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Cost-effectiveness of a single dose of the adjuvanted RSVPreF3 vaccine for the prevention of respiratory syncytial virus (RSV) among patients with chronic obstructive pulmonary disease in Italy

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) increases the risk of severe respiratory syncytial virus (RSV)-related disease. This analysis evaluated the potential public health impact and cost-effectiveness of RSV vaccination with a single dose of adjuvanted RSVPreF3 vaccine over five years in people aged 60–74 years with COPD in Italy.

Research design and methods: A static multi-cohort Markov model estimated RSV-related events, costs, and quality-adjusted life-years (QALY) over five years in people aged 60–74 years with COPD in Italy vaccinated with one dose of adjuvanted RSVPreF3, versus no vaccination. Vaccine efficacy and waning data were based on AReSVi-006 Phase III clinical trial results. Other input data came from published literature and official databases. Sensitivity analyses were conducted.

Results: A single dose of adjuvanted RSVPreF3 vaccine (75% coverage) was projected to reduce RSV-related acute respiratory infections by 29% and RSV-related hospitalizations and deaths by 38% among patients with COPD aged 60–74 years in Italy. The incremental cost-effectiveness ratio (health system perspective) was €1,306/QALY.

Conclusions: These results indicated that a single dose of adjuvanted RSVPreF3 vaccine in patients with COPD aged 60–74 years in Italy is a cost-effective preventive option that could potentially reduce RSV-related disease burden and costs over five years.

Keywords: chronic obstructive pulmonary disease; cost-effectiveness; Italy; respiratory syncytial virus; vaccination

1 Introduction

Respiratory syncytial virus (RSV) is an important cause of acute respiratory infection (ARI) [1]. In temperate climates, it generally circulates in the winter and spring, and is active between November and April in Italy [2,3]. Older adults, people living in long-term care facilities, and people with certain underlying clinical conditions, such as heart or lung disease (e.g., chronic obstructive pulmonary disease [COPD]) or impaired immunity, are at higher risk of severe outcomes, including RSV-related hospitalization or death [1,4,5]. Individuals with COPD have a 3–13-fold higher incidence of RSV infection and 5–10-fold higher risk of RSV-related hospitalization compared with those without COPD [6-9]. Additionally, RSV infection in COPD patients is associated with a worsening of their pre-existing clinical conditions, including COPD exacerbations, with potential for long-term subsequent decline in lung function [10,11].

RSV-related events result in a substantial clinical and economic burden on the healthcare system [12-16]. Across the European Union (EU), the annual number of RSV-related hospitalizations in adults has been estimated at 158,229, of which 92% were in adults aged 65 years or over [12]. In Italy, the disease burden attributable to RSV in adults aged 60 years and over has been estimated at 291,394 RSV-related ARI cases, 26,162 RSV-related hospitalizations, and 1,866 RSV-related in-hospital deaths in 2019 [13]. The in-hospital mortality rate has been estimated at 7.2% [14]. This RSV-related disease burden translates into a considerable economic burden of healthcare resource use and costs in Italy [15,16]. In patients aged 60 years or over with COPD hospitalized for RSV in Italy, the estimated mean total healthcare cost for the index hospitalization and 12 months of follow-up was €11,629 per patient [16]. The actual clinical and economic burden of RSV disease may be even higher than

currently reported due to limitations in studies, such as the absence of a unified case definition and the use of diagnostic tests with suboptimal sensitivity [17].

Following decades of research and development, three RSV vaccines have now been approved by both the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and are currently recommended in the adult/older adult populations, especially in those individuals at increased risk (AIR): two protein subunit vaccines — International Nonproprietary Name (INN)-RSV vaccine (recombinant, adjuvanted) (AREXVY*,* GSK) and INN-RSV vaccine (bivalent, recombinant) (ABRYSVO, Pfizer)—and one messenger ribonucleic acid (mRNA)-based vaccine, INN-RSV mRNA vaccine (mRESVIA, Moderna) [18-27]. In a clinical trial in adults aged 60 years or over, vaccine efficacy (VE) of a single dose of adjuvanted RSVPreF3 vaccine was 82.6% (96.95% confidence interval [CI] 57.9, 94.1) against RSV-related lower respiratory tract disease (LRTD) and 71.7% (95% CI 56.2, 82.3) against RSV-ARI in the first season (median follow-up 6.7 months), and the vaccine had an acceptable safety profile [28]. In subjects with at least one pre-existing condition of interest (COPD, asthma, any chronic respiratory or pulmonary disease, chronic heart failure (cardiorespiratory condition), diabetes mellitus type 1 or type 2, and advanced liver or renal disease (endocrine or metabolic condition), VE against RSV-related LRTD was 94.6% (95% CI 65.9 to 99.9) [28], and in subjects with at least one cardiorespiratory condition, the VE was 92.1% (95% CI 46.7, 99.8) [29]. Recent data have reported VE against RSV-LRTD over three seasons (median follow-up 30.6 months) at 62.9% (97.5% CI 46.7, 74.8) [30]. The VE against RSV-LRTD over three seasons was 64.7% (95% CI 45.1, 78.1) in subjects with at least one pre-existing condition of interest, and 68.1% (95% CI 45.7, 82.3) in subjects with at least one cardiorespiratory condition [30]. An Italian modeling study has estimated that vaccinating adults aged 75 years or over, and AIR adults aged 60 years or over,

with a single dose of adjuvanted RSVPreF3 vaccine at the target coverage rate for influenza vaccine (75%) [31] could reduce RSV-LRTD events by 43% over a 3-year period, leading to substantial potential public health benefits [32,33].

