A systematic review of the economic evaluation for Covid-19 vaccination for age groups elderly and adult in European countries

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Quote or Dedication page

To my other half,

Who needed to be a “super mom” during my 2 years of master’s degree,

…

This is for you…

And to my son,

Happy 10^{th} birthday.

Love you to the moon and back…

ABSTRACT

A systematic review of the economic evaluation for Covid-19 vaccination between age groups elderly and adults in European countries

Aim: This systematic review aimed to identify empirical evidence of the cost-effectiveness of Covid-19 vaccination programs within European countries among elderly and adult age groups. The result further acted as a parameter to assess the cost-effectiveness of a similar program in Sweden.

Method: A literature search was conducted in the Medline, Embase, PscyInfo, CINAHL and Tuft CEA, Cochrane and INAHTA databases in February 2023 with PICO as inclusion criteria. The inclusion criteria are economic evaluation articles with age-group separation, age-group based vaccinated European residents as population, Covid-19 vaccination as intervention and non-vaccinated European residents as control. The search was conducted by two reviewers with SBU search strategy. Handsearch was done on relevant websites and reference lists of selected articles. It was continued with title/abstract screening, full-text screening, and quality and risk of bias assessment with SBU checklist. The reporting follows guidelines from the Mastrigt articles.

Results: The screening resulted in 5,720 reports, title/abstract screening yielded 160 reports and after full text screening, four articles remained. Two articles with moderate quality were selected for further analysis. The economic evidence indicated that Covid-19 vaccination is cost-effective in the elderly age group. Transferability to Sweden was hindered by the contrast difference in the data source.

Conclusion: According to reviewed studies, the Covid-19 vaccination policy in the elderly population is cost-effective. The inclusion of the adult age group in the program depends on the vaccines' prices for it to be cost-effective. In-house health economic research is needed to assess the cost-effectiveness of the Swedish Covid-19 vaccination program.

Keywords: Covid-19, vaccination, age group, European, cost-effective

CONTENT

ABBREVIATIONS

COVID-19	Coronavirus disease 2019
GDP	Gross Domestic Product
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
WHO	World Health Organization
DNA	Deoxyribo Nucleic Acid
PCR	Polymerase Chain Reaction
UN	United Nations
UNESCO	United Nations Educational, Scientific and Cultural Organization
PPE	Personal Protective Equipment
SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
MPH	Master of Public Health
PICO	Population, Intervention, Control and Outcome
SBU	Statens beredning för medicinsk och social utvärdering (Swedish Health Technology Assessment Agency)
GP	General Practitioner

DKK	Danish Kronor (currency in Denmark)
SEK	Swedish Kronor (currency in Sweden)
PLN	Polish zloty (currency in Poland)
SKR	Sveriges Kommuner och Regioner
QALY	Quality Adjusted Life Year
ICU	Intensive Care Unit

1 INTRODUCTION

Covid-19: The Disease

Covid-19 is the official term coined by WHO on 11 February 2020, to replace the previous name for the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). This disease was once called as Wuhan virus, reflecting its geographic location where the virus was first identified in December 2019 (3). It is characterized as highly contagious and potentially leading to a fatal outcome. On 11 March 2020, WHO declared the outbreak as a pandemic (4).

The virus DNA shares 96% similarity with the coronavirus variant found in bats, which categorized Covid-19 as a zoonotic origin (5). There are documented cases of the spread of the virus from human to animals, and from animals to human (6).

The most distinguished symptoms from early Covid-19 are loss of smell and loss of taste, aside from regular symptoms of viral respiratory disease, such as fever, cough, headache and breathing difficulties (7, 8). The fact that the occurrence of these symptoms shows up from day one up until fourteen days after exposure to the virus and one-third of infected people show no symptoms (9) and asymptomatic infected people are contagious for up to 20 days, increases the virus's transmission rate (10).

One unique symptom of Covid-19 is neurological (such as loss of smell and taste) which leads to the hypothesis that the virus has the ability to penetrate the blood-brain barrier in the central nervous system (11). This hypothesis is considered as the basis to explain the mental health issues experienced by some Covid-19 patients (12).

Compared to other viral respiratory diseases, 14% of Covid-19 patients progresses to have severe symptoms and 5% manifested into critical conditions (13). High rates of cardiovascular complications are due to the body's reaction to the virus by triggering systemic inflammation in the hearts (14) and leading to poor prognosis when the inflammation creates thrombosis (15). Thrombosis (blood clot formation) especially in the lungs (pulmonary embolisms) and brain (ischemic events) plays the primary role in the case mortality of Covid-19 patients (10).

Mild Covid-19 cases with symptoms resembling the common cold typically subside within 14 days, while the more serious cases take up to six weeks to recover (16). Half of the infected people continue to suffer the long term Covid-19 symptoms, such as fatigue for weeks or months (17), and in some extreme cases, organ damage is observed (18). The risk of the long term Covid-19 is higher in elderly, smokers and patients with existing severe diseases (19).

The transmission goes through the common pathway of viral respiratory disease which is airborne (20) and the virus itself can stay infective for 7 days, especially in poorly ventilated indoor areas (21). This increases the complexity of disease management.

