Economic burden and health-related quality-of-life of respiratory syncytial virus (RSV) and influenza infection in European community-dwelling older adults

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Abstract

Background

Respiratory syncytial virus (RSV) and influenza virus infections result in a considerable mortality and morbidity among the ageing population globally. Influenza vaccination for older adults before the seasonal influenza epidemic has been evaluated to be cost-effective in many countries. Interventions against RSV in older adults are in the pipeline, and evaluating their cost-effectiveness is crucial for decision-making. To inform such evaluations, our aim was to estimate average costs and health-related quality-of-life (HRQoL) in older adults with RSV and influenza infection.

Methods

The European "RESCEU" observational cohort study followed 1040 relatively healthy community-dwelling older adults aged 60 years and above during two consecutive winter seasons. Healthcare resource use and HRQoL were collected and analyzed during RSV episodes, and also during influenza episodes. Country-specific unit cost data were mainly obtained from national databases. Direct costs were estimated from a patient, healthcare provider, and healthcare payers' perspective, whereas indirect costs were estimated from a societal perspective. Due to small sample size, no formal statistical comparisons were made.

Results

Thirty-six RSV and 60 influenza episodes were reported, including one hospitalization. Means [medians] (1^{st}-3^{rd} quartile) of €26.4[5.5](0-47.3) direct and €4.4[0](0-0) indirect costs were reported per non-hospitalized RSV episode, and €42.5[36](3.3-66.7) direct and €32.1[0](0-0) indirect costs per non-hospitalized influenza episode. For RSV episodes, the utility value

decreased from 0.896[0.928](0.854-0.953) to 0.801[0.854](0.712-0.937) from pre-season to one week after symptom onset; for influenza, the change was from 0.872[0.895](0.828-0.953) to 0.664[0.686](0.574-0.797).

Conclusion

The average costs and HRQoL estimates of older adults treated outside the hospital can be used to inform the design of future studies and the decision-making regarding interventions to prevent RSV infection in older adults. Larger studies are needed to provide better country-specific and complementary cost estimates and to allow for formal statistical comparison of costs between RSV and influenza.

Key words: RSV, flu, influenza, cost, productivity loss, health-related quality-of-life, elderly, outpatients, EQ5D, prospective study

Introduction

Acute respiratory tract infections (ARTIs) in older adults are commonly caused by respiratory syncytial virus (RSV) and influenza viruses. A recent meta-analysis estimated that the incidence rate of RSV-associated ARTI in older adults ≥65 years was 6.7 per 1000 persons per year in industrialized countries and 14.5% of them were admitted to hospitals, with a 1.6% in-hospital case fatality ratio [1]. Similarly, adults 65 years and above are at particularly high risk for complications associated with influenza, leading to significant numbers of influenza–related hospitalizations and deaths [2-4]. Seasonal influenza vaccination programmes for older adults have been evaluated to be cost-effective and are implemented in many countries [5-7]. Currently, no RSV vaccine is available to protect older adults, but several candidates are undergoing phase 3 clinical trials [8-10]; hence, it is essential for policymakers to evaluate the cost-effectiveness of targeting older adults with those interventions. To inform such an evaluation, reliable estimates of cost and health-related quality-of-life (HRQoL) associated with RSV infection in older adults are crucial.

Limited direct and indirect RSV-related cost data on older adults are available. Two recent studies compared RSV-related hospitalization costs with influenza or other ARTIs and found no statistically significant differences in average cost per admission [11, 12]. Another study estimated the RSV-related costs of ambulatory visits and prescribed medication greater than $2000 among older adults in the United States (US) [13]. To our knowledge, no European data on RSV-related costs of older adults in community settings are available. European and US per-person healthcare costs are known to differ substantially [14].

The few studies that measured HRQoL among RSV patients focused on infants and their parents

[15, 16]. Cost-effectiveness analyses of RSV interventions in older adults have used influenza data as a proxy [17, 18]. One study showed that RSV patients reported worse HRQoL than influenza patients, but this was only for hospitalized patients [19].

The principal aim of our study is to estimate the average costs and HRQoL in community-dwelling older adults with RSV and with influenza, using data from a large prospective cohort study [20].