The objective of the present analysis was to build on these results by evaluating the potential public health impact and cost-effectiveness of RSV vaccination with a single dose of the adjuvanted RSVPreF3 vaccine over five years in people aged 60–74 years with COPD in Italy.

2 Methods

2.1 Model overview

2.1.1 Model structure

The analysis used a previously published static multi-cohort Markov model [32,34,35] to estimate the expected number of RSV-related health outcomes and costs over five consecutive RSV seasons in adults aged 60–74 years with COPD in Italy. The model compared a single dose of adjuvanted RSVPreF3 vaccine at three coverage rates versus no RSV vaccination. The model had a one-month cycle time. The model structure, states, and transitions have been described elsewhere [32]. The model structure and data inputs were validated by three of the authors, who are Italian experts in public health and epidemiology (GEC), health economics (FR), and pneumology (FDM). The analysis for adults aged 60–74 years with COPD was conducted from the perspective of the Italian National Healthcare System, with an analysis from the societal perspective conducted for the age group 60–69 years, as the retirement age in Italy is 67 years. Costs and outcomes were discounted at 3% per year in accordance with Italian guidelines [36]. The incremental cost-effectiveness ratio (ICER) for vaccination with adjuvanted RSVPreF3 vaccine versus

no vaccination was calculated and compared against willingness-to-pay (WTP) thresholds of €30,000, €50,000, and €105,000 per quality-adjusted life-year (QALY), based on previous pharmacoeconomic literature [37-42].

2.1.2 Vaccine efficacy and waning

It was assumed that the adjuvanted RSVPreF3 vaccine was administered in October. VE was based on data over three seasons of follow-up (median follow-up 30.6 months) from the AReSVi-006 phase III clinical trial [30]. Estimates of VE post-vaccination beyond the trial period were extrapolated over a 5-year horizon using multivariable Cox regression modeling as described elsewhere [43]. A 5-year time horizon was chosen to capture the residual duration of VE, which was projected to last beyond the median 30.6-month follow-up of the AreSvi-006 study, in line with recent cost-effectiveness analyses of RSV vaccination [43-46]. VE at time (t), measured in days post-vaccination, was estimated for RSV-LRTD as $VE(t) = 1 - e(-3.6786 + 0.4465 * \ln(t + 10))$, and for RSV-ARI as $VE(t) = 1 - e(-2.5614 + 0.3125 * \ln(t + 10))$. Estimated VE peaked in the second month after vaccination, at 75.5% for RSV-ARI and 86.8% for RSV-LRTD, and gradually declined thereafter; the projected VE at month 60 was 19.6% for RSV-ARI and 28.2% for RSV-LRTD [43]. The model assumed that VE in the first month was 50% of the maximum value. Confidence intervals were calculated for use in sensitivity analysis [43]. For simplicity, the same VE estimates were applied to all age groups in the model.

2.2 Model inputs

Data inputs were based on a previous analysis [33], using country-specific data where possible, and inputs from studies in comparable countries when country-specific data were unavailable.

2.2.1 Demographic and coverage data

Age-stratified data on the general Italian population aged 60–74 years were obtained from official Italian national statistics [47]. The proportion of individuals with COPD in each age group was taken from Italian data [48], and applied to the general population data to calculate the population with COPD (Supplementary Table 1). Average annual incidence of all-cause mortality in the population with COPD was derived from official Italian national statistics [49], and from an observational retrospective healthcare database cohort study evaluating the impact of COPD on mortality in Germany [50].

Three vaccination coverage rates were modeled, using influenza vaccination coverage in Italy as a proxy:

- 11.8%, reflecting the influenza vaccination rate for adults aged 45–64 years during the 2023–2024 season [51];
- 75%, based on the minimum target for influenza vaccination coverage in Italy [31];
- 95%, based on the optimal target for influenza vaccination coverage in Italy [31].

2.2.2 Epidemiology data

Epidemiology input data are summarized in Supplementary Table 1. Incidence data for RSV-ARI were taken from a European study [52], with the same value used for all age groups due to a lack of age-stratified data. The annual rate of RSV cases was distributed across months using seasonality data reported from the Lombardy region during 2023–2024 [53]. The proportion of RSV-LRTD cases was based on data from the AReSVi-006 trial over three seasons [30].

2.2.3 Healthcare resource utilization and cost data

The model estimated numbers of RSV-ARI and RSV-LRTD cases. Healthcare resources for RSV-LRTD cases included outpatient visits, antibiotic use, emergency department (ED) visits, hospitalizations, intensive care unit (ICU) admissions, and in-hospital mortality. It was assumed that all RSV-LRTD cases required at least one outpatient visit, and input data for antibiotic use [54], ED visits [55], hospitalizations [55,56], ICU admissions [55-57], and in-hospital mortality [55-57] were based on published literature (Supplementary Table 2).

In an exploratory analysis, the model also estimated numbers of the following RSV-LRTD-related complications, based on published studies: COPD exacerbations [56] [55,57]; pneumonia [55,56,58]; stroke [55-57]; need for oxygen support [55-57]; and need for systemic corticosteroids [55,56,58].

