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SUPPLEMENT ARTICLE

Exploratory Analysis of the Economically Justifiable Price of a Hypothetical RSV Vaccine for Older Adults in the Netherlands and the United Kingdom

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Background: In older adults, the burden of respiratory syncytial virus (RSV) resembles that of influenza and may even be considered worse due to the lack of preventive interventions. This study was performed to identify the available literature on RSV infection in older adults, and to provide updated exploratory results of the cost-effectiveness of a hypothetical RSV vaccine in the Netherlands and the United Kingdom.

Methods: A literature search was performed in Medline and EMBASE on 11 November 2019, which served as input for a static decision-tree model that was used to estimate the EJP, for an RSV vaccine applying different willingness-to-pay (WTP) thresholds. WTP thresholds applied were €20 000 and €50 000 per quality-adjusted life-year for the Netherlands, and £20 000 and £30 000 per quality-adjusted life-year for the United Kingdom. Analyses were—in line with country-specific guidelines—conducted from a societal perspective for the Netherlands and a third-party payer perspective for the United Kingdom. The robustness of the cost-effectiveness results was tested in sensitivity analysis.

Results: After screening the literature, 3 studies for the Netherlands and 6 for the United Kingdom remained to populate the country-specific models. In the base case analysis for the Netherlands (mean RSV incidence, 3.32%), justifiable vaccine prices of €16.38 and €50.03 were found, based on applying the lower and higher WTP thresholds, respectively. Similarly, for the United Kingdom (mean incidence, 7.13%), vaccine prices of £72.29 and £109.74 were found, respectively.

Conclusion: RSV vaccination may well be cost-effective in both the Netherlands and the United Kingdom, depending on the exact RSV incidence, vaccine effectiveness and price. However, sensitivity analysis showed that the results were robust based on varying the different parameter estimates and assumptions. With RSV vaccines reaching the final stages of development, a strong need exists for cost-effectiveness studies to understand economically justifiable pricing of the vaccine.

Keywords. Respiratory Syncytial Virus; Elderly; Older adults; Cost-effectiveness; The Netherlands; United Kingdom.

Annually, respiratory illnesses cause a high burden for aging populations. Respiratory syncytial virus (RSV) is one of the pathogens causing respiratory illness with related hospital admissions and deaths every year [1–7]. Clinical symptoms of RSV infection are often nonspecific, as with to other pathogens, for example, influenza and potentially coronavirus disease 2019. Moreover, RSV has seasonal patterns with epidemic waves during fall, winter, and early spring [8], cocirculating with influenza. In older adults, the burden of RSV resembles that of influenza but many unknowns exist on incidence and severity. Hospitalization data for older adults in the United States have shown that RSV versus influenza admissions are associated with significantly worse morbidity and mortality [9]. With the aging population, the impact of RSV can be expected to increase. Whereas for infants at high risk of developing severe RSV the recombinant humanized monoclonal antibody palivizumab is available [10], no standardized treatment against RSV exists for older adults and no vaccine is yet available for RSV.

To protect the aging population against RSV, the pharmaceutical industry initiated the development of vaccines for older adults [11–14]. The significant disease burden of RSV and promising RSV candidate vaccines, urge the need to assess the public health and economic consequences of an RSV vaccine. Notably, in the current article, an economic model to assess the cost-effectiveness of RSV vaccination in older adults is presented. Two previous studies have assessed the cost-effectiveness of a (hypothetical) RSV vaccine in older adults, one in the United States and one in the Netherlands [15, 16]. Here, the aim

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was to explore the cost-effectiveness of a potential RSV vaccine in the Netherlands and the United Kingdom. Both countries use economic analysis as basis for decisions-making processes to implement a vaccination via national immunization programs.

METHODS

A cost-effectiveness analysis was conducted comparing vaccination with a hypothetical RSV vaccine in Dutch and British older adults with no vaccination, incorporating the effects and costs related to RSV disease and vaccination. A literature search was performed in Medline and EMBASE on 11 November 2019 (Supplementary Data I), which served as inputs for a static decision-tree model that was used to estimate the economically justifiable price (EJP) for an RSV vaccine based applying different willingness-to-pay (WTP) thresholds. The model structure and cohort characteristics used as input, such as RSV incidence, resource use (eg, hospitalizations), mortality rates, costs, and utilities for quality-adjusted life-years (QALYs) are presented in Supplementary Data II Tables 1, 2, 3, 4, and 5. As national health technology assessment guidelines differ among both countries, different acceptable costs for the hypothetical vaccine were estimated, taking a third-party payer perspective for the United Kingdom, including direct costs only (eg, costs for healthcare, treatment), and a societal perspective for the Netherlands, including direct and indirect costs (eg, productivity losses) [17, 18].