Methods

The REspiratory Syncytial virus Consortium in EUrope (RESCEU) older adult study (Clinicaltrials.gov: NCT03621930) was conducted to investigate the incidence and severity of RSV infection in relatively healthy community-dwelling older adults aged 60 years and above, as well as their healthcare resource use and HRQoL [20]. It was a prospective, observational cohort study that was conducted in three countries, Belgium, the United Kingdom (UK), and the Netherlands during two consecutive RSV seasons (October 1st to May 1st in 2017-2018 and 2018-2019). Eligible patients[1] were recruited via 17 general practitioners' (GP) offices and had a pre-season home visit to establish their baseline characteristics. During the RSV season, patients were contacted weekly, and if they had any ARTI symptoms for at least one day, they underwent a point-of-care polymerase chain reaction (PCR) test at home within 72 hours, with RSV and influenza infections confirmed within 24 hours after the nasopharyngeal sample was taken. Patients recorded their daily symptoms and medication use until symptom-free in a diary they received during the first home visit. The diary also included weekly questions on work

[1] The calculated sampling size for primary outcome of RSV incidence was 1000, calculated based on annual medically attended (MA) RSV incidence rate from literature. More details on the sampling size calculation are available in the study protocol and primary analysis [20].

absenteeism, usual activities, and HRQoL, and on resource use during the episode. A post-season home visit was also conducted within two months after the RSV season to collect data and samples from patients, similar to the pre-season visit. Participants gave informed consent and were followed up during one RSV season (Details are available in [20]).

Cost

Unit costs were collected according to the resource use data extracted from the diary. Country-specific national prices were used for unit healthcare visits and medication. Cost of productivity losses per paid-work day was estimated based on the gross average annual salary using the human capital approach [21]. Costs were inflated and converted to euro year 2020 values using harmonised indices of health sector consumer prices and annual nominal exchange rates from Eurostat [22, 23]. Details are reported in the Supplementary Methods 2-4.

We reported costs from the perspectives of the patient, healthcare provider, healthcare payers (= patient + healthcare provider, direct costs), and society (= direct + indirect costs), accounting for key healthcare system and reference case economic evaluation differences (see Supplementary Method 1).

Direct costs per episode were obtained by multiplying the healthcare use data (from the diary) by the unit cost per type. Indirect costs per episode were obtained by multiplying workdays lost (diary) with the average salary per day. These direct and indirect costs were summed to obtain the total costs per episode. (see Supplementary Methods 2-4).

Health-related quality-of-life

EQ-5D-5L [24, 25] was used to collect HRQoL data during the pre- and post-season home visit, and the first home visit of each ARTI episode (Week 0: W0), as well as each week after symptom

onset over a four-week period (W1 till W4) or until the patient was symptom-free. EQ-5D-5L contains a descriptive system and a visual analogue scale (VAS) to record a respondent's health status on the day of the survey (see Supplementary Method 5). The EQ-5D-5L states of each patient were converted into health utility values using the corresponding country-specific value set [26].

Descriptive analysis

Costs and HRQoL are only presented for non-hospitalized community-dwelling older adults, since no RSV patient was hospitalized during this study, and the only hospitalized influenza patient was excluded from further analysis. We calculated summary statistics for RSV- and influenza-related direct and total costs. Summary statistics for VAS scores and EQ-5D utility values were obtained for each time point and compared to the pre- and post-season values. In addition, we calculated the percentage of respondents reporting problems on each EQ-5D dimension. Missing values are reported but not included to calculate summary statistics. Costs, VAS scores, and utility values were also evaluated in subgroups, stratified by whether professional medical care was sought (yes/no), disease severity (mild/moderate[2]), and influenza vaccination status (yes/no). Mean costs were also shown by country. All analyses were conducted in R (version 3.6.2) [27].

Results

Cost

In total, 36 PCR-confirmed RSV episodes and 59 PCR-confirmed influenza episodes were included in the cost analyses (Supplementary Figure 1). Patients' baseline characteristics and resource use per episode are reported in Supplementary Tables 2 and 3.

[2] Moderate: any non-hospital medical-attendance or new or increased used of medications.