The nasopharyngeal swab is the most common method to collect samples for testing, although nasal swabs and sputum may also be used (22). Several testing methods are accepted as the basis for treatment while testing with the PCR (polymerase chain reaction) technique provides highest accuracy result (23).

While young children experience a low infection rate (24), the elderly population and pregnant women (25) are classified as at increased risk of becoming seriously ill from Covid-19. It is estimated that the real infection rate in young children is higher than the reported number since most of the studies of Covid-19 infection in young children are based on the visit to health facilities (25).

Since there is no specific anti-viral medication is available yet, the primary treatment for Covid-19 patients is symptomatic and supportive care, such as fluid therapy and oxygen administration (26). While for mild cases, the most common medication is anti-inflammation and general condition improvement (27).

Preventive measures are the only effective measure to contain the spread of the virus before the invention of the vaccination. One of the most effective preventive measures is washing hands with soap since the virus envelope dissolves with soap exposure (28). The preventive measures that are commonly adopted by the health authorities are stay-at-home quarantine, wearing masks in public, crowd control, and recommendation to maintain safe distance in public (social distancing).

It is worth mentioning that the recent variant of Covid-19 has less severe symptoms than the early Covid-19 variant, for instance, Omicron variant which is more contagious but causes milder symptoms (24). While immunity is observed in people recovering from Covid-19, it is unknown if the immunity is long-lasting (29). It is also observed that Covid-19 reinfection has milder symptoms than the primary infection with the same variant.

Covid-19: The Disease Burden

<u>Economic aspect</u>

The Covid-19 pandemic triggered the second-largest global recession since the second world war (this recession was also be known as 'Covid-19 recession') (30). In its effort to curb the infection, the lockdown measure was adopted by most countries in the world (31). This non-pharmaceutical measure caused disruption in the supply chain, an inflation surge and a stock market crash (32).

The recession forced governments to provide huge stimulus to soften the impact on the population (33). However, this step was not possible for some governments, especially for low- and middle-income countries. Food insecurity unavoidably turned into famine occurred in several countries, such as East African countries (34).

Business, especially sectors that relied greatly on physical presence, was heavily impacted. This in turn resulted in an increasing unemployment rate and lower purchasing power and circled back to worsen the economy (31). Estimation from Cambridge University indicated that the Covid-19 pandemic could cost the global economy at $82 trillion over five years (35).

Aside from the bleak picture experienced by most businesses, the Covid-19 pandemic positively impacted pharmaceutical industries and e-commerce sales (36). Record earnings were announced by internet-based companies, such as social media, online gambling, and TV providers. Contrary to general downgrading conditions for most population, Oxfam reported that the Covid-19 pandemic doubled the fortunes of the world's 10 richest men (37). This widening economic discrepancies could cause UN Sustainable Development Goal harder to achieve, and instead, it reversed the progress made (38).

<u>Social aspect</u>

Politically, the Covid-19 pandemic was a 'make or break' factor for many governments in the world. New Zealand was one of the 'make' examples with the prime minister being reelected with a landslide victory (39). Most governments were more on the 'break' part, for example, Donald Trump was heavily criticized on his response and ignorance of the pandemic in the USA (40).

In the education world, formal physical teaching was moved to internet based. UNESCO estimated that 1,5 billion students were affected and the most vulnerably affected were from low-income families who could not afford internet access (41). Reports of mental health issues among students were all-time high with isolation and loneliness cited as the main cause (42).

Mental health was also considered as the main reason for healthcare personnel's absence from work. Increased stress and workload, and lack of access to required resources such as personal protective equipment (PPE) altogether with sickness from Covid-19 itself reduced the healthcare workforce significantly, complicating the management of Covid-19 further (43). From a different perspective, the Covid-19 pandemic positively changed the image of the healthcare professions such as nurses and physicians in public opinion and increased pride within the profession itself (44).

From an environmental standpoint, the Covid-19 pandemic provided healing time for the planet. Grounded airlines industry, lockdown measures and industrial slowdown had helped to mend the ozone layer (45). Although at almost the same time, the accumulation of PPE trash due to Covid-19 had been the main concern for environmentalists due to the non-recyclable character of PPE (46).

Covid-19: The Vaccine

Contrary to general knowledge that Covid-19 vaccine development was started from null, research into Covid-19 vaccines was a continuation of the previous research on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (47). The two diseases were caused by the same type of coronavirus, and the knowledge about coronavirus from these two diseases enabled the acceleration of the development of Covid-19 vaccines (47).

Supported by governments in funding and administration, especially from the high-income countries, the development of Covid-19 vaccines produced its first approved product in 2020 (48). It was made available to the public through emergency authorizations (48).

The vaccines were proven clinically effective in reducing the severity and death in vaccinated patients with Covid-19 infection (49). Based on modelling, it was estimated that these Covid-19 vaccines saved almost 20 million people from death due to Covid-19 during its first year of distribution (50).

Adverse events reported for the administration of these vaccines are mild, while serious adverse events are rare, with an incidence rate of 5 cases per 100,000 administration for myocarditis (51). Anaphylaxis reaction was recorded at one case per 400,000 administrations (52). The number of death after receiving Covid-19 vaccination was 1,645 deaths in the UK (United Kingdom) for the period between 9 December 2020 and 8 September 2021, however, the cause of death was not fully investigated or confirmed to be the vaccine itself (53).

