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SUPPLEMENT ARTICLE

Economic Burden and Health-Related Quality of Life of Respiratory Syncytial Virus and Influenza Infection in European Community-Dwelling Older Adults

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Background. Respiratory syncytial virus (RSV) and influenza virus infections result in a considerable mortality and morbidity among the aging 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 older during 2 consecutive winter seasons. Health care 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, health care provider, and health care 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 1 hospitalization. Means (median; first-third quartile) of €26.4 (€5.5; 0–47.3) direct and €4.4 (€0; 0–0) indirect costs were reported per nonhospitalized RSV episode, and €42.5 (€36; 3.3–66.7) direct and €32.1 (€0; 0–0) indirect costs per nonhospitalized 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 preseason to 1 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).

Conclusions. 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.

Clinical Trials Registration: NCT03621930.

Keywords. RSV; flu; influenza; cost; productivity loss; health-related quality of life; elderly; outpatients; EQ5D; prospective study.

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 aged ≥ 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 aged 65 years and older 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 programs 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.

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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 [13]. To our knowledge, no European data on RSV-related costs of older adults in community settings are available. European and US per-person health care 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 older, as well as their health care resource use and HRQoL [20]. It was a prospective, observational cohort study that was conducted in 3 countries, Belgium, the United Kingdom, and the Netherlands, during 2 consecutive RSV seasons (1 October to 1 May in 2017–2018 and 2018–2019). Eligible patients were recruited via 17 general practitioners' offices and had a preseason home visit to establish their baseline characteristics. The calculated sampling size for primary outcome of RSV incidence was 1000, calculated based on annual medically attended (MA) RSV incidence rate from the literature. More details on the sampling size calculation are available in the study protocol and primary analysis [20]. During the RSV season, patients were contacted weekly, and if they had any ARTI symptoms for at least 1 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 absenteeism, usual activities, and HRQoL, and on resource use during the episode. A postseason home visit was also conducted within 2 months after the RSV season to collect data and samples from patients, similar to the preseason visit. Participants gave informed consent and were followed up during 1 RSV season (details are available in Korsten et al [20]). The 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, Integrated Research Application System Ref 224156).

Cost

Unit costs were collected according to the resource use data extracted from the diary. Country-specific national prices were used for unit health care visits and medication. Cost of productivity losses per paid workday 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 harmonized 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, health care provider, health care payers (= patient + health care provider, direct costs), and society (= direct + indirect costs), accounting for key health care system and reference case economic evaluation differences (Supplementary Method 1).

Direct costs per episode were obtained by multiplying the health care 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 (Supplementary Methods 2–4).

Health-Related Quality of Life

EQ-5D-5L [24, 25] was used to collect HRQoL data during the pre- and postseason home visit, and the first home visit of each ARTI episode (week 0, W0), as well as each week after symptom onset over a 4-week period (W1 to 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 (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 nonhospitalized community-dwelling older adults, because 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-related 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 postseason 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), and influenza vaccination status (yes/no). Moderate disease severity was defined as any nonhospital medical attendance or new or increased used of medications. 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.

Table 1 shows the direct costs per RSV episode to be €11.7 (median, €3.4; first-third quartile [Q1–Q3], 0–12.2), €14.6 (median, €0; Q1–Q3, 0–23.2), and €26.4 (median, €5.5; Q1–Q3, 0–47.3) from the patient's, health care provider's, and health care payers' perspective, respectively. The mean cost of productivity losses was €4.4 (median, €0; Q1–Q3, 0–0) per episode and the mean total costs were €30.8 (median, €5.5; Q1–Q3, 0–50) from a societal perspective. The mean and median costs were higher per influenza episode from all 4 perspectives, but there was a large overlap in interquartile ranges (Table 1). (Comparisons made here and below were all based on the observed data but not on statistical tests.) One patient reported productivity loss of 1 day during an RSV episode, whereas 2 patients reported 4 and 9 days' productivity loss during influenza.

Thirty-one percent of RSV and 57.6% of influenza episodes were 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 costs than non-MA episodes. Median medication costs seem slightly higher for an RSV than for an influenza episode from the patient's perspective, and vice versa from the health care 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. United Kingdom patients had higher health care visit costs from a health care provider's (National Health Service) perspective, whereas Belgian and Dutch patients had higher medication costs from the patients and health care 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).