Unit costs for healthcare resources in Italy were based on published studies [59,60] [61,62] and data from the Italian Ministry of Health [63,64] and are summarized in Supplementary Table 2. The cost per dose for the adjuvanted RSVPreF3 vaccine was taken from the Agenzia Italiana del Farmaco [65], and vaccine administration costs were based on a study of influenza vaccination [66]. All costs were adjusted for inflation to October 2024 using the Italian consumer price indices from the ISTAT Rivaluta database [67].

2.2.4 Indirect cost data

Indirect costs were calculated only for the COPD population aged 60–69 because the retirement age in Italy is 67 years. Productivity losses for RSV-ARI and RSV-LRTD events were estimated based on mean salary data in Italy for 2022 [68], adjusted for inflation to 2023, and labor force participation rates [69,70] (Supplementary Table 2).

The mean number of days absent from work for upper respiratory tract disease (URTD) or non-medically-attended RSV was assumed to be 2 days, the mean number of days absent from work for RSV-LRTD requiring an outpatient visit was 4.8 days [61]. The mean number of days absent from work for hospitalized RSV-LRTD was assumed to be 18.7 days among patients aged ≥ 60 years, based on a previous study to be published soon.

2.2.5 Utility data

Utility data used in the analysis are summarized in Supplementary Table 2. Age-specific baseline utility data for the general Italian population were derived from a published study using the EQ-5D-5L generic quality of life (QoL) instrument [71]. The number of QALYs lost due to each episode of RSV-URTD or RSV-LRTD was based on data on utility loss during RSV episodes from a European study in older adults [72]. The analysis did not include QALY losses due to adverse events because the rates of grade 3 adverse events in the AReSVi-006 trial were very low [28].

2.3 Sensitivity analyses

2.3.1 Univariate sensitivity analysis

A univariate deterministic sensitivity analysis (UDSA) was conducted to test the effect on the ICER of varying key parameters by 20% from the base-case value.

2.3.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed by assigning probability distributions to key parameters and running 1,000 Monte Carlo simulations with parameter values sampled from the distributions. The cost parameters followed a gamma distribution, whereas other parameters followed beta distributions.

3 Results

3.1 Public health impact

Table 1 shows the number of RSV-ARI and RSV-LRTD cases, RSV-LRTD cases receiving antibiotics, emergency department visits, RSV-LRTD hospitalizations, ICU admissions, and in-hospital deaths in Italian adults aged 60–74 years with COPD estimated by the model over a five-year period with no vaccination or with a single dose of adjuvanted RSVPreF3 vaccine at three coverage rates. Vaccination coverage at 11.8% was projected to reduce RSV-ARI cases by 5% and the other outcomes by 6%, while vaccination coverage at 75% was projected to reduce RSV-ARI cases by 29% and the other outcomes by 38%, and vaccination coverage at 95% was projected to reduce RSV-ARI cases by 37% and the other outcomes by 48%. Data for RSV-ARI, RSV-LRTD, RSV-LRTD hospitalizations, and RSV-related mortality are presented graphically in Figure 1A.

[Table 1 here]

[Figure 1 here]

Table 1 and Figure 1B show the estimated number of complications in hospitalized RSV-LRTD cases over 5 years with no vaccination and at three coverage rates. The projected reduction in all the modeled complications was 6% with vaccination coverage at 11.8%, 38% with vaccination coverage at 75%, and 48% with vaccination coverage at 95%.

3.2 Number needed to vaccinate

With vaccination coverage at 75%, the estimated number needed to vaccinate (NNV) to prevent one RSV-LRTD case in the Italian population aged 60–74 years with

COPD was 10, and to prevent one RSV-LRTD-related hospitalization, the NNV was 27. To prevent one RSV-LRTD-related ICU admission, the NNV was 320, and to prevent one RSV-related in-hospital death, the NNV was 223.

3.3 Cost-effectiveness

Table 2 summarizes the results of the cost-effectiveness analysis comparing vaccination with adjuvanted RSVPreF3 vaccine at 75% coverage versus no vaccination in Italian adults aged 60–74 years with COPD over five years. From the perspective of the Italian National Healthcare System, the direct cost of vaccination was estimated at approximately €79 million (approximately €76 million for vaccine purchase plus approximately €3 million for vaccine administration), and the projected saving in direct healthcare costs for RSV-LRTD cases was approximately €54 million, resulting in a projected net increase in direct healthcare costs of approximately €25 million (Table 2). Vaccination was projected to reduce the QALY loss due to RSV-related illness and death by 18,962, mainly by avoiding QALY loss due to RSV-related deaths (Table 2). Overall, the ICER for vaccination with adjuvanted RSVPreF3 vaccine was estimated at €1,306 per QALY gained (Table 2).

From the societal perspective, vaccination was also projected to save approximately €8 million in indirect costs in the population aged 60–69 years with COPD (Italian retirement age is 67 years), and the ICER was estimated at €871 per QALY gained (Table 2).

[Table 2 here]

3.4 Sensitivity analysis

Figure 2 shows the results of the UDSA for the cost-effectiveness of vaccination with

the adjuvanted RSVPreF3 vaccine at 75% coverage versus no vaccination in Italian adults aged 60–74 years with COPD over five years from the perspective of the Italian National Healthcare System (Figure 2A) and the societal perspective (Figure 2B). The most important drivers from both perspectives were vaccine efficacy against RSV-LRTD, the purchase price of the adjuvanted RSVPreF3 vaccine, the proportion of RSV-ARI events that were RSV-LRTD, and the annual incidence of RSV-ARI (Figure 2).

