Figure 1). Thirty-six patients experienced an RSV-ARTI, while 56 patients experienced 57 influenza-positive ARTI. The remaining 657 ARTI episodes experienced by 583 patients were neither RSV nor influenza positive and were thus classified as other ARTI. Characteristics of the study population are described in Table 1.

Clinical Symptoms

Patient-reported symptoms and vital signs collected during the home visit are displayed in Table 2. Measured fever (≥38°C) was observed in 25% (14/57) of influenza-ARTI, 11% (4/36) of RSV-ARTI, and 5% (33/657) of other ARTI during the complete illness course. The feeling of being feverish was present in 65% (37/57) of influenza-ARTI, 33% (12/36) of RSV-ARTI, and 29% (191/657) of other ARTI. Patients with RSV-ARTI and those with influenza-ARTI more often experienced production of sputum (phlegm), dyspnea, and headache compared to other ARTI. Patients with RSV-ARTI as well as those with influenza-ARTI more often felt ill and indicated more disturbances in their daily activities compared to other ARTI. Vital signs collected during the home visit showed that patients with influenza-ARTI more often had a fever compared to other ARTI (16% vs 2%, $P < .001$) but not compared to RSV-ARTI (6%, $P = .19$). While an increased respiratory rate (>20/min) and lower saturation (<95% SaO_2) were more often observed in those with RSV-ARTI and influenza-ARTI, these differences were not significant compared to other ARTI.

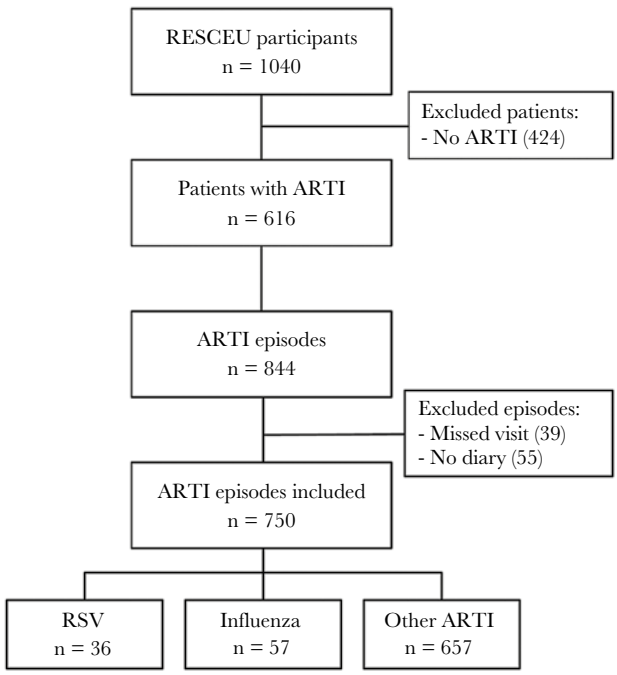

Figure 1. Flowchart of study participants and respiratory episodes. Abbreviations: ARTI, acute respiratory tract infection; RESCEU, Respiratory Syncytial Virus Consortium in Europe; RSV, respiratory syncytial virus.

Table 1. Characteristics of Study Participants

Characteristic	Patients With ARTI Included in Current Study (n = 616)			Total RESCEU Study Population (n = 1040)
	Patients With RSV (n = 36)	Patients With Influenza (n = 56[a])	Patients With Other ARTI (n = 583)	
Age				
Median, y (range)	75 (63–89)	71 (60–90)	75 (60–100)	75 (60–100)
Age older than 75 y	20 (56)	25 (44)	302 (52)	562 (54)
Female sex	20 (56)	28 (49)	320 (55)	554 (54)
Comorbidity[b]				
Cardiovascular	7 (19)	10 (18)	121 (21)	212 (21)
Lung	5 (14)	7 (12)	76 (13)	120 (12)
Diabetes	2 (6)	5 (9)	59 (10)	80 (8)
Allergies, any[c]	11 (29)	15 (27)	167 (29)	276 (27)
Hay fever	3 (9)	2 (4)	32 (6)	59 (6)
House dust mite	0 (0)	4 (7)	22 (4)	32 (3)
Pneumococcal vaccination[d]	4 (12)	10 (21)	71 (14)	118 (13)
Influenza vaccination[e]	30 (86	44 (79)	444 (79)	752 (76)
Smoking status				
Current smoker	3 (8)	5 (9)	35 (6)	80 (8)
Former smoker	14 (39)	17 (30)	241 (41)	409 (39)

Data are No. (%) except where indicated. Numbers represent individual participants. Missing data < 1% is not shown; if more than 1% is missing, the percentages are given as footnote.

