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Influential drivers of the cost-effectiveness of respiratory syncytial virus vaccination in European older adults: a multi-country analysis

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Abstract

Background We aimed to identify influential drivers of the cost-effectiveness of older adult respiratory syncytial virus (RSV) vaccination in Denmark, Finland, the Netherlands and Valencia-Spain.

Methods A static multi-cohort model was parameterised using country- and age-specific hospitalisations using three approaches: (A) the International Classification of Diseases (ICD)-coded hospitalisations, (B) laboratory RSV-confirmed hospitalisations and (C) time-series modelling (TSM). Plausible hypothetical RSV vaccine characteristics were derived from two protein subunit vaccines for adults aged ≥60 years. A full incremental analysis was conducted by comparing three RSV vaccination strategies: (1) in adults aged ≥60 years ("60y+"); (2) in adults aged ≥65 years ("65y+"); (3) in adults aged ≥75 years ("75y+") to "no intervention" and to each other. Both costs and quality-adjusted life-years (QALYs) were discounted at country-specific discount rates and the analysis was conducted from both the healthcare payers' and societal perspectives. Value of information, probabilistic sensitivity and scenario analyses identified influential drivers.

Results Besides vaccine price, the hospitalisation estimates were most influential: (A) Using adjusted RSV-ICD-coded hospitalisations at a vaccine price of €150 per dose, no intervention was cost-effective up to willingness-to-pay (WTP) values of €150,000 per QALY gained in Denmark and the Netherlands, and up to €124,000 per QALY gained in Finland. (B) Using the adjusted RSV-confirmed dataset, the findings were consistent in Denmark and comparable in Finland. In Spain-Valencia, the 75y+ strategy became cost-effective at WTP >€55,000. (C) Using TSM-based estimates, the 75y+ strategy was cost-effective at WTP >€45,000, >€101,000, >€41,000 and >€114,000 in Denmark, Finland, the Netherlands and Spain-Valencia, respectively. Sensitivity analyses showed that the (in-hospital) case fatality ratio and the specification of its age dependency were both influential. Duration of protection was found more influential than a variety of plausible waning patterns over the duration of protection.

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Conclusions Data gaps and uncertainties on the RSV-related burden in older adults persist and influence the cost-effectiveness of RSV vaccination. More refined age- and country-specific data on the RSV attributable burden are crucial to aid decision making.

Keywords RSV, Respiratory, Vaccination, Policy, Ageing population, Economic evaluation, Cost-utility analysis, Cost-effectiveness analysis, Uncertainty

Background

Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infections (RTI) in both young children and older adults. Among adults aged 60 years and above (60y+), a meta-analysis estimated 5.2 million RSV cases, 470,000 hospitalisations and 33,000 in-hospital deaths across high-income countries in 2019 [1]. With ageing populations in these countries, this disease burden is expected to increase.

RSV is contagious and seasonal, and it typically peaks during the winter months in Europe, in line with several other respiratory pathogens. RSV leads to a substantial burden, exerting pressure on healthcare resources [2]. The RSV-related disease burden among European older adults has not been well established, in terms of country- and age-specific hospitalisation rates, which are essential ingredients for cost-effectiveness analyses. Previous systematic reviews included multiple studies that reported hospitalisation rates, but the majority of these studies were conducted outside of Europe [1, 3].

In 2023, two protein subunit RSV vaccines, Arexvy® (GSK) and Abrysvo® (Pfizer), were approved for the prevention of RSV disease among adults aged 60y+ and marketed in several high-income countries. In 2024, an mRNA-based vaccine mResvia® (Moderna) was also approved [4]. All vaccines have demonstrated protective efficacy lasting for more than one season, with waning immunity observed in the second season [5–8].

Recommendations on RSV immunisation in older adults were made by several National Immunisation Technical Advisory Groups. In the USA, the Advisory Committee on Immunization Practices (ACIP) recommended a single-dose RSV vaccine for all adults 75y+ and adults aged 60–74 years who are at increased risk for severe RSV disease [9]. In the United Kingdom (UK), the Joint Committee on Vaccination and Immunisation (JCVI) was in favour of a programme for older adults aged 75 years and above (75y+), and suggested in 2024/2025 a cohort programme focusing on adults turning 75 years from 1st September 2024, along with a one-time catch-up programme for those aged 75–79 on that date [10]. Cost-effectiveness analyses were conducted to inform these ACIP and JCVI recommendations.

The PROMISE (Preparing for RSV Immunisation and Surveillance in Europe) Consortium (https://imi-promise.eu/) aimed to produce new evidence on the burden of RSV disease in Europe, before and after the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). For instance, data on RSV International Classification of Diseases (ICD)-coded and RSV-confirmed hospitalisations were collected using national or regional registries in several countries. Moreover, time-series modelling (TSM) was employed to estimate the RSV-attributable hospitalisations for these countries.

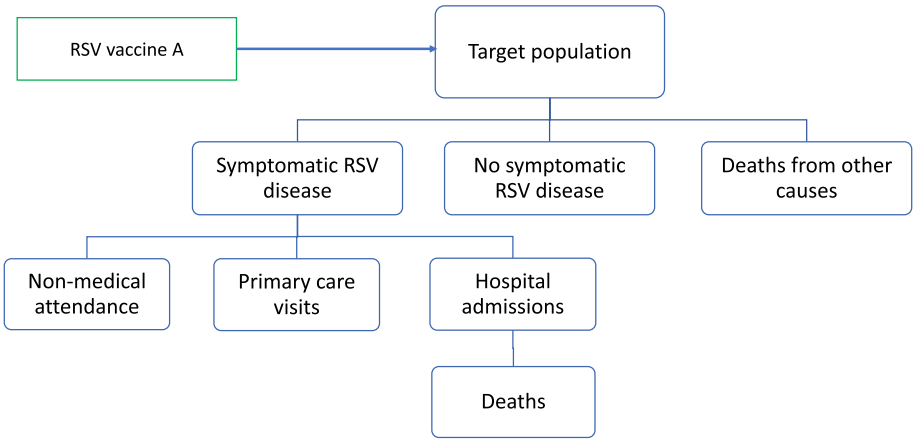
We used the data on RSV hospitalisations generated by the PROMISE project to identify and explore the influential parameters and assumptions driving the cost-effectiveness of RSV vaccination strategies among older adults in four European countries: Denmark, Finland, the Netherlands and Spain-Valencia. The choice of these countries was guided by the timely availability of data of sufficient quality and detail within the PROMISE project (June 2024).

Methods

Cost-effectiveness model

We developed a static multi-cohort model (Figure 1) named Multi-Country Model Application for RSV Cost-Effectiveness poLicy for Adults (MCMARCELA). The modelled population consists of adults aged 60 to 99 years, who were tracked monthly over a 5-year time horizon, which aligns with the expected maximum protective duration of RSV vaccine [11]. The model considered costs and quality-adjusted life-years (QALYs) lost for RSV cases seen in primary care, admitted to hospitals and symptomatic RSV cases requiring no medical attendance (non-MA). It also assumed that RSV-related mortality occurs only in a hospital setting. Premature RSV-related deaths were calculated from the model using hospital-fatality ratios to estimate QALYs lost over the remaining life-expectancy at the age of death. The model did not separately account for RSV cases requiring only an outpatient visit in hospital or an emergency department visit without admission, because such type of data was not available for most of the countries considered.

The model made comparisons between four strategies: "no intervention" and three age-based single-dose universal RSV vaccination strategies among older adults. Each vaccination strategy was modelled as if a single



Primary care visits were estimated from hospitalisations, and non-medical attendance were estimated from primary care visits.

Fig 1 Model structure

Primary care visits were estimated from hospitalisations, and non-medical attendance were estimated from primary care visits

dose were offered to everyone in an age band at the same time in October, prior to the start of the first RSV season included in the the 5-year time horizon:

I. 60 years and above up to 99 years ("60y+" strategy) based on the approved age indication,
II. 65 years and above up to 99 years ("65y+" strategy) considering the universal influenza vaccination programmes in many European countries,
III. 75 years and above up to 99 years ("75y+" strategy) based on the JCVI and ACIP recommendation.