[Figure 2 here]

Figure 3 shows the results of the PSA from the Italian National Healthcare System perspective (Figure 3A) and the societal perspective (Figure 3B). From both perspectives, all the simulation results fall below all three of the WTP thresholds considered (€30,000 per QALY, €50,000 per QALY, and €105,000 per QALY), indicating that vaccinating Italian adults aged 60–74 years with COPD with a single dose of the adjuvanted RSVPreF3 vaccine would be considered cost-effective.

[Figure 3 here]

4 Discussion

This study is the first, to our knowledge, to evaluate the cost-effectiveness of a vaccination program using a single dose of adjuvanted RSVPreF3 vaccine compared with no vaccination over a 5-year period in the population aged 60–74 years with COPD in Italy. The results indicated that a single dose of adjuvanted RSVPreF3 vaccine at a vaccination coverage of 75% could reduce the projected numbers of RSV-ARI events by 29% and reduce projected direct healthcare costs and projected numbers of RSV-LRTD events, RSV-LRTD-related hospitalizations, and RSV-related deaths by 38%. The NNV to prevent one RSV-LRTD case was 10, and to prevent

one RSV-LRTD-related hospitalization, the NNV was 27. The NNV for RSV-LRTD-related hospitalization compares favorably with results from a previous evaluation of RSV vaccination in the general population aged 60 years and over in 11 European countries, where the NNV to prevent one RSV-LRTD-related hospitalization ranged from 173 to 210 [73], illustrating the potential effect of focusing RSV vaccination on the specific risk group of people with COPD. For comparison with other diseases, the median estimated NNV for a coronavirus disease 2019 (COVID-19) vaccine booster dose to prevent one COVID-19 hospitalization in the winter of 2021–2022 was 205 [74], the NNV for universal infant rotavirus vaccination in France to prevent one rotavirus-related hospitalization was estimated at 24.15–27.44 [75], and the NNV for pneumococcal conjugate vaccination of adults aged 65 years or over to prevent one hospitalization for community-acquired pneumonia over a 5-year period in the US was estimated at 576 [76].

The cost-effectiveness analysis results indicated that projected savings in direct healthcare costs and indirect costs (in the population aged 60–69 years) could partially offset the direct cost of the adjuvanted RSVPreF3 vaccination program. Vaccination was projected to reduce the QALY loss due to RSV-related illness and death by 18,962, mainly by avoiding QALY loss due to RSV-related deaths. The estimated ICER for a single dose of adjuvanted RSVPreF3 vaccine at a vaccination coverage of 75% in Italian adults aged 60–74 years with COPD, compared with no vaccination, was €1,306 per QALY gained from the perspective of the Italian National Healthcare System, and €871 per QALY gained from the societal perspective. The ICER results from both perspectives in this analysis were well below the three selected thresholds of €30,000, €50,000, and €105,000 per QALY gained. In the PSA, 100% of simulations remained below all three thresholds, indicating that the results were robust to variation in input parameters. As no official WTP threshold

exists in Italy, multiple thresholds were used. More specifically, the values of €30,000 and €50,000 were selected based on commonly used thresholds in the Italian pharmacoeconomic literature [38-41]. A cost-effectiveness threshold of £20,000–30,000 per QALY is also used in the United Kingdom (UK) guidance [77]. The higher threshold of €105,000 per QALY gained corresponds to three times the per-capita gross domestic product (GDP) of Italy in 2022 (i.e., approximately €35,000 [41]). This approach is consistent with the findings of a recent European systematic review, which reported that, in the absence of an official national cost-effectiveness threshold, most cost-effectiveness studies apply values ranging from one to three times per-capita GDP [42]. Other publications using different models have also assessed the potential impact of RSV vaccination on public health outcomes and costs, although the analyses were not conducted in the population with COPD. In Germany, the potential cost-effectiveness of RSV vaccination (with a discount rate of 3% per year) was estimated at €21,900–€38,700 per QALY in the population aged 75 years or over, €29,700–€51,400 per QALY in the population aged 65 years or over, and €37,500–€64,200 per QALY in the population aged 60 years or over [78]. Postma et al. [79] estimated the impact of vaccinating the population aged 60 years or over in Belgium against RSV, compared with no vaccination, using a static cohort model. This study estimated that a generic RSV vaccine with a five-year duration of protection and vaccine coverage of 59.1% could potentially avoid 224,601 RSV-ARI cases, 5,353 RSV-related hospitalizations, 728 RSV-related deaths, and €51,033,613 in RSV-related direct healthcare costs, approximately a one-third reduction compared with no vaccination. None of these studies are directly comparable with the present analysis, as they were not conducted in the COPD population. However, they indicate that RSV vaccination would be expected to have a substantial potential public health impact and that RSV vaccination could be considered cost-effective using established thresholds, which is broadly consistent

with the findings of the current study.