Abbreviations: ARTI, acute respiratory tract infection; RESCEU, Respiratory Syncytial Virus Consortium in Europe; RSV, respiratory syncytial virus.

[a]One patient experienced 2 separate influenza B infections during follow-up.

[b]Cardiovascular comorbidity included all arrhythmias, structural heart diseases, angina, and cardiac events such as infarction, percutaneous coronary intervention, and bypass surgery. Hypertension was not included in this definition. Lung disease included asthma, chronic obstructive pulmonary disease, chronic bronchitis, and emphysema. Diabetes was defined as either type.

[c]Missing n = 12 (2%).

[d]Missing n = 56 (10%).

[e]Missing n = 19 (3%).

Performance of the ILI Case Definitions for RSV

Sensitivity of the ILI and modified ILI case definitions was low for RSV-ARTI (11% for ILI, 33% for modified ILI; Table 3 and Figure 2). The AUC was 0.52 for both ILI case definitions.

Table 2. Clinical Symptoms of Respiratory Episodes

Patient-Reported Symptoms	RSV-ARTI Episodes (n = 36)	Influenza-ARTI Episodes (n = 57)	Other ARTI Episodes (n = 657)
Rhinitis	36 (100)	55 (96)	624 (95)
Cough	35 (97)	55 (96)	572 (87)
Wheeze	16 (44)	26 (46)	223 (34)
Phlegm	34 (94)	52 (91)	466 (71)**
Dyspnea	24 (67)	42 (74)	309 (47)*
Fever (≥38°C)	2 (6)	11 (19)	26 (4)
Feeling feverish	12 (33)	37 (65)**	191 (29)
Headache	27 (75)	45 (79)	348 (53)*
Myalgia	19 (53)	41 (72)	263 (40)
Disturbed sleep	26 (72	51 (89)*	440 (67)
Feeling unwell	33 (91)	56 (98)	499 (76)*
Disturbance in daily activity	27 (75)	51 (89)	348 (53)**
Vital signs from home visit[a]			
Temperature baseline, mean (SD)	36.4°C (0.5)	36.4°C (0.7)	36.5°C (0.6)
Temperature ARTI, mean (SD)	36.6°C (0.6)	36.9°C (1.0)*	36.5°C (0.6)
Temperature increase, mean (SD)[b]	0.2°C (0.6)	0.5°C (0.8)	0°C (0.7)
Fever, ≥38°C	2 (6)	9 (16)	13 (2)
Respiratory rate/min, mean (SD)	17 (5)	17 (5)	17 (4)
Respiratory rate > 20/min	6 (17)	8 (14)	63 (10)
Saturation, mean (SD)	96% (2)	96% (2)	97% (2)*
Saturation, SaO_2 < 95%	5 (14)	10 (18)	39 (6)
Heart rate, bpm, mean (SD)	74 (12)	76 (12)	71 (11)
Composite fever, ≥38°C[c]	4 (11)	14 (25)	33 (5)

Data are No. (%) except where indicated. Numbers represent respiratory episodes unless stated otherwise.

Abbreviations: ARTI, acute respiratory tract infection; bpm, beats per minute; RSV, respiratory syncytial virus.

Statistical significance compared to RSV-ARTI: *P < .05, **P < .01, ***P < .001 (not indicated if nonsignificant).

[a]Measured by the study team during the ARTI visit unless otherwise indicated.

[b]Compared to baseline measurement before the season.

[c]Patient reported or measured during ARTI home visit.

Performance of the case definitions in the subcohort of 178 medically attended patients (11 medically attended RSV-ARTI) showed similar results (Table 3). The sensitivity in identifying influenza was 25% for ILI and 65% for modified ILI with an AUC of 0.59 and 0.69, respectively (Supplementary Table 1).

Exploration of Alternative Case Definitions

Infectious productive cough (IPC) was defined as a respiratory infection with cough and production of sputum/phlegm as discriminating symptom irrespective of the presence of fever. IPC identified 94% of RSV cases (2 missed cases) but specificity was only 30%, resulting in an AUC of 0.62 (Supplementary Table 2). The second alternative, IPC without fever, specifically excluded cases with fever to discriminate RSV from influenza (Box 2). IPC without fever identified 61% of RSV cases with a specificity of 55% resulting in an AUC of 0.58 (Supplementary Table 2 and Figure 2). Bootstrapped results and performance in those with medical attendance showed similar results (Supplementary Tables 3 and 4).