This analysis was conducted separately from a healthcare payers' (HCP) perspective considering only direct medical costs and from a societal perspective, additionally including costs associated with productivity losses of patients. Both costs and QALYs were discounted at rates recommended by the country-specific pharmacoeconomic guidelines (see Additional file 1*: S.* Table 1–6) [12–15].

Model input parameters and assumptions

Each input parameter is described in detail in Additional file 1: section 1, *S.* Table 1–5 and *S.* Figure 1–7, and all parameters are summarised in Additional file 1*:* S. Table 6.

In brief, for Denmark, Finland and the Netherlands, RSV-ICD-coded hospitalisations by age and calendar month were estimated retrospectively using national registries [16]. The RSV-confirmed data were also obtained in Denmark and Finland using the same registries [17]. In Valencia, a region of Spain, the RSV-confirmed hospitalisations were collected retrospectively through their regional active hospital-based surveillance network (descriptions in previous publications [18, 19]). The catchment area represented 21% of the overall population in Valencia (approximately 1 million), or 0.2% of the population in Spain. Patients meeting preliminary inclusion criteria and meeting the influenza-like illness (ILI) case definition [20] were included and systematically tested for RSV with a multiplex polymerase chain reaction (PCR) test. RSV-confirmed data was adjusted to the RSV season as active surveillance was not performed throughout the whole year [21]. The brief description of the data collection methods is in Additional file 1*:* section 1.1.1, and the full details are available elsewhere [21–23]. Moreover, multiple studies have demonstrated that diagnostic testing underestimates the overall RSV-related disease burden. A systematic review in high-income countries suggested using an adjustment factor of 2.2 to account for diagnostic under-ascertainment of admissions [24]. Accordingly, we applied this adjustment factor to both RSV-ICD-coded and RSV-confirmed hospitalisations in our base case analyses (Additional file 1*: S.* Figure 1–3) and conducted scenario analyses without applying this adjustment factor for comparison.

Subsequently, a TSM analysis was conducted to attribute respiratory tract infection (RTI) hospital admissions to RSV, using the number of positive virological isolates of respiratory pathogens, including influenza A and B, SARS-CoV-2 and RSV, over time as covariates. Under

this approach influenza and RSV laboratory test frequency was regressed against RTI incidence over time, to determine the proportion of RTI cases that were attributable to the two viruses [22]. In Spain-Valencia, ILI was used instead of RTI in the TSM analysis and an inference on missing weeks without active surveillance was performed in order to account for the fact that data was not available throughout the whole year. The brief description of the TSM analysis is in Additional file 1*:* section 1.1.1.3, Additional file 1*: S.* Figure 4, and the full details are available elsewhere [21].

To account for uncertainty on the choice of source data for the hospitalisation estimates, we explored the cost-effectiveness of using

(1) The RSV-ICD-coded hospitalisations with an adjustment factor of 2.2 for diagnostic under-ascertainment, except for Spain-Valencia due to insufficient sample size [24].
(2) The RSV-confirmed hospitalisations with the adjustment factor of 2.2 (except for the Netherlands due to data unavailability),
(3) The TSM estimated RSV-attributable hospitalisations.

The differences among the three hospitalisation datasets are illustrated in Additional file 1*: S.* Figures 1–4. We used the average data over three or four seasons (depending on data availability) prior to the COVID-19 pandemic (2016/2017 to 2019/2020).

In the absence of country-specific data, the RSV-related primary care episodes by age were estimated based on a meta-analysis of US studies [25], which were found for every RSV hospitalisation in adults aged 60y+, and 8.5 RSV primary care episodes occurred on average. We additionally used higher estimates of 12.5 RSV-related primary care episodes based on a UK modelling study performed by Fleming et al. in a scenario analysis [26]. A multi-country prospective study among European community-dwelling older adults provided an estimate of 2.27 non-MA episodes per primary care episode [27, 28] (*more details on RSV-related primary care and non-MA episodes are in* Additional file 1*:* section 1.1.4). We used 7.13% (95% CI 5.4–9.36) for the in-hospital case fatality ratio (hCFR) for all 60y+ based on a meta-analysis conducted by Savic et al. in high-income countries [1]. The age-specific RSV-confirmed hCFRs in Finland were used in scenario analysis (*more details on RSV-related in-hospital deaths are in* Additional file 1: section 1.1.3 and Additional file 1*: S.* Figure 6*).*

In order to focus on identifying general drivers of cost-effectiveness of RSV vaccination among older adults, and to avoid detractions due to minute interpretative differences in differently defined product-specific clinical endpoints, we consider in this analysis the use of a hypothetical RSV vaccine. We used plausible efficacy (mean and 95% CI) values against non-MA episodes, primary care episodes, hospitalisations and deaths by combining information available at the time of the analysis for both Arexvy® and Abrysvo® (Table 1) [5, 6]. Based on waning

Table 1 Phase 3 vaccine efficacy data of Arexvy® and Abrysvo® and the efficacy values of an RSV hypothetical vaccine

Arexvy® (GSK)			**Abrysvo® (Pfizer)**		
Endpoints	Season 1 (full season)	Season 2 (full season)	Endpoints	Season 1 (full season)	Season 2 (full season)
			ARI ≥1 symptom	62.1% (95% CI 37.1–77.9)	Not shared in public domain yet
ARI ≥2 symptoms or sign	71.7% (95% CI 56.2–82.3)	40.6% (95% CI 19.0–57.0)			
LRTD ≥2 symptoms including ≥1 sign or ≥3 symptoms	82.6% (96.95% CI 57.9–94.1)	56.1% (95% CI 28.2–74.4)	LRTD ≥2 symptoms or signs	66.7% (96.66% CI 28.8–85.8)	55.7% (95% CI 34.7–70.4)
			LRTD ≥3 symptoms or signs	85.7% (96.66% CI 32.0–98.7)	77.8% (95% CI 51.4–91.1)
Severe LRTD (≥2 signs or defined as severe by investigator)	94.1% (95% CI 62.4–99.9)	64.2% (95% CI 61.6–93.4%)			
RSV hypothetical vaccine					
Vaccine efficacy against		Season 1 (full season)		Season 2 (full season)	
Non-MA		65% (35–85%)		35% (15–60%)	
Primary care		65% (35–85%)		35% (15–60%)	
Hospitalisation		80% (35–95%)		55% (25–80%)	
Death		90% (60–100%)		60% (55–95%)	

Abbreviations: *ARI* acute respiratory infection, *LRTD* lower respiratory tract disease

assumptions made in published cost-effectiveness analyses for older adults [29–33], we explored 13 waning scenarios accommodating a range for the duration: of protection from 18 to 48 months (Additional file 1*:* section 1.15*,* Additional file 1: *S.* Table 1). We also explored a scenario with lower efficacy in adults aged 80 years and above (Additional file 1*:* S. Table 2) [34, 35]. The RSV vaccine price was assumed to be €150 per dose for all countries in this study [36]. RSV vaccination coverage was based on country- and age-specific influenza vaccination coverage (Additional file 1*:* S. Table 6) [37–40].

Country-specific costs were obtained for hospitalisations (including intensive care unit admissions), primary care consultations and vaccine administration (Additional file 1*:* section 1.1.7*, S.* Table 3–5) [14, 41–44]. A cost of €4.06 per non-MA episode was used for all countries based on a European multi-country prospective study [28]. From a societal perspective, the costs of productivity losses were estimated using the human capital approach: the age- and country-specific daily salaries were adjusted by employment rates and multiplied by the number of workdays lost [45, 46]. We accounted for one and two lost workdays per non-MA and primary care episode, respectively [47], and the country-specific length of hospital stay plus three lost workdays per hospitalised case for patients who were employed (e.g. without correction for weekends, national holidays). Productivity losses due to RSV-associated premature deaths were not included in order to avoid double counting [48]. All costs were inflated to their 2023 value using the country-specific consumer price index (CPI) of all sectors, and those reported in local currency were converted to euro (€) using the annual exchange rates of 2023 [49, 50].