This study had a number of limitations. First, the results were not adjusted for under-estimation of the RSV burden, potentially leading to under-estimation of the impact of vaccination. Indeed, the incidence data available to populate our model may not fully capture the true RSV disease burden due to a number of factors, including under-ascertainment (cases who do not seek healthcare), under-reporting (cases who seek healthcare but are not captured by surveillance systems), and under-detection (cases not detected by the diagnostic techniques in use) [80,81]. Future research could consider adjusting modeled RSV incidence to allow for under-ascertainment of disease burden. Second, age-stratified incidence data were not available, and the use of the same incidence rate across all age groups would not capture any variation in RSV susceptibility by age. Third, regarding VE, waning beyond the AReSVi-006 phase III clinical trial median follow-up period relies on extrapolation rather than reported clinical data. Although our approach is aligned with recent cost-effectiveness analyses of RSV vaccination [43-46], extrapolating VE beyond the 30.6-month empirical data using Cox regression models introduces uncertainty. Additionally, a constant VE was assumed across all age and risk groups for model simplicity. This assumption reflects the limited availability of stratified VE data by age and comorbidity from clinical trials and may not fully capture the real-world vaccine efficacy. Fourth, country-specific data were not available for Italy for some of the parameters in the model (for example, the proportion of RSV-LRTD cases hospitalized was based on data from a study in the US [55]). More detailed country-specific data could be valuable for further evaluations of adjuvanted RSVPreF3 vaccine in Italy and could strengthen the generalizability of our results. Fifth, the analysis used a static model and therefore could not capture potential indirect effects of vaccination on disease transmission (herd protection). This may have further

contributed to under-estimating the potential impact of vaccination. However, given the limited evidence available on herd protection against RSV, we considered this approach appropriate. Sixth, transitions between URTD and LRTD could not be included in the model, whereas such transitions can occur in real life, and thus the model may not correctly reflect the number of RSV-related events. Development of a dynamic model for use in future studies could be valuable to investigate the impact of such transitions and indirect effects. The analysis also assumed that RSV-URTD incurred no healthcare resource usage, which may be an under-estimation of its impact. Seventh, although the AReSVi-006 phase III clinical trial did not demonstrate reductions in RSV-LRTD-related complications (i.e., COPD exacerbation, stroke, pneumonia, oxygen support, corticosteroid use) following vaccination, our model included estimates of these complications based on literature sources. However, the estimation of complications was part of an exploratory analysis, and the resulting data were not used to calculate costs and, therefore, did not influence the economic results. Lastly, in line with recent cost-effectiveness analyses of RSV vaccination, we selected a 5-year time horizon [43-46]. As opposed to a lifelong horizon, a shorter horizon does not account for any potential long-term impacts of RSV-related hospitalization, such as re-hospitalizations or long-term functional decline, under-estimating the disease burden of RSV in patients with COPD and the potential benefits of vaccination.

5 Conclusion

The results of this modeling study indicated that a single dose of adjuvanted RSVPreF3 vaccine in patients with COPD aged 60–74 years in Italy could potentially result in substantial reductions in RSV-related disease burden over a 5-year period. Projected savings in direct healthcare costs for RSV-related events could potentially

offset some of the costs of a vaccination program, and the estimated ICER was well below commonly used cost-effectiveness thresholds from both the societal and healthcare system perspectives. These data may help to support decision-makers and clinicians considering vaccination strategies in Italy.

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Declaration of interest

AP and EZ are employed by GSK and hold financial equities in GSK. GL is employed by GSK. FDM received consulting fees, honoraria for presentations, speakers bureaus, educational events, and support for attending meetings and/or travel from AZ, BI, GSK, Menarini, Sanofi, Chiesi, Neopharmed Gentili, and Zambon. FR declares scientific consultancy for GSK. GEC received consulting fees and honoraria for presentations, speakers bureaus, educational events from GSK. The author also declares having participated to the Advisory Board at GSK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Table 1. Projected public health impact over a 5-year time horizon of vaccination of Italian adults aged 60–74 years with COPD with a single dose of adjuvanted RSVPreF3 vaccine at three levels of coverage, compared with no vaccination

	No vaccination	**Adjuvanted RSVPreF3 vaccination**								
		11.8% coverage			**75% coverage**			**95% coverage**		
	Number of cases	**Number of cases**	**Difference vs no vaccination**	**% difference vs no vaccination**	**Number of cases**	**Difference vs no vaccination**	**% difference vs no vaccination**	**Number of cases**	**Difference vs no vaccination**	**% difference vs no vaccination**
Adults aged 60–74 years with COPD			565,063							
Vaccinated adults aged 60–74 years with COPD		66,677			423,797			536,810		
Outcome										
RSV-ARI	149,845	142,904	-6,941	-5%	105,727	-44,118	-29%	93,962	-55,883	-37%
RSV-LRTD [a]	107,034	100,645	-6,389	-6%	66,424	-40,610	-38%	55,595	-51,439	-48%
Receiving antibiotics	67,705	63,664	-4,042	-6%	42,017	-25,688	-38%	35,167	-32,538	-48%

Emergency department visit	5,352	5,032	-319	-6%	3,321	-2,030	-38%	2,780	-2,572	-48%
RSV-LRTD hospitalizations	40,628	38,202	-2,427	-6%	25,205	-15,424	-38%	21,092	-19,537	-48%
Intensive care unit admission	3,494	3,285	-209	-6%	2,168	-1,326	-38%	1,814	-1,680	-48%
In-hospital mortality	4,997	4,699	-298	-6%	3,100	-1,897	-38%	2,594	-2,403	-48%
RSV-LRTD-related complications										
Outcome										
COPD exacerbation	21,084	19,825	-1,259	-6%	13,080	-8,004	-38%	10,945	-10,139	-48%
Pneumonia	6,201	5,831	-370	-6%	3,847	-2,354	-38%	3,219	-2,982	-48%
Stroke	3,496	3,287	-209	-6%	2,169	-1,327	-38%	1,815	-1,681	-48%
Requiring oxygen support	2,519	2,369	-150	-6%	1,563	-956	-38%	1,308	-1,211	-48%
Requiring systemic corticosteroids	26,651	25,060	-1,591	-6%	16,534	-10,118	-38%	13,836	-12,816	-48%