Table 1 shows the mean [median](1st - 3rd quartile) direct costs per RSV episode to be €11.7 [3.4](0-12.2), €14.6 [0](0-23.2) and €26.4 [5.5](0-47.3) from the patient's, healthcare provider's and healthcare payers' perspective, respectively. The mean cost of productivity losses was €4.4 [0](0-0) per episode and the mean total costs were €30.8 [5.5](0-50) from a societal perspective. The mean and median costs were higher[3] per influenza episode from all four perspectives, but interquartile ranges overlapped largely (Table 1). One patient reported productivity loss of one day during an RSV episode, whereas two patients reported four respectively nine days productivity loss during influenza.

Thirty-one percent of RSV and 57.6% of influenza episodes were medically attended (MA) (Supplementary Table 4). Mean and median direct costs were similar for RSV and influenza non-MA episodes, as well as for RSV and influenza MA episodes. MA episodes incurred higher[3] costs than non-MA episodes. Median medication costs seem slightly higher[3] for an RSV than for an influenza episode from the patient's perspective, and vice versa from the healthcare provider's perspective, but the interquartile ranges again overlapped widely (Supplementary Table 4).

Subgroup costs by severity levels and influenza vaccination status are reported in Supplementary Tables 5 and 6. UK patients had higher[3] healthcare visit costs from a healthcare provider's (National Health Service; NHS) perspective, whereas Belgian and Dutch patients had higher[3] medication costs from the patients and healthcare provider's perspectives, but sample sizes were very small (ranging between 7 and 15 RSV episodes and between 16 and 22 influenza episodes, Supplementary Figure 2).

[3] Note that comparisons made here and below were all based on the observed data but not on statistical tests.

Health-related quality-of-life

Thirty-four PCR-confirmed RSV episodes and 56 PCR-confirmed influenza episodes had available HRQoL diary data (Supplementary Figure 1). Pre-season, around 41.2-53.6% and 32.0% of older adults reported problems with pain/discomfort and mobility, respectively, and only 1.8-3.0% reported problems with self-care (Supplementary Table 7). A higher proportion of patients reported problems during RSV and influenza episodes than pre- and post-season on all five EQ-5D dimensions up to three weeks after symptom onset (two weeks for mobility). At W0, all patients reported at least slight problems in each EQ-5D dimension. Usual activities were affected the most during both the RSV and influenza episodes, and the number of patients reporting any problem increased from 8.8% (pre-season) to 52.9% (W1) for RSV and from 19.6% to 84.6% for influenza. "Having any problem" was reported more frequently for influenza than for RSV episodes, on all dimensions during all timepoints after symptom onset (Supplementary Table 7). Note that older adults who experienced an influenza episode reported more[3] problems on three of the five dimensions pre-season than the group of older adults who experienced an RSV episode. Changes in EQ-5D utility values and VAS scores are presented in Figure 1. For RSV episodes, the mean [median](1st-3rd quartile) utility value decreased markedly from pre-season to W1 (from 0.896 [0.928](0.854-0.953) to 0.801 [0.854](0.712-0.937)), and then increased weekly. In W3, the mean utility value almost returned to its pre-season level. The W4 and post-season mean utility values of RSV episodes were higher[3] than the pre-season value. Compared to the mean utility value of RSV episodes, the value of influenza episodes decreased to a larger[3] extent from baseline to W1 (from 0.872 [0.895](0.828-0.953) to 0.664 [0.686](0.574-0.797)) and bounced back slower, with interquartile ranges largely overlapping. The changes in mean and median VAS scores

followed a similar trend as the mean utility values but were less[3] pronounced (Figure 1). RSV episodes had higher[3] utility values than influenza episodes at each time point, in both the MA and non-MA groups, and when only considering persons vaccinated against influenza, although this was not the case for VAS scores. Detailed subgroup analyses[4] and description of two patients diagnosed with RSV and influenza in a single season are presented in Supplementary Result 3.4.

Discussion

Since data on the economic burden and HRQoL of RSV in community-dwelling older adults is scarce, our study aimed to fill the knowledge gap and found an average total cost of €30.8 [5.5](0-50) and the utility value decreased from 0.896 [0.928](0.854-0.953) to 0.801 [0.854](0.712-0.937) one week after symptom onset compared to pre-season for a non-hospitalized RSV episode. This study also found that using direct costs related to influenza infection might be acceptable as a proxy for RSV infection in older adults in the ambulatory care setting or not seeking medical care. This seems, however, not true for HRQoL. Results should be interpreted with care given the small sample sizes and wide interquartile ranges.