QALY losses due to RSV deaths were estimated using remaining life expectancy at age of death and standard age-specific utility values by country [51, 52] (Additional file 1*:* section 1.1.8). A prospective study in European older adults estimated an average QALY loss of 0.004 (95% CI 0.001–0.010) per non-MA or primary care episode [47]. There was no utility value available for individuals aged 60y+ who were hospitalised with RSV. Hence, we assumed QALY losses of 0.01023 (95% CI 0.0089–0.0170) based on another European multi-country prospective study among RSV-hospitalised infants' parents [53], this value was comparable to QALY losses in hospitalised influenza patients [47]. However, in scenario analysis, we also assumed alternative average QALY losses of 0.0185 (CI 0.0053–0.0347) for non-hospitalised patients and 0.0193 (CI 0.0095–0.0316) for hospitalised patients, based on a 2022 US ACIP meeting, subsequently published in Hutton et al. [54].

Analytical approach

We conducted a full incremental analysis of costs and effects arising in all strategies to identify the cost-effective programme for willingness-to-pay (WTP) values ranging from €0 to €150,000 per QALY gained [48, 55, 56].

To evaluate the impact of uncertain input parameters on the estimated cost-effectiveness, the expected value of partial perfect information (EVPPI) was calculated over a range of WTP values through probabilistic sensitivity analysis [57]. A probabilistic price threshold analysis was also performed for each country applying the method demonstrated by Pieters and colleagues [58].

To explore the impact of key assumptions and input parameters, we also conducted deterministic scenario analyses including 16 scenarios on input parameters such as burden of disease, higher QALY losses, RSV seasonality, price per dose, the impact of the COVID-19 pandemic (Additional file 1*: S.* Figure 5) and age-specific hCFR (Additional file 1*: S.* Figure 6) and 13 scenarios on vaccine characteristics (Additional file 1*: S.* Figure 7: i.e. efficacy, duration of protection, waning curves). An overview of scenarios analyses was summarised in Additional file 1*: S.* Tables 7 and section 1.4. All analyses were conducted in R version 4.3.2.

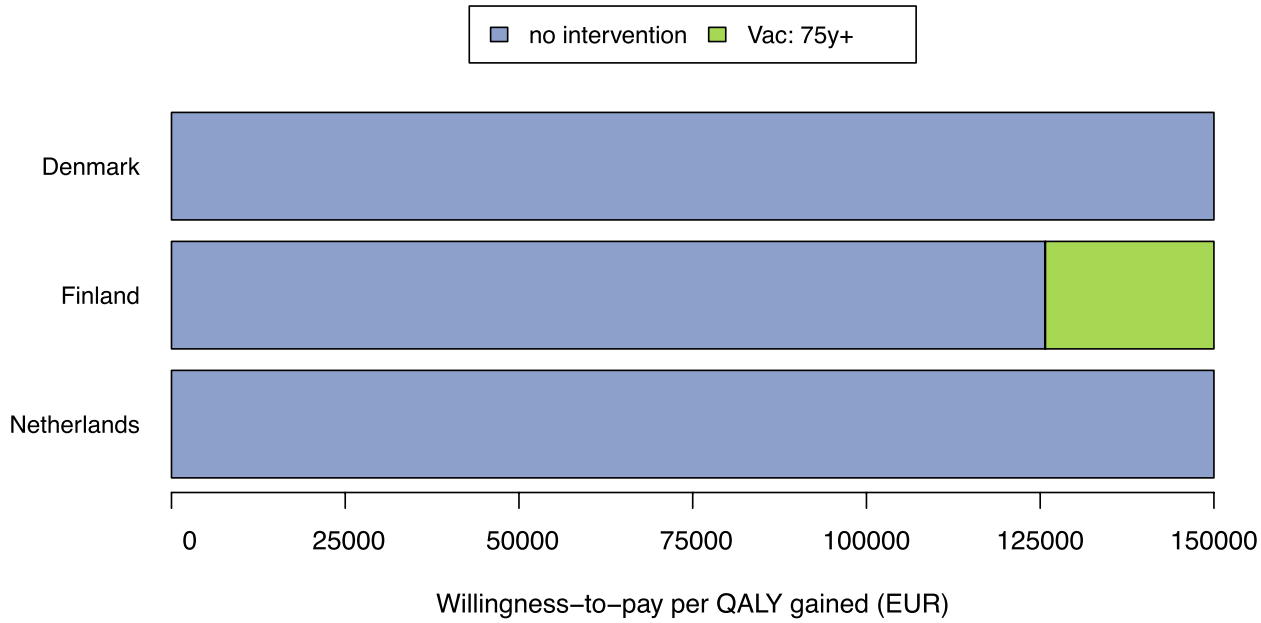
Results

A summary of the findings is presented in the section below, while additional results are illustrated in Additional file 1: section 2: S. Table: 8–14 and S. Figure 8–20

RSV health and economic burden without vaccination

Over a 5-year time horizon, (1) using the adjusted RSV-ICD-coded dataset (Additional file 1*: S.* Table 8), we estimated 30,910, 252,679 and 316,814 RSV cases (including non-MA, primary care episodes and hospitalisations), as well as 580, 4529 and 8663 discounted QALY losses among adults 60y+ in Denmark, Finland and the Netherlands, respectively. From the HCP and societal perspectives, the discounted costs were €3.6 and 4.0 million in Demark, €30.1 and €33.4 million in Finland and €76.2 and €90.3 million in the Netherlands, respectively.

(2) Using the adjusted RSV-confirmed hospitalisation dataset (Additional file 1*: S.* Table 10), the estimated RSV cases were 84,852 in Denmark, 326,588 in Finland and 74,083 in Spain-Valencia, as well as 1575, 5895 and 1530 discounted QALY losses among adults 60y+ in Denmark, Finland and Spain-Valencia, respectively. From the HCP and societal perspectives, the discounted costs were €9.9 and 11.0 million in Denmark, €40.1 and €43.2 million in Finland and €10.4 and €10.7 million in Spain-Valencia, respectively.



Note: The RSV vaccine price per dose assumed is €150.

Abbreviations: QALY: quality-adjusted life-year, EUR: euro

Fig 2 Using adjusted RSV-ICD-coded disease burden: preferred strategy based on cost-effectiveness analysis from the healthcare payers' perspective

Note: The RSV vaccine price per dose assumed is €150. Abbreviations: QALY: quality-adjusted life-year, EUR: euro

