Broader societal consequences of RSV infection among Danish COPD patients over 60 years - a systematic review, meta-analysis and health economic analysis of Abrysvo.

DEPARTMENT OF HEALTH, SCIENCE, AND TECHNOLOGY
AALBORG UNIVERSITY
Masters Thesis, MEDICAL MARKET ACCESS
PROJECT GROUP 1007

AALBORG UNIVERSITY

School of Health Science and Technology
Medicine with Industrial Specialization
Medical Market Access
Aalborg University
https://www.hst.aau.dk/

Title:
Broader societal consequences of RSV infection among Danish COPD patients over 60 years - a systematic review, meta-analysis and health economic evaluation of ABRYSVO.

Project Type:
Masters Thesis - 4th semester

Project Period:
February 9th, 2025 - May 28th, 2025

Project Group:
Group 1007

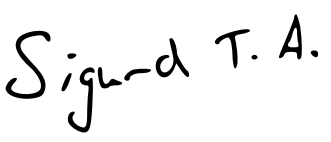
Author(s):
Sigurd Trudslev Andersson
Lykke Hilding-Hamann

Supervisor(s):
Nasrin Tayyari Dehbarez
Daniel Sloth Hauberg

Page number: 46

Date of Submission:
May 23rd, 2025

Aalborg University, 23th May, 2025



Lykke Hilding-Hamann
Student number: 20194768

Sigurd Trudslev Andersson
Student number: 20202984

Abstract

Background: Respiratory Syncytial Virus (RSV) is one of the leading causes of lower respiratory tract infections, a condition that often leads to exacerbations of varying degrees in Chronic obstructive pulmonary disease (COPD) patients. In Denmark, there are an estimated 400.000 COPD patients who risk RSV-related exacerbations, hospital admissions, and ultimately death. Currently, no national immunization program is in place to prevent infection with RSV. Instead, the Standard of Care is based on symptomatic treatment, once infection and exacerbation have occurred. This study aims to assess the cost-effectiveness and budget impact of implementing nationwide vaccination of COPD patients over 60 years with Pfizer's RSV vaccine ABRYSVO.

Methods: A cost-utility analysis (CUA) based on a Markov model was conducted to address the aim. Input parameters; baseline health related quality of life (HRQoL) in COPD patients and HRQoL during exacerbation of COPD, were derived from two systematic reviews and meta-analyses. Other input parameters were sourced through gray literature searches and register data, with some requiring various degrees of arithmetic calculations. The Markov model included 20 cycles, each 1 year long. The ABRYSVO scenario included 31 possible health states, while the non-vaccination scenario included 16 health states. A state tracker was utilized to calculate the accumulation of disutility attributable to RSV-caused exacerbations to avoid a so-called state explosion. The robustness of the results was assessed using deterministic (DSA) and probabilistic sensitivity analysis (PSA), while a budget impact analysis (BIA) was conducted to determine the budgetary implications of implementing ABRYSVO as the standard of care.

Results: The CUA results provided an incremental Quality Adjusted Life Years gain of $0,00456$ and an incremental cost of $1.086,26$ DKK. This translates to an incremental cost-effectiveness ratio of $238.067,79$ DKK, proving that, with a theoretical Willingness To Pay (WTP) of 450.000 DKK, ABRYSVO provides a cost-effective option for preventive treatment. Additionally, the BIA showed that year 1 would see an increased spending of $247.869.037,77$ DKK, while year 3 would see a saving of $17.760.743,25$ DKK. Moreover, the PSA showed that at the theoretical WTP of 450.000 DKK, ABRYSVO is cost-effective in approximately 66% of scenarios. While sensitivity analyses using $\pm$ 15% variation in WTP showed a probability of cost effectiveness of approximately 57% and 74% respectively.

Conclusion: At a WTP threshold of 450.000 DKK, ABRYSVO provides a predominantly cost-effective treatment option. Additionally, the BIA was relatively high in the first year and tapered off in the subsequent years. The results display a higher quality of life for COPD patients due to reduced infection and overall severity. Furthermore, the implementation will reduce strain on the health sector and combat antibiotic resistance.

List of abbreviations

AECOPD - Acute Exacerbations of Chronic Obstructive Pulmonary Disease
CASP - Critical Appraisal Skills Programme
CEAC - Cost-Effectiveness Acceptability Curve
CHEERS - Consolidated Health Economic Evaluation Reporting Standards
CIs - Confidence Intervals
COPD - Chronic Obstructive Pulmonary Disease
DAM - Decision Analytic Model
DMC - Danish Medicines Council
DSA - Deterministic Sensitivity Analysis
ERD - Enhanced Respiratory Disease
FEV_1 - Forced Expiratory Volume in One Second
FVC - Forced Vital Capacity
GOLD - Global Initiative for Chronic Obstructive Lung Disease
HEAP - Health Economic Analysis Plan
HRQoL - Health-Related Quality of Life
ICE - Incremental Cost-Effectiveness
ICUs - Intensive Care Units
ISPOR - International Society for Pharmacoeconomics and Outcomes Research
MeSH - Medical Subject Headings
MRC - Medical Research Council
PIO - Population-Intervention-Outcome
pre-F - Pre-Fusion
PRISMA - Reporting Items for Systematic Reviews and Meta-Analyses
PSA - Probabilistic Sensitivity Analysis
QALY - Quality Adjusted Life Year
RCT - Randomised Controlled Trial
RoB - Risk of Bias
RSV - Respiratory Syncytial Virus
SD - Standard Deviation
SoC - Standard of Care
WTP - Willingness-to-Pay

Contents

Introduction 1

On a global scale, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death and the eighth leading cause of poor health[1]. In Denmark, COPD is at its highest, estimated to affect 400.000 of the aging population[2], out of which up to 60.000 live with severe to very severe COPD[3]. COPD patients are particularly susceptible to disease exacerbations caused by bacterial or viral infections, which can lead to hospitalizations, lower quality of life, and, in the worst case, death[4]. On an annual basis, 15.000 Danish COPD patients are admitted to the hospital with acute exacerbations, which puts significant pressure on the healthcare system[3]. In recent years, these acute exacerbations of chronic obstructive pulmonary disease (AECOPD) hospitalizations have had a 30-day mortality of $15 - 20\%$[3]. In addition, a study by Jackson et al. 2024 has shown that severe exacerbations affect the already reduced health-related quality of life (HRQoL) of COPD patients by -0.025 as measured by using the EuroQol 5 Dimension (EQ-5D) quality of life questionnaire[5]. Although some patients recover from exacerbations, they experience a sustained decline in quality of life compared to their pre-exacerbation state[6]. The magnitude of COPD and the above-mentioned factors underscores the critical importance of preventing exacerbations to maintain and improve the quality of life for COPD patients.

Respiratory infections are well-established triggers of exacerbations and are linked to more severe disease progression[7]. In response, Denmark has introduced prophylactic vaccination programs targeting major epidemic and pandemic threats. While vaccines are available for purchase, high-risk groups, e.g., COPD patients, are offered free annual influenza and COVID-19 vaccines and subsidies for pneumonia and respiratory syncytial virus (RSV) vaccines[8].
In recent years, there has been increasing focus on RSV as a common respiratory infection that causes high morbidity and mortality among infants globally. In contrast, recent research additionally shows that RSV also causes a significant burden of disease among the elderly population, especially those with comorbidities and compromised immune systems[9]. Two U.S.-based studies, Branche et al. 2022 and Falsey et al. 2005, and one European study by Korsten et al. 2021 estimate that $3-7\%$ of individuals aged 65 and older are infected with RSV annually, accounting for $3-10\%$ of all lower respiratory tract infections in this age group[10, 11, 12]. A meta-analysis by Savic et al. 2023 found that $1,6\%$ of elderly ≥ 60 years in high-income countries experienced RSV infection. Additionally, $0,2\%$ were hospitalized with RSV, for which the mortality of the hospitalized was $7,1\%$[13]. Specifically, in Denmark, the estimated hospitalization rate for RSV in adults ≥ 45 years is 2 in 1.000. However, the hospitalization rate is significantly higher in

COPD patients[14]. Osei et al. 2023 found that RSV-associated respiratory tract infections accounted for 12.6% of all respiratory tract infection-related hospitalizations among Danish COPD patients[14].

RSV patients only receive supportive care, including respiratory support with supplemental oxygen and Continuous Positive Airway Pressure, and there is a lack of specific treatment for them, which is reflected in the high number of RSV-related hospitalizations[15]. This remained the standard approach for many years until 2023, when the first RSV vaccines were introduced to the market. These vaccines offer significant potential to prevent severe, treatment-requiring RSV infections[9]. By doing so, they may help preserve patients' quality of life and reduce strain and resource use within hospitals. Currently, no official immunization program exist for RSV vaccination in aging COPD patients in Denmark[16, 17]. Therefore, this project aims to evaluate ABRYSVO by Pfizer as the preferred prophylactic RSV vaccine for Danish COPD patients aged 60 and above. Clinically, ABRYSVO demonstrated an efficacy of 66.7% in preventing the first occurrence of RSV-related lower respiratory tract infections presenting with two or more symptoms, and 85.7% for cases with three or more symptoms[18]. These results underscore its strong preventative properties and represent a compelling opportunity to protect particularly high-risk patient populations, such as COPD patients.

Background 2

This chapter will provide essential background knowledge to establish a broad understanding of the burden of COPD and its association with RSV. Focus will be placed on the epidemiology, progression, and complications of COPD, and the role of RSV as a significant trigger of exacerbations. Additionally, the ABRYSVO vaccine by Pfizer will be introduced, along with its clinical effects and potential advantages for COPD patients. This introduction will lay the foundation for comprehending the relevance and objectives of the subsequent analysis.

2.1 Chronic obstructive pulmonary disease

As previously mentioned, COPD imposes a heavy disease burden, accounting for 3.5 million deaths worldwide in 2021, translating to 5% of deaths globally[1]. A study by Boers et al. 2023 estimated that COPD affected around 480 million people worldwide in 2020, with projections suggesting a rise to 600 million cases by 2050[19]. This indicates that the burden of COPD is likely to remain significant in the future. A similar tendency is noticeable in Denmark, where COPD persists as an important public health challenge. The prevalence of COPD cases in Denmark has reached record levels, and is progressing with annual new diagnoses ranging from 4.450 to 10.272 between 2015 to 2020[20]. Moreover, the disease is singularly accountable for 3.500 deaths each year[2]. This high prevalence, incidence, and mortality rate has substantial economic implications for the healthcare system and society. In a national Danish study, direct costs, elderly care, and nursing home expenses for COPD patients were found to be roughly three times those of the general population. Especially, severe exacerbations were a central cost driver[21]. Zooming out, the economic burden of COPD globally is foreseen to increase during the coming decades, underlining the necessity for effective management and prophylaxis strategies[22].
Besides the societal toll, marked by increased strain on healthcare systems and substantial economic costs, there are the individuals living with COPD every day, real people behind the statistics, facing ongoing physical, emotional, and social challenges. The study by Wang et al 2025 estimated that COPD accounts for 79.78 million disability-adjusted life years globally, a measure that encompasses premature mortality and years lived with reduced quality of life, shedding a light on the detrimental individual burden of the disease[23].

The disease COPD itself is a chronic, incurable lung disease. It typically develops over $20 - 30$ years, during which lung tissue is gradually destroyed[24]. It is a smoking-related disease, with

8 out of 10 cases in Denmark caused by tobacco smoke. It is estimated that $40 - 50\%$ of smokers develop COPD, and of these, approximately 25% go on to develop clinically significant COPD. In addition, environmental and genetic factors also influence disease development[25]. The term "obstructive" refers to the narrowing of the airways, which makes it difficult for air to move in and out of the lungs. COPD inflicts a persistent state of inflammation in the lungs, known as bronchitis, which causes swelling of the airways and increased mucus production. The inflammatory state is a sign of an overactive immune response, destroying lung tissue, specifically the alveoli, where oxygen is transferred to the blood, a condition known as emphysema[24].

COPD should always be suspected in patients over the age of 35 with a significant smoking history who present with shortness of breath, chronic cough, or frequent respiratory infections[25]. The diagnosis is made through a lung function test called spirometry, which measures forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the $\frac{FEV_1}{FVC}$ ratio. If the $\frac{FEV_1}{FVC}$ ratio is below 0.7, it indicates airway obstruction, which may suggest COPD (except in individuals over 70, who may naturally have values as low as 0.65 without it necessarily being pathological). To confirm the diagnosis, the measured FEV_1 value is compared to the predicted value in %, calculated based on sex, age, height, and ethnicity. This value determines the severity of COPD following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1-4 criteria[25]. The spirometric classification of COPD according to GOLD stages 1–4 is as follows:

- **GOLD Stage 1:** $\frac{FEV_1}{FVC} < 0.7$ and $FEV_1 \geq 80\%$
- **GOLD Stage 2:** $\frac{FEV_1}{FVC} < 0.7$ and FEV_1 between $50 - 80\%$
- **GOLD Stage 3:** $\frac{FEV_1}{FVC} < 0.7$ and FEV_1 between $30 - 50\%$
- **GOLD Stage 4:** $\frac{FEV_1}{FVC} < 0.7$ and FEV_1 less than 30% [25].

The spirometry values significantly impact the patient's survival prognosis. The severity of disease and medical treatment is primarily determined by the patient's daily symptoms, dyspnea, lung function level, and risk of future exacerbations based on the propensity for exacerbations during the last year[25]. In a revision of the GOLD classification, the severity of COPD is further divided into groups A, B, and E. This subdivision is based on the patient's Medical Research Council (MRC) dyspnea score and the frequency of exacerbations in the previous year. The MRC score ranges from 1 to 5, describing how apnea affects daily physical activities. Patients in GOLD group A typically experience few symptoms, reflected by an MRC score below 3, and are considered at low risk for exacerbations, defined as fewer than two exacerbations within the past year and no hospital admissions related to COPD. In GOLD group B, patients report more symptoms (MRC score of 3 or higher) but still fall into the low-risk category for exacerbations. Conversely, GOLD group E includes patients who are at high risk for exacerbations, either having had two or more in the last year or at least one that required hospitalization, regardless of the severity of their daily symptoms[25].

It is now clear that COPD patients are particularly vulnerable to exacerbations. The phe-

nomenon covers an acute worsening of respiratory symptoms and/or productive cough lasting longer than 14 days. These symptoms can be accompanied by tachypnea and tachycardia. As previously outlined, AECOPD can vary in frequency and severity, ranging from mild to moderate and severe. Mild AECOPD calls for increased treatment with short-acting bronchodilators, which the patients administer at home[3]. Because these exacerbations do not require additional prescribed medication, patients seldom seek medical assistance, which could explain why they are not recorded in registers[26]. Moderate AECOPD involves treatment with either antibiotics and/or systemic steroids. In severe cases, patients are hospitalized or at least assessed in the emergency department, in some instances accompanied by acute respiratory failure. As mentioned, 30-day mortality for AECOPD caused hospitalizations in Denmark is $15 - 20\%$ [3]. A bacterial or viral infection most commonly causes AECOPD. However, particle pollution and tobacco smoke can also be triggers. Virus infections typically cause more severe and prolonged symptoms and increase hospitalization risk. AECOPD, regardless of infectious agent, causes acute local inflammation, which can progress into a systemic response. The inflammatory condition induces bronchoconstriction, hypersecretion of mucus, and mucosal edema, narrowing the air ducts[3].
Physiologically, this makes exhalation of air more difficult, preventing the patient from emptying their lungs. Over time, this will develop into dynamic hyperinflation, when air becomes trapped in the lungs, increasing lung volume and making breathing more difficult. Furthermore, the respiratory muscles, the diaphragm and intercostal muscles, are affected, working under poorer conditions and growing fatigued due to the increased volume and breathing difficulty. Internally in the lungs, ventilation/perfusion mismatch may occur, which describes the balance between perfusion and ventilation of the lung tissue. In COPD and especially AECOPD, areas of the lungs may be poorly ventilated whilst still being perfused and vice versa, resulting in inefficient gas exchange of oxygen and CO_2[3]. As COPD is a smoking-related disease, risk factors include tobacco smoking, but also having had previous exacerbations, bronchiectasis, reduced lung function, and a high number of comorbidities[27]. AECOPD increases the use of healthcare resources, in terms of visits to the emergency room and possible hospitalization, leading to a substantially higher economic burden[28]. Moreover, the HRQoL is impacted both during and continually after experiencing moderate and severe exacerbations, as reported in Jackson et al. 2024 showing disutilities of 0.055 for moderate AECOPD and an additional disutility of 0.035 for severe AECOPD[6]. This emphasizes that focusing on preventive measures could improve health and quality of life.