We found much lower direct costs compared to the only other study that measured ambulatory costs of RSV infection in older adults ≥65 years; on average €75.2[65.3](51.8-83.6) total costs and €34.3[30.3](16.6-48.3) medication costs per MA RSV episode compared to $1597 in costs of ambulatory consultations and $2022 in prescription medicine costs (65-74 years), based on a commercial claims database analysis in the US [13]. The mean number of healthcare consultations per RSV episode was similar between the two studies, where we estimated 1.2[1](1-1) GP visits

[4] Note that any observed differences in subgroup results can be due to random error given the small sample sizes

compared to the estimation of 2.7 (age 75-84 years) and 0.7 visits (age 85 years and above) in the US study. Hence the differences are likely explained by differences in pricing as a consequence of predominantly private health insurance in the US versus public health insurance in Europe [28]. Our costs of influenza (€42.5[36](3.3-66.7) healthcare visits costs and €19.1[7.80](1-24.8) medication cost) are comparable to the estimated mean costs of healthcare visits (€39 and €43, assuming lowest and highest unit price) and medication (€14 and €23) for MA influenza from a Belgian study including children and adults [29]. The medication costs of non-MA influenza-like illness (ILI) episodes were also comparable (€6.3[1.2](0-12.2) vs. €3-7) [29]. A cost analysis in 15 European countries among patients with ILI estimated a mean cost of €69 from a healthcare payer's perspective (13 years and above) [30], which were also comparable with our findings of €75.2[65.3](51.8-83.6) and €69.1[58.53](40.89-77.14) per RSV and influenza MA episodes. The average cost per non-hospitalized RSV episode in older adults seems lower than in infants [13, 16], indicating generally milder infections. However, given the large number of the aging population and the incidence rate, the overall RSV disease burden could be substantial in Europe. Hodgson et al [15] reported EQ-5D profiles among RSV patients (aged 15 years and above) and found more problems were reported during the infection period than at baseline on all five EQ-5D dimensions. Since they focused on younger adults, problems on mobility and self-care were reported less often than in our study [15]. A decrease of 0.095 (from 0.896[0.928](0.854-0.953) to 0.801[0.854](0.712-0.937)) in utility value was observed in our study one week after symptom onset. This HRQoL decline was less pronounced than what was previously reported for patients with RSV; Hodgson et al [15] estimated a 0.452 utility loss on the worst day compared to baseline whereas Diez-Gandia et al [16] reported 31.5% decrease in HRQoL scores in day 7 after RSV

infection. Potentially ‘worst day’, in terms of HRQoL, occurred fewer than seven days after disease onset; we also observed a lower utility of 0.606[0.701](0.579-0.705) at W0 (on average 3.75 days after disease onset). In addition, Hodgson’s data were collected retrospectively, while our study collected data during the episode and, therefore, complied more with the intended use of EQ-5D. Furthermore, our utility values were generated through EQ-5D-5L value sets based on preference weighting, but Diez-Gandia’s HRQoL utilities were calculated using an unweighted method with a self-developed questionnaire; thus, discrepancies in HRQoL values can be expected [31]. Hodgson et al used EQ-5D-3L instead of EQ-5D-5L, while the latter was reported as having better measurement properties and discriminatory power among patients than EQ-5D-3L [32]. Meijboom et al assumed utilities of MA RSV patients at 0.46 per day over a seven-day period [18], which was lower than what we found (0.801[0.854](0.712-0.937) at W1). However, they considered high- and low-risk patients and took their estimates from the influenza literature [33, 34].