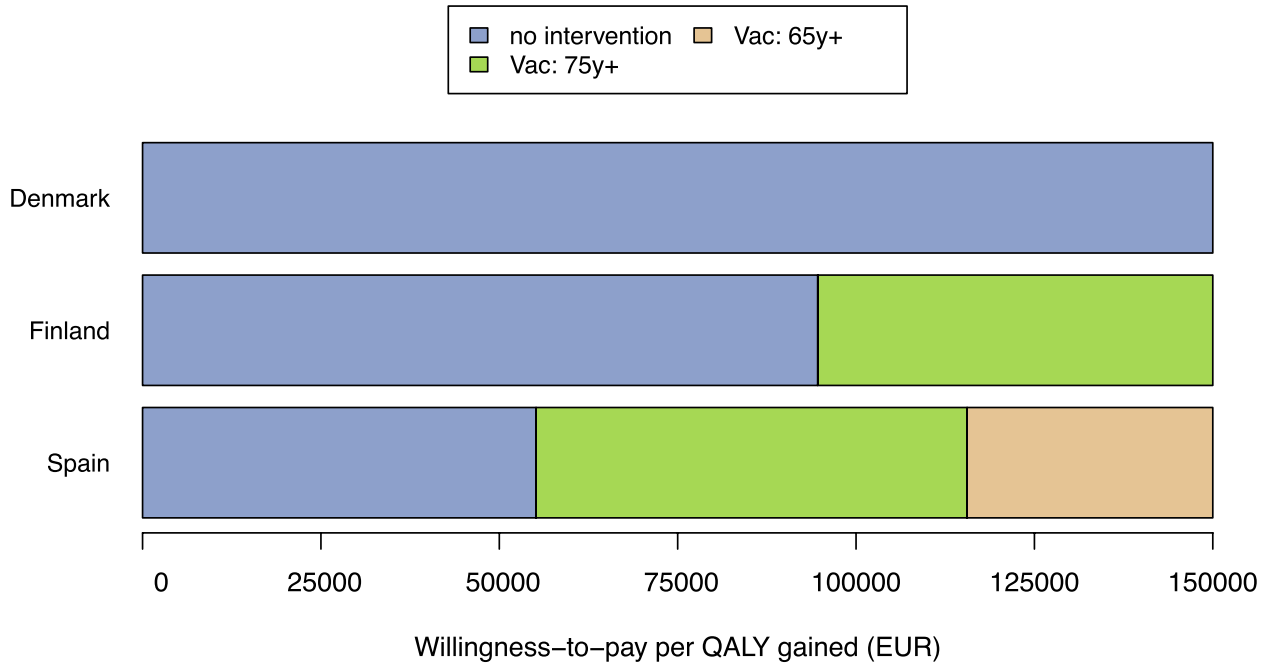
(3) Using the TSM RSV-attributable estimates (Additional file 1*: S.* Table 12), we observed 24- and 9-fold higher RSV-attributable cases (0.7 million) in Demark compared with the adjusted RSV-ICD-coded and adjusted RSV-confirmed hospitalisations, respectively. Consequently, there were higher QALY losses and direct medical and indirect medical costs. In the Netherlands, 4-fold higher RSV-attributable cases (1.3 million) were estimated compared with using the adjusted RSV-ICD-coded dataset. However, both in Finland and Spain-Valencia, the RSV-attributable cases from the TSM were 11% (289,516) and 49% (37,895) lower than the adjusted RSV-confirmed estimates, respectively. Consequently, large differences were observed in the discounted QALY losses, and the direct and indirect costs attributable to RSV. Despite the large differences in baseline disease burden while using different datasets, it was consistent that the 75–84 years age group had the highest number of hospitalisations (except the Netherlands using adjusted RSV-ICD-coded dataset); consequently, the highest number of primary care and non-MA episodes, and discounted medical costs. However, the highest discounted QALY losses mainly occurred in the 65–74y age group (except Spain-Valencia). Most indirect costs due to productivity losses occurred in the 60–64 years age group, as it had the highest active labour force participation.

RSV-burden averted with single-dose one-time vaccination over 2 years protection

Irrespective of the hospitalisation data source, in every country the 60y+ strategy had the greatest impact on disease burden in terms of cases, hospitalisations and deaths averted, QALYs gained and direct and indirect medical costs averted. However, this was also the most expensive strategy with one-time vaccination costs of €195 million, €139 million, €482 million and €30 million in Denmark, Finland, the Netherlands and Spain-Valencia, respectively. Detailed RSV burden averted estimates are presented in Additional file 1*: S.* Table 9, 11 and 13 by strategy, country and methodological approach.

Cost-effectiveness

In general, more expansive vaccination strategies became cost-effective for the HCP with increasing WTP values per QALY gained (Figures 2, 3 and 4). A societal perspective increased the potential cost savings per averted case, but the overall results remained comparable with the HCP perspective (Additional file 1*: S.* Figures 8, 9, 11, 12, 14 and 15).



Note: The RSV vaccine price per dose assumed is €150. Spain: Valencia region in this analysis

Abbreviations: QALY: quality-adjusted life-year, EUR: euro

Fig 3 Using adjusted RSV-confirmed disease burden: preferred strategy based on cost-effectiveness analysis from the healthcare payers' perspective.

Note: The RSV vaccine price per dose assumed is €150. Spain: Valencia region in this analysis. Abbreviations: QALY: quality-adjusted life-year, EUR: euro

(1) Using the adjusted RSV-ICD-coded hospitalisations (Figure 2), "no intervention" was cost-effective up to a WTP value of €150,000 per QALY gained for the HCP in Denmark and the Netherlands. In Finland, the 75y+ would be preferred at WTP values exceeding €124,000.

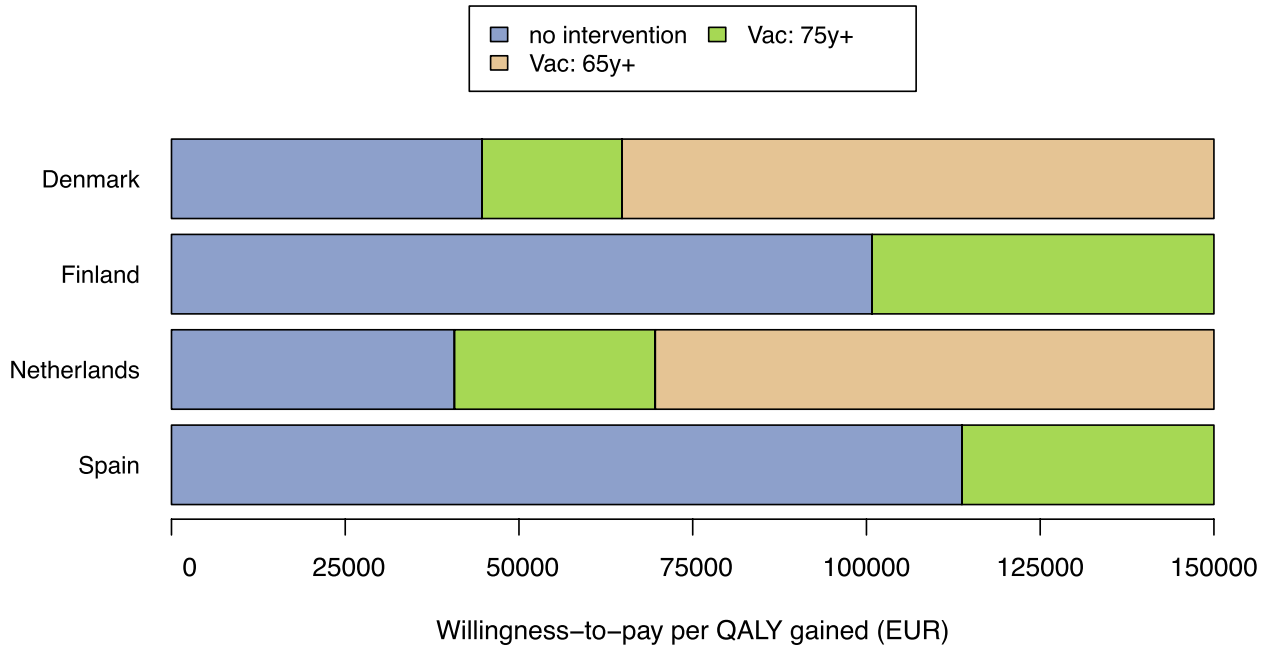
(2) Using the RSV-confirmed hospitalisations (Figure 3), the finding was consistent for Denmark that "no intervention" is cost-effective, whereas in Finland the 75y+ strategy became preferred at lower WTP values (≥95,000) versus using adjusted RSV-ICD-coded hospitalisations. In Spain-Valencia, the 75y+ and 65y+ strategies became cost-effective at WTP values above €55,000 and €116,000, respectively.

(3) Using the TSM estimates (Figure 4), the 75y+ strategy was preferred if the WTP value exceeded €45,000 in Denmark, €101,000 in Finland, €41,000 in the Netherlands and €114,000 in Spain-Valencia. The 65y+ strategy became the preferred strategy at higher WTP values of €65,000 in Denmark, and €70,000 in the Netherlands. In Finland and Spain-Valencia, 65y+ strategy was not preferred up to a WTP value of €150,000.