Model Structure

A static model using a decision tree was applied, as for this study 1 RSV season was modeled. A dynamic model, including downstream effects of vaccination on transmission, was not undertaken with the static approach, reflecting a conservative modeling approach. The assumption here is that the RSV infection is acquired once (Supplementary Data II Figure 1). Applying a 1-year time horizon is aligned with an estimated duration of protection with vaccination of 1 year [19]. This timeline also aligns well with the annual influenza vaccination as implemented in both countries [20]. The model was developed using Microsoft Office Excel 2016 software, a valid and generally accepted program for decision-tree models developed to estimate the cost-effectiveness for reimbursement authorities.

In line with the national influenza recommendations, the target populations considered eligible for the vaccine consist of older adults, aged ≥60 years for the Netherlands and ≥65 years for the United Kingdom, and were divided into age groups, 60–64, 65–74, 75–84, or ≥85 years for the Netherlands and 65–74 or ≥75 years for the United Kingdom, who are at high or low risk for RSV disease [21, 22]. Country-specific cutoffs for age categories were chosen in line with the granularity in the data available for the inputs. High risk was defined as the presence of chronic disease (ie, diabetes, multiple sclerosis, and chronic cardiac, respiratory, or liver disease), again in line with the classification for influenza vaccination [23]. The presence of chronic conditions may enhance immunosenescence in older adults and thus possibly increase the risk of acquiring an infectious disease like RSV and/or developing more severe complications owing to the occurrence of infection [24]. Within the model, on the occurrence of an RSV infection, patients could either stay at home with no visit to a healthcare provider (HCP), visit their general practitioner (GP), be hospitalized, or die.

RSV Vaccine

The EJP of the RSV vaccine was calculated based on the WTP thresholds for the Netherlands and the United Kingdom. One-off administration costs for vaccination were estimated for both countries based on data from published sources [25, 26]. In the absence of data, the vaccine efficacy (VE) was based on the effectiveness of influenza vaccination in older adults, as well as data from a phase 3 clinical trial for RSV maternal vaccination (Table 1) [27, 28]. Influenza data may suggest approximately 50% VE against pneumonia hospitalizations and deaths in older adults [29]. A range for the VE with lower and higher VE was applied for the threshold analysis. Coverage rates were analyzed and implemented for the total cost and QALYs estimated (Supplementary Data II Table 1), however, this does not influence cost-effectiveness in the static model structure chosen.

Cost-effectiveness and Threshold Analysis

The incremental cost-effectiveness ratio (ICER) summarizes the costs and effects of the hypothetical RSV vaccine versus nonpreventive treatment, calculated by dividing differences in costs and by differences in QALYs. Obviously, owing to the absence of an RSV vaccine, the price is uncertain. Therefore, a threshold analysis was performed to calculate the EJP with a WTP threshold of €20 000 for the Netherlands and £20 000 for the United Kingdom, as often applied for vaccines in the

Table 1. Respiratory Syncytial Virus Vaccine Efficacy by Disease Outcome

	Assumed VE in Older Adults, %		
Disease Outcome	Low	Base Case	High
Medically significant RSV LRTI (cases with no HCP and cases with GP visits)	30	40	50
RSV LRTI with hospitalization	40	50	60
RSV LRTI with severe hypoxemia, SpO2<92% (death)	50	60	70

Abbreviations; GP, general practitioner; HCP, healthcare provider; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; VE, vaccine efficacy.

Netherlands [30] and the United Kingdom [18, 31]. ICERs below this threshold are considered cost-effective. We also included less strict thresholds of €50 000 and £30 000, the next formally introduced thresholds for the Netherlands and the United Kingdom, respectively [31–33]. The threshold analysis portrays the impact of the VEs on the price as well as possible variability in RSV incidence. Notably, to analyze the effect of RSV incidence on prices, we used a range of 1%–10% for the probability of acquiring an RSV infection of about 3.3% and 7.1%, on average, identified in the literature for the Netherlands and the United Kingdom, respectively (Supplementary Materials data II Table 3). The relative risk of hospitalization after infection was kept constant in the model [3, 21].