Another challenge in managing COPD is that it is a largely underdiagnosed disease, with late diagnoses due to its slow build and deterioration. Initially, the symptoms are gradual and nonspecific, often consisting of a chronic cough and mild dyspnea. These symptoms are frequently dismissed or attributed to aging or smoking habits[25]. This diagnosis uncertainty and lack of awareness among patients and healthcare professionals culminate in delayed detection. The consequences of this issue include that the disease often progresses to a moderate or severe stage before detection, where it has already caused irreversible damage to the lung tissue,

reducing the effect of treatments[25]. Furthermore, COPD is often accompanied by various comorbidities, especially among the elderly. Common multimorbidities consist of cardiovascular disease, diabetes, depression, and musculoskeletal disorders, and all constitute complicating factors in the management and exacerbation of disease[29, 30].

2.2 Respiratory syncytial virus

RSV is an enveloped, single-stranded, negative-sense RNA virus that causes lower respiratory tract infections. Regarding virus classification, it belongs to the Pneumovirus genus of the Paramyxoviridae family[9]. The virus entails two subtypes; subtype A and subtype B. Luckily, RSV does not possess the ability to undergo genome reassortment due to its nonsegmented structure, and therefore does not pose a threat in terms of creating new RSV variants with pandemic potential[9]. The RSV genome is made up of 10 genes that encode a total of 11 proteins. The composition includes three non-structural and eight structural proteins, of which glycoprotein F is particularly significant for the development of vaccines, as it is crucial for the fusion of the virus and the cell membrane[31].
The virus was first detected in a herd of chimpanzees in 1956, and a year later in infants with lower respiratory tract infection[9]. Since then, it has been noted that RSV has a seasonal variation, where both subtypes often flourish simultaneously and occur as epidemics every year. The period overlaps with the influenza season, starting in December, reaching its peak in February, and ebbing in April[32]. An infection with RSV leads to partial and short-term immunity, meaning one can be reinfected at 3-10 year intervals[33]. An RSV infection is characterized by cold-like symptoms lasting 1-2 weeks. Among healthy adults, the infection is asymptomatic in 40% of cases. The virus has an incubation period of 4-10 days, and patients will usually be contagious and PCR-positive for 11 days[9].
It infects through the eyes, nose, or mouth, and spreads through respiratory droplets[34]. In older healthy children and adults, RSV infection typically doesn't result in severe disease but causes illness similar to the common cold[35, 34]. However, in infants, neonates, and adults with underlying comorbidities, such as heart and lung disease and weakened immune systems, RSV poses a threat of developing severe disease[34, 35].

2.2.1 Burden of RSV

The burden of RSV is often discussed in the case of infants and neonates, since they are at greater risk of developing severe RSV infections than healthy adults, partly due to a lower level of IgG antibodies[36]. Also older adults are at risk of developing severe disease after RSV infection, especially those with underlying comorbidities such as COPD [37]. A study conducted by Penders et. al. 2025 found that COPD patients accounted for 30.8% of RSV infections requiring inpatient care [38]. These patients had an adjusted RSV incidence rate ratio of approximately 9.7, when compared with the background population, and a mortality rate of $2.8\% - 17.8\%$. This means that COPD patients are approximately 9.7 times more likely

to be hospitalized with an RSV infection than the average adult, and in this case, they have up to a 17.8% risk of dying [38]. This is especially concerning given Western society's aging population [39]. The healthcare sector risks seeing an increase in the number of RSV-related complications requiring medical attention.
In the context of the COPD populations, this implies that RSV-induced exacerbations and especially severe cases ramp up the cost as they result in hospital admissions, emergency care, consultations with general practitioners, and increased use of medications and prescriptions[3]. Indirect costs increase due to the productivity loss of those who require sick leave, health deterioration leading to early retirement, and caregiver burden[40]. This is especially relevant in elderly populations with multimorbidities, which make up a significant percentage of the Danish population living with COPD. In severe cases, long-term care and rehabilitation can also be necessary[40]. Additionally, the higher incidence rate in the autumn and winter leads to an increased burden for the hospital sector when they are already experiencing peak loads from other pathogens[41].
All in all, this begs the question of whether it is feasible to continue ignoring the burden of RSV in the older, comorbid population and handling the disease course in hospitals with supportive care. Conversely, from a medical, social, and economic standpoint, it might be more favorable to utilize the innovative, preventive measures that reside in the medical arsenal of the modern health care system.

2.2.2 Vaccine

There have long been ongoing efforts to develop an effective vaccine against RSV infection. The search for a vaccine that effectively protects against RSV began in the 1960's - around a decade after RSV was first discovered[42]. Effective vaccines did, however, only reach the market in 2023[43], with the development and first approval of vaccines such as ABRYSVO by Pfizer, AREXVY by GSK, or Beyfortus by AstraZeneca and Sanofi[43, 44, 45, 46]. These three preventive strategies differ in several ways, with ABRYSVO being a bivalent vaccine, containing F-proteins from both the RSV-A and the RSV-B strands[44]. AREXVY is a monovalent vaccine containing F-proteins from only the RSV-A strand and an adjuvant[45]. Lastly, Beyfortus is a monoclonal antibody, meaning that it works by binding directly to the virus and neutralizing it[46].

Throughout the development efforts, an ongoing problem with the development of an effective RSV vaccine has been the occurrence of Enhanced Respiratory Disease (ERD). ERD happens when an RSV-naive individual receives an RSV vaccination, but instead of protecting the individual against RSV infection, it increases the risk of a severe case of the disease [42]. The reason for ERD has been that the vaccine resulted in the induction of neutralizing antibodies, which did not properly neutralize the RSV virus. These vaccines also lead to a Th-2 immune cell biased immune response, resulting in airway hyperactivity and mucus hypersecretion [47]. As such, earlier attempts to develop an RSV vaccine have led to disease courses that were more

severe than if the patient had not been vaccinated [42].
In recent times, increased knowledge of the etiology and pathological mechanisms of RSV has allowed researchers to address the issues of ERD. A particularly valuable insight in the development of the vaccine has been that the majority of the neutralizing activity of RSV antibodies is delivered by the Pre-Fusion (pre-F) conformation of the antibody [42].

The ABRYSVO RSV vaccine from Pfizer is developed as a recombinant bivalent Pre-F conformation of the RSV F-protein based on both the RSV-A and RSV-B subtypes [9]. The vaccine includes 120 µg RSVPreF antibody: 60 µg from RSV-A, and 60 µg from RSV-B [9]. The inclusion of both subtypes of RSV is intended to provide the most optimal protection against both strands of the RSV pathogen.
In Denmark, older adults over 60 with COPD can receive a conditional subsidy for vaccination with AREXVY [48]. Additionally, the Danish Medicines Council (DMC) recently provided a partial recommendation for Beyfortus as a preventative treatment for premature children who are at increased risk of being infected with RSV within their first life year [16].

Aim of Study 3

This project aims to explore the potential health benefits and economic value of administering and providing full reimbursement of the ABRYSVO vaccine against RSV for COPD patients over 60 years.

The project will encompass:

- Systematic Literature Reviews and Meta-Analyses to determine:
  - The baseline HRQoL of COPD patients
  - The proportion of AECOPD cases attributable to RSV infection
- Gray Literature Search to find:
  - The burden of RSV-induced AECOPD
- Health Economic Evaluation including:
  - Cost Utility Analysis
    - Markov Model
    - Deterministic Sensitivity Analysis
    - Probabilistic Sensitivity Analysis
  - Budget Impact Analysis

Through these steps, the investigation is intended to assess whether vaccination with ABRYSVO may convey a cost-effective preventive measure and prove a valuable strategic addition to the Danish immunization program. By tying the clinical evidence to an economic evaluation, this project will contribute to the ongoing efforts to prioritize and implement preventative healthcare strategies for Danish COPD patients.

Method 4

This chapter outlines the methods and guidelines employed throughout the project, from gathering data to the analysis.

4.1 Systematic reviews

4.1.1 Search Strategy

As a fundamental part of the data collection for this project, two systematic reviews were executed in the Medical Research Database, PubMed, managed by the National Institutes of Health. Pubmed contains over 30 million records dedicated to health sciences research[49], and was chosen as the preferred database, providing a starting point for a comprehensive collection of inputs to the economic evaluation model. Further context and insights were obtained via searches of gray literature, chain searches, and additional applicable sources. The systematic reviews were carried out per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensuring a structured procedure with clear documentation and transparency[50]. A comprehensive breakdown of the reported items and their locations within the project can be found in Appendix B. Before conducting the two systematic reviews, review protocols were developed and are attached in Digital Exam Appendix.

The first systematic review aimed to identify and analyze HRQoL values in COPD patients, and the second aimed to establish the percentage of COPD exacerbations caused by RSV. This included investigating the primary outcome of interest: the incidence of RSV in COPD patients hospitalized with an exacerbation. Secondary outcomes of interest were also included in the search string, including the hospitalizations and mortality caused by RSV infections in this population.
The systematic reviews were structured, aligning with the Population-Intervention-Outcome (PIO) model. The search blocks were established to achieve a focused block search, improving the accuracy and applicability of the retrieved studies. Three facets were formed for the systematic reviews to identify and perform block searches. The PIO facets for each search can be seen in Table 4.1.
To enhance the comprehensiveness of the search, both synonymous free-text terms and controlled vocabulary terms, including medical subject headings (MeSH) terms, were employed using the PubMed thesaurus. The search strings were composed by Boolean operators, with *'OR'* connecting the terms within each facet and *'AND'* linking the facets together. The search terms

Criteria	Search for HRQoL Values in COPD Patients	Search for COPD exacerbations caused by RSV
Population	Studies focused on COPD patients	Studies focused on COPD patients
Intervention/ Exposure	Quality of life measures, specifically the EQ-5D and EuroQol instruments.	RSV infections and vaccines
Outcome	Health-related quality of life, including terms such as QALY and HRQoL.	RSV-related consequences in COPD patients, such as incidence rates, hospitalizations, mortality, and disease exacerbations.

Table 4.1. Population, intervention, and outcome framework for the two systematic reviews for COPD patients.

and constructed search strings are detailed in Appendix A.

4.1.2 Eligibility Criteria

Specific inclusion and exclusion criteria were established to facilitate a comprehensive review of appropriate literature encompassing HRQoL values and RSV infections in COPD patients. These criteria were designed to ensure the relevance and suitability of the literature for the project's objectives. Moreover, they were crafted to align the investigated conditions and reported outcomes with this project's aims while focusing on pertinent patient populations. Each review's inclusion and exclusion criteria are detailed in Table 4.2. Specifically, an age limitation was applied in both of the the searches. Study populations in the uncovered literature had to include patients older than 35 years. Studies including children or young adults ≥ 35 were excluded. These criteria were applied according to Danish clinical guideline platform, Sundhed.dk, which states *"COPD should be suspected in individuals over the age of* 35 *who present with respiratory symptoms such as cough, increased mucus production, and dyspnea, and who are current or former smokers."*[25]. The rationale for setting these criteria was to ensure that the study population reflected the characteristics of the Danish COPD patients. Furthermore, since the economic evaluation of this project is conducted on patients aged 60 and above, it was deemed most appropriate to exclude data from significantly younger patients to ensure the results were representative of an older population.

Search for HRQoL Values in COPD Patients		Search for COPD Exacerbations Caused by RSV	
Inclusion Criteria	**Exclusion Criteria**	**Inclusion Criteria**	**Exclusion Criteria**
• Studies including COPD patients. • Studies focusing on COPD exacerbations and their impact on HRQoL. • Studies involving adult patients ($\geq$ 35 years) and including all age groups. • Studies reporting HRQoL data using EQ-5D-5L, and HRQoL assessed using validated measurement instruments.	• Studies involving children, young adults (<35 years), or patients without COPD. • Studies that do not focus on COPD exacerbations but rather on specific COPD treatments. • Studies that investigate specific subpopulations of COPD patients. • Studies that do not report HRQoL measurements related to COPD. • Studies not using EQ-5D-5L. • Studies focusing only on clinical outcomes (e.g., mortality, hospitalization) without HRQoL assessments. • Studies not available in full-text. • Studies not available in English or Danish.	• Studies focused on COPD patients. • Studies involving adult patients ($\geq$ 35 years) and including all age groups. • Studies conducted in humans. • Studies including cases of RSV. • Studies reporting outcome measures of incidence, hospital admittance, mortality, and/or exacerbations of COPD related to RSV infection.	• Studies that do not report the proportion of COPD exacerbations caused by RSV infection. • Studies involving children, young adults (<35 years), or patients without COPD. • Studies not available in full-text. • Studies not available in English or Danish.

Table 4.2. Inclusion and Exclusion criteria for the review for HRQoL values in COPD patients and COPD exacerbations caused by RSV. HRQoL - health-related quality of life. COPD - chronic obstructive pulmonary disease.

4.1.3 Selection Process

The studies obtained from the systematic reviews on HRQoL values and COPD exacerbations caused by RSV underwent independent reviewing and categorization by two authors simultaneously, adhering to the established inclusion and exclusion criteria outlined in Table 4.2[51]. Duplicate records were initially removed using the screening tool Rayyan[52]. The screening process comprised three stages: title screening, abstract screening, and a full-text review. The total selection process was simplified by Rayyan, employing blinding techniques to reduce bias[52, 51]. Both authors performed the title, abstract, and full-text screening phases. Disagreements concerning study inclusion were handled via collective discussions among the authors at the end of each screening phase until agreement was reached[51].

4.1.4 Risk of Bias Assessment

A thorough risk of bias (RoB) assessment was undertaken to ensure the reliability and validity of the included studies. Both authors of this project evaluated each study to minimize selection bias and maintain consistency. If studies were identified as having a high RoB, they were excluded from the analysis. The tool used to evaluate the methodological quality of the articles was the Critical Appraisal Skills Programme (CASP) checklists, as they provide a uniform, structured procedure for appraising medical literature. CASP checklists are widely utilized in evidence-based practice, especially in healthcare and social sciences[53]. The CASP checklists were selected to ensure consistency across various included study designs. The primary common focus of the CASP checklist includes study design, study population, methodological rigor, reporting of the results, and transferability throughout the studies.

The following CASP checklists were applied based on the varying study designs: *Systematic*

Reviews with Meta-Analysis of Observational Studies, *Randomised Controlled Trial (RCT) Checklist*, *Cross-Sectional Studies Checklist*, *Case Control Study Checklist*, and *Cohort Study Checklist*. These instruments feature structured questions designed for particular study designs, allowing for the evaluation of reliability, applicability, and methodological strengths and weaknesses.

4.1.5 Data Management

The data, which were later used for meta-analysis in this project, were managed according to two steps: first, relevant data were extracted from the appropriate studies, and then the data were converted to ensure suitability for use in a meta-analysis.

Data Collection Process

All relevant data were collected from the identified studies and stored in a data sheet as an .xlsx document. In both searches, the data collected encompassed study ID, year of publication, country of origin, sample size, and proportion of male participants. Additionally, the incidence of RSV (%), and the number of exacerbations were collected for the review investigating COPD exacerbations caused by RSV, and HRQoL-score and standard deviation (SD) in the review for HRQoL in COPD patients, respectively. Both authors conducted data extraction collectively to ensure the consistency and reliability of the extracted data.