In all four countries and using all hospitalisation data, the 60y+ strategy was not preferred up to a WTP value of €150,000.

Influence of price

Variations in the vaccine price from €50 to €250 per dose changed the preferred strategy over a wide range of WTP levels from the HCP perspective. (1) Using the adjusted RSV-ICD-coded dataset (Additional file 1*: S.* Figure 17), 'no intervention' was cost-effective in Denmark irrespective of WTP per QALY. However, at €50 per dose, in Finland the 75y+ strategy was cost-effective at a WTP value of €40,000, whereas in the Netherlands the 75y+ strategy could be cost-effective at a WTP value of €80,000. (2) Using the adjusted RSV-confirmed dataset (Additional file 1*: S.* Figure 18), findings are consistent in Denmark and comparable in Finland versus adjusted ICD-coded hospitalisation. In Spain-Valencia, at €50 per dose, the 75y+ strategy would be cost-effective at a WTP value of €20,000 per QALY gained. (3) Using TSM estimates (Figure 5) and a price of €50 per dose, the 75y+ strategy would be cost-effective at a WTP of €20,000 per



Note: The RSV vaccine price per dose assumed is €150. Spain: Valencia region in this analysis

Abbreviations: QALY: quality-adjusted life-year, EUR: euro

Fig 4 Using time-series-modelling RSV estimates: preferred strategy based on cost-effectiveness analysis from the healthcare payers' perspective

Note: The RSV vaccine price per dose assumed is €150. Spain: Valencia region in this analysis. Abbreviations: QALY: quality-adjusted life-year, EUR: euro

QALY gained in Denmark, €30,000 in Finland, €10,000 in the Netherlands and €50,000 in Spain-Valencia. The 65y+ strategy would become cost-effective at higher WTP ranges per QALY gained: €30,000 in Denmark and the Netherlands, €80,000 in Finland and €100,000 in Spain-Valencia. The 60y+ strategy might become cost-effective in Denmark and the Netherlands at WTP values of €100,000 and €120,000 per QALY gained, respectively. The price reductions led to sharp decreases in the WTP level at which strategies became cost-effective for Denmark and the Netherlands. This effect was less pronounced for Finland and Spain-Valencia. Overall, decision uncertainty was highest nearby the WTP values at which the cost-effective strategy switched.

Highly influential factors on the optimal strategy (other than price)

Choice of datasets

The choice of optimal strategy at a given WTP level and price depended in all countries heavily on the choice of dataset to estimate the incidence of RSV hospitalisations (RSV-ICD-coded, RSV-confirmed and RSV-attributable).

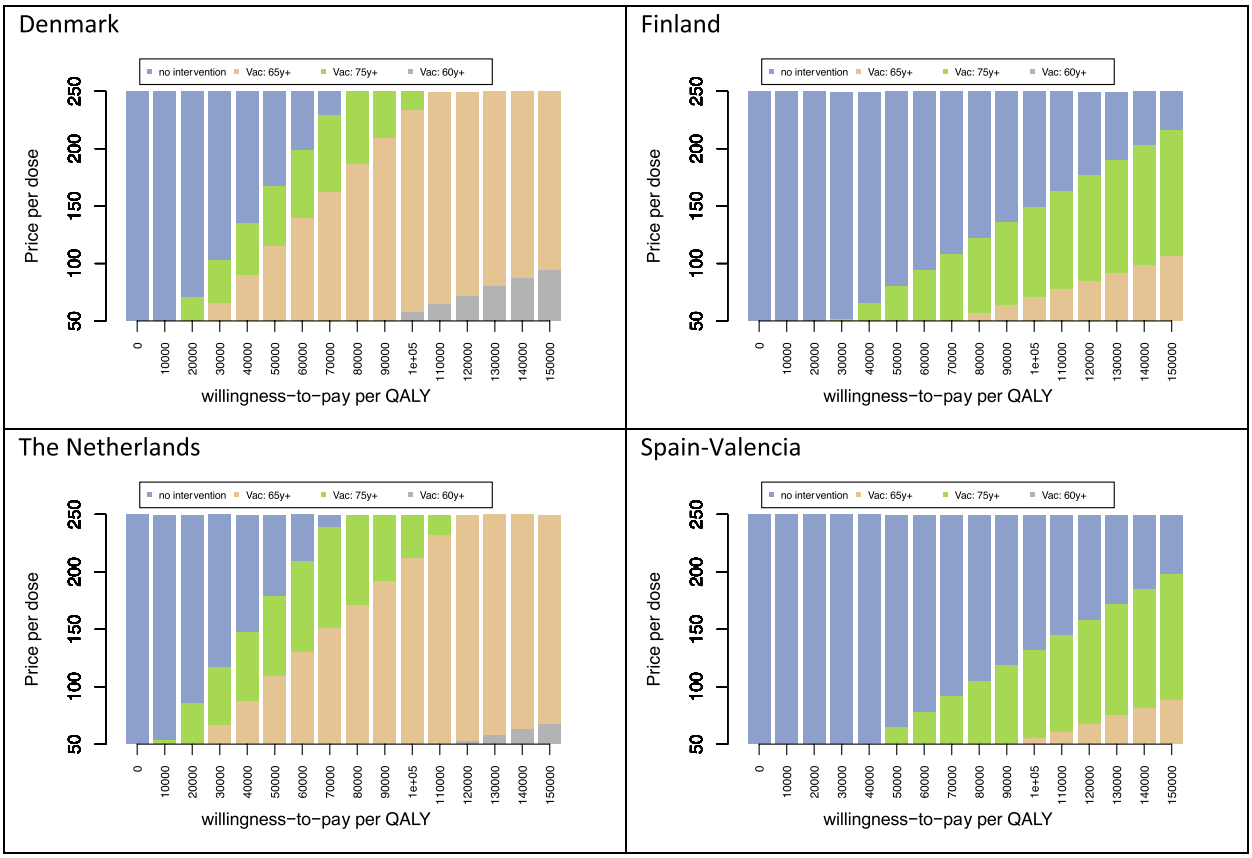
Hospital case fatality ratio (non-age specific and age specific)

The hCFR was identified as another key driver. The EVPPI graphs demonstrated that the uncertainty around the non-age-specific hCFR caused the most decision uncertainty for all countries across all three datasets (Figure 6 and Additional file 1*: S.* Figures 10, 13 and 16).

Compared with assuming non-age-specific hCFR for adults 60y+, using relatively higher hCFRs among adults 75y+ made the 75y+ strategy preferred at lower WTP values, whereas lower hCFRs in the 60–64 years and 65–74 years age groups made the 65y+ strategy only preferable over the 75y+ strategy at much higher WTP values (Additional file 1*: S.* Figure 20).

RSV vaccine efficacy values against mortality

As illustrated by the EVPPI graphs, the uncertainty around first- and second-year RSV vaccine efficacy values against mortality were the top-ranking influential drivers (Figure 6, Additional file 1*: S.* Figures 10, 13 and 16), because approximately. 80% of the QALY gains came from the RSV-related deaths averted across all four countries.



Abbreviation: TSM: time-series modelling; HCP: healthcare payers' perspective; QALY: quality-adjusted life-year

Fig 5 Using TSM estimates: Price threshold analysis showing the cost-effective strategy at different WTP thresholds from HCP's perspective

Abbreviation: TSM: time-series modelling; HCP: healthcare payers' perspective; QALY: quality-adjusted life-year

QALY losses due to non-medically attended cases

The large number of non-MA cases make the estimate of the number of non-MA episodes per primary care visit over its relatively wide uncertainty interval (2.27 [uniform distribution: 1.14–3.41]) influential for the costs per QALY gained estimates (Figure 6, Additional file 1*: S.* Figures 10, 13 and 16).