It is reported that some of the public members are reluctant to participate in the Covid-19 vaccination due to fear of cardiac adverse events, such as myocarditis (54). This fact is highlighted as one potential hindrance to increasing vaccination coverage (54). While in a different publication, it is mentioned that the mental stress triggered by the fear of side effects from Covid-19 vaccination could cause a higher incidence of side effects itself (55). Mental stress induces constriction of blood vessels which could exacerbate the formation of blood clots and heart attacks which might appear shortly after the vaccination (55).Booster doses are recommended due to the data that immunity from these vaccines tapered off over time (56). Challenges from newly found Covid-19 variants require continuous and intensive research to keep up with the virus mutation. While the speed slowed down after the peak of the pandemic in 2021, the research is still ongoing since the aim of the scientists and regulatory authorities worldwide is to have omnipotent single Covid-19 vaccines (57).

The controversy

As of March 2023, around 13 billion doses of Covid-19 vaccines were administered (58) and around half of these doses were designated for high-income countries with a total population of only 14% of the world's population (59). The inequality of vaccine distribution was estimated as the main cause of the mutation of the virus and could potentially reduce the effectiveness of the current vaccines (60).

Covid-19 vaccines were mostly provided free of charge by the governments to its population and the cost was shouldered by the taxpayers. This reality triggered questions to the vaccine producers (pharmaceutical companies) if it was ethical for these companies to make a huge profit from the pandemic, considering the research to create the vaccines was mostly also funded by the taxpayers through governments (61).

The pharmaceutical companies behind the Covid-19 vaccines also enjoy governments' protection from any liability such as negligence related to the vaccines they produced (62).

The further controversy of Covid-19 research was the period of developing these vaccines. While it takes years for regular vaccines and medications to be deemed safe and receive approval from regulatory authorities, Covid-19 vaccines took only 11 months from their conception to distribution to the population (63). This raised concern related to the safety of these vaccines and became the main reason for the anti-vaccine movement around the globe (64).

Swedish situation

Based on the last data in March 2023, Folkhälsomyndigheten (public health agency in Sweden) recorded a total case of 2,7 million Covid-19 cases since the beginning of the pandemic in 2020 (65). The first Covid-19 case in Sweden was confirmed on 31st January 2020 (65). The total death case due to Covid-19 up to March 2023 was more than 23,500 deaths and this total death number put Sweden as 18th place in Europe's death related to the Covid-19 pandemic (66).

IHME (The Institute for Health Metrics and Evaluation) COVID model estimated many Covid-19 related deaths in Sweden as excess and avoidable (67). The hypothesis arose from the controversial policies taken by the Swedish government during the pandemic (68).

Contrary to the strict lockdown implemented by other countries, there were no legal restrictions applied to the Swedish population (69). Public Health Agency of Sweden put out recommendations on steps to reduce the infection rate and the public was expected to follow this recommendation voluntarily (70). While the policy managed to slow down the economic downturn (71), Swedish healthcare was under immense pressure to cope with regular service and was overwhelmed with cases of Covid-19 infection (72).

Sweden's unique strategy in tackling the Covid-19 pandemic caused more severe impact compared to other developed countries, especially in the beginning of the pandemic (73). As elaborated by Pashakhanlou, as on February 17, 2021, the death toll in Sweden was 12,598 while in Norway was 607, in Finland was 725 and in Denmark was 2319 (73).

This information is in line with the report from National Commission established by the Swedish Government in June 2020 to examine the Covid-19 management in Sweden. The total excess mortality in 2020–2021 was 0.79%, which was lower than other European countries which suggested that the voluntary measures were appropriate and guaranteed Swedes' personal freedom (74). Even though the Swedish COVID-19 Commission concluded that during the first wave, earlier and more extensive action should have been taken (74).

In December 2020, Sweden began its vaccination program (75). Despite Sweden vaccination progress was being marked as slow compared to other countries such as Denmark and Poland (76, 77), as of March 2023, Folkhälsomyndigheten reported that 86,4% of the population aged 18 years and older already received Covid-19 vaccination (75). The coverage of vaccination in Denmark is recorded at 82% and Poland at 60% based on data from WHO dated 04 June 2023 (78). The author recommends the readers to the WHO reference website for the full comparison data between countries: https://covid19.who.int/table (78).

European countries have different age limit and criteria for their Covid-19 vaccination strategies. Although several countries prioritized medical personnels in the first phase of Covid-19 vaccination program, most countries allocated this phase for elderly population. The difference can be seen in table 1 (79).