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). Preseason, 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

Table 1. Descriptive Analysis: Mean Direct, Indirect, and Total Costs per Respiratory Syncytial Virus (RSV) and per Influenza Episode from 4 Perspectives

	RSV (n = 36)				Influenza (n = 59)			
Perspective	Patient	Health Care Provider	Health Care Payer	Societal	Patient	Health Care Provider	Health Care 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)

Data are € 2020 value (median; first–third quartile).

problems with self-care (Supplementary Table 7). A higher proportion of patients reported problems during RSV and influenza episodes than pre- and postseason on all 5 EQ-5D dimensions up to 3 weeks after symptom onset (2 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% (preseason) 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 time points after symptom onset (Supplementary Table 7). Note that older adults who experienced an influenza episode reported more problems on 3 of the 5 dimensions preseason 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 utility value decreased markedly from preseason to W1 (from 0.896 [median, 0.928; Q1–Q3, 0.854–0.953] to 0.801 [median, 0.854; Q1–Q3, 0.712–0.937]), and then increased weekly. In W3, the mean utility value almost returned to its preseason level. The W4 and postseason mean utility values of RSV episodes were higher than the preseason value. Compared to the mean utility value of RSV episodes, the value of influenza episodes decreased to a larger extent from baseline to W1 (from 0.872 [median, 0.895; Q1–Q3, 0.828–0.953] to 0.664 [median, 0.686; Q1–Q3, 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 pronounced (Figure 1).

RSV episodes had higher 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 and description of 2 patients diagnosed with RSV and influenza in a single season are presented in Supplementary Result 3.4. (Any observed differences in subgroup results can be due to random error given the small sample sizes.)