Adjustment factor for diagnostic under-ascertainment

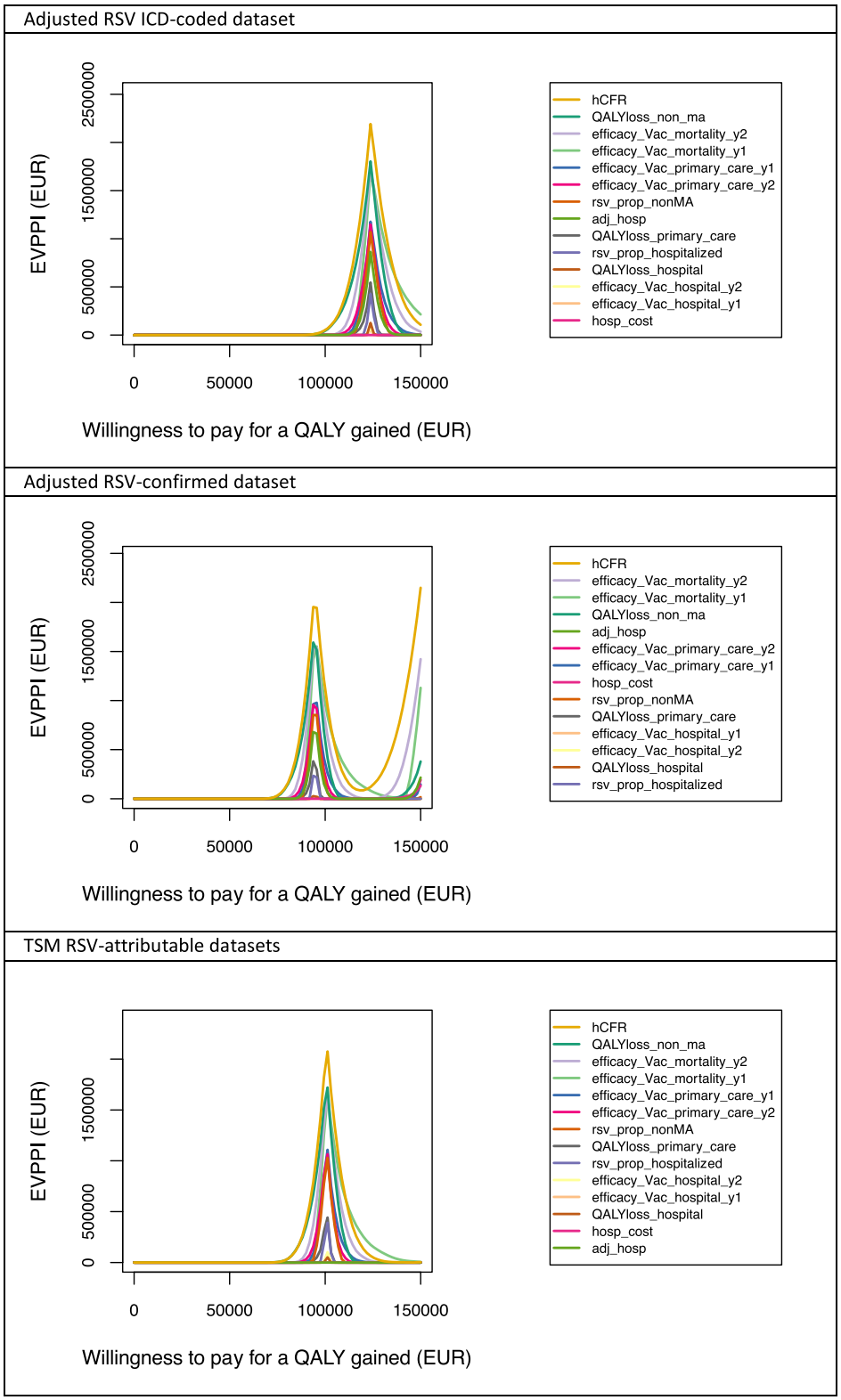
The adjustment factor of 2.2 for diagnostic under-ascertainment of hospitalised cases was also influential when using the RSV-ICD-coded and RSV-confirmed datasets (Additional file 1*: S.* Figures 20). Its parametric uncertainty was influential when using the adjusted RSV-ICD-coded and adjusted RSV-confirmed datasets (Figure 6 and Additional file 1*: S.* Figures 10 and 13).

Other influential factors on the optimal strategy

The duration of protective efficacy showed more impact than the type of waning curve assumed (Additional file 1*: S.* Figure 19). Scenarios considering a seasonal shift of RSV as observed during the COVID-19 pandemic, administering RSV vaccine prior to a "mild" season and applying lower vaccine efficacy in adults 80y+ all yielded negative impacts on the cost-effectiveness results compared to the reference analysis. Scenarios administering RSV vaccine prior to a "severe" season, using higher QALY losses associated with RSV illness and a higher ratio of hospital to primary care, led to more expansive cost-effective strategies (Additional file 1*: S.* Figure 15). Nevertheless, RSV vaccine coverage increases in the 60–64 years age group had limited impact (Additional file 1*: S.* Figure 15), in the context of comparing multiple age-based RSV strategies using a single RSV vaccine at price of €150 per dose.

Discussion

We performed a full incremental analysis comparing no intervention and three vaccination strategies in adults aged 60, 65 and 75 years and above to each other using a hypothetical RSV vaccine which bridged phase 3 trial efficacy data available up to June 2024. Our analyses used



Abbreviations: RSV: respiratory syncytial virus; TSM: time-series modelling, QALY: quality-adjusted life-year

Fig 6 Expected value of partial perfect information for Finland, using three different hospitalisation datasets

Abbreviations: RSV: respiratory syncytial virus; TSM: time-series modelling, QALY: quality-adjusted life-year, adj_hosp: adjustment factor of hospital admissions data, y: year, Vac: vaccine, hCFR: in-hospital case fatality ratio, prop: proportion

three hospitalisation datasets in four countries to explore the influential drivers of the cost-effectiveness of RSV vaccination in European older adults. Although there are substantial differences observed among countries in term of cost-effectiveness, the influential drivers are consistent across countries. We found that apart from the vaccine price, the key driver of decision uncertainty regarding which strategy is cost-effective in all countries is the choice of the RSV hospital admissions dataset to use. The top-ranking uncertainty drivers are the non-age-specific hCFR, the vaccine efficacy values against mortality and the adjustment for diagnostic under-ascertainment of hospitalised cases, when using the adjusted RSV-ICD-coded and RSV-confirmed datasets. The uncertainty around the ratio of non-MA cases per primary care visit was also particularly influential.

Since RSV clinical symptoms are indistinguishable from those of many other respiratory virus infections and laboratory testing for RSV is relatively rare in older European adults, RSV-ICD-coded hospitalisation rates can substantially underestimate the disease burden, especially in countries without routine RSV testing [17, 27]. We, therefore, investigated the impact of using RSV-ICD-coded (except Spain-Valencia), RSV-confirmed (except the Netherlands) or TSM model-based RSV-attributable hospitalisations to inform RSV hospitalisation rates. We showed this impact to be very high. For instance, after applying an adjustment factor of 2.2 to the RSV-ICD-coded hospitalisations and RSV-confirmed, no intervention was cost-effective up to the WTP value of €150,000 per QALY gained in Denmark and the Netherlands, and up to €124,000 per QALY gained in Finland. No intervention was cost-effective up to a WTP value of €55,000, in Spain-Valencia when using adjusted RSV-confirmed hospitalisations. However, model-based analyses of TSM data yielded increased age-specific RSV attributability, and when using the resulting hospitalisation rates, the 75y+ strategy was shown to be cost-effective at much lower WTP values per QALY gained in Denmark and the Netherlands.