[a] All RSV-LRTD cases assumed to require an outpatient visit

ARI, acute respiratory infection; COPD chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus

Table 2. Projected cost-effectiveness of vaccination of Italian adults aged 60–74 years with COPD with a single dose of adjuvanted RSVPreF3 vaccine over a 5-year time horizon at 75% vaccine coverage, compared with no vaccination, from the National Healthcare System perspective and the societal perspective (for population aged 60–69 years only)

	No vaccination	**Vaccination with adjuvanted RSVPreF3 vaccine at 75% coverage**	**Incremental (vaccination minus no vaccination)**
National Healthcare System perspective			
Total direct healthcare costs (€)	**141,752,042**	**166,515,281**	**24,763,239**
Direct RSV-LRTD-related medical costs	141,752,042	87,151,278	-54,600,764
Direct vaccine purchase costs	0	76,283,505	76,283,505
Direct vaccine administration costs	0	3,080,497	3,080,497
Total QALYs lost	**48,439**	**29,477**	**-18,962**
RSV-URTD events	235	214	-21
RSV-LRTD events	1,264	777	-487
RSV-related deaths	46,940	28,486	-18,454
ICER (cost (€) per QALY gained)			**1,306**
Societal perspective [a]			
Total direct healthcare costs (€)	141,752,042	166,515,281	24,763,239
Total indirect costs (€)	22,941,310	14,683,294	-8,258,015
Total QALYs lost	48,438	29,477	-18,961
ICER (cost (€) per QALY gained)			**871**

COPD chronic obstructive pulmonary disease; ICER, incremental cost-effectiveness ratio; LRTD, lower respiratory tract disease; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus; URTD, upper respiratory tract disease

[a] Analysis from the societal perspective conducted for individuals with COPD aged 60–69 years, as retirement age in Italy is 67 years.

Figure 1. Projected public health impact on (A) RSV-related outcomes and (B) RSV-LRTD-related complications over a 5-year time horizon of vaccination of Italian adults aged 60–74 years with COPD with a single dose of adjuvanted RSVPreF3 vaccine at three levels of coverage, compared with no vaccination

ARI, acute respiratory infection; COPD chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus

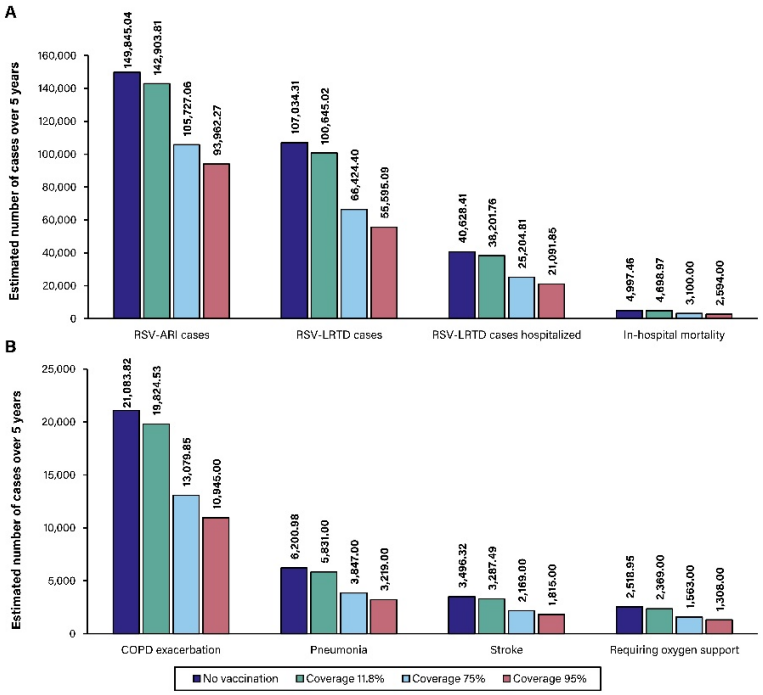


Figure 2. Results of the univariate deterministic sensitivity analysis for the cost-effectiveness of a single dose of the adjuvanted RSVPreF3 vaccine over a 5-year time horizon in Italian adults aged 60–74 years with COPD at vaccine coverage of 75% from (A) the Italian National Healthcare System perspective and (B) the societal perspective (for adults aged 60–69 years with COPD)

ARI, acute respiratory infection; COPD chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus

A 20% variation was considered for all parameters.