Data Conversion

One study included patients in the age group 18-35. This data could not be used directly in the meta-analysis due to a contradiction with the exclusion criteria. However, since the study reported stratified results for age groups 18-39, 40-65, and 66-102, it was possible to exclude the younger subpopulation and calculate pooled HRQoL and SD for the population in the age group 40-102. The pooled SD was calculated using the formula below[54]:

$$s_{pooled} = \sqrt{\frac{\sum SSD_i}{\sum(r_i - n)}} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}} \tag{4.1}$$

In formula 4.1, n_1 and n_2 represent the respective sample sizes, whereas s_1 and s_2 represent the respective SDs.
To calculate the pooled or weighted HRQoL, an inverse variance weighting method was used, where a lower weight is given to variables with higher variance. This ensures that more precise estimates are given a higher weight. The calculations were performed with the following formula[55]:

$$\tilde{Y} = \frac{\sum_{i=1}^{n} \omega_i Y_i}{\sum_{i=1}^{n} \omega_i} = \frac{\frac{1}{Var(Y_1)} \times Y_1 + \frac{1}{Var(Y_2)} \times Y_2}{\frac{1}{Var(Y_1)} + \frac{1}{Var(Y_2)}} \tag{4.2}$$

In formula 4.2 Y_1 and Y_2 represent the HRQoL of the respective subpopulations and $Var(Y_1)$ and $Var(Y_2)$ represent the variance of the two subpopulations.

The last step in the data conversion was to calculate the variance of the studies based on the SDs, since none of the studies reported the variance directly. However, the SD is simply the square root of the variance, so the variance can conversely be calculated by squaring the SD [56].

Data Preparation

Data analysis was conducted in the statistical software *R* [57]. Once the necessary data conversion steps had been completed, the extracted data was loaded directly into R as an .xlsx document. The loaded dataset was subsequently assessed for completeness to ensure no data was missing.

4.2 Meta Analysis

Two meta-analyses were conducted using the data gathered from the systematic reviews to aggregate data for use in later cost-utility modeling[58]. One was conducted to collect data regarding the average HRQoL observed in COPD patients, and the other to collect data regarding the average incidence of RSV infection in COPD patients hospitalized with AECOPD. A meta-analytic framework was chosen given its ability to synthesize evidence based on multiple studies, providing greater statistical power and more reliable findings[58].
The meta-analysis was conducted using statistical software *R*, given its extensive analytical capabilities provided through the wide range of publicly available packages. The meta-analysis in this project utilized the $metafor$ and *tidyverse* packages, which make it possible to conduct meta-analyses and create visualizations such as forest and funnel plots[59, 60]. The rma function was employed to perform a random effects meta-analysis, while the functions $forest.rma$ and $funnel.rma$ were used to create visualizations in the form of forest and funnel plots. Additionally, influence and leave-one-out analyses were conducted using the $influence$ and $leave1out$ packages, to assess the individual impact of studies on the heterogeneity and overall outcome measures.
Additionally, an Egger's regression test was conducted using the $regtest$ function to support any funnel plot findings. Egger's regression is a statistical method used to assess the asymmetry found in a funnel plot, and thereby a way to assess publication bias in meta-analyses[61]. A low p-value from the eggers regression indicates a statistically significant presence of publication bias[61]. Publication bias arises, when the likelihood of a study being published is related to its results and the statistical significance of these results[61].
The meta-analysis assumed that the included studies produce inferences of the same underlying construct - HRQoL in COPD patients. Thus, a random effect model was deemed suitable, due to its ability to account for both within and between study variability. As such, the random effects model allows for a synthesis of data based on studies with different populations and methods[58]. Furthermore, confidence intervals (CIs) of the included studies were used to assess the precision of the individual study findings. Narrow CIs represent more precise estimates, while wide CIs

represent less precise estimates[62].

Assessment of Heterogeneity

Heterogeneity of the included studies was assessed using I^2 values. The I^2 represents the proportion of variability that can not be attributed to random chance alone, but must instead be attributed to heterogeneity[58]. Some argue that using fixed thresholds to describe heterogeneity is inappropriate since the consequence of inconsistency depends on the study context. However, Cochrane reports the following tentative thresholds:

- $0 - 40\%$ might not be important
- $30 - 60\%$ might represent moderate heterogeneity
- $50 - 90\%$ might represent substantial heterogeneity
- $90 - 100\%$ might represent considerable heterogeneity[58].

Assessment of Publication Bias

Publication bias arises when studies that fail to report positive or statistically significant results are not published. As such, published studies might be systematically unrepresentative of the investigated population. This poses a threat to the validity of meta-analytic findings[63]. Thus, assessing the presence of publication bias in the utilized data is crucial to ensure the validity and reliability of the study findings. This project evaluated publication bias via funnel plots and Egger's regression test. In a funnel plot, the effect size of the study is plotted against its standard error, providing a visual way of inspecting the presence of publication bias[64]. Egger's regression test produces a measure describing the asymmetry of the studies' distribution, whereby it provides a quantitative way of assessing the presence of publication bias[61].

4.3 Health Economic Modeling

To assess whether a recommendation resulting in full reimbursement of the RSV vaccine, ABRYSVO by Pfizer for adults over the age of 60 years, suffering from COPD, would be cost-effective, a decision analytic model (DAM) was carried out. The DAM offers a framework that consolidates various data types, such as clinical measures and resource use. This allows it to inform decision-making regarding resource allocation within the healthcare sector, enabling more efficient prioritization of scarce resources[65]. The DAM framework ensures the incorporation of uncertainty arising from input parameters through the use of deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA)[65]. The PSA was conducted using a second-order Monte Carlo simulation.

The most appropriate DAM for this scenario would be a CUA conducted using a Markov model. The Markov model was chosen based on its structural ability to accommodate longer time horizons and its ability to return to previously experienced health states, making it suitable for simulating the course of chronic conditions, such as COPD[65]. The model was simulated using a limited societal perspective, meaning that it included all relevant costs, encompassing medical

costs, hospitalization costs, vaccination costs, transportation costs, GP costs, and patient-related costs such as the value of alternative time, while productivity loss was not included. The use of a limited societal perspective aligns with the recommendations of the DMC[66]. All the specifics of the model can be seen in Table 4.3. The Markov model was developed and executed using Microsoft Excel, as the DMC demands that applications for Health Technology Assessments are carried out in this specific software[66].
A health economic analysis plan (HEAP) was designed before undertaking the economic evaluation. The completed HEAP is attached in Digital Exam Appendix. To ensure appropriate structure and reporting of the health economic evaluation it adhered to the checklist, Consolidated Health Economic Evaluation Reporting Standards (CHEERS) from 2022[67], which can be found in Appendix D.

	Health economic analysis
Alternatives	- ABRYSVO scenario - Non-Vaccination scenario
Model Type	- Markov Model
Analysis method	- Cost-utility analysis
Outcome measures	- QALY - Life Years
Number of Cycles	- 20
Cycle Length	- 1 Year
Time horizon	- 20 Years
Cost perspective	- Limited societal perspective
Sensitivity analysis	- Deterministic and probabilistic

Table 4.3. *Framework of the health economic model.*

4.3.1 Markov Model

A Markov Model works by defining a set of health states, which the patients in the model can occupy at any given time point, in any given cycle[65]. Between each cycle, the Markov Model lets the patients transition between health states based on distinct transition probabilities, defining the probability of transitioning from one state to another[65].
Now, the Markov model is subject to an intrinsic underlying property, the Markovian assumption. This property states that the model is memoryless, meaning that the future state a patient can transition to relies solely on the current state the patient occupies[65]. Additionally, the Model states must be mutually exclusive and exhaustive, meaning that a patient can not occupy more than one state at a time, and patients can not appear or disappear from the

model[65].
In the Markov model, the cycle length was set to one year, and the model was allowed to undergo 20 cycles, accumulating to a time horizon of 20 years. The 20-year time horizon was based on the age of the patients upon introduction to the model, at 60 years of age, as well as the average Danish lifespan of approximately 80 years. By allowing the model to run for 20 cycles, the patients in the model reach the average life expectancy before the model concludes[68].

Parameters

The parameters used in constructing the model consisted of various probabilities of events occurring or not occurring, utility values, and costs.

Probabilities

The probabilities used in the model were found using a mix of methods, including systematic review, meta-analysis, gray literature search, and arithmetic calculations. These probabilities define the patient transitions between the states of the Markov Model. A more elaborate explanation of the probabilities and how they were obtained can be found in the Appendix C in Table C.1.

Utilities

The primary outcome measure used in the model is the Quality Adjusted Life Year (QALY). A QALY is a compound measure combining length of life with quality of life. This makes the QALY a suitable outcome measure for health economic evaluation, where it is necessary to compare the effects of interventions in widely different disease areas with no naturally comparable outcome measure[65]. The quality of life aspect of the QALY is measured using a validated and standardized HRQoL Questionnaire, such as the EQ-5D or the SF-6D[65].
The utilities used in the model were obtained using a mix of methods, including systematic review, meta-analysis, and gray literature search. A more elaborate explanation of the utilities and how they were obtained can be found in the Appendix C in Table C.2.

Costs

All costs and measures of resource use included in this project are based on register data provided by Pfizer. This data combines register records of resource use and contacts to the health care sector following COPD exacerbation, with the price reported through DRG-tariffs. The vaccine cost was identified on Medicinpriser.dk, while transportation time and alternative patient time were calculated according to the recommendations of the DMC[66, 69]. Table 4.4 shows the breakdown of the calculated cost resulting from event cost and pertaining frequency for each possible event, including *Severe infection*, *Moderate infection*, *Vaccination* and *No event*. The cost presented are *Alternative time*, *Transportation*, *Hospitalization Cost*, *Vaccine Cost* and *Total*.

	Alternative Time	Transportation	Hospitalization Cost	Vaccine Cost	Total
Severe Infection	13.958,76 DKK	413,23 DKK	85.010,39 DKK	0 DKK	99.382,39 DKK
Moderate Infection	225,42 DKK	45,44 DKK	279,07 DKK	0 DKK	549,94 DKK
Vaccination	188,00 DKK	37,90 DKK	0 DKK	1.449,77 DKK	1.675,67 DKK
No Event	0 DKK	0 DKK	0 DKK	0 DKK	0 DKK

Table 4.4. Cost breakdown by event type used in the Markov model. All prices are in the Danish currency, Danske Kroner (DKK).

Health states and transitions

The model was structured around two primary scenarios: ABRYSVO scenario and a non-vaccination scenario, with the latter representing the standard of care (SoC). The health states and transitions in the model were designed to mimic the clinical reality and immunological dynamics over a three-year period. The time horizon was motivated by evidence showing that reinfection is plausible after approximately 3 years[9]. Moreover, Center for Disease Control reports that ABRYSVO is effective for at least two years, with data from Pfizer showing significant immunity throughout year three as well[70].

The model included 31 discrete health states in the vaccination scenario, allowing 181 possible transitions. In the no-vaccination scenario, there were 16 health states giving way to 61 transitions. Each health state describes a distinctive combination of clinical status, immunological state (e.g., post-infection immunity or vaccination effectiveness), and year within the 3-year simulation cycle. To imitate the time-dependent aspects of vaccine and infection-induced immunity, the health states were sorted into year 1, 2, and 3 segments in both the vaccinated and unvaccinated cohorts. In the vaccinated cohorts, *"Vaccinated 1"* represents the year of vaccination, whereas *"Vaccinated 2"* and *"Vaccinated 3"* capture the vaccine-induced immunity over time, assuming no revaccination happens in those years.
Similarly, the unvaccinated cohorts advance via "*Unvaccinated (y1–3)*" states, without acquiring immunity through vaccination, facilitating the comparison of immunity trajectories. In the case of infection, the state *"Infected 1"* symbolizes active infection and the associated health burdens, whereas *"Infected 2"* and *"Infected 3"* simulate post-infection immunity in the subsequent years, reducing the risk of reinfection.

The year-based health states, ranging from 1-3, were modeled as tunnel states, as individuals cannot stay in the exact time-year indefinitely. The tunnel states enable transitioning through the annual structure of the model systematically. Tunnel states facilitate time-dependent effects within the otherwise memoryless Markov model[71]. The health state *"Death"* was an absorbing state; once an individual enters *"Death"*, no further transitions occur, marking an irreversible exit from the model[72].

All transitions were controlled by probabilities, which were gathered empirically through the meta-analyses or from published literature. Calculating the transition probabilities, it was ensured that the transition probabilities from any given health state summed to 1 for probabilistic coherence. As an example of one of the transition probability calculations, *"Transition from unvaccinated (y3) healthy to unvaccinated (y1) infected 1 moderate"* can be seen below:

$$(1 - \text{Annual\_Mortality\_Rate}) \times \text{Infection\_Probability\_Moderate}$$

The values of the specific parameters used in the model, including probabilities and utilities, can be seen in Table 4.5. For additional information, such as parameter description, how it was obtained, and source, refer to Appendix C.

Probability Name	Value
Annual Mortality Rate	0,258865551
RSV Caused Exacerbations	0,0938
Moderate - Severe ratio	5,977804158 : 1
Infection Probability	0,024622500
Infection Probability Moderate	0,021093811
Infection Probability Severe	0,003528689
Acute Severe Infected Mortality	0,175
Severe Infected Mortality	0,38856408
Vaccine Compliance	0,76
Post Infection Immunity y1	0,82940
Post Infection Immunity y2	0,69180
Post Infection Immunity y3	0,53080
Vaccine Effectiveness y1	0,82940
Vaccine Effectivevess y2	0,69180
Vaccine Effectiveness y3	0,53080

Utility Name	Value
Baseline HRQoL	0,79
Acute Moderate HRQoL Loss	0,055
Chronic Moderate HRQoL Loss	0,014
Acute Severe HRQoL Loss	0,09
Chronic Severe HRQoL Loss	0,025

Table 4.5. Overview of parameter inputs of the model, including probabilities and utilities.

Markov trace

A Markov trace was created for each scenario to simulate the evolution of the cohorts over time. Its purpose is to capture the proportion of the cohort within each health state at a given time, to facilitate the calculation of cumulative clinical and economic outcomes. The model was conducted with a cycle length of one year and ran for 20 cycles. Three cumulative trace tables showing *Costs*, *Life years*, and *QALYs* were generated for each cycle. Each of these outcomes was recorded in undiscounted and discounted values, using an annual discount rate of 3,5% as per the Danish Finance Ministry[73].

As mentioned earlier, the Markov model is memoryless, which means that the transition probabilities only reflect the current state, involving no prior history[71]. This posed a challenge regarding the estimation of QALYs, where previous disease experiences and severity influenced HRQoL acutely and chronically.

State Tracker

The need to keep track of the chronic loss of HRQoL resulting from an RSV-caused exacerbation arose throughout the model, challenging the memoryless conditions. Therefore, it was decided to employ the use of tracker variables to acommodate this issue[71]. Tracker variables offer a way to keep track of event accumulation in the live population of the simulation[74, 71]. Thus, by employing tracker states, it is possible to calculate the cumulative loss of HRQoL sustained through the RSV-caused exacerbation, while avoiding so so-called state explosion[71]. State explosion happens through excessive use of tunnel states, leading to an extreme number of possible health states, and state transition probabilities, resulting in an overly complicated model [71]. Using an external state tracker yields a simpler model while accounting for the cumulative effects of the RSV-induced exacerbation.
The state tracker was developed to monitor 11 different events and parameters. These include the per-cycle number of severe and moderate exacerbations, deaths, death rate, moderate and severe infection burden, acute and chronic utility loss, base QALY, QALYs experienced in each specific cycle, and cumulative QALY.
The severe and moderate infection burden represents the accumulated number of severe and moderate exacerbations experienced at any point by patients still alive in the model. The acute and severe loss represents the number of QALY lost in each cycle due to moderate or severe RSV-related exacerbations. The Base QALY represents the QALY that would have been had no patients experienced an exacerbation in that specific cycle. In contrast, the QALY cycle is calculated by subtracting the acute and severe loss from the base QALY. Lastly, the cumulative QALY is calculated. The state tracker was built based on the values from the Markov trace, as well as the original input values, also used in the Markov trace.

4.3.2 Sensitivity analysis

Sensitivity analyses were carried out to investigate the robustness of the outcomes from the CUA. Essentially, a sensitivity analysis aims to test whether the results change if the estimates of the parameters are varied in the model[65]. This project includes DSA and PSA, investigating parameter uncertainty. The analyses will be subjected to a speculative willingness-to-pay (WTP) threshold of 450.000 DKK, according to a WTP investigation by Nordic Market Access presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [75].