Deterministic, Probabilistic Sensitivity, and Scenario Analyses

A deterministic sensitivity analysis was performed to reveal the impact of parameter variability on the ICER. For the acquisition costs, we used the estimated EJP in the base case at the lowest WTP threshold. These costs were also varied by using the minimum and maximum values obtained after the threshold analysis. If the acquisition costs were <1 (ie, <1€ or <1£), 1€ or 1£ was applied. Minimum and maximum values for cost of hospitalization, vaccination coverage, and the percentage of the high-risk group were included for deterministic analyses. Given the high uncertainty, the overall RSV incidence was varied by ±50%, that is, a range of approximately 1.7%–5% and 3%–12% for the Netherlands and the United Kingdom, respectively. Other input parameters were varied ±10% from the base case value and presented in a tornado diagram.

To explore further variation in the base case, the following scenario analyses were performed: (1) without discounting QALYs, (2) considering only GP visits and hospitalization incidence rates (excluding cases without any HCP context), (3) targeted vaccination of the high-risk group, (4) vaccination of the ≥75-year-old population, and (5) inclusion of vaccination acquisition costs only (waiving the administration costs). For the Netherlands, we excluded the indirect healthcare costs in a further specific scenario. In the last scenario for the United Kingdom, incidence data were taken from Cromer et al [7] instead of Fleming et al [3].

A probabilistic sensitivity analysis (PSA) was performed to assess the parameter uncertainty on the ICER outcome. The ICER was calculated 1000 times based on variable parameter input according to the distributions/ranges (Supplementary Data II Tables 2, 4 and 5). A beta distribution was applied for the incidence, VE, proportion of patients staying at home, and QALY losses. A gamma distribution was applied for costs and duration of illness. For the proportion of high-risk individuals, a beta-PERT distribution was applied, using the parameter's minimum, modus, and maximum values. Results of the PSA were presented in a cost-effectiveness plane and a cost-effectiveness acceptability curve.

RESULTS

Base Case

If the hypothetical RSV vaccine would be given to the 4.3 million aged ≥60 years in the Netherlands, 31 628 symptomatic RSV infections could be prevented (Supplementary data III Table 1), including 8827 GP visits, 608 hospitalizations, and 309 deaths. Implementing RSV vaccination for the 11.8 million aged ≥65 years in the United Kingdom, could avert 238 930 symptomatic RSV cases, as well as 65 235 GP visits, 6277 hospitalizations, and 4320 deaths (Supplementary data III Table 2).

For the Netherlands, based on thresholds of €20 000 and €50 000 per QALY, economically justifiable vaccine acquisition prices of €16.38 and €50.03, respectively, were calculated. For the United Kingdom, based on the ICER thresholds of £20 000 and £30 000 per QALY, economically justifiable vaccine acquisition prices of £72.29 and £109.74, respectively, were calculated.

The EJP varied significantly in both countries (Table 2). A lower VE resulted in a reduction of the EJP and vice versa; for example, for the Netherlands, on average a 30% increase (high VE) or decrease (low VE) of the base case EJP was found with the corresponding threshold of €20 000 per QALY. For the United Kingdom, the EJP of the base case increased (high VE) or decreased (low VE) on average 22%, with a threshold of £20 000 per QALY.

Sensitivity Analysis

Deterministic Sensitivity Analysis

The deterministic sensitivity analyses showed that vaccination cost, RSV incidence, and QALYs lost per hospitalization have the highest impact on the ICER in both countries (Supplementary Data III Figure 1). In addition, mortality rate, QALYs lost per RSV-related death, and VE against death, showed a significant impact on the ICER for RSV vaccination in the Netherlands and the United Kingdom.

Scenario Analysis

Results of the scenario analysis can be found in Supplementary data III Table 3. The scenario of only including the GP visit and hospitalization incidence rates resulted in a small increase of the ICER for both countries. Limiting vaccination to the high-risk population or changing the population eligible for vaccination to those aged ≥75 years significantly lowered the ICER for both countries. In the Netherlands, a significant reduction was observed when administration costs were excluded, and a slight increase when indirect healthcare costs were excluded. Furthermore, the UK-specific scenario with incidence data from Cromer et al [7], resulted in an ICER of £17 424 per QALY.