Table 1. European countries and the Covid-19 vaccination initial strategies

Country name	Covid-19 vaccination first priority
Slovakia	health workers, medical students, social service home staff, armed forces and some infrastructure workers are being offered the vaccine in the first round, while patients over age 65 and the chronically ill are not eligible until the second round
Spain	residents and workers in assisted-living nursing homes, as well as care centers for highly disabled

	people in addition to front line healthcare and social care workers
Latvia	health workers treating COVID-19 patients and professionals working in Emergency Medical Services (EMS) are in the top priority group
Lithuania	those who work directly with Covid-19 patients
Netherlands	hospital and nursing home personnel over other groups, including older people and those with pre-existing conditions
Austria, Germany and the United Kingdom	80 years and over before planning to move incrementally to younger age groups
Estonia	those 70 years and over
Portugal	people aged 50 years or older, but only if they have one of a short list of chronic conditions

(This table is created based on data from Cylus, J., et al (79))

Role of economic evaluation in the vaccination program

The scarce resource is the main reason of having an economic evaluation in decision-making in health care (80). Economic analysis of health care technology, which defines as all types of health care intervention, including vaccination is an inseparable part of health care policy to ensure optimal allocation of the available resources resonance with maximum health benefit received by the population (81). The main concept for health intervention is the benefits need to outweigh the risks (82).

In general, there are three types of full economic evaluations: cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA) (83). The difference between these three types is the outcome measurements (for instance, CEA focuses on non-monetary outcomes such as life years gained, while CBA focuses on net monetary benefit) (83).

There are several factors in deciding which type of economic evaluation to use such as preference of the country's regulatory authority and the effects it wants to achieve (84). Regardless of the type, the main idea of economic evaluation is comparing the benefit and costs of health interventions.

The benefit is directly or indirectly influenced by the risk of disease. Certain diseases cause higher mortality/morbidity than other diseases and directly impact the patients. The population also suffers indirectly from the disease, for example, quarantine and limitation of movement in infectious diseases with the high risk of transmission and mortality, such as Covid-19 (85).

The cost is directly influenced by the price of the intervention itself, such as vaccine price, the administration of the vaccines and the minimum number of effective boosters required. The indirect cost can be interpreted as the loss due to the planned intervention, for instance, employees take time off from work to get the treatment or the incapacity due to the treatment (86).

The vaccination itself differs from other types of health interventions due to the nature of vaccination as prevention. The risk of infectious disease is not isolated to a single individual but to a population at risk. This expresses as more value in prevention intervention such as vaccination for the population at risk. Vaccinations are general interventions in a specific part of the population. This implies that vaccination's value is not the same in different populations. For example, the malaria vaccine which is now being trialed is valued more in sub-Saharan countries compared to European countries (87).

A particular feature of vaccination is its mass effects on the population in the form of herd immunity (88). Herd immunity can be translated as indirect protection for unvaccinated individuals when most of the population is immune to the disease, either through vaccination or through previous infection (89).

Another feature of vaccination which also affects the economic evaluation concept for vaccination is the long-term benefit of vaccination. The averted healthcare spending and avoided productivity loss due to sickness to both specific individuals and associated populations, such as family members are the basis of benefit calculation in economic evaluation for vaccination programs (90).

Altogether with herd immunity as another long-term benefit of vaccination implies the importance of modelling in the economic evaluation of vaccination programs (91). Modelling is defined in this context as a simulation of effect and resource allocation for the alternatives in the health intervention. By referencing the models, the policy-makers are provided with a basis for deciding which intervention to take for the population (92).

Systematic review in economic evaluation

In general, most economic evaluation is done with a focus on a specific scope, such as geographically (municipality, region), organization or program. These types of economic evaluations are based on the data from the registry, real world data and could also include collecting outcome data such as quality-of-life estimates (80). A systematic review collects and summarizes the information on these available economic evaluation reports (93).

Although initially systematic review arose from randomized controlled trials (RCTs), the methodology has evolved in engaging diverse types of data to support decision-making (94). Systematic review offers the policy-makers useful information regarding various circumstances (95) affecting cost-effectiveness profiles of each health intervention which could not be provided by simple and straightforward economic evaluation, for instance, economic evaluation of a health program in a specific municipality.

Specific attention to the assumptions and background of the economic evaluation modelling needs to be considered to ensure the result is transferable. Transferring economic evaluation results is more context-specific than effectiveness evaluation, therefore it is crucial to capture these similarities and differences in the reviews, for example, in one area, it takes at least three visits before the patient is confirmed to have an operation, while in another region, two visits are considered adequate (96).

Covid-19 vaccination program in Sweden

Referring to the Covid-19 pandemic, as in other countries, Sweden rolled out its Covid-19 vaccination program in several phases. The phases followed a principle of priority order with the ones with the greatest need as the first group who received vaccination. The definition of greatest need follows the WHO recommendation to assess the criteria based on the severity risk of the disease, death rate, vaccine efficacy and community acceptance (97). It was decided by

Folkhälsomyndigheten as the official agency in disseminating vaccination to the Swedish population (98).

For the first phase, the targeted group was elderly care homes for both the inhabitants and staff and healthcare workers who work with risk groups. The second phase was for healthy individuals aged 70 or above and adults with functional impairments. Medical healthcare professionals were included in phase two. The third phase included other adults in the risk group, while the rest of the population above 18 years old were included in the fourth phase (98).

Vaccination for children under 18 was limited only for ages 12 and above and it started as a continuation from the fourth phase (99). Sweden was against vaccinating children under 12, citing that the no extra benefit in vaccinating this age group compared to the risks (100).