The TSM-based approach used in this analysis is a method commonly used to estimate the burden of many other diseases such as influenza [59]. In our analysis, we used laboratory test data series on four pathogens (influenza A, influenza B, SARS-CoV-2 and RSV) that cause RTIs (in Spain-Valencia, ILI was used as a proxy for RTI). Although these are four highly important pathogens for RTIs, this is not an exhaustive inclusion of potential causative pathogens and, therefore, the attributable fractions estimated for each or some of these pathogens to RTI hospitalisation may be overestimations, although this was partially adjusted for by including a constant term. Although reduced, there is still a possibility that the TSM-based approach underestimates the disease burden due to the characteristics of various RSV diagnostic testing approaches that affect input data used for TSM [60]. On the other hand, RSV-ICD-coded hospital admission data are likely to substantially underestimate RSV-related hospital admissions [17, 61]. RSV diagnostic tests were also not systematically performed except in Spain-Valencia. When adjusting RSV-ICD-coded and RSV-confirmed datasets with the diagnostic under-ascertainment factor of 2.2, the findings were substantially different than those using TSM estimates in Denmark. The large differences were also observed in the Netherlands when comparing the adjusted RSV-ICD-coded hospitalisation with the TSM estimates. However, the results of using three datasets were comparable in Finland. In Spain-Valencia, the adjusted-RSV-confirmed dataset showed more favourable results for RSV vaccination. This could be explained by the fact that testing was already systematic in all included in patients in Spain-Valencia. However, the use of ILI as inclusion criteria (in Spain-Valencia) is known to underestimate the real RSV burden in the surveillance networks compared to other case definitions an under-ascertainment that has not been corrected for here [27, 62, 63]. Hence, the adjustment factor and its uncertainty need to be interpreted with caution, taking into account country-specific coding and testing practices.

Moreover, the hCFR and the specification of its age dependency were influential (Additional file 1*: S.* Figures 10, 13, 15 and 20). Despite the efforts to link the RSV-confirmed deaths with hospital and mortality registries of multiple countries, we were only able to use the age-specific hCFR for Finland, which had a sufficient sample size and was compliant with the applicable data privacy law. Importantly, we demonstrated that acknowledging the age-dependent nature of the hCFR is important when selecting optimal age-based RSV vaccination strategies in older adults.

Our price threshold analysis showed that different "vaccine price per dose" thresholds exist for different "WTP per QALY" levels, implying different optimal choices of strategies. When considering vaccination strategies among 60y+, 65y+ and 75y+, the strategy protecting the oldest (75y+) age group is first selected from the HCP perspective. With increasing WTP values or decreases in price, the 65y+ and 60y+ strategies might become the optimal strategy. Embedded in our calculations is the budget impact. Clearly, the smaller older-age cohorts have a budgetary advantage over larger younger-age ones. In many countries, budget-impact considerations may determine the choice of preferred strategy as much as cost-effectiveness considerations do. For instance, Hodgson and colleagues assumed 1 year protection and estimated the threshold price at which the 75y+ strategy

can be cost-effective at a much higher price (£20.71) than the price (£3.63) at which it would be considered affordable, given a UK-set budget constraint for an individual programme of £20 million annually during the first 3 years of implementation [64].

By exploring many different waning efficacy profiles, we found that duration of protection is more influential than the type of waning curve to achieve a cost-effective result. However, this is for a single vaccine analysis and is likely to become more nuanced in head-to-head comparisons of different vaccine brands, especially so when vaccines are marketed to compete more on marginal differences in age-specific protective efficacy over time than on more influential differences in price-setting. Given the trial-based information available, with different case definitions of the clinical endpoints of the licenced vaccines, such a head-to-head comparison is beyond the scope of this paper.

We assumed the RSV vaccines would be administered prior to the expected RSV season in Europe in October (with instant protection) in order to maximise the effectiveness. However, depending on the country, influenza, pneumococcal and COVID-19 vaccines are also typically administered in the last quarter of the calendar year in the same target populations, which can lead to implementation challenges for RSV vaccines due to crowded schedules. Given that RSV vaccines protect longer than one season, a year-round programme might be considered, possibly together with the pneumococcal or herpes zoster vaccine among older adults. However, given the clear seasonal pattern of RSV in Europe, a year-round programme would be less effective than a seasonal programme due to waning protection. Moreover, the coverage of pneumococcal vaccines is generally lower than the coverage of influenza vaccines among adults 65 years and above in Europe. Joint recommendations for RSV, pneumococcal, influenza and COVID-19 vaccine before winter might simplify the communication and reduce the number of visits. Combining vaccination programmes or applying a (upcoming) multi-antigen combination vaccine (i.e. COVID-19, RSV and influenza) will not only reduce the direct and indirect cost of vaccine delivery, but may also increase overall vaccination coverage, thus providing broader protection against respiratory illness during winter months. The potential future expansion of intranasal vaccines for respiratory viruses may further contribute positively to vaccination coverage [65, 66].

This is the first analysis that assessed the cost-effectiveness of three age-based RSV vaccination strategies among older adults in more than two countries and identified the key evidence gaps that were most influential to cost-effectiveness. Previous analyses on a single country or two countries did not explore the sensitivity to different data sources, the influence of a shift in seasonality and the severity of a season [31, 32, 47, 64, 67]. Our results are comparable with two cost-effectiveness analyses published in 2023, which applied vaccine protection over two RSV seasons. Moghadas and colleagues evaluated both marketed RSV vaccines in the US among adults aged 60y+ from a societal perspective. They concluded that both vaccines can be cost-effective at a price of $235 (~€219) and $245 (~€228) per dose given a WTP value of $95,000 (~€88,000) per QALY gained, with sensitivity analyses on WTP values of $80,000 (~€75,000) and $120,000 (~110,000) per QALY gained [31]. Using the time-series estimates, we find that from the HCP's perspective and at an RSV vaccine price of €200 per dose, the 65y+ strategy would be cost-effective only at high WTP values of €90,000 and €100,000 per QALY gained in Denmark and the Netherlands, respectively. We used age-specific hospitalisation rates, which led to much higher estimates for the 85y+ age group (~366 per 100,000 in the Netherlands and 533 per 100,000 in Denmark) in comparison to Moghadas et al (214 per 100,000 for any adult aged 60y+, with a 54.8% proportion in 85y+) [31]. However, Moghadas et al. included both market and non-market productivity losses due to RSV premature deaths based on US guidelines. Using a cost-utility framework as prescribed by the pharmacoeconomic guidelines for the countries in our study, we did not include such monetised productivity costs. Wang and colleagues conducted a cost-effectiveness analysis in Hong Kong and used adjusted hospitalisation rates ranging from 23.0 to 221.4 per 100,000 in the 60–64 years and 75y+ age groups, respectively [32]. By adjusting ICD-coded hospitalisations, our analysis estimated a lower rate in Denmark (4.2 and 17.8 per 100,000), the Netherlands (0.4 and 2.2 per 100,000) and Spain (2.6 and 13.1 per 100,000), but a higher rate in Finland (37.1 and 168.0 per 100,000). The Hong Kong analysis also generally highlighted the price and disease burden as influential drivers for the cost-effectiveness analysis, as did previous analyses, which assumed protection over one RSV season [47, 64, 67].

Unlike in the UK, where the WTP thresholds of £20,000 (~€24,000) and £30,000 (~€35,000) per QALY gained from the National Health Service (NHS) perspective are clearly indicated, the four European countries in our analysis do not have an explicit WTP reference value [68]. In Denmark, a WTP value of DKK 88,000 (~€12,000) per QALY gained was estimated via a population survey in 2001, which might need updating [69]. In Finland, infant varicella, pneumococcal and rotavirus vaccination programmes were considered to be cost-effective at WTP values ranging from €15,000 to €25,000

per QALY gained from HCP perspective [70]. In the Netherlands, the reference values of €20,000, €50,000 and €80,000 per QALY gained depended on the disease severity and perspective [71]. However, in 2023 the Dutch prevention working group recommended a threshold of €50,000 per QALY gained for public health interventions, including vaccines [72]. In Spain, a threshold of €30,000 from the NHS perspective is commonly cited [73]. Instead of using one or multiple arbitrary threshold values, our analysis presented findings over a range of WTP values (€0–150,000 per QALY gained) to assess the influence of the WTP value on the optimal choice.