Probabilistic Sensitivity Analysis

The PSA revealed that the probability for our hypothetical RSV vaccine to be cost-effective in the Netherlands is 0.44 at a WTP threshold of €20 000 per QALY, applying the base-case vaccine

Table 2. Cost-effectiveness/Pricing Threshold Analysis of Respiratory Syncytial Virus (RSV) Vaccination in the Netherlands and the United Kingdom by Willingness-to-Pay Threshold and RSV Incidence

	EJP by RSV Incidence, € or £											
Country and WTP Threshold	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	3.32%[a]	**7**.13%[a]
EJP for the Netherlands, €												
WTP threshold: €20 000/QALY												
Low VE	−2.00	2.05	9.13	16.21	23.28	30.36	37.43	44.51	51.59	58.66	11.36	…
Base case	−3.51	5.08	13.67	22.26	30.85	39.44	48.03	56.62	65.21	73.80	16.38	…
High VE	−5.02	8.11	18.21	28.31	38.41	48.52	58.62	68.72	78.82	88.93	21.40	…
WTP threshold: €50 000 per QALY												
Low VE	3.41	18.92	34.44	49.95	65.46	80.97	96.49	112.00	127.51	143.02	39.34	…
Base case	6.64	25.38	44.11	62.85	81.59	100.33	119.06	137.80	156.54	175.28	50.03	…
High VE	9.86	31.83	53.79	75.75	97.71	119.68	141.64	163.60	185.57	207.53	60.73	…
EJP for the United Kingdom, £												
WTP threshold: £20 000/QALY												
Low VE	−1.63	8.07	17.78	27.49	37.19	46.90	56.61	66.31	76.02	85.73	…	57.90
Base Case	0.38	12.11	23.83	35.56	47.28	59.01	70.73	82.45	94.18	105.90	…	72.29
High VE	2.40	16.14	29.89	43.63	57.37	71.11	84.85	98.60	112.34	126.08	…	86.69
WTP threshold: £30 000/QALY												
Low VE	2.73	16.80	30.87	44.94	59.01	73.08	87.15	101.22	115.30	129.37	…	89.03
Base case	5.63	22.61	39.58	56.55	73.52	90.50	107.47	124.44	141.42	158.39	…	109.74
High VE	8.54	28.41	48.29	68.16	88.04	107.91	127.79	147.66	167.54	187.41	…	130.44

Abbreviations: EJP, economically justifiable price; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus; VE, vaccine efficacy; WTP, willingness-to-pay.

[a]In the base case analysis, 3.32% was the mean RSV incidence for the Netherlands, and 7.13% the mean RSV incidence for the United Kingdom.

price of €16.38 (Supplementary Data III Figure 2). If a WTP threshold of €50 000 per QALY is used, the probability of being cost-effective increased to 1. In the United Kingdom the probability of our hypothetical RSV vaccine with a price of £72.29 being cost-effective is 0.59 with a WTP threshold of £20 000, which increased to 1 for a WTP threshold of £30 000.

DISCUSSION

This study shows a significant impact of RSV incidence and VE on the maximum EJP resulting from a cost-effectiveness analysis of RSV vaccination of older adults in the Netherlands and the United Kingdom. It should be noted that the EJP must be interpreted differently for the Netherlands and the United Kingdom, as a different perspective was applied (ie, a societal perspective for the Netherlands and a third-party payer perspective for the United Kingdom). This leads to a higher price compared with a third-party payer perspective for the Netherlands, because more costs were saved when applying the broader societal perspective.

In the construction of the cost-effectiveness model, the literature search revealed that epidemiologic data on RSV in the aging population in Europe are scarce. Moreover, many countries lack sufficient surveillance systems for RSV infection [34, 35]. Measuring the burden of respiratory diseases in adults is difficult because hospitalization and/or deaths commonly occur days or weeks after the initial infection [36]. At this stage, it is possible that the virus is no longer detectable, and diagnostic classifications may miss the infection as the underlying cause. In addition, in older adults, secondary infections or exacerbations of an underlying illness may occur, and the causal infection may also not be recognized [3].

Published mathematical estimations were used to derive an incidence rate, because no data were available [3, 16]. In the absence of recognition of a high RSV burden in older adults, these estimates have a high likelihood of underdiagnosis and underreporting of RSV, in particular applying to the older estimates for the Netherlands. If more recent UK incidence rate estimates were applied for the cost-effectiveness analysis of the Netherlands, the vaccine price was comparable to the UK estimate (price, €71.52 vs €72.29). Owing to uncertainty of the RSV incidence data, different incidence rates varying from 1% to 10% were used for the economic analysis. The lack of evidence on the RSV incidence emphasizes the importance of RESCEU (REspiratory Syncytial virus Consortium in EUrope), which strives to develop robust evidence of the RSV disease burden throughout Europe [37].