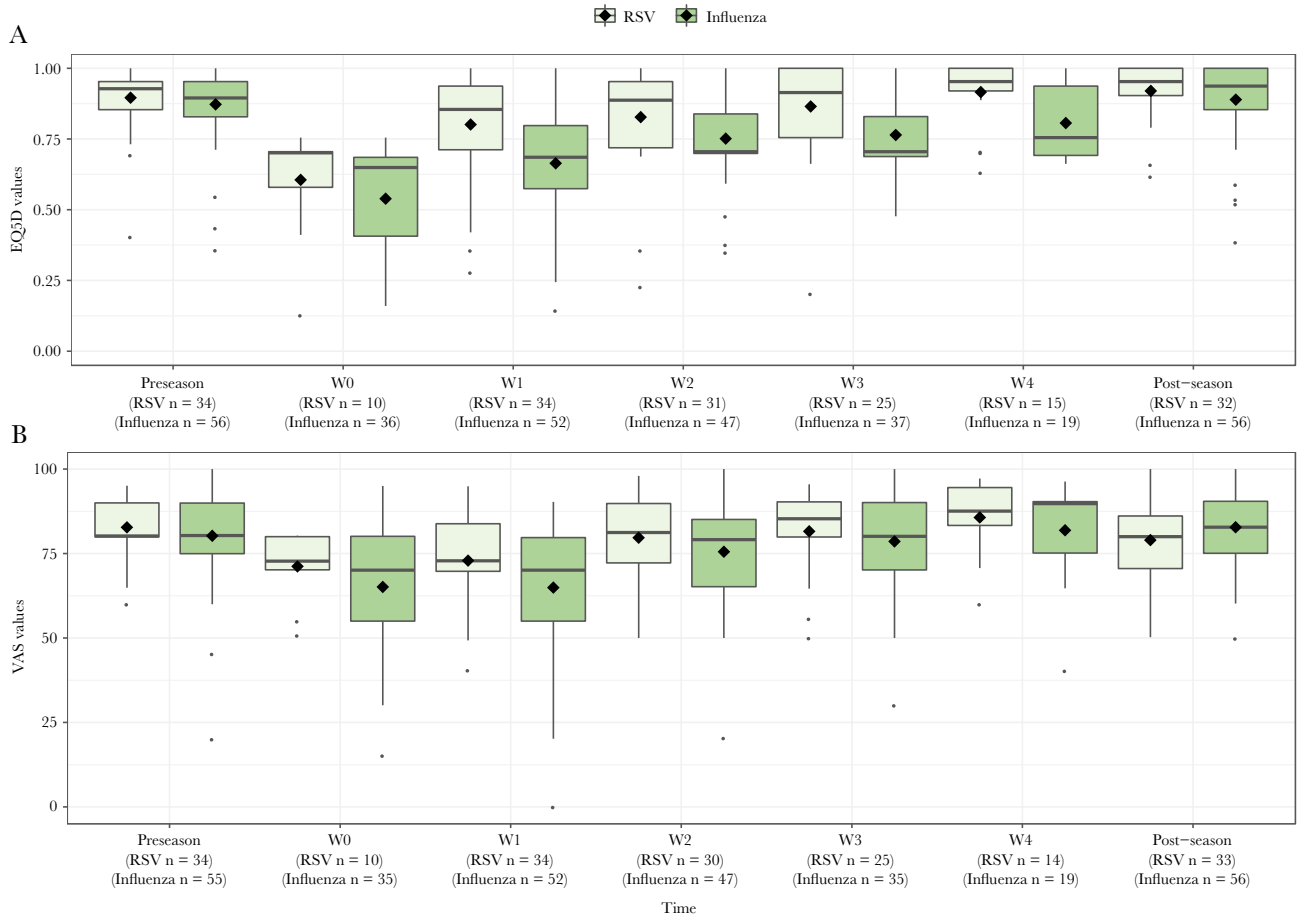

Figure 1. Boxplots of EQ-5D-5L utility values (*A*) and EQ-visual analogue scale scores (VAS, *B*) for respiratory syncytial virus (RSV) and influenza episodes.n represents the number of episodes. In the boxplots, black diamonds and horizontal solid black lines represent mean and median, respectively. Boxes are interquartile range (first to third quartile), the vertical black lines are the range between Q1 −1.5 × interquartile range (IQR) and Q3 + 1.5 × IQR (Q1, Q3 = first, third quartile; IQR = Q3–Q1), and small dots are outliers.

DISCUSSION

Because data on the economic burden and HRQoL of RSV in community-dwelling older adults are scarce, our study aimed to fill the knowledge gap and found an average total cost of €30.8 (median, €5.5; Q1–Q3, 0–50) and the utility value decreased from 0.896 (median, 0.928; Q1–Q3, 0.854–0.953) to 0.801 (median, 0.854; Q1–Q3, 0.712–0.937) 1 week after symptom onset compared to preseason for a nonhospitalized 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 aged ≥ 65 years; on average €75.2 (median, €65.3; Q1–Q3, 51.8–83.6) total costs and €34.3 (median, €30.3; Q1–Q3, 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 United States [13]. The mean number of health care consultations per RSV episode was similar between the 2 studies, where we estimated 1.2 (median, 1; Q1–Q3, 1–1) general practitioner visits compared to the estimation of 2.7 (age 75–84 years) and 0.7 visits (age 85 years and older) in the US study. Hence, the differences are likely explained by differences in pricing as a consequence of predominantly private health insurance in the United States versus public health insurance in Europe [28]. Our costs of influenza (€42.5 [median, €36; Q1–Q3, 3.3–66.7] health care visits costs and €19.1 [median, €7.80; Q1–Q3, 1–24.8] medication cost) are comparable to the estimated mean costs of health care 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 [median, €1.2; Q1–Q3, 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 health care payer's perspective (aged 13 years and older) [30], which were also comparable with our findings of €75.2 (median, €65.3; Q1–Q3, 51.8–83.6) and €69.1 (median, €58.53; Q1–Q3, 40.89–77.14) per RSV and influenza MA episodes, respectively. The average cost per nonhospitalized 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 older) and found more problems were reported during the infection period than at baseline on all 5 EQ-5D dimensions. Because 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 [median, 0.928; Q1–Q3, 0.854–0.953] to 0.801 [median, 0.854; Q1–Q3, 0.712–0.937]) in utility value was observed in our study 1 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 Díez-Gandía et al [16] reported a 31.5% decrease in HRQoL scores in day 7 after RSV infection. Potentially, the "worst day," in terms of HRQoL, occurred fewer than 7 days after disease onset; we also observed a lower utility of 0.606 (median, 0.701; Q1–Q3, 0.579–0.705) at W0 (on average 3.75 days after disease onset). In addition, Hodgson's data were collected retrospectively [15], 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 Díez-Gandía's HRQoL utilities were calculated using an unweighted method with a self-developed questionnaire [16]; thus, discrepancies in HRQoL values can be expected [31]. Hodgson et al used EQ-5D-3L instead of EQ-5D-5L [15], 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 7-day period [18], which was lower than what we found (0.801 [median, 0.854; Q1–Q3, 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 could either reflect a real difference or could 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 Falsey's 2021 study [19] included RSV participants being older (mean age, 67.3 years; median, 70 years) and having more chronic diseases than the influenza patients (mean age, 64.4 years; median 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 1 week after symptom onset for influenza to be 0.664 (median, 0.686; Q1–Q3, 0.574–0.797), which is similar to that 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].

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 3 countries with different health care 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 nonmedical care home visit at W0, may have influenced health care-seeking behavior, 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 3 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 that 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.

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.

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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