In our study, better HRQoL was observed in RSV patients than in influenza patients. This can either reflect a real difference or can be due to random error. Better HRQoL for RSV than for influenza patients was similar to Falsey’s study in 2005 [35], where RSV infection resulted in lower functional impairment compared to influenza infection, but contradictory to Falsey’s 2021 study [19], which showed RSV patients reported more severe symptoms and lower VAS scores than influenza patients. Note that Falysey’s 2021 study included RSV participants being older (mean age [median]: 67.3 [70] years) and having more chronic diseases than the influenza patients (64.4 [65.5] years). Additionally, in our study, RSV patients reported better HRQoL in terms of mean utility values and VAS scores than influenza patients at baseline, where initial poorer health

can lead to a more impactful health event (Supplementary Table 2). More importantly, their study recruited non-European hospitalized patients, whose illness episode and health scoring preferences are difficult to compare to ours. We estimated utility one week after symptom onset for influenza to be 0.664[0.686](0.574-0.797), which is similar as previously reported for Belgian patients of all ages [29]. We observed a larger impact on HRQoL in MA patients than non-MA patients, in line with previous studies [15, 29]. Older adults vaccinated against influenza had worse HRQoL at baseline, but better HRQoL during their influenza episode than their unvaccinated counterparts. The observation at baseline may result from random error or from influenza vaccine uptake being greater in people with more comorbidities. The observation during the episode supports that influenza vaccination reduces severity and, thus, limits the decrease of HRQoL due to influenza infection [36, 37].

Limitations and strengths

Our study has several limitations. First, despite this prospective observational study having recruited 1040 participants, only 36 RSV episodes were identified, and none of the participants were hospitalized. Due to the small sample size, we did not perform formal statistical tests, therefore, observed differences can either reflect real differences or can be due to random error. Second, we pooled data from three countries with different healthcare systems and country-specific unit costs. Country-specific analysis could have been more informative if the sample size was sufficient. Third, HRQoL was not measured for all episodes close to symptom onset because of the difficulty in scheduling the first home visit (W0) of each ARTI episode within 72 hours after symptom onset. Fourth, participation in the study, which included a non-medical care home

visit at W0, may have influenced healthcare-seeking behaviour, despite explicit messaging that the home visit was not a medical care consultation. Fifth, when evaluating the indirect cost from a societal perspective, the loss of unpaid activities could not be considered due to absence of data.

Our study has important strengths. First, the prospective "healthy" cohort design of our study enabled us to recruit and follow up representative community-dwelling patients over their infection episodes with minimal recall bias. Second, we made efforts to diversify our sample in three European countries and used country-specific national tariffs for cost analyses to reflect the reality as much as possible. Third, we were able to make direct comparisons between RSV and influenza episodes from the same cohort, validating previous studies which used influenza cost information as a proxy for RSV costs. Fourth, we used EQ-5D-5L and country-specific utility value sets to estimate HRQoL, which can reflect the general public's preferences for different health states and such information is essential for policy making based on health economic evaluation.

Implications

To our knowledge, this is the first study presenting economic burden and HRQoL estimates based on data collected directly from older adults with RSV infection treated outside the hospital. The average costs and HRQoL estimates can be used to inform decision-making regarding interventions to prevent RSV infection in older adults. Larger studies are needed to test differences statistically and to provide better country-specific and complementary cost estimates. This may be difficult to accomplish using a prospective design.

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Ethics approval

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 ref 17/LO/1210, IRAS Ref: 224156).

Declaration of interests

LB declares regular interaction with pharmaceutical and other industrial partners, but has not received personal fees or other personal benefits. The University Medical Center Utrecht as received major funding (>€100,000 per industrial partner) for investigator-initiated studies from AbbVie, MedImmune, Janssen, Pfizer, the Bill and Melinda Gates Foundation, and MeMed Diagnostics. UMCU has received major cash or in-kind funding as part of the public private partnership IMI-funded RESCEU project from GSK, Novavax, Janssen, AstraZeneca, Pfizer and Sanofi. UMCU has received major funding by Julius Clinical for participating in the INFORM study. PB declares consulting fees from Pfizer and GSK on two occasions for discussions on economic evaluation and the payments were made to the University of Antwerp. NH declares

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Tables and Figures

Table 1: Descriptive analysis: mean direct, indirect, and total costs per respiratory syncytial virus (RSV) and per influenza episode [median] (1st – 3rd quartile) from four perspectives (in € 2020 value)