Deterministic sensitivity analysis

A DSA was conducted employing a one-way sensitivity analysis and presented in a tornado diagram, including cost, transition probabilities, and utility measures. The tornado diagram portrays how varying each parameter within a probable range affects the model outcome. It eventually arranges the parameters with the most significant impact at the top of the diagram, giving it the appearance of a tornado, hence the name. In the one-way sensitivity analysis, one distinct parameter varies whilst the remaining parameters stay at their respective base-case

values. This strategy enables an assessment of each parameter and its influence on the overall outcome, providing insight into which parameters particularly drive the results of the model and thereby where the most significant uncertainties lie[65].

In the DSA, different levels of uncertainty were applied to the model parameters. The parameters for which CI were available were used directly, including the disutility values for moderate chronic and acute exacerbations, baseline HRQoL, and infection probability. For the parameters without specified CIs, an uncertainty level of ±15% was applied, as this was deemed most realistic. This applied to costing and disutility values for both *severe chronic and acute exacerbations*, *annual mortality rate*, *infection probability moderate and severe*, *post infection immunity year 1 to year 3*, *vaccine compliance*, and *vaccine effectiveness year 1 to year 3*. Explicitly, for the mortality rate for severe exacerbations, the source reported $15-20\%$, therefore, this was set at an average of 17.5%, with fixed lower and upper bounds of 15% and 20% to reflect likely deviation. Data for the DSA was extracted from the model in Excel, and the visualization of the tornado diagram was coded in the program *R*[57].

Probabilistic sensitivity analysis

Whereas the DSA tested one parameter at a time, a PSA was conducted to assess all parameter uncertainties simultaneously using stochastic functions. The distributions employed in the PSA encompassed Gamma distributions, which reflected costs as they can not have a negative value, and often have a right-skewed distribution. Meanwhile, Beta distributions were used for transition probabilities and utilities, as these are in the defined interval between zero and one[76, 65]. The PSA was implemented as a Second-order Monte Carlo simulation extracted from the model in Excel and captured using Visual Basic for Applications. A second-order Monte Carlo simulation was suitable in this model, as it incorporates variability in the model parameters, in contrast to a first-order simulation, thereby providing a more extensive estimation of the uncertainty in the model[77]. To ensure that the simulation results were appropriately robust, the PSA was executed with 10.000 iterations, in which 10.000 random samples were pulled from the fixed distributions of each parameter to simulate its variation[78].
Similarly to the DSA, varying levels of uncertainty were applied to the model parameters. The same levels of uncertainty as used in the DSA were applied for parameters with reported CIs and the mortality rate for severe exacerbations; please refer to the section above for details. ±15% uncertainty was applied to the parameters mentioned above, except for the chronic and acute disutility for severe exacerbations from the study by Jackson et al. 2024 which was assigned ±20% uncertainty[6]. Specific for the PSA, the cost elements *"Alternative time"*, and *"Hospitalisation cost"* were assigned an uncertainty of ±10%. However, *"transportation costs"* and *"vaccine cost"* were not varied. Since it was assumed that compliance with the RSV-immunization program would be the same as that for influenza (76%), it was chosen not to vary it in the PSA. However, to see the impact of this specific parameter on the base-case results, it was assessed in the DSA. The discounting rate was varied in neither of the sensitivity analyses.

The PSA data were exported to *R*, where a cost-effectiveness acceptability curve (CEAC) and an incremental cost-effectiveness (ICE) scatterplot were created to visualize the results of the PSA. The CEAC was constructed to display the probability at which an intervention is cost-effective relative to differing WTP thresholds[65]. Additionally, the CEAC was subject to a sensitivity analysis on the WTP, which was varied by ± 15%. The ICE-scatterplot is a visualisation of the distribution of the calculated ICERs and the associated range of feasible values[65].

4.3.3 Budget Impact Analysis

As per the recommendations by the DMC, this project will provide a BIA alongside the CUA[66]. A BIA is an economic assessment tool that estimates the financial consequences associated with adopting new interventions, specifically by investigating the foreseen changes in healthcare costs with their implementation. The analysis evaluates the affordability of the intervention and its economic implications associated with implementation compared to the existing practice[79]. BIAs are more frequently required as supplementation for cost-effectiveness analyses. They strengthen the CUA by supplying real-world understanding of the new intervention's affordability and financial feasibility. These results are particularly important for decision-makers in charge of managing and planning healthcare budgets, as they supply them with budgetary implications for the first five years in addition to the value for money from the CUA[79].

This DAM was chosen to investigate how costs and expenditures will affect the Danish healthcare sector if the ABRYSVO vaccine were to be recommended and reimbursed for COPD patients aged 60 and above. To display the changes, two scenarios were derived from the Markov model: a scenario where vaccination is recommended and a scenario with no recommendation for vaccination, which reflects the current state regarding recommendations on preventative RSV vaccines.

Specifically for the BIA, $6,000$ patients were added to the cohort each year to simulate the influx of individuals entering the 60+ age group and newly diagnosed cases. This was calculated based on an annual diagnosis rate and the most recent population count of Denmark[80, 81]. It was assumed that the number of existing COPD patients transitioning from age 59, where vaccination is not offered, to age 60, where vaccination is provided, matches the number of newly diagnosed cases.

The BIA is calculated to reflect the change in expenses if the ABRYSVO vaccine has 100% market share vs if it has 0% market share. The costs reported in the BIA are based on the yearly, per-patient cost of the Markov model multiplied by the number of patients still alive. The BIA will be presented as an annual, and undiscounted cost for the first five years separately[66]. This analysis obeys ISPOR's principles of good practice for BIAs. Additionally, BIAs are typically reported as undiscounted since they are meant to reflect the actual impact on cash flow, not the current value of future expenses. Moreover, BIAs are designed for the decision makers, who are accountable for the budgets and need to know the actual expense/savings, not the future

value. Additionally, the short time horizon of BIAs, typically 5 years, means that the discount rate doesn't have the same impact as it would over the longer time spans, often seen in other health economic models[79, 82]

The framework in the analysis has been created to inform decision-makers and add paramount layers to the overall assessment of ABRYSVO. The budget holder is recognized as the Danish healthcare system, funded by the Danish government, which is accountable for financing hospital services and preventive treatment options, influenced by the implementation of intervention[79]. The estimates used in the BIA are derived from the Markov model constructed for the CUA, with the addition of the annual incidence of new COPD diagnoses and the number of COPD patients turning 60. Both scenarios consider population size, resource utilization, and associated costs to reflect the distinctions and potential impact that implementing preventative measures like ABRYSVO might inflict on the healthcare system and the pertaining budget.

Ultimately, the BIA underwent a DSA on the initial patient population, varying it by $\pm 15\%$ to account for uncertainty in the estimated prevalence of COPD in Denmark[83].

5 Results

This section outlines the results of the analyses conducted throughout the project. Initially, the findings from the systematic reviews will be described, along with subsequent RoB assessments and a description of the included studies for each search. Thereafter, moving into the meta-analysis conducted based on the extracted data from the yield of the systematic reviews. Lastly, the health economic evaluation findings will be presented, followed by sensitivity analyses and ultimately the BIA.

5.1 Study Identification

The systematic review investigating HRQoL in COPD patients was undertaken in PubMed on the 24th of February 2025. The search yielded 276 records. An *"available in full text"* filter was applied in PubMed, leaving 274 records eligible for screening. The initial screening of titles led to 208 exclusions; 66 records remained for abstract screening. Ultimately, 30 records qualified for full-text reading, where 24 records were excluded due to various exclusion criteria. Six articles were included for RoB assessment. A visual presentation of the entire systematic review is documented in the PRISMA flowchart Figure 5.1 below.

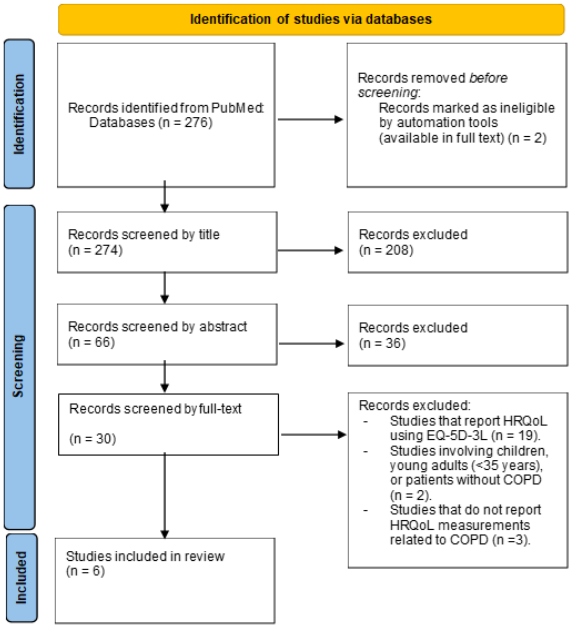


Figure 5.1. PRISMA 2020 flow diagram of the systematic review investigating EQ-5D Health-Related Quality of Life in chronic obstructive pulmonary disease patients.

The second search, which aimed to identify data on COPD exacerbations caused by RSV, was undertaken in PubMed on March 17, 2025. 138 records were identified. The filters *"available in full-text"* and *"Human"* were applied in PubMed, leaving 113 records eligible for screening. During the initial title screening, 49 records were excluded, and additional 34 records were excluded during abstract screening. Ultimately, 30 records were screened by full-text, of which 17 studies were excluded due to contradicting the exclusion criteria. 13 records were included for further analysis. The screening process is visualized in the PRISMA flowchart in Figure 5.2. Ultimately, another study was removed after the screening process as the population overlapped with another study, preventing data duplication and leaving 12 studies for RoB assessment.

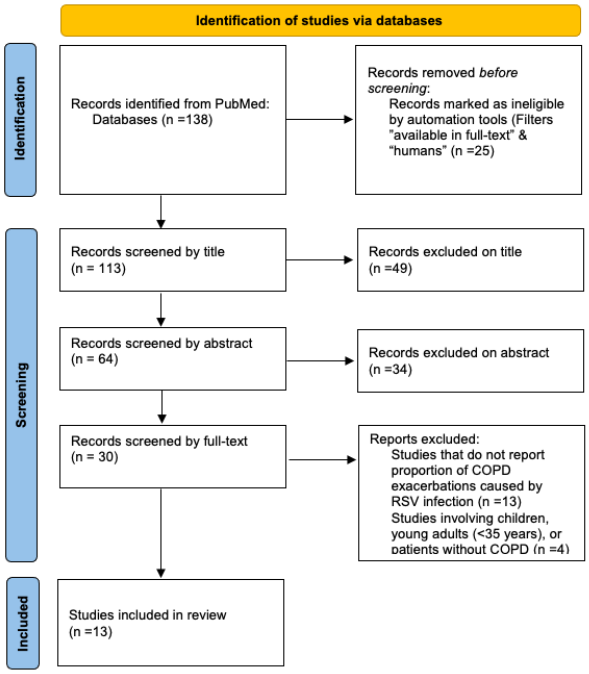


Figure 5.2. PRISMA 2020 flow diagram of the systematic review investigating chronic obstructive pulmonary disease exacerbations caused by respiratory syncytial virus.

5.1.1 Risk of Bias Assessment

During the RoB assessments, each study underwent a systematic examination to identify potential sources of bias that might impact both validity and reliability.

The evaluation of the six identified studies in the systematic reviews for HRQoL values in COPD patients involved analyzing two systematic reviews with meta-analysis of observational studies, one RCT, and three cross-sectional studies using the CASP checklists for the individual study designs[53].

The three cross-sectional studies by Lin et al. 2014, Choi et al. 2020 and Garcia-Gordillo et al. 2017 exhibited focused research questions and appropriate methods[84, 85, 86]. Their recruitment and measurement methods were robust, and their data collection and analysis were rigorous, with clear results presentations. All three studies were deemed of high quality, providing valuable insights into HRQoL in COPD patients. The two systematic reviews with

meta-analyses of observational studies were assessed. This revealed that the study by Guo et al. 2020 was transparent in its design and methodologically sound. Qualifying it as a high-quality study eligible for further analysis, as the results indicated the study to provide significant impact and strong validity[87]. However, the study by Salant et al. 2024 was excluded due to high heterogeneity and a lack of RoB assessment in its included studies[88]. Moreover, the RCT study by Jackson et al. 2024 assessed with the CASP checklist was reported to have high quality and strong validity, which permitted this study to be further analyzed[6]. Ultimately, five studies qualified for further analysis.

Regarding the search evaluating the COPD exacerbations caused by RSV, 12 studies were assessed using the CASP checklist for the study designs: two case-control studies and ten cohort studies. The ten cohort studies were evaluated in three general categories: methodological approach, reporting, and weighting of results, in which all included studies were deemed to have a high methodological approach in terms of presenting the issue, exposure and outcome measurements, handling of confounding, and appropriate follow-up periods. In addition, they had well-defined results with high reliability, and the studies were assessed to have high transferability while being consistent with other published evidence in the field. All ten cohort studies showed high quality based on RoB assessment with CASP and were therefore included for further analysis.
The same general categories applied to the case control study checklists, where the two studies reported the same positive findings as in the cohort studies above, except for the study by Hutchinson et al. 2007 having an imprecise estimate of treatment effect due to a wide CI[89], and the study by Hosseini et al. 2015 was unable to tell wether the estimate of treatment effect was precise or not[90]. However, both studies were deemed eligible for further analysis, due to their qualities in methodological rigor and the transferability of the results. Therefore, all 12 studies proceeded to further analysis. The completed CASP checklists for all studies included in the two systematic reviews are attached in the Digital Exam Appendix.

5.1.2 Studies Excluded Due to Missing Data

The study by Choi et al. 2020, did not report the standard deviation for the HRQoL values[85]. In an attempt to still utilize the data from this study, the author was contacted via e-mail found through ResearchGate. However, since no reply was received before the decided cut-off date of March 12^{th}, the study was excluded from later analysis.

5.1.3 Description of Included Studies

The search investigating HRQoL in COPD patients included four studies after reviewing all CASP assessments. Three of the included studies aimed to estimate the impact of COPD on patients' quality of life and were eligible for a meta-analysis. The study designs span

one systematic review and meta-analysis, and two cross-sectional observational studies. The standard HRQoL measurement tool between studies was EuroQol's EQ-5D-5L[65]. The studies were published between 2014 and 2020, and originated from Spain, China, and the USA[84, 87, 86]. An overview of the data extracted for the meta-analysis can be seen in the Table 5.1. For an extended table of study characteristics, visit the Appendix A.2.

Author	Year of Publication	Country	HRQoL	SD	Sample Size	Gender (Male %)	Variance
Garcia-Gordillo et al.	2017	Spain	0.75	0.30	1001	48.67	0.09
Guo J et al.	2020	China	0.8	0.19	18746	66	0.0361
Lin F-J et al.	2014	USA	0.79	0.15	670	58.7	0.0225

Table 5.1. Summary of HRQoL measurements in COPD patients. HRQoL - health-related quality of life. COPD - chronic obstructive pulmonary disease.

A fourth study, the study by Jackson et al. 2024, was included in the search on COPD HRQoL[6]. However, it was not incorporated in the meta-analysis, as it did not report baseline HRQoL values in COPD patients. Rather, it informed the economic model by providing acute and chronic disutility values regarding COPD patients experiencing moderate and severe exacerbations. The study by Jackson et al. 2024 was a multicenter trial, coordinated by AstraZeneca. It had a population size of $8,498$ patients, of whom 59.7% were male. The study reported acute disutility for current moderate exacerbation of 0.055, (95% CI[0.048, 0.062]), and an additional impact on top of severe exacerbation of 0.035, (95% CI[0.014, 0.055]), accumulating to a disutility of 0.090 for current severe exacerbation. After an exacerbation, chronic disutilites persisted. Each previous moderate exacerbation yielded a chronic disutility of 0.014, (95% CI [0.011, 0.016]), and the severe exacerbation added 0.011, (95% CI [0.003, 0.018]), summing to a disutility of 0.025 for previous severe exacerbation[6]. These disutility values were employed in the Markov model to account for the loss in HRQoL during and after experiencing moderate and severe exacerbations.