Table 3. Performance of ILI Case Definitions for RSV-ARTI

	RSV-ARTI (n = 36)	MA-RSV-ARTI (n = 11)
ILI[a]		
No. (%)	4 (11)	1 (9)
Sensitivity (95% CI)	11 (3–26)	9 (0–41)
Specificity (95% CI)	93 (91–95)	84 (77–89)
LR+ (95% CI)	1.6 (.6–4.2)	0.6 (.1–3.7)
LR– (95% CI)	1.0 (.9–1.1)	1.1 (.9–1.3)
PPV (95% CI)	8 (2–18)	4 (0–18)
NPV (95% CI)	95 (94–97)	93 (88–97)
AUC	0.52	0.46
Modified ILI[a]		
No. (%)	12 (33)	4 (36)
Sensitivity (95% CI)	33 (19–51)	36 (11–69)
Specificity (95% CI)	70 (67–74)	58 (50–66)
LR+ (95% CI)	1.1 (.7–1.8)	0.9 (.9–1.0)
LR– (95% CI)	1.0 (.8–1.2)	1.1 (.7–1.8)
PPV (95% CI)	5 (3–9)	5 (2–13)
NPV (95% CI)	95 (93–97)	93 (86–97)
AUC	0.52	0.47

Abbreviations: ARTI, acute respiratory tract infection; AUC, area under the receiver operating characteristic curve; CI, confidence interval; ILI, influenza-like illness; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MA, medically attended; NPV, negative predictive value; PPV, positive predictive value; RSV, respiratory syncytial virus.

[a]ILI includes measured temperature ≥ 38°C while the modified ILI includes also the feeling of being feverish.

Targeted Testing for RSV

By testing everyone with an ARTI, 21 tested patients were required to identify 1 case of RSV. Targeted testing using ILI required just 13 tested ILI cases per case of RSV. But because the proportion of ILI within ARTI was low, 188 screened ARTI cases were needed to identify the 13 ILI cases required for 1 case of RSV. IPC required 23 ARTI cases to be screened to find 16 IPC patients that had to be tested to identify 1 case of RSV (Table 4).

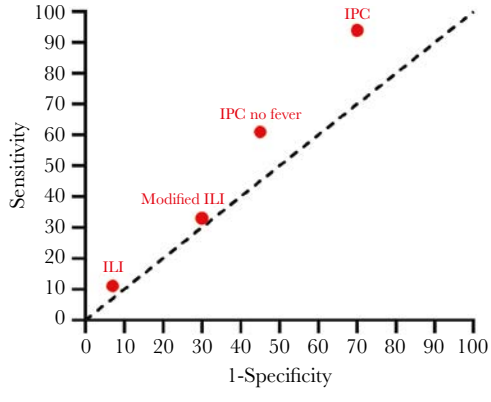

Figure 2. Area under the curve plot of performance of case definitions for respiratory syncytial virus. ILI includes measured temperature ≥ 38°C while modified ILI includes also the feeling of being feverish. Abbreviations: ILI, influenza-like illness; IPC, infectious productive cough.

Box 2. Alternative Case Definitions

Alternative 1: Infectious productive cough	Acute respiratory infection with: • cough with sputum/phlegm production
Alternative 2: Infectious productive cough without fever	Acute respiratory infection with: • cough with sputum/phlegm production WITHOUT • measured fever or feeling feverish

DISCUSSION

In this study we investigated the performance of the WHO ILI and a modified ILI case definition in identifying RSV infection in community-dwelling older adults. Sensitivity for RSV-ARTI was poor for ILI (11%) and modified ILI (33%) with an AUC of 0.52, indicating the inability of both case definitions to discriminate RSV-ARTI from other respiratory infections. Alternative case definitions formulated in this study were unable to substantially improve identification of RSV-ARTI.

Complementary to previous studies performed in children and adults [7–10], we confirm that RSV is not captured well by ILI in community-dwelling older adults. Fever is less frequently reported in RSV infections compared to influenza infections [7, 16–19]. Moreover, age might also negatively influence occurrence of fever as shown for newborns [8, 9, 20], but also for the elderly who may lack a robust febrile response in up to one-third of acute infections [21]. The latter can be caused by a lower baseline temperature (simply not reaching the fever threshold) or because of diminished febrile responses [21]. As observed in our study, occurrence of fever or even a significant increase in body temperature compared to baseline was low, which negatively impacts the sensitivity of ILI for RSV.

The strength of this study is the prospective design with a focus on the older adult community population. To our knowledge, this study represents the largest cohort of community-dwelling older adults to date in which the WHO ILI case definition was tested. Medical attendance was not required to trigger viral testing in those with respiratory symptoms, which limits the risk of selection bias for more severe disease. Because of intensive follow-up, we tested 95% of the ARTI episodes and had complete symptom diary data available in 93% of those episodes.