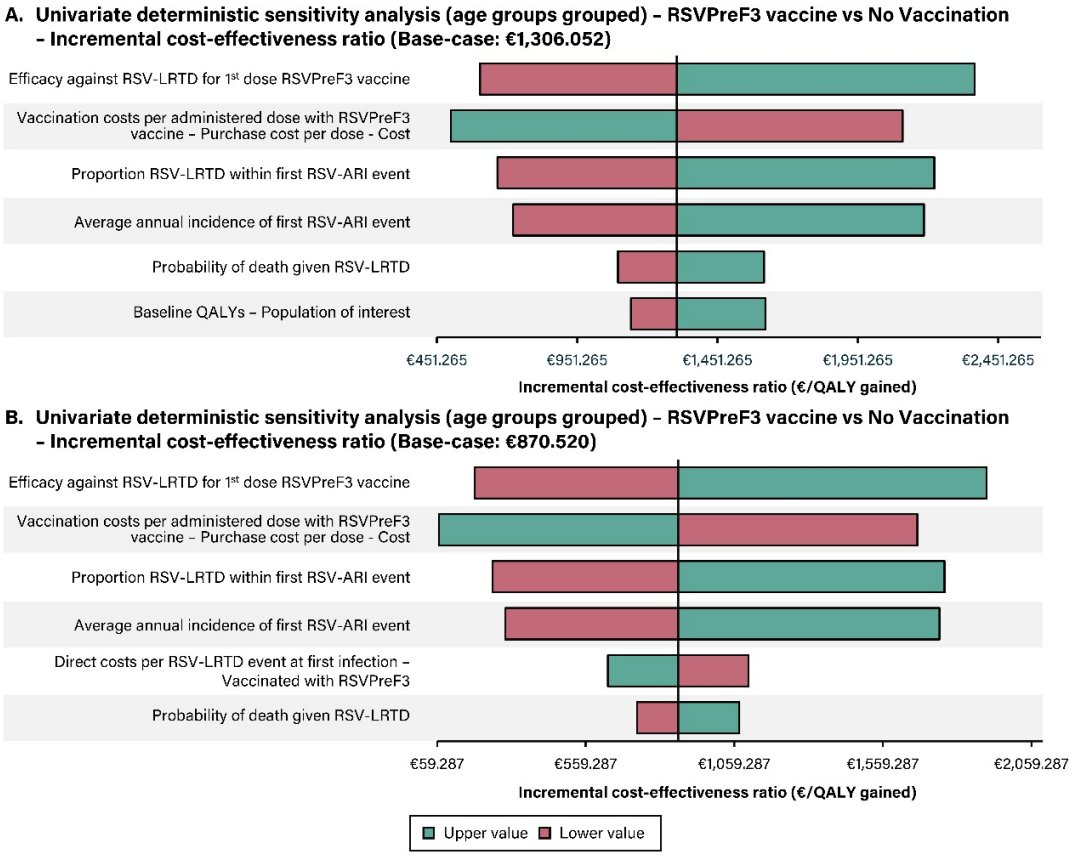
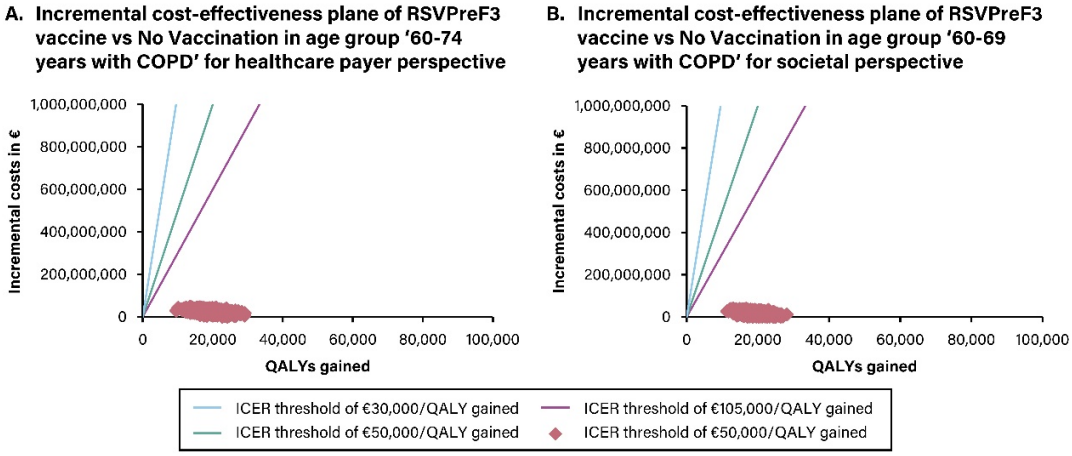


Figure 3. Results of the probabilistic sensitivity analysis for the cost-effectiveness of a single dose of the adjuvanted RSVPreF3 vaccine in Italy over a 5-year time horizon in Italian adults aged 60–74 years with COPD at vaccine coverage of 75% from (A) the Italian National Healthcare System perspective and (B) the societal perspective (for adults aged 60–69 years with COPD)

COPD chronic obstructive pulmonary disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus



Abbreviations

AIR, at increased risk;

ARI, acute respiratory infection;

CI, confidence interval;

COPD, chronic obstructive pulmonary disease;

COVID-19, coronavirus disease 2019;

ED, emergency department;

EMA, European Medicines Agency;

EU, European Union;

FDA, Food and Drug Administration;

GDP, gross domestic product;

ICER, incremental cost-effectiveness ratio;

ICU, intensive care unit;

INN, International Nonproprietary Name;

LRTD, lower respiratory tract disease;

mRNA, messenger ribonucleic acid;

NNV, number needed to vaccinate;

PSA, probabilistic sensitivity analysis;

QALY, quality-adjusted life-year;

QoL, quality of life;

RSV, respiratory syncytial virus;

UDSA, univariate deterministic sensitivity analysis;

UK, United Kingdom;

URTD, upper respiratory tract disease;

US, United States;

VE, vaccine efficacy;