Regarding vaccination for children under 12, it is arguable that vaccines could add extra protection since children rarely experience serious symptoms due to Covid-19 (101). On the other hand, safety profiles of the vaccines in the children age groups have not been fully established (102). It should provide clear evidence that the benefit outweigh the risk before a health intervention be approved to be given to children (103).

Theoretical framework for this study

Limited resources constantly put the decision makers in delicate situations in their effort to provide health care service to the population. As highlighted by Mitton, C. and Donaldson, C. that “In essence, as there are more claims on resources than there are resources available, some form of priority setting must occur. That is, resources are scarce and there is thus a need, regardless of how many resources are available in total, to make choices about what to fund and what not to fund.” (104)

There are three ethical principles in guiding priority setting in the health service (105). These three ethical principles act as theoretical framework for this study. They are human dignity principle, the needs and solidarity principle and the cost effectiveness principle. Although there are several reports suggesting Covid-19 vaccination fulfill the third principle of cost effectiveness, however these reports are focusing on the vaccination in general, with the comparison with status quo (no vaccination).

The implementation of Sweden's Covid-19 vaccination was rolled out in phases with certain risk and age group being prioritized over the others. This decision was based only on two of these ethical principles which are the human dignity principle and the needs and solidarity principle. The principle of cost effectiveness is left unanswered.

This systematic review contributes to confirming the Covid-19 vaccination policy which prioritizes the elderly age group population over other age groups is valid based on cost-effectiveness ground. This is crucial since the early consideration of this policy was not based on concrete economic evaluation.

Justification for this thesis

It is a common practice by some authorities, for instance, the Swedish government to exercise cost-effectiveness analysis for health policies before adopting it as mentioned on the Folkhälsomyndigheten website that it uses health economics as the basis of prioritization of which medication or vaccine or policy to implement (106).

An early estimation was made regarding economic valuation of Covid-19 vaccination shows the benefit of the effective Covid-19 vaccination in tackling the impact on GDP and relevant sectors (107). One study provides an estimated value of €744–€956 per dose with societal perspective (108). These highlight that the Covid-19 vaccination is economically acceptable although these studies do not provide explanation regarding specific part of population, such as age-group.

In the prioritization order of vaccination against Covid-19, the Swedish and other governments relied on the risk of disease of each targeted group (109). In the Covid-19 vaccination plan, the elderly population is the priority. The reason is this age group population suffer the most severely when infected by the Covid-19 virus, due to a declining immune system and the inflammaging process (age-related pathological immunological characteristic) (110).

Aside from this biological consideration, the analysis of cost-effectiveness of this policy remains questionable. There is a knowledge gap to understand whether the approach for vaccination prioritization solely based on the biological condition of the targeted group is a cost-effective allocation of resources.

As elaborated by Giubilini, A. that this type of policy requires consideration of intrinsic and instrumental values (111). Intrinsic values are measurable means such as cost-effectiveness and instrumental values are described as the impact on society, for instance prioritizing front-line healthcare workers are more valuable due to their roles (111). In his article, Giubilini explained further that "It is a mistake to simply assume that prioritizing the most vulnerable is the best strategy. Although that could end up being the best approach, whether it is or not, requires careful ethical and empirical analysis." (111)

There is no study yet, at the time this systematic review is composed, that provides information on cost-effectiveness of the prioritization plan for Covid-19 vaccination in Sweden. This systematic review focuses on collecting economic evaluation information from other countries in the European continent for the same program with the consideration that these countries have the most similarity with Sweden in geographical location, governance system and economic situation compared to other continents (transferability purpose).

This study is aimed at gaining evidence into benefit risk profile of Covid-19 vaccination in the elderly age group and in the adult age group and use this information to determine if the decision to vaccinate elderly age group as the first prioritization over adult age group is economically acceptable. By providing this information, this study could contribute to reviewing if the Swedish policy of prioritization for vaccination against Covid-19 is the best approach and could be a basis for deciding future policies in the pandemic or similar situations.

2 AIM

The aim of this systematic review is to identify empirical evidence of the cost-effectiveness of Covid-19 vaccination programs among the elderly age group and adult age groups within European countries.

Research question(s)

1. How is the balance between the benefit and cost of the Covid-19 vaccination program within European countries in the elderly age group?

2. How is the balance between the benefits and costs of the Covid-19 vaccination program within European countries in the adult age group?

3. If choices to implement Covid-19 vaccination must be made between the elderly age group and the adult age group, for instance, due to limited resources, which group should be favored based on cost-effectiveness grounds?

3 METHODS

Protocol

The literature search was developed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement (112). The early phase of this study was developed as teamwork with a colleague from the same MPH program at the University of Gothenburg as the author and included a process of defining PICO (Population, Intervention, Control and Outcome) and search strategies, title and abstract screening, full-text screening, and quality assessment.

The process of data extraction and data analysis were performed individually since the aim of the study for each team member was different. This study focuses on the age group: adults and elderly while the other team member study focuses on the age group: children and elderly.

The assessment of the result follows the SBU checklist, while the reporting of the result follows the reporting guidelines from Expert Review of Pharmacoeconomics & Outcomes Research articles. The guidance comprised of three separate articles, and it is intended specific for economic evaluation in health care (83, 113, 114). The analysis conducted in this study follows this guideline and is presented in each subheading in the next chapter 4 (Result) and chapter 5 (Discussion).