Limitations also deserve discussion. First, the number of RSV and influenza cases was low, which could have affected the performance of the case definitions. Bootstrapped results showed similar results and the observed symptomology was comparable to other studies [22, 23], which is reassuring. Second, the performance of case definitions is dependent on the clinical setting. Surveillance often takes place in a medical setting where disease is more severe and not in community-dwelling patients. We observed mainly mild disease, although results were similar in those with medical attendance. Generalizability to hospitalized patients is uncertain because RSV-related hospitalization did not occur in our study. Third, patients were not obliged to measure temperature when they felt feverish. This could have negatively affected ILI performance because ILI requires a measured fever to fulfil to the case definition. We therefore also used a modified ILI case definition requiring only the feeling of being feverish. Nevertheless, temperature was measured in 97% of the home visits and we showed that temperature was not substantially higher upon respiratory infection in those with RSV compared to baseline. The median timing of the home visits in those with RSV-ARTI was 1 day after the peak of symptoms. Additionally, while temperature was measured using different methods during the ARTI visits (tympanic membrane 50%, axillary 30%, infrared 10%, and oral 8%), 91% of patients were measured by the same method at baseline and during the study visit for an ARTI.

Worldwide RSV surveillance is largely dependent on the ILI and ARI case definitions [6]. ARI was not included in our analysis because we used ARI symptoms as criterion for sampling of ARTI episodes. RSV vaccines for older adults are currently in a late stage of clinical development. While clinical trials are able to show vaccine efficacy (performance of an intervention under ideal circumstances), we need good surveillance to measure vaccine effectiveness (real-world performance) after implementation. By using estimates of disease burden before and after implementation of a new vaccine in combination with vaccine coverage it is possible to calculate the impact of vaccine introduction. However, the impact of vaccination will be underestimated if estimates are obtained from a surveillance system in which the majority of the burden is not captured. The impact of future RSV vaccine introduction might go unnoticed if ILI is used for surveillance.

We show that in older adults the proportion of RSV in those who fulfil the ILI case definition is much lower (7.5%) (Supplementary Table 4) compared to 19%–45% for influenza [24, 25]. Consequently, even in the unrealistic scenario

Table 4. Performance of Case Definitions for RSV Surveillance and Targeted Testing

Case Definition	Proportion of Case Definition Within ARTI, %	Proportion of RSV Within Case Definition, %	Total Tested per RSV Case [a]	Total Screened per RSV Case [b]
ARTI	100	4.8	21	21
ILI	7.1	7.5	13	188
Modified ILI	29.7	5.4	19	62
IPC	70.9	6.4	16	23
IPC no fever	45.5	6.5	15	33

Abbreviations: ARTI, acute respiratory tract infection; ILI, influenza-like illness; IPC, infectious productive cough.

[a]1/proportion RSV within case definition.

[b]Total screened = total tested/proportion case definition within ARTI.

of a 100% effective vaccine, trends in case definition incidence would find at most a 7.5% reduction. These reductions might go unnoticed because of considerable variation in RSV seasonality [26], suboptimal vaccination coverage, and real-world vaccination procedures. Additionally, a reduction in RSV ARTI might be compensated by ARTI due to other respiratory pathogens. This phenomenon was seen for influenza when an unchanged incidence of ILI was observed despite a reduction in laboratory-confirmed influenza [24]. Unfortunately, we were not able to formulate an alternative RSV case definition that was able to increase the proportion of RSV and substantially increase discriminative performance (Supplementary Table 1). This suggests that there might not be a simple clinical case definition that can discriminate RSV from other respiratory infections. Additional diagnostic testing therefore seems inevitable to accurately determine the impact of RSV vaccination.

Vaccine effectiveness can be measured by determining the odds of vaccination between laboratory-confirmed cases and controls that fulfil a certain case definition using a test-negative design [27]. Large studies will be required to accurately determine RSV vaccine effectiveness because of the low proportion of RSV in currently available case definitions. The choice of which case definition to use for targeted sampling in these studies is crucial to decrease the costs and limit the risk of selection bias. The alternative case definitions from our study could improve this targeted sampling process as shown in Table 4. However, these alternative case definitions were developed with a relatively low number of cases and validation in other settings and larger groups of patients is still needed to confirm their performance.

CONCLUSION

In this study we showed that the syndromic WHO case definition for ILI underestimated the confirmed RSV occurrence by 9-fold in community-dwelling older adults. This is important because worldwide surveillance for RSV is largely dependent on the case definition for ILI. With the current surveillance programs, we risk being unable to measure the vaccine effectiveness of RSV vaccines. Because RSV vaccines are currently in a late stage of clinical development, there is an urgent need to determine the best approach to measure the impact of RSV vaccine introduction in older adults.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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