In the systematic review on COPD exacerbations caused by RSV, 12 studies were identified. The studies examined various virological and bacteriological factors. Some studies focused solely on RSV, while others investigated bacterial and viral contributions to AECOPD. Their common denominator is that they report the proportion of exacerbations caused by RSV, enabling a quantification of their results to estimate an infection probability for the Markov model. The data extracted from the studies for the meta-analysis are shown in Table 5.2, and for the extended table of study characteristics, visit Appendix A.4.
The 12 included studies were published between 2001 and 2024 and carried out across various countries, including the UK, USA, China, Iran, South Korea, Canada, and Australia. The

Author (Year)	Country of Origin	Incidence of RSV (%)	Number of Exacerbations	Population Size	Male (%)
Seemungal et al. (2001)	UK	11.30952381	168	83	71.1
Camargo et al. (2008)	USA	8.00000000	76	76	68.0
Dai et al. (2015)	China	3.703703704	81	81	75.0
Dimopoulos et al. (2011)	Greece	40.50000000	200	200	75.0
Hosseini et al. (2015)	Iran	7.647058824	170	170	54.7
Jang et al. (2021)	South Korea	14.80000000	262	192	80.7
Kherad et al. (2010)	Switzerland	0.986842105	304	86	64.0
Ko et al. (2007)	Hong Kong	2.300000000	505	373	82.3
Hutchinson et al. (2007)	Australia	0.675675676	148	92	63.0
Kwak et al. (2016)	South Korea	14.10000000	278	213	65.7
Serres et al. (2009)	Canada	7.000000000	108	108	54.6
Wiseman et al. (2024)	UK, Netherlands	8.700000000	310	377	66.3

Table 5.2. Summary of data from the studies reporting RSV incidence in COPD exacerbations for the meta-analysis. RSV - Respiratory syncytial virus. COPD - chronic obstructive pulmonary disease

studies were primarily prospective cohort or observational studies, reporting varying sample sizes from 76 to 643 episodes. A majority of the studies assessed hospitalized patients with AECOPD, and some included stable COPD comparators[89, 90]. The method used for RSV detection was RT-PCR, other molecular diagnostics, or nasopharyngeal swabs. The incidence of RSV in the studies varied significantly from $< 1\%$ to 40.5%, depending on study population, detection methods, and geographic setting.

5.2 Results of the Meta-analysis

A meta-analytic framework was utilized to aggregate the extracted data, described in Section 4.1.5, which was identified through the systematic reviews. This approach provided a synthesized overall estimate of the average HRQoL experienced by a COPD patient and the average incidence rate of RSV infection among COPD patients hospitalized with an acute exacerbation. In addition to the meta-analysis itself, forest plots provide a visual representation of the findings. Meanwhile, Egger's regression and funnel plots provide a numerical and visual assessment of the publication bias in the meta-analytic dataset.

5.2.1 Overall HRQoL

The study by Garcia-Gordillo et al. 2017 found the average HRQoL among probed COPD patients to be 0.75 (95% CI [0.15 to 1.35]), the study by Guo J et al. 2020 found it to be 0.80 (95% CI [0.43 to 1.17])[86, 87]. Lastly, Lin F-J et al. 2014 found it to be 0.79 (95% CI [0.5 to 1.08])[84]. The meta-analytic aggregation of the above-mentioned study findings results in an

overall HRQoL of 0.79 (95% CI [0.57 to 1.00]) for COPD patients. Meanwhile, the heterogeneity test yields a heterogeneity of 0.0% , indicating no heterogeneity. This corresponds with the high P-value, indicating no significant heterogeneity in the study populations. Additionally, the CIs of all the studies' results overlap, indicating similar findings.

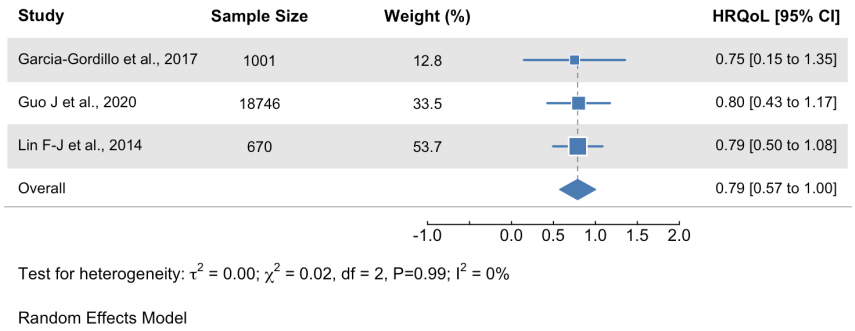


Figure 5.3. Forest Plot of the overall HRQoL experienced by patients with a COPD diagnosis. HRQoL - health-related quality of life. COPD - chronic obstructive pulmonary disease.

To further assess the heterogeneity present in the included studies, a funnel plot was created and is depicted in Figure 5.4. This shows a relatively symmetrical distribution of studies around the mean value, with no studies falling outside the pseudo 95% CIs. This indicates that no publication bias is present in the included studies. The findings from the funnel plot are supported by Egger's regression test, which yielded a result $z = -0.1072, p = 0.9146$ that indicates non-significant funnel plot asymmetry.

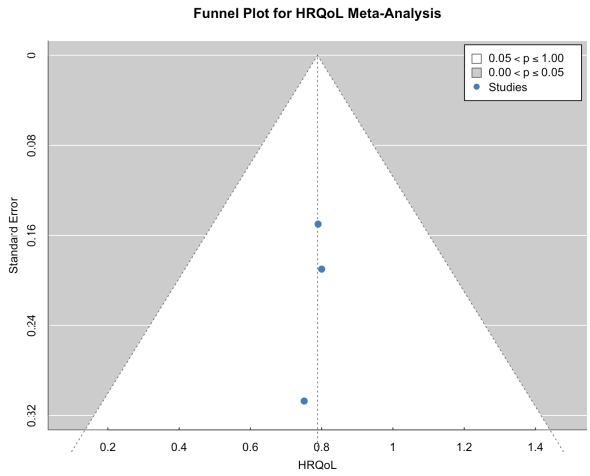


Figure 5.4. Funnel Plot of publication bias analysis of the overall HRQoL experienced by patients with a COPD diagnosis. HRQoL - health-related quality of life. COPD - chronic obstructive pulmonary disease.

5.2.2 RSV caused exacerbations

The studies included in this meta-analysis found incidences of RSV infection in patients hospitalized with acute COPD exacerbations ranging from 0.68% to 40.5%. The aggregated incidence of RSV in patients hospitalized with AECOPD was 9.38% (95% CI [6% to 13%]).

Meanwhile, the heterogeneity test yields an I^2-statistic of 94.37%, indicating a high level of heterogeneity. Additionally, $P < 0.01$ and the fact that not all the studies' CIs overlap hints at the presence of heterogeneity in the meta-analysis. This could be explained by relative outliers such as the study by Dimopoulos et al. 2011, which reports a much higher incidence rate than the other studies[91]. The studies by Kherad et al. 2010, Ko et al. 2007, and Hutchinson et al. 2007 all report incidence rates close to 0% and could contribute to the overall heterogeneity of the meta-analysis[92, 89, 93]. Given the high heterogeneity of the meta-analysis, an influence analysis was also carried out, which indicated that the study by Dimopoulos et al. 2011 contributed significantly to the overall estimate[91]. As such, a leave-one-out analysis was conducted to assess how the iterative removal of each single study might impact the heterogeneity measure. This analysis found that the single removal of every study, except Dimopoulos et al. 2011, had a negligible impact on the heterogeneity estimate[91]. However, when the Dimopoulos et al. 2011 study was removed, a relatively significant reduction in heterogeneity was observed, resulting in an I^2-statistic of 88.12% , hence, a still considerably high heterogeneity.

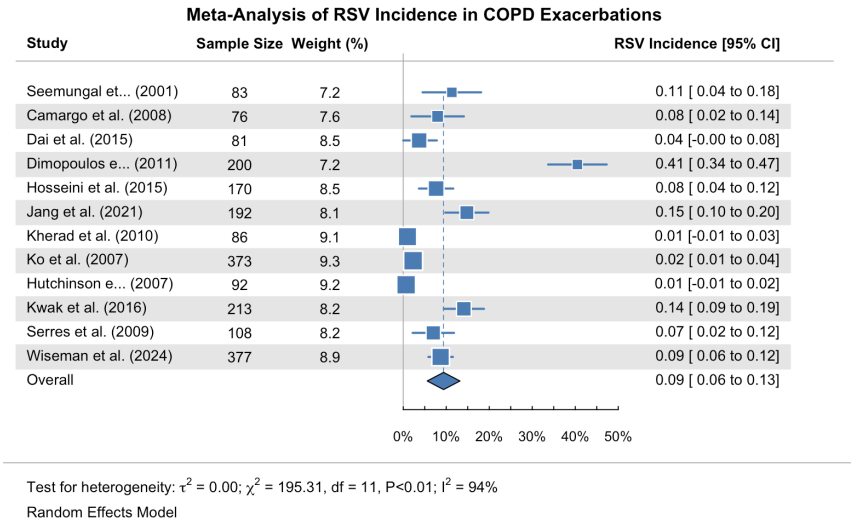


Figure 5.5. Forest Plot of proportion of acute COPD exacerbations caused by RSV. RSV - respiratory syncytial virus. COPD - chronic obstructive pulmonary disease.

To further assess the heterogeneity present in the studies included in the meta-analysis, a funnel plot was created and is displayed in Figure 5.6. This plot shows some outliers with five studies falling outside the pseudo 95% CIs: four below and one above. This indicates that a certain amount of publication bias might be present in the studies included in the meta-analysis. This is supported by the results of Egger's regression test, which yielded a result $z = 4.9075, p < .0001$ indicating significant funnel plot asymmetry. Given the positive nature of this asymmetry, it is likely driven by the Dimopoulos et al. 2011[91].

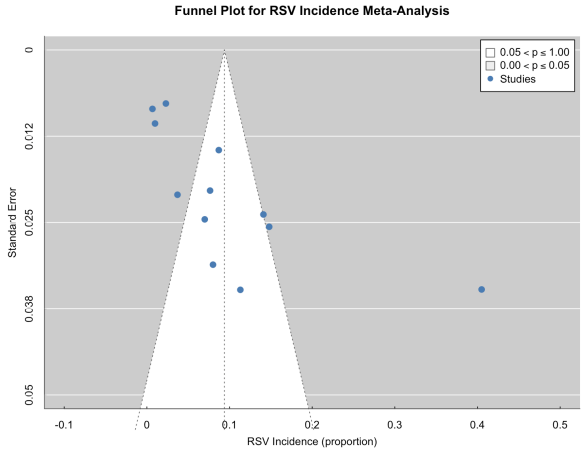


Figure 5.6. Funnel Plot of publication bias analysis of the proportion of acute COPD exacerbations caused by RSV. RSV - respiratory syncytial virus. COPD - chronic obstructive pulmonary disease.

5.3 Health Economic Modeling

5.3.1 Base Case Results

The discounted results of the Base Case analysis can be seen in Table 5.3, which shows that the ABRYSVO scenario yields approximately $0,0046$ additional QALY, while introducing an incremental expense of $1.086,26$ DKK per patient. This results in an ICER of $238.067,79$ DKK per additional QALY, which generally would be considered cost-effective.

Results	**ABRYSVO scenario**	**Non-vaccination scenario**	**Incremental**
Cost (DKK)	2.007,64 kr.	921,38 kr.	1.086,26 kr.
Life-Years	2,59781005	2,59515363	0,00265641
QALYs	2,0511091	2,0465463	0,0045628
ICER (DKK per QALY)			**238.067,79 kr.**

Table 5.3. Discounted Base Case Results of the decision analytic model.

5.3.2 Sensitivity Analysis

Deterministic Sensitivity Analysis

A one-way sensitivity analysis was conducted to assess the robustness of the base-case results by varying the input parameters one by one. The results of the one-way sensitivity analysis of the model's ICER can be seen in the Tornado diagram in Figure 5.7. Each bar in the diagram depicts the influence of varying one parameter across its assigned uncertainty range whilst holding the remaining parameters constant.
Out of the 20 parameters tested, the ICER was most sensitive to *"infection probability moderate"*

and *"infection probability"*, shifting the ICER by up to 400.000 DKK in both directions. Additional influential parameters included *"Vaccination cost"*, *"Annual mortality rate"*, and *"infection probability severe"*, highlighting that both economic and clinical parameters impact the ICER. Additionally, *"Vaccine effectiveness - y1"* and *"Baseline HRQoL"* have some influence on QALY-related outputs.

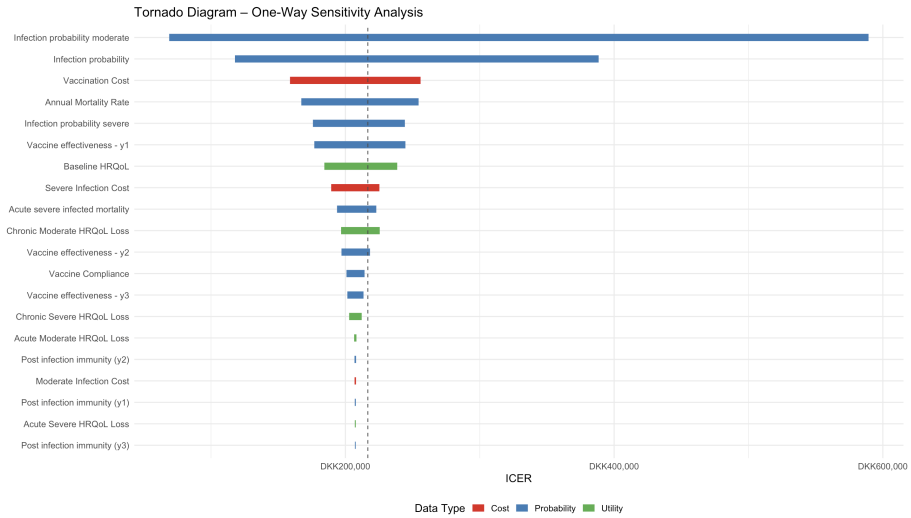


Figure 5.7. This tornado diagram depicts the impact of individual parameter uncertainty on the ICER. Parameters are arranged by impact, with wider bars indicating greater sensitivity. Blue bars represent probabilities, red bars indicate cost, and green bars mark utility values. The vertical dashed line depicts the base-case ICER. ICER - Incremental cost-effectiveness ratio

Probabilistic Sensitivity Analysis

PSAs were performed to address the uncertainty related to the model parameters. This was accomplished by running 10.000 iterations of the Markov model, utilizing second-order Monte Carlo simulations to integrate the variability in input estimates and assess the robustness of the model outcomes.

10.000 iterations of incremental cost-effectiveness pairs from the PSA were arranged in an ICE-scatterplot, as seen in Figure 5.8. Incremental QALYs are represented on the x-axis with positive values, whereas Incremental Cost in DKK is represented on the y-axis, ranging between negative and positive values. The iterations are all located within the coordinate system's north- and southeastern quadrants. Their placement indicates that the ABRYSVO scenario generally improves QALY, whilst the cost ranges from cost savings to additional incremental costs. However, most iterations are in the northeastern quadrant, representing additional costs. The red ellipse marks the 95% CI region, where most of the iterations lie. A speculative WTP threshold set to 450.000 DKK was plotted to provide bounds for the maximum cost per QALY that is deemed cost-effective[75].

The majority of the iteration points are located below and to the right of the graph, implying that the ABRYSVO scenario is highly likely to be cost-effective. Conversely, the share above the WTP line indicates that the intervention is not cost-effective under some assumptions. Worthy of note are the iterations in the negative cost area, suggesting that some simulations improve

QALY and are less costly than the current treatment options.