WTP, willingness-to-pay

Cost-effectiveness of a single dose of the adjuvanted RSVPreF3 vaccine for the prevention of respiratory syncytial virus (RSV) among patients with chronic obstructive pulmonary disease in Italy

Supplementary Material

Supplementary Table 1. Data inputs for demographics, seasonality, and epidemiology

Parameter	Base-case value	Source
Population		[1]
60–64 years	4,288,466	
65–69 years	3,668,021	
70–74 years	3,251,392	
Proportion with COPD		[2]
60–64 years	2.85%	
65–69 years	6.40%	
70–74 years	6.40%	
Population with COPD		[1,2]
60–64 years	122,221	
65–69 years	234,753	
70–74 years	208,089	
Average annual incidence all-cause mortality among population with COPD		[3,4]
60–64 years	1.00%	
65–69 years	1.63%	
70–74 years	2.74%	

75–79 years	4.81%	
80–84 years	8.71%	
85–89 years	17.00%	
90–94 years	30.82%	
95–99 years	48.49%	
100+ years	83.81%	
RSV seasonality by month[a]		[5]
January 2024	363.00%	
February 2024	249.00%	
March 2024	76.00%	
April 24	38.00%	
May 2024	0.00%	
June 2024	0.00%	
July 2024	0.00%	
August 2024	0.00%	
September 2024	0.00%	
October 2023	21.00%	
November 2023	118.00%	
December 2023	335.00%	
RSV epidemiology		
Mean annual incidence of medically attended cases of RSV-ARI per person per year, all age groups	5.67%	[6]
Proportion of RSV-ARI events that are LRTD, all age groups	71.43%	Calculated from data over three RSV seasons from the AReSVi-006 trial [7]. Among trial participants with

		at least 1 pre-existing cardiorespiratory condition, 85 RSV cases were classified as LRTD out of the total 119 cases observed in the placebo arm

ARI, acute respiratory infection; COPD chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus

[a] Monthly values are normalized to the annual mean (100%); therefore, the incidence during peak months may exceed 100%.

Supplementary Table 2. Data inputs for healthcare resource utilization, unit costs, indirect costs, baseline utility and QALY loss in patients with COPD experiencing RSV

Parameter	Base-case value	Source
Healthcare resource utilization for RSV-LRTD cases		
Cases requiring outpatient visit, all age groups	100%	Assumption
Cases receiving antibiotics		[8]
60–64 years	63.10%	
65–69 years	63.30%	
70–74 years	63.30%	
Cases requiring emergency department visit, all age groups	5.00%	[9]
Cases requiring hospitalization		Calculated from [9,10]
60–64 years	18.15%	

65–69 years	43.57%	
70–74 years	43.57%	
Hospitalized cases admitted to intensive care unit	5.00%	Calculated from [9-11]
60–64 years	1.56%	
65–69 years	3.75%	
70–74 years	3.75%	
In-hospital mortality		Calculated from [9-11]
60–64 years	2.23%	
65–69 years	5.36%	
70–74 years	5.36%	
Cases with complications		
COPD exacerbations		Calculated from [9-11]
60–64 years	9.42%	
65–69 years	22.61%	
70–74 years	22.61%	
Pneumonia		Calculated from [9,10,12]
60–64 years	2.77%	
65–69 years	6.65%	
70–74 years	6.65%	
Stroke		Calculated from [9-11]
60–64 years	1.56%	

65–69 years	3.75%	
70–74 years	3.75%	
Oxygen support		Calculated from [9-11]
60–64 years	1.13%	
65–69 years	2.70%	
70–74 years	2.70%	
Treatment with systemic corticosteroids		Calculated from [9,10,12]
60–64 years	11.91%	
65–69 years	28.58%	
70–74 years	28.58%	
Unit costs for healthcare resources and vaccination		
Outpatient visits	€ 148.09	[13]
Prescribed antibiotics	€ 130.37	[14]
Emergency department visits	€ 430.55	[15]
Hospitalization [a]	€ 3,958.27	[16,17]
Intensive care unit	€ 13,028.17	[18]
Adjuvanted RSVPreF3 vaccine cost per dose [b]	€ 180.00	[19]
Vaccine administration cost per dose	€ 7.29	[20]
Indirect costs		Calculated from

(age 60–69 only)				[21-23], adjusted for inflation to 2023
Productivity loss per RSV-URTD event				
60–64 years	€ 92.46			
65–69 years	€ 58.86			
Productivity loss per RSV-LRTD event				
60–64 years	€ 338.55			
65–69 years	€ 319.47			

Baseline utility in Italian general population

	Mean EQ-5D-5L utility		**Weighted average used in model**	
Age group	**Males**	**Females**		[24]
60–64 years	0.919	0.895	0.907	
65–74 years	0.907	0.877	0.892	
75–109 years	0.879	0.829	0.853	

QALY loss applied to transition events in model

Event	**QALY loss**	**Source**
RSV-URTD	0.006	[25]
RSV-LRTD	0.013	[25]

[a] Based on the mean total cost of diagnosis-related-group (DRG) 79, DRG 80, DRG 089, DRG 090, DRG 092, DRG093, DRG 096, DRG 097, and DRG 088. Includes the costs of COPD complications

[b] Maximum price for the Italian National Healthcare System

COPD chronic obstructive pulmonary disease; LRTD, EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; lower respiratory tract disease; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus; URTD, upper respiratory tract disease

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