Eligibility Criteria

Study Design

The inclusion criterion for the articles was economic evaluation articles relevant to Covid-19 vaccination. The economic evaluation included cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). The comparison group (control) was essential to highlight the difference in the cost and benefit aspects of Covid-19 vaccination.

Population

The population was specified as Covid-19 vaccinated European residents with age group separation. Due to a variety of definitions for age groups in different countries, this study avoided using exact age limitations. This study used the age group as defined in the included studies instead.

The definition for Europe is in line with the geographical definition from the Center for European Studies which is an area from the Atlantic to the Ural Mountains and the Arctic to the Mediterranean (115).

Intervention

The intervention was Covid-19 vaccination and was not limited to the number of doses, boosters, type of vaccines, manufacturers, and period of vaccine administration.

Control

The control group of this study was a population who was unvaccinated with Covid-19 vaccines.

Outcome

The outcome of secondary data for this study was the reported outcome such as difference in costs, cost per avoided infection, cost per QALY and net monetary benefit.

Search strategy

Literature searches

The search strategy was adapted to accommodate Population, Intervention, Control and Outcome (PICO) and due to resources limitation, only articles in English were included. The year of publication was from 2019 onwards (up to February 2023) since the Covid-19 pandemic started at the end of 2019. These were the databases utilized for this study:

- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- EMBASE (Excerpta Medica Database)
- PsychINFO (Psychological Information Database)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)

The search term (Appendix 1) used for this study was taken from the Swedish HTA website so as to ensure compliance with the transferability of this study for Swedish circumstances (116). The SBU is an official Swedish agency responsible for doing health technology assessments. For further information about SBU, the readers are recommended to go to its website (https://www.sbu.se/en/).

For instance, a search term of health economic studies was taken from another SBU publication. The SBU publication which is used as reference for this purpose has specific health economic search terms for each specific database. The publication is titled: Wheelchairs and wheelchair accessories, a systematic review and assessment of medical, economic, social and ethical aspects (117).

In this specific example, on page 28, search term for health economy for CINAHL database is provided. This search strategy is agreed upon discussion with the supervisor and aligned with the answer given by SBU to the clarification email from the author of this study (see Appendix 3).

Another example was the Covid-19 search term. The search term was taken from SBU publication titled: Covid-19 and pregnancy (118). The Covid-19 search term is defined in the appendices of this report and specified to specific databases.

Grey literatures searches were done for these selective websites: WHO (World Health Organization (WHO)), Folkhälsomyndigheten (public health agency in Sweden - Folkhälsomyndigheten — Myndigheten för folkhälsofrågor (folkhalsomyndigheten.se)) and EMA (European Medicines Agency - European Medicines Agency | (europa.eu)) with the same PICO criteria and synonym. The reason for limiting the hand searches to these three websites was time and resource limitations. The database searches and grey literature searches were done individually by each team member and results were combined to ensure no articles were left behind.

Complementary searches

Hand searches

An extra search into the reference list from the included articles was done to detect potential literature. Potential literature found during this extra search went through an extra search into its reference list. The process was repeated until the reference lists were exhaustive of potential literature.

Economic evaluation databases

Further search into health economic databases was done. The economic databases utilized for this study were:

- Tuft CEA
- Cochrane
- INAHTA

Two other economic databases were excluded, which were NHS HEED (last update was in March 2015) and HEED (no longer accessible) (83) (Appendix 1).

Title and abstract screening

The following phase was de-duplication which was done with EndNote management tool (119). The result of de-duplication was then exported to Rayyan. Rayyan is an application used to help expedite the screening of titles and abstracts. For further information on Rayyan, the author refer the readers to the Rayyan website (Rayyan - AI Powered Tool for Systematic Literature Reviews) and reference article (120).

The title and abstracts of the articles that were not according to eligibility criteria were excluded, and this process was done individually by each team member, followed by consensus between team members. Ambiguous articles were decided to be included in the full-text screening phase.

The result from Rayyan was exported back to EndNote in which it was already determined which articles belonged to which team member (labelling). Full-text articles were retrieved in EndNote, and for articles which cannot be retrieved with EndNote, manual searching on the internet was done.

Full text screening

The full-text screening was documented with separate Microsoft Excel done by and for each team member. The result was two final lists of articles, one for each team member according to the age group as in each's research question. The reasons for excluding each article were documented (Appendix 2). Assurance of these final lists was done via consensus discussions.

Quality assessment

The step quality assessment was conducted with an SBU-model-based quality assessment checklist. Clarification with the SBU unit was done per email to ensure the checklist used is the most updated (Appendix 3).

The quality checklist from the SBU has two types, model based, and trial based. Since the content of the reports did not derive from trial/experiment and the reports determined alternate outcomes and its economic evaluations based on modelling, it is agreed with the supervisor to proceed with the model-based quality assessment checklist.

The SBU checklist has been constructed to complement SBU's purpose by including parameters for identifying bias and transferability. This supports the transferability of this study into the Swedish setting.

In finalizing the quality assessment step, reconciliation was done with the team member and the study supervisor to ensure all parties were on the same page with the result of chosen articles. The whole process of defining PICO, searching, screening and quality assessment was conducted between the 16th of January and the 5th of April 2023.