	RSV (N=36)				Influenza (N=59)			
Perspective	Patient	Healthcare provider	Healthcare payer	Societal	Patient	Healthcare provider	Healthcare payer	Societal
Health care visits	0.78 [0] (0 - 0)	11.74 [0] (0 - 23.06)	12.52 [0] (0 - 27.06)		1.76 [0] (0 - 2.00)	21.67 [23.06] (0 – 35.00)	23.44 [27.06] (0 – 35.00)	
Medication	10.97 [2.7] (0 - 12.2)	2.88 [0] (0 - 0.55)	13.85 [5.54] (0 - 18.39)		14.44 [3.12] (0 - 17.63)	4.62 [0] (0 - 4.1)	19.06 [7.80] (0.97 - 24.83)	
Direct cost	**11.74 [3.42] (0 - 12.2)**	**14.62 [0] (0 - 23.22)**	**26.37 [5.54] (0 - 47.31)**		**16.2 [4.00] (0.21 - 22.9)**	**26.29 [23.06] (0 - 40)**	**42.49 [35.98] (3.34 - 66.7)**	
Productivity loss				4.38 [0] (0 - 0)				32.07 [0] (0 - 0)
Total costs				**30.75 [5.54] (0 - 50.02)**				**74.56 [36.90] (5.42 - 73.53)**

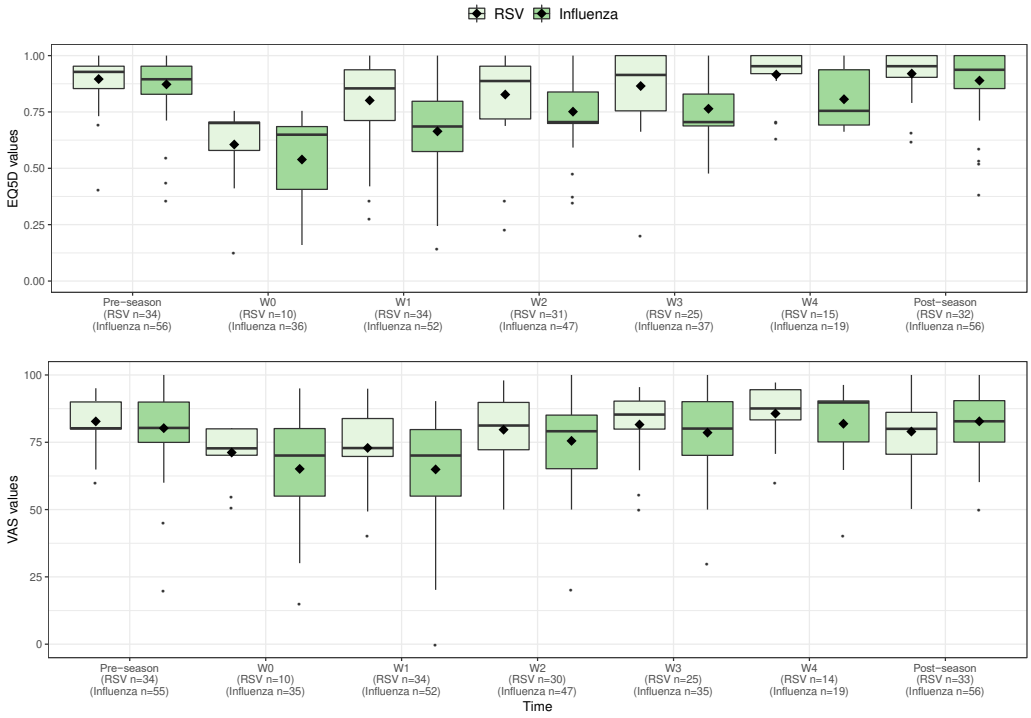

Figure 1: Boxplots of EQ-5D-5L utility values (top) and EQ-Visual Analogue Scale scores (VAS, bottom) for respiratory syncytial virus (RSV) and Influenza episodes.

N represents the number of episodes. In the boxplots, black diamond shaped dots and horizontal solid black lines represent mean and median, respectively. Boxes are interquartile range (1st to 3rd quartile), the vertical black lines are for a range between Q1 – 1.5×IQR and Q3 + 1.5×IQR (Q1, Q3=1st, 3rd quartile; IQR=Q3-Q1) and black round dots are outliers.

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