Our study has some additional strengths. It used the most recent country-specific data to populate the model according to country-specific pharmacoeconomic guidelines. Considerable differences in the RSV health and economic burden exist between countries, and policy makers should reflect on these when making decisions. Most strikingly, RSV seasonality changed during the COVID-19 pandemic in many countries. Therefore, we simulated an off-season hospital admission peak (4 months earlier) observed during the pandemic and found the results would be less favourable because administering RSV vaccine in October would miss either a portion or the entirety of the seasonal peak. We also investigated RSV vaccine introduction in a country with a biannual seasonal pattern and found that is considerably more beneficial to introduce the vaccine first prior to a predicted "severe" season than a "mild" season. Furthermore, we explored multiple vaccine efficacy waning scenarios in combination with duration of protection based on the latest clinical data and demonstrated that the duration of protection have more impact than the type of waning curve assumed. Finally, extensive sensitivity analyses were performed using a wide range of WTP values to investigate the sensitivity of the optimal choice of strategy to the adopted WTP level.

Although we believe we posed a relevant well-defined research question, we failed to include some possibly important aspects of RSV disease and vaccination. First, we investigated age-based and not risk group-based strategies, the results may not be transferable. Second, we investigated one-time RSV vaccination, but did not attempt to model scenarios with repetitive vaccination of cohorts over time. Future refined information on vaccine effectiveness and durability may allow the evaluation of such strategies realistically in future. Third, the costs and QALY losses associated with vaccine-related adverse events were not accounted for, which may lead to slightly optimistic estimates of the cost-effectiveness of RSV vaccination strategies. We note however that costs and quality of life data to inform such aspects are lacking, and that costs of vaccine-related adverse events for a minority of vaccine recipients are likely to be dwarfed by the uncertainty that exists around the vaccine price for all vaccine recipients. Fourth, the burden on caregivers of older adults was not quantified, which may underestimate the RSV disease burden and the societal benefits of vaccination.

There are a few limitations regarding data availability. The hCFR was used to estimate RSV-related deaths in the inpatient setting. However, deaths that occurred in community setting (i.e. nursing home) were not captured due to the lack of data, hence possibly underestimating the cost-effectiveness of the RSV vaccine. Moreover, when using TSM estimates, the hospitalisation rate of a wide age group (18–64 years) was applied to a small subgroup (60–64 years) in all four countries due to data limitations. However, the impact on the overall insights from this analysis was negligible. We were unable to explicitly evaluate the impact of potentially disproportionately prevented re-admissions, long-term consequences due to RSV hospitalisation (e.g. transfer to a nursing home instead of home after discharge), and RSV vaccine's potential prevention of exacerbations of chronic respiratory disease and cardiac events [74], mainly because the occurrence of, and effectiveness against, these endpoints were unavailable.

More research insights on RSV are urgently needed to consistently inform decision-making processes. More refined age-, risk group- and country-specific RSV burden data are crucial. Evidence-based vaccine introduction decisions will require greater investment in enhanced RSV surveillance and better data linkage systems to enable accurate assessments of the age- and country-specific RSV burden, especially in tertiary and primary care settings, such as those established in Finland. Longitudinal studies may provide insights into the long-term impacts of RSV on different populations, including high-risk older adults and those with underlying conditions. It is also essential to improve the accuracy and consistency of diagnostic testing and coding for respiratory illnesses, including RSV, in medical records, especially in older adults. Standardised diagnostic testing and coding practices across healthcare systems may help improve the estimation of RSV-related hospitalisations and the reliability of disease burden estimates.

Conclusions

Large data gaps and uncertainties around the RSV burden among older adults persist in many European countries, contributing to substantial uncertainties regarding the cost-effectiveness of intervention programmes. Ongoing research is urgently needed; otherwise, costly and potentially suboptimal decisions risk being made,

leading to substantial opportunity costs due to the large target populations to be vaccinated.

Abbreviations

ACIP	Advisory Committee on Immunization Practices
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPI	Consumer price index
ENL	Expected net loss
EVPPI	Expected value of partial perfect information
hCFR	In-hospital case fatality ratio
HCP	Healthcare payers
ICD	International Classification of Diseases
ILI	Influenza-like illness
JCVI	Joint Committee on Vaccination and Immunisation
MA	Medical attendance
MCMARCELA	Multi-Country Model Application for RSV Cost-Effectiveness poLicy for Adults
PCR	Polymerase chain reaction
PROMISE	Preparing for RSV Immunisation and Surveillance in Europe
QALY	Quality-adjusted life-years
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TSM	Time-series modelling
UK	United Kingdom
US	United States
WTP	Willingness-to-pay
Y	Year

Supplementary Information

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Additional file 1. Provides full details on input parameters, methodology, base case results and extensive scenario analyses. Tables 1- 13. (short title). S. Table 1: Waning scenarios. S. Table 2: Vaccine efficacy. S. Table 3: RSV-confirmed hospitalisation cost. S. Table 4: Mean length of stay data and cost per hospitalisation episode in the Netherlands. S. Table 5: RSV-confirmed hospitalisation cost per episode in Spain-Valencia. S. Table 6: Input parameters. S. Table 7: Scenarios unrelated to the assumed waning characteristics. S. Table 8: Adjusted RSV-coded disease and economic burden. S. Table 9: Burden averted using adjusted RSV-ICD-10-coded data. S. Table 10: Adjusted RSV-confirmed disease and economic burden. S. Table 11: Burden averted: using the adjusted RSV-confirmed data. S. Table 12: RSV-attributable disease and economic burden. S. Table 13: Burden averted: using RSV-attributable data. Figure 1-20 (short title). S. Fig1: RSV-ICD-coded admissions in Finland and the Netherlands. S. Fig2: RSV-ICD-coded admissions in Denmark. S. Fig3: RSV-confirmed hospital admissions. S. Fig4: RSV-attributable hospital admissions. S. Fig5: COVID-19 pandemic and an"atypical" peak. S. Fig6: In-hospital case fatality ratios. S. Fig7: Waning scenarios. S. Fig8: Incremental cost-effectiveness plane (adjusted RSV-ICD-coded). S. Fig9: Cost-effectiveness acceptability curves and expected net loss curves (adjusted RSV-ICD-coded). S. Fig10: The expected value of partial perfect information (adjusted RSV-ICD-coded). S. Fig11: Incremental cost-effectiveness plane (adjusted RSV-confirmed). S. Fig12: Cost-effectiveness acceptability curves and expected net loss curves (adjusted RSV-confirmed). S. Fig13: The expected value of partial perfect information (adjusted RSV-confirmed). S. Fig14: Incremental cost-effectiveness plane (TSM estimates). S. Fig15: cost-effectiveness acceptability curves and expected net loss curves (TSM estimates). S. Fig16: the expected value of partial perfect information (TSM estimates). S. Fig17: Price threshold analysis (adjusted RSV-ICD-coded). S. Fig18: Price threshold analysis (adjusted RSV-confirmed). S. Fig19: Outputs of scenarios: assumed waning characteristics. S. Figure 20: Outputs of scenarios: others

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Authors' contributions

PB and HN initiated and supervised the study. XL, LW, JB and PB conceptualised the study. XL analysed input data, performed literature searches and auxiliary data collection. XL, LW and JB wrote the cost-effectiveness model codes. XL performed the cost-effectiveness analyses. CKJ, AUF and TL conducted national/regional database analyses, and collected and validated data in Denmark, Spain-Valencia, and Finland, respectively. CKJ, ROY and TL led and estimated the time-series model-based hospitalisation estimates. HS, AOS and JDD provided implementation, resource use and cost data for Finland and Spain. HN, MJ, JB and PB advised on model parameters, intervention characteristics and scenario analyses. XL, LW, JB and PB wrote the initial manuscript draft. All authors read and approved the final manuscript.

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Data availability

Almost all the data analysed and generated during this study are included in this article and its supplementary files. Formal requests for additional data can be made to the corresponding author (XL) or the senior authors (PB).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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