Data extraction

The information in included studies were reported based on the template according to Mastrigt, et al. which is specific to health economics studies (83). The following data items were summarized from each study: authors and publication details, funding source, conflict of interest, location setting, patient characteristics, type of intervention, control information, eligibility criteria, study perspective, type of economic evaluations, analytical approach, time horizon, discount rate (cost and effects), inflation rate, reference year, choice of health economics modelling, type and category of costs, information regarding the source of data for cost and effect, methods for identifying cost and effect, measurement of cost and effect, ICER, sensitivity analysis and the result of sensitivity analysis, and the conclusion from the authors. Extracted data were summarized in a table (Appendix 4).

Analysis of transferability to Swedish circumstances

The literature search was developed following PRISMA protocol and utilized search term developed by SBU. This strategy with SBU search term aims to accommodate easy adaptation for the result to be used in Swedish setting. This is based on the concept that SBU used the same search term for its earlier publications.

The next phase is quality assessment and this phase utilized SBU checklist. This checklist is developed by SBU to assess quality of the publications, risk of bias and early assessment for transferability of the result. The same aim as literature search phase is the motivation to use SBU checklist.

In order to accommodate comparison between articles, all cost was converted into Swedish kronor (SEK) based on the currency exchange rate in the year 2020 (121). For example, the cost in Poland was first converted to Euro with the exchange rate as mentioned in the Orlewska articles (1 euro = 4,4 PLN) (122) and the result was converted into the SEK based on historical 2020 rate (121).

There is no cost-effectiveness analysis conducted for Covid-19 vaccination in Sweden in this study, for instance, ICER is not calculated. Some data items taken from Sweden are used for the purpose of comparing with data from the included reports, such as unit cost and effect. This comparison serves as the basis of transferability assessment if the setting in either Orlewska or Debrabant match Swedish setting.

The reporting guideline consideration

Kylie Porritt, a researcher from Joanna Briggs Institute, elaborated in her article that “While conducting a systematic review is a step-by-step process, it's also characterized by plurality. No single methodology is advocated by all organizations that develop and conduct systematic reviews.” (123)

There are several reporting guidelines available for this systematic review. One of them is synthesis without meta-analysis (SWiM) reporting guideline. The data in the two final included reports used as sources for this study cannot be combined to be developed further as meta-analysis. Lack of description of the methods used, as can be found in Debrabant article, categorized this study as "narrative synthesis" according to SWiM article (124). Further information regarding the SWiM reporting guidelines can be read from the reference source (124).

Another reporting guideline considered for this study is PRISMA reporting guidelines. However, as elaborated in SWiM article that PRISMA has limitation in "certain aspects such as the methods for presentation and synthesis, and no reporting guideline exists for synthesis without meta-analysis of effect estimates." (124), thus the author excludes the possibility of presenting the result with PRISMA reporting guideline.

Another reporting guideline is taken from articles from Expert Review of Pharmacoeconomics & Outcomes Research articles. In order to simplify the naming of this guideline, the author called it Mastrigt, based on the name of one of the authors. The guidance comprised of 3 (three) separate articles (83, 113, 114). For further information, the author suggests that the reader check the following references (83, 113, 114).

The author and the supervisor agreed to present the result of this study following Mastrigt guidelines. The considerations are the Mastrigt guideline is intended specific for economic evaluation in health care and the author is more familiar with this guideline since this was part of this study's master course references. The analysis conducted in this study follows this guideline and is presented in each subheading in the next chapter 4 (Result) and chapter 5 (Discussion).

Ethical consideration

Ethical approval was not required due to the nature of this study as a systematic review. The source of data for this study was already published articles available in the public domain and neither patient consent was required since patient data remained aggregated (125, 126).

For both articles, the authors stated their names and roles, and both articles' authors provided information for conflict of interest. Regarding the source of funding, only Debrabant declared that the study was funded by the employer of the author, while no information is available for Orlewska regarding the funding.

Primary data collection was not done by the authors of Orlewska nor Debrabant. This implies that no handling of personal data in both Orlewska and Debrabant since the source of data was taken from either statistical agency or other reports' results. This is shown in both articles, and it is written in Debrabant in the ethics approval section. The Orlewska article does not contain specific ethics approval section.

Related to the funding aspect, as mentioned by Suri, H. that a systematic review takes up significant resources (126). However, this does not apply for this study since the author received no funding for this study. The author also declared that there is no conflict of interest in this study.

4 RESULTS

Study selection

The database searches resulted in 6,053 records. Grey literature searches into the website WHO, Folkhälsomyndigheten and EMA resulted in zero articles. After de-duplication, 5,720 articles remained. These articles went through the first stage of screening, based on title and abstract, and 160 articles were included. The second stage of screening, where the full text of each article was assessed for eligibility, reduced the number of reports to 3 (three) (122, 127, 128). The reasons for exclusion were documented (Appendix 2).

Extra hand searches into the reference list of the three included studies resulted in one report (129). Further screening of the reference list for the newly found report resulted in no relevant article.