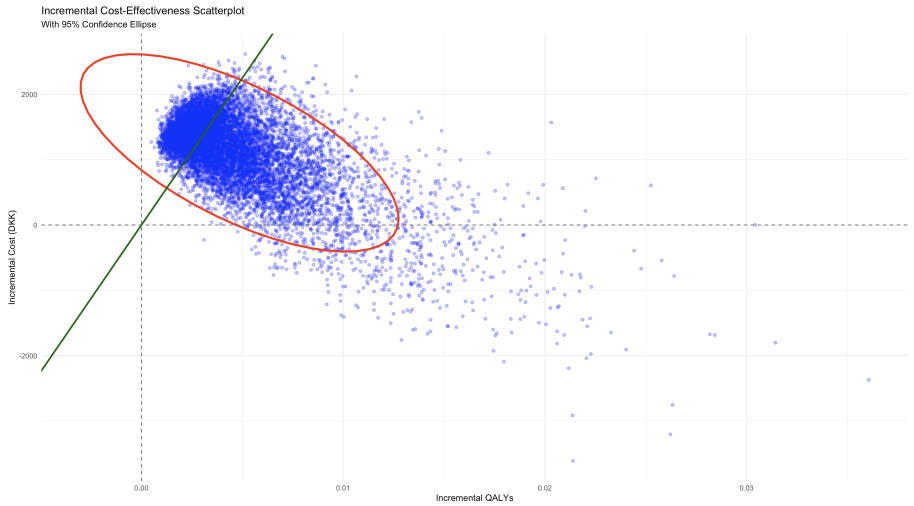


Figure 5.8. Incremental cost-effectiveness scatterplot for the ABRYSVO scenario, visually presenting the results of the PSA with 10.000 iterations. The iterations distributed in the north- and southeastern quadrants are seen on the graph, a willingness-to-pay threshold set to 450.000 DKK marked by the green graph, and a 95% CI ellipse. PSA - probabilistic sensitivity analysis

The CEAC created from the PSA data is presented in Figure 5.9. On the x-axis, the WTP threshold is placed, measured by DKK per QALY, ranging from 0 to 1.500.000 DKK. On the y-axis, the "probability cost-effective" is presented, describing the probability of the ABRYSVO scenario being cost-effective at each WTP threshold. The CEAC takes a classic S-shape, ascending from 0 to 1.000.000 DKK, and plateauing close to 100% at around 1.250.000 DKK per QALY. The dashed WTP threshold of 450.000 DKK, often used in Danish and European countries, is intersected by the CEAC at approximately 66% probability of cost-effectiveness[75]. Additionally, the CEAC was subject to sensitivity analysis in which the WTP was varied by ± 15%, yielding probabilities of cost effectiveness of approximately 57% and 74% respectively, as pictured in Figure 5.9.

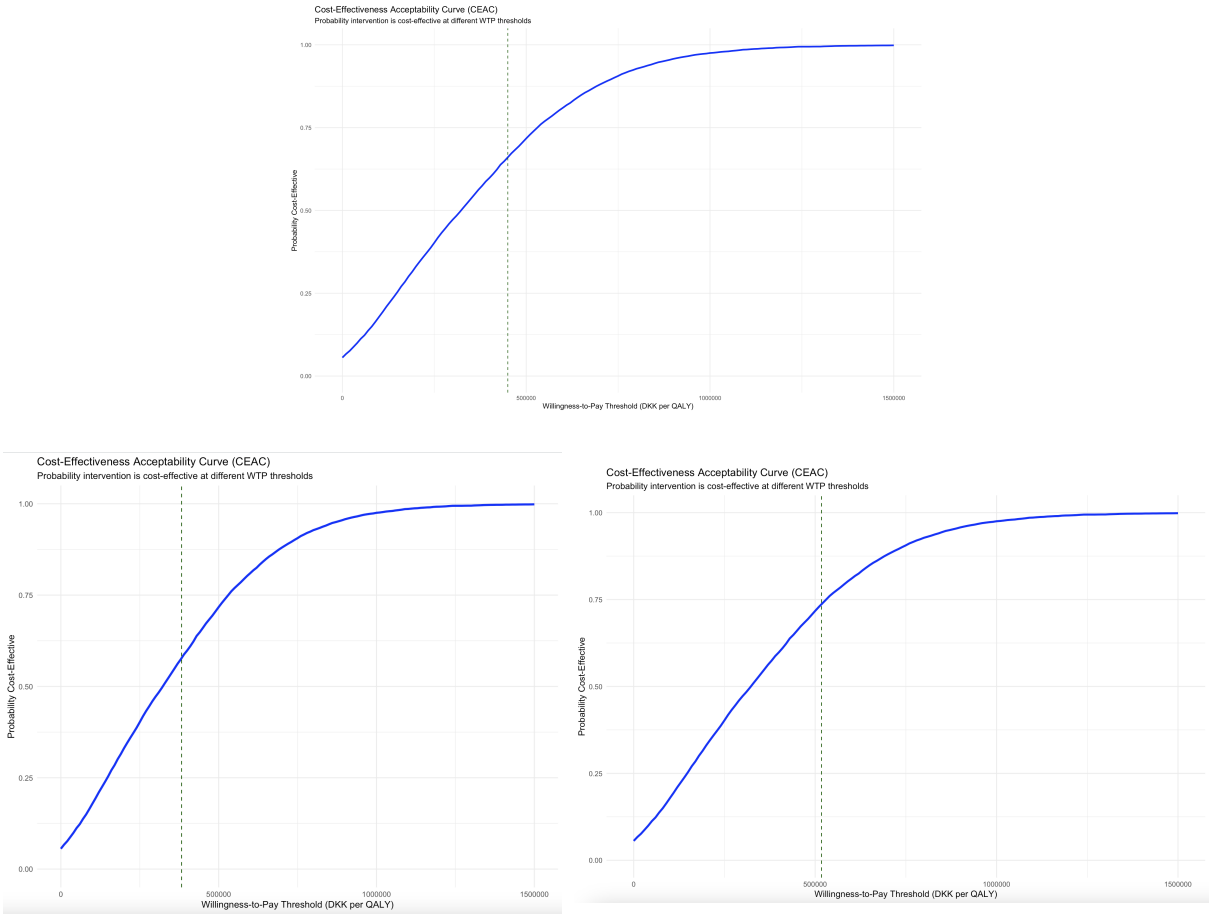


Figure 5.9. Cost-effectiveness acceptability curve analysis for the ABRYSVO scenario. The willingness-to-pay (WTP) on the x-axis runs from 0 to 1.500.000 DKK, and the probability of cost-effectiveness is presented along the y-axis. The top figure is presented with a WTP of 450.000 DKK. The bottom left and right figures show the lower WTP of 382.500 DKK and the upper WTP threshold of 517.500 DKK.

5.3.3 Budget Impact Analysis

In Table 5.4, a comparison of annual, undiscounted costs between the ABRYSVO scenario and the non-vaccination scenario can be seen, for the first five years after implementation.

Year	Cost ABRYSVO scenario	Cost non-vaccination scenario	Budget impact (DKK)
Year 1	333.790.780,20	85.921.742,40	247.869.037,77
Year 2	73.748.532,72	64.868.359,13	8.880.173,59
Year 3	30.470.687,35	48.231.430,59	−17.760.743,25
Year 4	117.743.336,60	37.351.870,19	80.391.466,40
Year 5	50.386.070,51	29.260.279,98	21.125.790,53

Table 5.4. The total annual cost comparison and budget impact in DKK between the ABRYSVO scenario and non-vaccination scenario.

The table shows that years 1, 2, 4, and 5 result in additional total costs, highlighted by a positive budget impact. However, in Year 3 the ABRYSVO scenario is less costly, producing a cost saving of 17.76 million DKK. Year 1 accounts for the most significant increase in cost, which is attributed to the initial implementation and scaling-up. Additionally the BIA was subject to

a DSA in which the base case patient population of 320.000 patients was varied by ± 15%. The results of this DSA can be seen in Table 5.5.

Year	BIA + 15%	BIA - 15%
Year 1	285.049.393,43	210.688.682,10
Year 2	4.867.523,51	3.597.734,77
Year 3	−25.860.796,93	−19.114.502,08
Year 4	87.499.134,10	64.673.273,03
Year 5	17.702.998,10	13.084.824,64

Table 5.5. Results of the DSA on the BIA, varying the initial patient population by ± 15%. DSA - Deterministic Sensitivity Analysis. BIA - Budget Impact Analysis.

6 Discussion

The discussion section of this project adheres to the suggested structure for discussions in scientific papers recommended by BMJ, described in the article by Docherty et al. 1999[94]. To ensure proper reporting, the discussion will go over the statement of principal findings, strengths and weaknesses of the study, and in relation to other studies, the meaning of the study, unanswered questions, and future research[94].

6.1 Statement of principal findings

The results of the base case CUA showed that vaccination with ABRYSVO in COPD patients over 60 yields a discounted ICER of 238.067, 79 DKK. Thus, when seen in the light of a WTP of around 450.000 DKK, the implementation of the ABRYSVO vaccine provides a cost-effective treatment option [75].
Additionally, the CEAC, based on the results of the 10.000 iteration PSA, shows that, at a WTP threshold of 450.000 DKK, the vaccine has a probability of being cost-effective of approximately 66%.
The BIA showed that the ABRYSVO scenario would cost 247.869.037, 77 DKK in year 1, 8.880.173, 59 DKK in year 2, −17.760.743, 24 DKK in year 3, 80.391.466, 40 DKK in year 4, and 21.125.790, 53 DKK in year 5. The drop in expenses, resulting in savings in year 3, can be attributed to a number of factors. Firstly, many patients had already received vaccinations in the previous years, meaning that vaccine expenses were lower in year 3. Additionally, the high degree of vaccine immunity results in fewer patients needing medical attention due to RSV-caused exacerbations, reducing medical costs. Then, in year 4, the budget impact sees a relatively large leap in expenses. This can be attributed to the fact that the vaccine's immunity has reduced, leading to more hospitalizations. Moreover, the cohort vaccinated in year 1 is now eligible for vaccination again. Together, these result in increased hospital and vaccine expenses.

6.2 Strengths and weaknesses of the study

A significant strength of the study is the methodological rigor employed throughout. The systematic review was conducted strongly, per the PRISMA guidelines, while risk of bias assessment was carried out according to the CASP checklist[50, 53]. The study's health economic analysis aligns with the recommendations of the CHEERS checklist[67]. The project's accordance with methodological guidelines helps ensure high reliability, reproducibility, and

validity.
Circling back, the systematic review on the proportion of COPD exacerbations caused by RSV was initially theoretically meant to capture secondary outcomes of RSV-related hospitalizations and mortality. However, it proved challenging to isolate parameters consistently throughout the studies, as most of the patients were hospitalized upon enrollment, and mortality was seldom reported for the isolated pathogen. Because of this lack of specific information on mortality rate and reporting inconsistency, it was impossible to incorporate hospitalization and mortality rates in the meta-analysis. As a result, the synthesis focused on the incidence of RSV infection in exacerbations, whilst other necessary clinical outcomes were excluded from the meta-analysis to sustain methodological rigor. Instead, the key parameters, hospitalization and mortality rates, were sourced from gray literature. More specifically, the Danish Respiratory Society and the official Danish platform for clinical guidelines (Lægehåndbogen) from Sundhed.dk[83, 25]. Since these sources are grounded in a Danish context, they will inevitably draw information from patient populations that differ from those utilized in the meta-analyses. This introduces a potential selection bias, which has the potential to reduce the internal consistency of the model and ultimately over- or underestimate the burden of RSV-caused exacerbations in COPD patients.

Using a Markov model to simulate the cost-effectiveness of the vaccine is well-suited as the condition examined is chronic, and the simulation runs over a relatively long time-horizon (20 years)[65]. Thus, the Markov model provides the simulation and the subsequent CUA with great detail. The model developed could, however, have been more granular, perhaps utilizing cycles that represent individual months, instead of full years, to capture the seasonal variability of RSV epidemics. Additionally, the memoryless nature of the Markov model proved suboptimal for the estimation of chronic utility loss sustained through RSV-caused exacerbations. One way of tackling this is the use of tunnel states. Indeed, the model does incorporate the use of some tunnel states to map the course of vaccination and post-infection immunity[65]. Using tunnel states to map the entire course of RSV-sustained HRQoL loss, however, would have resulted in an explosion of the number of health states and transitions. Therefore, to ensure a degree of simplicity and greater transparency of the model, it was decided to employ a state tracker through tracker variables[71]. This made it possible to construct a model with fewer states, while accounting for the accumulated loss of utility due to RSV-caused exacerbations[74].

Since RSV doesn't undergo RNA recombination in the same manner as Influenza does, it does not mutate in the same manner either[9]. This means that post-infection, patients will benefit from a longer span of immunity from the virus. This post-infection immunity was also incorporated in the model through tunnel states, and the level of immunity was assumed to be equal to the vaccine effectiveness[65]. It was likewise believed that the post-infection and vaccine-derived immunity could accumulate. Meaning that if a patient had the highest level of vaccine immunity and the highest level of post-infection immunity, their immunity level would be calculated as:

$$1 - ((1 - vaccineimmunity) * (1 - postinfectionimmunity))$$

This means that the highest possible level of immunity results in a reduced risk of infection of just over 97%. While this approach allowed the model to account for post-infection and vaccine immunity, the assumption that the two immunities accumulate might be slightly overoptimistic. This introduces the risk of overestimating the overall immunity, producing a slightly more favorable ICER than if the maximum immunity was assumed to cap at the maximum vaccine effectiveness of approximately 83%.

A common phenomenon in modeling health states was that the cohort could experience three different scenarios regarding exacerbations. Either a patient does not experience an exacerbation, they experience a moderate exacerbation, or they experience a severe exacerbation. While this approach allows the model to distinguish between the costs and utilities of the three scenarios, it is quite a rough distinction. This means there is a risk of over- or under-evaluation of utilities and expenses in edge scenarios, which could distort the project's cost-effectiveness estimates. Additionally, it was only possible to find Danish data on the yearly number of severe exacerbations[3]. Therefore, a British article was identified to specify the annual number of moderate exacerbations, which is not reported in Denmark, enabling the calculation of the ratio between severe and moderate exacerbations[95]. While this allowed the calculation of an estimated yearly number of moderate exacerbations in Denmark, the lack of directly reported, country-specific data introduces some uncertainty to the cost-effectiveness estimate of this project.
Furthermore, the model was developed to exclusively simulate exacerbations caused by RSV infection for both the vaccination and non-vaccination cohorts. This design is based on the assumption that all other types of exacerbations would be experienced in equal numbers for patients who receive the RSV vaccination and patients that didn't. While this might be true, the effects of the vaccine increasing survivability slightly increase the probability that a patient lives long enough to experience an exacerbation of another type. This means that the structure of the model could result in a slight underestimation of the utility loss of the vaccination cohort compared to the non-vaccination cohort, resulting in a slightly more optimistic cost-effectiveness estimate.

It was not possible to find an average annual mortality rate of COPD patients, and Danish records only show annual deaths of COPD patients that are a direct result of COPD. Thus, the annual mortality rate utilized in the model was obtained by interpolating a 10-year mortality rate of COPD patients of approximately 95%[25]. This yielded an annual mortality rate of just over 25%. Additionally, it was identified that patients suffering a severe exacerbation had a 17.5% risk of death during the exacerbation period[80]. Thus, to accurately model the loss of life and risk of death for patients suffering a severe exacerbation, the annual mortality rate and the additional mortality rate attributable to a severe exacerbation were multiplied. This produced an estimated mortality rate, in the year of a severe exacerbation, of approximately 38%. While direct measures of yearly mortality rates would have been optimal, allowing the model

to provide more precise, life-like estimates, this approach made it possible to give the model satisfactory mortality estimates. However, content with the mortality rates used in this project, Papaioannou et al. 2024 mention that based on Danish registry data on COPD patients, the 3-year mortality rate is between 10% and 36.9% depending on the severity of the disease[96]. This indicates that the identified estimates are not too far from reality.

The robustness of the results presented in this project was investigated through the use of DSA and PSA, increasing the methodological rigor. However, throughout the sensitivity analyses, some costs were kept constant. Transport costs were not varied, since a fixed rate is specified in the DMC guidelines[66]. Vaccine costs were likewise held constant, as list prices were used, and no deviation from the stated administration costs is expected[69]. Discounting was not varied either, as the applied rates align with national health economic guidelines and reflect standard practice in Danish cost-effectiveness evaluations[73].