Also owing to lack of data, the percentage of cases without HCP context, in both the United Kingdom and the Netherlands, is based on influenza data from the Netherlands [38] and is a fixed percentage in our analysis. A 1-way sensitivity analysis was performed using low and high percentages of cases without HCP contacts, as well as a scenario without those patients. The 1-way analysis on varying the percentage of cases without HCP contacts showed limited impact on the cost-effectiveness results (a difference of 2% from societal perspective in the Netherlands and 1% from third-party payer perspective in the United Kingdom). However, when cases without HCP contacts are ignored, an 6% and 20% increase in the ICER is observed following the third-party payer and societal perspective in the Netherlands, respectively. This difference is mainly caused the inclusion of additional societal costs, such as productivity losses for patients and caregivers, whereas the direct medical costs (healthcare costs) did not change. For the UK, only a 1% increase was observed through slight changes in QALYs gained, no costs were assumed in the absence of an HCP visit as only the third-party payer's perspective was applied.

The older adults most vulnerable for hospitalizations and death after acquiring an RSV infection are those ≥75 years old, as well as individuals in high-risk groups. In our analysis, we found that vaccination of these groups resulted in a lower ICER than vaccination of those aged ≥60 or ≥65 years in the Netherlands and the United Kingdom, respectively. Ergo, targeted vaccination seems to be an effective strategy to reduce the number of RSV hospitalizations and deaths in both countries. Vaccination of a smaller target population (ie, those aged ≥75 years) could prove to be more efficient and cost-effective [39]. However, universal vaccination of the ≥60-year-old population should not be excluded, as the burden of RSV can also be significant in the older general population, and optimal alignment with influenza vaccination may provide logistic benefits [3].

For the Netherlands, disutilities for laboratory-confirmed influenzalike illness cases were similar to those for laboratory-confirmed influenza cases [40]. Therefore, we assumed the QALY loss of an RSV-associated GP visit or hospitalization equal to that of an influenza-associated GP visit or hospitalization in the Netherlands [16]. Even though this is a well-substantiated assumption, specific RSV-related effects on quality of life could exist and warrant further inspection for optimally populating cost-effectiveness models of RSV vaccination. Although the QALY loss can be different, no distinction was made between the low- and high-risk groups. This could lead to an overestimation of QALYs for those in the high-risk group, as they may already have (multiple) comorbid conditions [41]. However, potentially more severe health outcomes in high-risk persons compared with low-risk persons can result in a higher QALY loss and may counterbalance. Notably, such changes in QALY loss resulted in only small changes in ICERs in the deterministic analysis.

A time horizon of 1 RSV season was applied. It is possible, however, that RSV vaccination has an effect in older adults that will last longer than 1 RSV season, as only the RSV-A and RSV-B strains cocirculate, and subsequent seasons may involve the same strain [42]. It can thus be argued that such longer protection could yield even more favorable cost-effectiveness results for older adults in the Netherlands and the United Kingdom. Moreover, the vaccine may protect the nonvaccinated through herd protection, which was conservatively not included in our model. However, older adults are generally typically not considered important transmitters of airborne infections, which could be considered as a conservative assumption.

Limitations of the current study relate to the estimated RSV incidence data available for the United Kingdom and the Netherlands. Together with the lack of VE data, it is not possible to draw firm conclusions regarding the maximum EJP. The deterministic analysis showed that the results depend heavily on the VE and vaccine price. In this economic analysis, VE in the older adults can only be assumed, because there is not yet a vaccine available. Furthermore, RSV infection in combination with influenza and pneumococcal disease may overwhelm a hospital's capacity to deliver good healthcare services during winter. In addition, coronavirus disease 2019 may play a role in next winters to come. Hence, reducing the RSV disease burden by vaccinating the aging population is core in maintaining sufficient capacity of these services and avoid shortages. Further epidemiologic research is needed to further elucidate incidence and severity of disease and health-services needs. Yet, and despite the limitations in this study, RSV vaccination may well be cost-effective if the vaccine is implemented in older adults for a reasonable price.

In conclusion, as RSV vaccines reach the final stages of development, there is a growing need for epidemiologic data on RSV to populate models on the economic impact of novel RSV vaccines. Despite still the lack of such data, our study shows that the implementation of RSV vaccination can be cost-effective in both the Netherlands and the United Kingdom if reasonable effectiveness and pricing are achieved.

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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