In the health economic analysis, the scenario where ABRYSVO is implemented in the national immunization program is compared to the current SoC, which is the non-vaccination scenario, with symptom treatment upon infection, in the case of RSV-related exacerbation[17]. While getting a subsidy for the vaccination against RSV is currently possible, the subsidy is conditional, and might apply if you are vaccinated with the GSK vaccine AREXVY. This means that whether or not a patient is entitled to reimbursement depends on whether or not a doctor assesses that the patient meets the defined reimbursement criteria[17, 48]. This means that the model does not account for the cost and utility gain sustained by patients, who potentially already receive vaccination against RSV with the AREXVY vaccine.
Contemporarily, the measure of compliance with the RSV vaccination program used in the model was assumed to be equal to that of the compliance with the existing Influenza vaccination program in Denmark[97]. Additionally, the BIA was conducted with a 100% market share from year 1. This might, however, be an overestimation since the Influenza vaccination program is well established and well known by citizens eligible to receive an Influenza vaccination. Furthermore, in a real-world scenario, the new treatment can not be expected to be implemented 100% from the start. This will lead to a higher BIA estimate in the first year, as every patient is assumed to be offered the vaccine. Moreover, to estimate the size of the patient pool that would be eligible to receive an RSV vaccination, it was assumed that 80% of COPD patients are over 60 years. This yielded a patient pool of 320.000 patients. This might represent an overestimation of patients eligible to receive vaccination with ABRYSVO. Together with the potentially overestimated vaccination compliance and market share, this might result in an inflated budget impact estimate. A DSA varying the initial patient population by $\pm$ 15% was carried out to assess the impact of the assumed size of the initial patient population. Even though the budget impact estimate is subject to the risk of overestimation, its application in this project demonstrates the methodological rigor. In its guidelines, the DMC strongly recommends using a BIA to inform decision-making regarding resource allocation[66].

This project's resulting ICER from the health economic analysis has been compared to a hypothetical WTP of 450.000 DKK[75]. In the same source, however, it is also reported that the WTP could be as high as 970.000 DKK, depending on the method used to estimate the WTP[75]. While no official threshold value exists in Denmark, other countries, such as Norway and the UK, have explicit WTP thresholds. In Norway, for example, the WTP ranges from $275.000 - 825.000$ NOK (approximately $178.000 - 535.000$ DKK), with higher levels of disease severity increasing the WTP[98]. Meanwhile, in the UK, a WTP threshold of $20.000 - 30.000$ GBP (approximately $177.000 - 265.000$ DKK) was established in 2004[99, 100]. However, since NICE established their WTP between 20.000 GBP and 30.000 GBP, more than 20 years have passed, meaning that the purchasing power of that WTP has been reduced by at least 30% as a result of inflation[100].
In light of the WTP in Norway and Britain, it is not far-fetched to argue that the 450.000 DKK per QALY WTP used as a reference in this project could be truthful. As such, this theoretical WTP is a clear strength of this project, as it provides decision makers with an anchor point against which they can assess whether or not the ABRYVSO vaccine offers a cost-effective treatment option.

6.3 Strengths and weaknesses in relation to other studies

When assessing the strengths and weaknesses of this project with regard to those of other studies, an obvious strength is that it seems to be the first study carried out in a Danish context. It has, at least, not been possible to uncover other studies conducting the same investigation using a Danish context.

In this project, data regarding the probability of experiencing an RSV-caused exacerbation and the baseline HRQoL of the average COPD patient were synthesized via meta-analyses. This represents a strength when comparing it with other similar studies, since most of these do not carry out meta-analyses of their own[101, 102]. One weakness of this project's meta-analytic approach was the relatively simplistic meta-analyses. More specifically, they do not include moderator analysis of the population characteristics. This means that the meta-analytic results do not account for age differences, comorbidities, country of origin, gender distribution, or method of RSV detection, etc. Instead, the results of the meta-analyses, including the pooled effect size and the heterogeneity, are solely based on the effect sizes reported in the individual studies, the variances of the included studies, and how much the individual studies' effect sizes differ from that of the pooled estimate. This omits the possibility of detecting subgroup differences while increasing the pooled estimates' heterogeneity.
Additionally, the register-based patient data regarding costs and patient characteristics, included in the Markov model, did not report comorbidities or gender distribution. Furthermore, the purpose of the Markov model and health economic assessment was not to explore variations in ABRYSVO's cost-effectiveness across subgroups with different comorbidities. Rather, the analysis aimed to represent the average COPD patient, estimating the potential health

benefits of ABRYSVO in this population and weighing them against the associated costs and savings. Therefore, including such subgroup parameters would likely not affect the pooled estimate and subsequent results of the health economic evaluation. More likely, it would result in increased heterogeneity measures, which, through its implications for the generalizability of the study, would be interesting in and of itself. Contrarily, the register data did provide age group-stratified data, making age-related subgroup analysis an interesting possible addition to the meta-analysis.

A potential improvement to the robustness of the meta-analytic result of the proportion of AE-COPD cases caused by RSV could have been obtained through moderator analysis of the RSV detection method. Of the 12 studies in the systematic review and meta-analysis, 9 used polymerase chain reaction-based methods with samples collected via nasopharyngeal swabs to detect RSV. The exceptions were the UK-based study, Seemungal et al. 2001, which used viral culture and serology, and reported an incidence of RSV of 11.3%[103]. Another study by Wiseman et al. 2024 with populations from the UK and the Netherlands employed a pentaplex serology assay and reported an RSV incidence of 8.7%[104]. Lastly, the study by Ko et al. 2007 from Hong Kong, China, where virus testing was performed using cell culture and immunofluorescent staining, found an incidence of 2.5%[92].

Although different detection methods were used across the studies, most applied comparable approaches, suggesting that the meta-analysis results are relatively reliable. However, methodological deviations in a few studies may have influenced the number of RSV cases detected in those studies.

The studies of the meta-analysis reported incidences of RSV between 0.6% in Hutchinson et al. 2007 to 40.5% in Dimopoulos et al. 2011[89, 91], which represents a relatively wide range. However, leave-one-out analyses also revealed that Dimopoulos et al. 2011 significantly impacted the heterogeneity of the meta-analysis, indicating that this study differs considerably from the others[91]. The meta-analysis included studies from across the globe. This raises the question of whether RSV detection and treatment practices are consistent across countries, as differences in climates, healthcare systems, diagnostic protocols, and access to care could influence detection and patient outcomes.

A 2008 report by the Danish Ministry of the Interior and Health states that the Danish healthcare sector is comparable to primarily Nordic and Northern European countries, including Sweden, Norway, Finland, the UK, Germany, and the Netherlands. These countries' healthcare systems, population lifestyles, and health status are similar to that of the Danish[105]. Nevertheless, this project also included studies originating from countries beyond those typically used for comparison, for example, Iran, South Korea, and China[90, 106, 107, 92, 108]. However, since the data reported and methods used in these studies were very similar to those carried out in countries more frequently compared to Denmark, it was decided to include them in the project. Additionally, all studies underwent a risk of bias assessment before inclusion, ensuring high methodological quality. The inclusion of these extra studies additionally serves to enhance statistical power.

This project employs register data, which allows for more precise estimation of resource use than

is possible in studies that do not employ robust register data, such as a study by Wang et al. 2023[102, 109]. Other similar studies seem to favor the use of decision trees with a short time horizon of 2 years: much shorter than the 20-year time horizon employed in the Markov model utilized in this project[101, 102].

When considering the chronic nature of COPD and the longer time horizon of the cost and utility consequences of RSV-related exacerbation, this represents a strength for this project. In contrast to other studies, which often seem to stratify their simulation into age groups, this approach was not implemented in this project[101]. This reduces the level of detail that is possible to obtain in the simulation, as age inevitably affects mortality and disease severity. Equal to that of the age stratification, other studies employ a more granular, monthly cycle length, allowing them to capture a greater level of detail, especially when assessing the seasonal nature of RSV epidemics[110, 101]. This would allow the model to provide greater information regarding the monthly stress RSV-caused exacerbations exert on the Danish hospitals. It would additionally allow a more detailed investigation into RSV's impact on the HRQoL of COPD patients of different ages. Hereby, it could help inform a more targeted and effective vaccine strategy.

Additionally, other studies have also included the consequences of vaccine-related adverse events on both costs and utilities in their simulations[101, 102]. This was not done in this project's simulations, which might lead to an ICER estimate that is slightly positively distorted when compared to that of the studies that do account for these factors. Some other studies also take into account that methods used to detect RSV infection do not capture 100% of cases, and thus, they include a multiplication factor to account for this [101, 102]. This approach was not used in this project, thus possibly leading to the underestimation of the proportion of exacerbations that RSV causes.

Other studies seem to favor a full societal perspective, accounting for productivity loss [101, 102]. This contrasts with the limited societal perspective employed in this project. However, since the results of this project are meant to be applied in a Danish context, and the DMC explicitly recommends the use of a limited societal perspective, the use of exactly that is a clear strength of the Danish applicability of this project [66]. However, including productivity loss would provide a clearer picture of the actual consequence of introducing a new intervention on the societal economy[111].

Lastly, this project employed post-infection immunity, which was implemented as a percentage reduction in the risk of reinfection. Other studies simply made it impossible to be reinfected the first year after infection, and then individuals could be reinfected again in year two after infection[102]. As such, the post-infection immunity approach of this project represents a more nuanced and perhaps life-like way of simulating post-infection immunity, leading to potentially more representative outcomes of the health economic analysis. This is supported by the ISPOR report by Mauskopf et al. 2007, which emphasizes that models should be designed to reflect real-world scenarios as closely as possible[82]. This project applies this principle by incorporating disease progression, immunization, and acute and chronic HRQoL disutilities. This approach enhances the validity and applicability of the method used in this study.

6.4 Meaning of the study

The base case result of this project, with an ICER of 238.067, 79 DKK, shows that implementation of the ABRYSVO vaccine for COPD patients over the age of 60, represents a cost-effective solution, if a WTP of around 450.000 DKK is assumed[75]. Moreover, via the PSA, the CEAC shows that implementation of ABRYSVO would prove cost-effective in approximately 66% of all scenarios. Additionally, the ICE scatterplot shows that most of the PSA iterations fall in the northeastern quadrant, with many below the WTP threshold of 450.000 DKK. Meanwhile, some iterations fall in the southeastern quadrant, highlighting the possibility of ABRYSVO being a dominant option.
A DSA was performed to test the implications of the hypothetical WTP employed in the CEAC plot. In this DSA, the WTP was varied by ± 15%. The result showed that in both cases, ABRYSVO still provided a predominantly cost-effective treatment option, with probabilities of cost-effectiveness of approximately 57% and 74%. As such, if seen only in the light of the ICER estimate, the use of ABRYSVO should be implemented as the SoC. However, payers rely not only on the ICER but also on the budget impact estimate.
The results of the budget impact highlight a relatively high starting cost of 247.869.037, 77 DKK, with costs becoming more manageable in the later years, while savings of 17.760.743, 25 DKK would be experienced in year 3. In years 4 and 5, the BIA increases expenses again. Therefore, a decision to implement would probably come down to the costs of initiating the vaccination program.

While not the project's primary concern, the risk of severe RSV-caused exacerbation was found to be 0, 0035 among the approximately 400.000 COPD patients in Denmark. Based on this project's calculations, this means that RSV is responsible for approximately 1400 COPD exacerbations requiring hospital admission. Not only do these hospital admissions cost money, but they also strain an already stressed hospital sector[112].
Additionally, most cases of RSV are recorded in the fall and especially in the winter, resulting in a peak strain in these seasons[9]. Thus, ABRYSVO provides a means to reduce strain on hospitals, free up beds, and facilitate the work capacity needed for other conditions. In this context, the opportunity cost concept provides an interesting discussion. It could be discussed whether the costs foregone through implementing ABRYSVO would have been better spent on increasing hospital capacity, as this would benefit not only COPD patients, but all patients in need of inpatient treatment. However, the new super-hospitals currently under construction all over Denmark will have a lower capacity than the existing hospitals[113]. Moreover, since 2007, there have been efforts to reduce the number of hospital beds by around 20%[113]. This introduces the necessity of increasing efficiency in the healthcare sector, whereby the need for hospital beds can be reduced. This argument favors implementing ABRYSVO vaccination as the SoC for COPD patients over 60 in Denmark.

Furthermore, many cases of RSV are initially misdiagnosed as bacterial infections, and as

such, many patients receive treatment with antibiotics, despite this not affecting the RSV exacerbation[114]. This project identified the incidence of a moderate or severe RSV-related exacerbation to be $0,0246$. This means that, annually, almost 10.000 patients experience an RSV-caused exacerbation, representing a large number of cases where there is a risk of mistreating with antibiotics. Complimentarily, ABRYSVO could offer a potential solution to reduce antibiotic consumption and, in turn, antibiotic resistance by reducing the number of RSV infections altogether, in which misdiagnosis can occur.
All in all, ABRYSVO offers a cost-effective way to increase the length and quality of life of COPD patients and a solution to reduce strain on the healthcare sector, which suffers from capacity constraints and antibiotic resistance.

6.5 Unanswered questions and future research

Despite the valuable insight this project has generated through its many comprehensive analyses, challenges arose during the process, pointing to suggestions for future research. Gaps in the literature were identified in multiple areas, necessitating sometimes inventive solutions in the form of extrapolations, interpolations of values and rates, and justified assumptions.
First, a significant limitation in this project's current field of knowledge is the lack of directly measured impact of RSV-caused exacerbation on HRQoL in COPD patients. In the Markov model, the disutility values applied were derived from general COPD patient exacerbation data, as no study was found that isolated the loss in HRQoL specific to RSV-related episodes[86, 87, 84]. The method used represents a commonly used, pragmatic solution. However, it introduces some level of uncertainty. Mainly, if AECOPD caused by RSV differs in disease burden and duration compared to other pathogens. To provide more suitable utilities in investigating the health benefits of ABRYSVO in preventing exacerbations, future funding should be prioritized to quantify the direct impact of RSV infection on HRQoL in COPD patients. This should be measured using validated instruments such as EQ-5D-5L.

Secondly, Denmark is recognized for its high-quality, comprehensive disease registries, which are routinely updated and maintained with a high level of clinical detail[109]. The Danish National Patient Registry does not contain a specific variable indicating whether patients are classified as having mild, moderate, or severe COPD disease or the severity and frequency of experienced exacerbations. Nevertheless, diagnoses are recorded using coded classification systems in the Danish patient registries that follow ICD-10 criteria[115]. These criteria distinguish between J*44.0: COPD with acute lower respiratory infection*, *J44.1: COPD with acute exacerbation*, and *J44.9: COPD, unspecified*, offering some means of identification[116].
Alternatively, severity may be inferred through proxy indicators available in the registries. For example, patients with severe disease are more likely to be admitted to intensive care units (ICUs). ICU admission data could approximate disease severity and classify patients accordingly. Other proxy measures could include hospitalization frequency and duration, or Medical use from the Danish National Prescription Registry. Ultimately, it was possible to identify how many

severe exacerbations occur annually in Denmark[3]. From there, the occurrence of moderate exacerbations was mapped out via ratios found in gray literature[95]. The meta-analyses synthesized the RSV incidence, which was afterwards applied to the distinct exacerbations. Although these solutions represent evidence-based empirical data, they are still estimates based on different populations and can add uncertainty to the model.

If the exacerbations occurring in the Danish population were better classified by coding exacerbation severity and causative pathogens, this would allow for more accurate health economic modeling and a sounder measure of the long-term disease burden. Additionally, conducting studies and collecting HRQoL could support analyses with disease-specific impacts beyond survival and hospitalization alone.

A valuable investigation for further research would also be to estimate the number needed to vaccinate to prevent RSV-caused exacerbations resulting in hospitalization or death. This metric can potentially provide valuable context for assessing preventative RSV vaccination strategies' clinical effectiveness and efficiency [117]. Even though this project offers a strong cost-effectiveness case established on the model outcomes, utilizing real-world evidence provided by national vaccination programs could refine these estimates and support broader implementation decisions for ABRYSVO.

Finally, future research should aspire to investigate longitudinal outcomes of RSV infection, now that preventative measures have been taken to market. These analyses should particularly focus on elderly adults with multimorbidities, where the functional and economic consequences and quality of life may be underestimated in the long term[30].

Conclusion 7

The results of the conducted CUA showed that implementing the ABRYSVO vaccine in COPD patients over 60 provides a cost-effective treatment option when viewed in the light of a theoretical WTP of 450.000 DKK. Danish decision makers could use this information to justify widespread implementation and reimbursement of the ABRYSVO vaccine in the investigated population. The budget impact analysis did, however, also show a relatively significant impact on the public expenses in the first year. Nevertheless, this is reduced in the following years, as more people are vaccinated, and smaller cohorts must be offered the vaccine every year.

On a human level, ABRYSVO can help COPD patients experience fewer and milder exacerbations, thereby maintaining better health and functionality and ultimately improving their quality of life, as exhibited in the project's results. ABRYSVO can alleviate some fear among vulnerable elderly COPD patients of contracting infections and suffering severe disease courses that leave them chronically debilitated.

Moreover, ABRYSVO helps ease the burden on the hospital system by reducing admissions and freeing up beds and staff resources. By preventing RSV cases, often mistaken for bacterial infections, ABRYSVO also lowers the risk of unnecessary antibiotic use, addressing a critical challenge in healthcare and combating the rise of antibiotic resistance.

This project delivers robust evidence and well-reasoned arguments demonstrating why ABRYSVO represents a highly valuable and strategic addition to the Danish immunization program. It highlights the vaccine's potential to improve public health outcomes, reduce healthcare burdens, and address pressing challenges of RSV infections.

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Search strategy A

A.1 Systematic search: COPD utilities

Block search

	AND		
	Population (P)	**Intervention/Exposure (I)**	**Outcome (O)**
OR	Controlled Vocabulary (MeSH Terms): Pulmonary Disease, Chronic Obstructive [MeSH Terms] Free Text Terms (Title/Abstract): COPD [Title/Abstract] "COPD exacerbation*" [Title/Abstract] "Chronic obstructive pulmonary disease*" [Title/Abstract] "Exacerbations of chronic obstructive pulmonary disease" [Title/Abstract] Results: 110,900	Controlled Vocabulary (MeSH Terms): Free Text Terms (Title/Abstract): EQ-5D [Title/Abstract] EQ-5D-5L [Title/Abstract] EuroQol [Title/Abstract] Results: 19,017	Controlled Vocabulary (MeSH Terms): Quality of life [MeSH Terms] Free Text Terms (Title/Abstract): "Health-related quality of life" [Title/Abstract] "Health related quality of life" [Title/Abstract] QALY [Title/Abstract] HRQoL [Title/Abstract] Results: 329,886

Table A.1. The search blocks for the COPD utility search are based on the PICO framework, combined by boolean operators; OR/AND.

Search string in PubMed on the 24/02/25: 276 hits:

```
(((((Pulmonary Disease, Chronic Obstructive[MeSH Terms])
OR (COPD[Title/Abstract]))
OR ("COPD exacerbation*"[Title/Abstract]))
OR ("chronic obstructive pulmonary disease"[Title/Abstract]))
OR ("exacerbations of chronic obstructive pulmonary disease"[Title/Abstract]))
AND ((((EQ-5D[Title/Abstract])
OR (EQ-5D-5L[Title/Abstract]))
OR (EuroQol[Title/Abstract])))
AND (((((Quality of life[MeSH Terms])
OR ("Health-related quality of life"[Title/Abstract]))
OR ("Health related quality of life"[Title/Abstract]))
OR (QALY[Title/Abstract]))
OR (HRQoL[Title/Abstract]))
```

Author (Year)	Title	Country of Origin	Study Design	Journal of Publication	HRQoL Measurement Tool	Population Characteristics	Population Size
Lin et al. (2014)	Measuring health-related quality of life in chronic obstructive pulmonary disease: properties of the EQ-5D-5L and PROMIS-43 short form	USA	Multi-center, cross-sectional	BMC Medical Research Methodology	EQ-5D-5L, PROMIS-43	COPD patients, mean age 68.5 years, 58% male	670
Guo et al. (2020)	Moderate and severe exacerbations have a significant impact on health-related quality of life, utility, and lung function in patients with chronic obstructive pulmonary disease: A meta-analysis	China	Meta-analysis	International Journal of Surgery	SGRQ, CAT, EQ-5D-5L	COPD patients, 24% with $\geq$1 severe exacerbation in the previous year	18,746
Garcia-Gordillo et al. (2017)	A Cross-sectional Assessment of Health-related Quality of Life among Patients with Chronic Obstructive Pulmonary Disease	Spain	Cross-sectional	Iran J Public Health	EQ-5D-5L	COPD patients, 48.67% male, 51.33% female	1,130
Dan Jackson et al. (2024)	Associations between the EQ-5D-5L and exacerbations of chronic obstructive pulmonary disease in the ETHOS trial	International multi-center	Randomized controlled trial	Quality of life journal	EQ-5D-5L	COPD patients	8572

Table A.2. Study characteristics from the search identifying HRQoL in COPD patients - health-related quality of life. COPD - chronic obstructive pulmonary disease.

A.1.1 Included studies

A.2 Systematic search: RSV in COPD patients

Block search

	AND		
	Population (P)	**Intervention/Exposure (I)**	**Outcome (O)**
OR	Controlled Vocabulary (MeSH Terms): Pulmonary Disease, Chronic Obstructive [MeSH Terms] Free Text Terms (Title/Abstract): COPD [Title/Abstract] "Chronic obstructive pulmonary disease"[Title/Abstract] "Pulmonary Disease, Chronic Obstructive"[Title/Abstract] Results: 111,429	Controlled Vocabulary (MeSH Terms): Respiratory Syncytial Viruses [MeSH Terms] Respiratory Syncytial Virus Infections [MeSH Terms] Respiratory Syncytial Virus Vaccines [MeSH Terms] Free Text Terms (Title/Abstract): "Respiratory Syncytial Virus Infection*" [Title/Abstract] "Respiratory Syncytial Virus*" [Title/Abstract] RSV [Title/Abstract] "Respiratory Syncytial Virus Vaccine*" [Title/Abstract] Results: 26,292	Controlled Vocabulary (MeSH Terms): Incidence [MeSH Terms] Hospitalization [MeSH Terms] Mortality [MeSH Terms] Disease Exacerbation [MeSH Terms] Free Text Terms (Title/Abstract): "COPD exacerbation*" [Title/Abstract] "Exacerbations of chronic obstructive pulmonary disease" [Title/Abstract] "Incidence" [Title/Abstract] "Hospitalization*" [Title/Abstract] "Mortality" [Title/Abstract] "Disease exacerbation*" [Title/Abstract] Results: 2,804,311

Table A.3. The search blocks for the RSV search based on the PICO framework, combined by boolean operators; OR/AND.

Search string in PubMed on the 17/03/2025: 138 hits

```
((((((Pulmonary Disease, Chronic Obstructive[MeSH Terms]) OR (COPD[Title/Abstract]))
OR ("chronic obstructive pulmonary disease"[Title/Abstract])))
OR (Pulmonary Disease, Chronic Obstructive[Title/Abstract]))
AND (((((((Respiratory Syncytial Viruses[MeSH Terms]) OR (Respiratory Syncytial Virus
Infections[MeSH Terms])) OR ("Respiratory Syncytial Virus Infection*"[Title/Abstract]))
OR ("Respiratory Syncytial Virus*"[Title/Abstract])) OR (RSV[Title/Abstract])) OR
(Respiratory Syncytial Virus Vaccines[MeSH Terms])) OR ("Respiratory Syncytial Virus
Vaccine*"[Title/Abstract])) OR (RSV[Title/Abstract])))
AND ((((((((((incidence[MeSH Terms]) OR (hospitalization[MeSH Terms])) OR
(Mortality[MeSH Terms])) OR (disease exacerbation[MeSH Terms]))
OR ("COPD exacerbation*"[Title/Abstract])) OR ("exacerbations of chronic obstructive
pulmonary disease"[Title/Abstract])) OR (incidence[Title/Abstract]))
OR (hospitalization*[Title/Abstract])) OR (Mortality[Title/Abstract]))
OR ("disease exacerbation*"[Title/Abstract]))
```

A.2.1 Included articles

Author (Year)	Title	Country of Origin	Study Design	Journal of Publication	Population Characteristics	Population Size
Seemungal et al. (2001)	Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease	UK	Prospective cohort study	American Journal of Respiratory and Critical Care Medicine	Patients with COPD experiencing exacerbations	83 patients
Camargo et al. (2008)	Viral pathogens in acute exacerbations of chronic obstructive pulmonary disease	USA	Prospective, observational study	Intern Emerg Med	COPD patients presenting to the ED with <10 days of AECOPD symptoms	76 patients
Dai et al. (2015)	Respiratory infectious phenotypes in acute exacerbation of COPD: an aid to length of stay and COPD Assessment Test	China	Cohort study	International Journal of COPD	Patients with AECOPD	81 patients
Dimopoulos et al. (2011)	Viral epidemiology of acute exacerbations of chronic obstructive pulmonary disease	Greece	Cohort study	Pulmonary Pharmacology & Therapeutics	Patients with AECOPD	200 patients
Hosseini et al. (2015)	Association between respiratory viruses and exacerbation of COPD: a case-control study	Iran	Case-control study	Infectious Diseases	Patients with AECOPD and stable COPD	266 patients (170 with AECOPD, 96 with stable COPD)
Jang et al. (2021)	Incidence and Prognostic Factors of Respiratory Viral Infections in Severe Acute Exacerbation of Chronic Obstructive Pulmonary Disease	South Korea	Retrospective study	International Journal of Chronic Obstructive Pulmonary Disease	Patients with severe AECOPD	192 patients
Kherad et al. (2010)	Upper-Respiratory Viral Infection, Biomarkers, and COPD Exacerbations	Switzerland	Prospective cohort study	CHEST	Patients with AECOPD	304 patients with 3 cases of RSV
Ko et al. (2007)	A 1-Year Prospective Study of the Infectious Etiology in Patients Hospitalized With Acute Exacerbations of COPD	Hong Kong	Prospective study	CHEST	Patients with AECOPD	643 episodes among 373 patients
Hutchinson et al. (2007)	A community-based, time-matched, case-control study of respiratory viruses and exacerbations of COPD	Australia	Case-control study	Respiratory Medicine	Patients with AECOPD	148 exacerbations
Kwak et al. (2016)	Prevalence and risk factors of respiratory viral infections in exacerbations of chronic obstructive pulmonary disease	South Korea	Prospective study	The Tohoku Journal of Experimental Medicine	Patients with AECOPD	278 cases from 213 patients (RSV detected in 12 patients)
Serres et al. (2009)	Importance of viral and bacterial infections in chronic obstructive pulmonary disease exacerbations	Canada	Prospective study	Journal of Clinical Virology	Patients with AECOPD	108 patients with AECOPD (8 (7%) with RSV)
Wiseman et al. (2024)	Respiratory Syncytial Virus-related Community Obstructive Pulmonary Disease Exacerbations and novel diagnostics	UK, Netherlands	Prospective study	American Journal of Respiratory and Critical Care Medicine	Patients with AECOPD and stable COPD	377 patients

Table A.4. Summary of included studies examining RSV infection in AECOPD populations. AECOPD: acute exacerbation of chronic obstructive pulmonary disease.

PRISMA Checklist B

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Front Page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 9
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10-15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 10-11 & Appendix A
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 13-14
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 15-23
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 12-13
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 14-15
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 10-15
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 13-15
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 14-15
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 15
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 24-25
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 25-26
Study characteristics	17	Cite each included study and present its characteristics.	Page 27-28 & Appendix A
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 25-26 & Appendix C
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 27-28 & Appendix A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 26-28
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 28-31
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 28-31
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 30
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 29-31
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 28-31
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 40-41
	23b	Discuss any limitations of the evidence included in the review.	Page 36-42
	23c	Discuss any limitations of the review processes used.	Page 37
	23d	Discuss implications of the results for practice, policy, and future research.	Page 42-45
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 10 & Appendix G
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Input Parameters C

Probability Name	Description	Value	Method	Source
Annual Mortality Rate	Annual rate of patients dying	0,258865551	10 Year mortality Interpolated to a yearly basis	[25]
RSV Caused Exacerbations	Proportion of exacerbations caused by RSV	0,0938	Meta-analysis	5.5
Moderate - Severe ratio	Ratio between moderate and severe exacerbations	1 : 5,977804158	Calculated from article results	[95]
Infection Probability	Overall risk of RSV infection and subsequent exacerbation	0,024622500	Based on RSV Caused Exacerbations, yearly number of exa's and COPD patients in Denmark	[83]
Infection Probability Moderate	Risk of RSV infection and Subsequent moderate exacerbation	0,021093811	Based on Infection Probability and ratio between Severe and Moderate Exas	5.5, [95]
Infection Probability Severe	Risk of RSV infection and Subsequent severe exacerbation	0,003528689	Based on Infection Probability and ratio between Severe and Moderate Exas	5.5, [95]
Acute Severe Infected Mortality	Additional risk of dying in relation to a severe exacerbation	0,175	Average of 15-20% acute mortality rate of severe Exa's in Denmark	[3]
Severe Infected Mortality	Combined risk of dying from, Annual Mortality Rate and Acute Severe Infected Mortality	0,38856408	Calculated from Annual Mortality rate and Acute Severe Infected Mortality	[25, 3]
Vaccine Compliance	The annual uptake of the vaccine in the target population	0,76	Assumption based on the annual compliance to the Danish Influenza vaccination program	[97]
Post Infection Immunity y1	Reduced risk of infection the first year after being infected due to post infection immunity	0,82940	Assumed to be equal to Vaccine Effectiveness y1	Assumption
Post Infection Immunity y2	Reduced risk of infection the second year after being infected due to post infection immunity	0,69180	Assumed to be equal to Vaccine Effectiveness y2	Assumption
Post Infection Immunity y3	Reduced risk of infection the third year after being infected due to post infection immunity	0,53080	Assumed to be equal to Vaccine Effectiveness y3	Assumption
Vaccine Effectiveness y1	Reduced risk of infection the first year after being vaccinated	0,82940	Based on Pfizer Data	Pfizer Data
Vaccine Effectivevess y2	Reduced risk of infection the second year after being vaccinated	0,69180	Based on Pfizer Data	Pfizer Data
Vaccine Effectiveness y3	Reduced risk of infection the third year after being vaccinated	0,53080	Based on Pfizer Data	Pfizer Data

Table C.1. *Model Probabilities*

Utility Name	Description	Value	Method	Source
Baseline HRQoL	The Baseline HRQoL of COPD patients	0,79	Meta-analysis	5.3
Acute Moderate HRQoL Loss	The loss of HRQoL endured in the 30 days post a moderate exacerbation	0,055	Literature Review	[6]
Chronic Moderate HRQoL Loss	The persisting loss of HRQoL endured for the rest of the patients life time after a moderate exacerbation	0,014	Literature Review	[6]
Acute Severe HRQoL Loss	The loss of HRQoL endured in the 30 days post a severe exacerbation	0,09	Literature Review	[6]
Chronic Severe HRQoL Loss	The persisting loss of HRQoL endured for the rest of the patients life time after a severe exacerbation	0,025	Literature Review	[6]

Table C.2. *Model Utilities*

Consolidated Health Economic Evaluation Reporting Standards

D

CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Front Page
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Page 1 - 9
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Page 15 & Appendix E
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 11
Setting and location	6	Provide relevant contextual information that may influence findings.	Page 11
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 16
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 15
Time horizon	9	State the time horizon for the study and why appropriate.	Page 16
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 19
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Page 16 & 17
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 19
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Page 16 - 20

Topic	No.	Item	Location where item is reported
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Page 17
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	N/A
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Page 16-20
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Page 12-23
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	N/A
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	N/A
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Page 20-23
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	N/A
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Page 24-31
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Page 31
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Page 31-34
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	N/A
Discussion			

Topic	No.	Item	Location where item is reported
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Page 36-45
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	N/A
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	N/A

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008