Complementary searches into three health economics databases resulted in one article, which was from the Tuft CEA registry. This article was a duplication of an article found in Embase therefore it was omitted. The screening and selection process was illustrated in the PRISMA flow diagram (Figure 1).

Quality assessment

The quality assessment was done on the four articles with a checklist from the Swedish HTA agency (SBU). The quality assessment was done separately by each team member and the supervisor of this study. Individual results were discussed between team members and the supervisor to reach a consensus.

There are two articles deemed as low quality (128, 129) and excluded for the next step. One article with low quality is titled: "Does natural and hybrid immunity obviate the need for frequent vaccine boosters against SARS-CoV-2 in the endemic phase? (128) It was considered low quality because the article has no source for cost and effect (simulation only) and no clear information on the method used. Another article with low quality is titled: "Pharmaco Economics Analysis of COVID-19 Vaccines in Ukraine." (129) The reason for low quality is inadequate information regarding method and missing calculation for economic evaluation in the article. The conclusion for these two low quality articles was consensus between the team members and the supervisor.

The other two articles (122, 127) are considered moderate and included in the data extraction phase. The quality assessment checklist can be found in Appendix 3.

Data extraction

The following was a summary description of the detailed information in the data extraction table (Appendix 4). The data extraction table was based on Mastrigt, et al (114).

Publication information

To simplify the naming of the two articles, the last name of the first author is used in this study. The first article with the title "Cost-effectiveness analysis of COVID-19 vaccination in Poland" is called Orlewska (122), and the second article with the title "The Cost-Effectiveness of a COVID-19 Vaccine in a Danish Context" is called Debrabant (127).

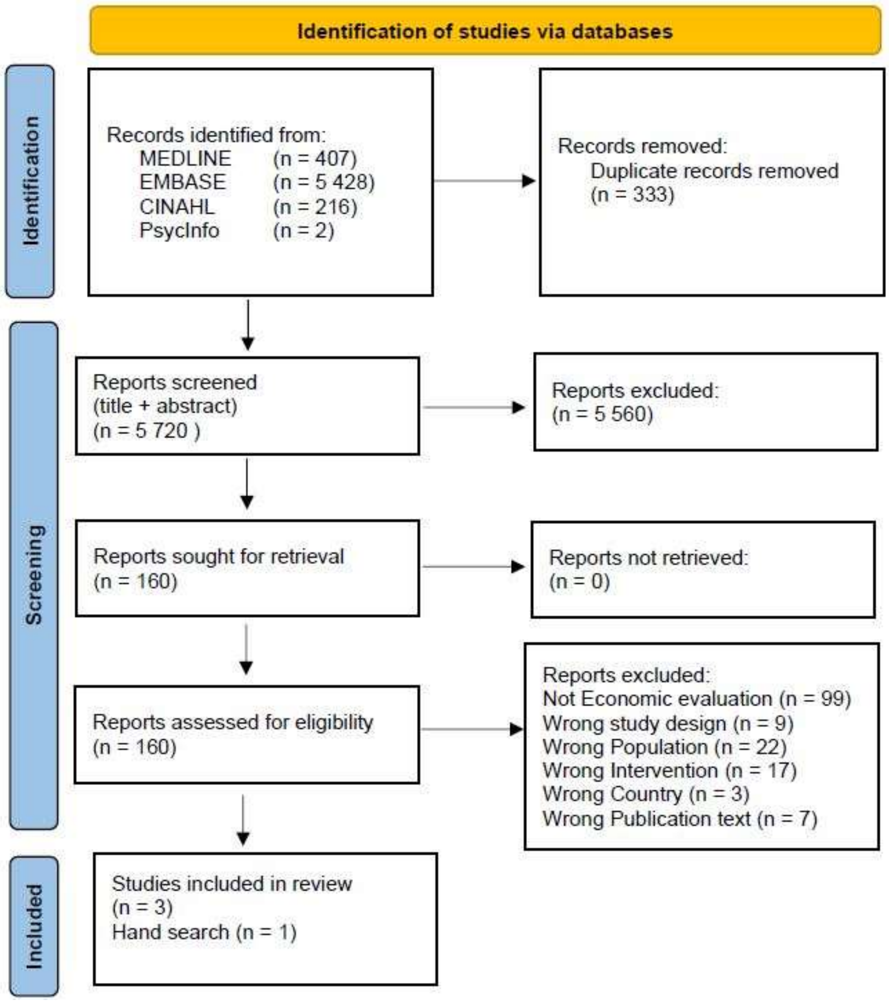


Figure 1. PRISMA flowchart

Both articles were published in medical journals in 2021 and the authors stated that there is no conflict of interest, however only Debrabant stated the source of funding for the study.

<u>Analytical approach and time horizon of the study</u>

Both articles' analytical approaches were model-based. Orlewska used Markov model with the transition probabilities from disease progression and Pfizer vaccine trial, combined with real cost data from its country's statistical agency. Orlewska's time horizon was 1 year.

Debrabant engages the dynamic transition model, a model developed by the Danish Ministry of Health. The model is considered as the most suitable for communicable diseases and vaccination programs (130). time horizon for Debrabant was 6 months.

Study perspective and country setting

Based on the method handbook from Swedish HTA, the perspective used in Swedish health economic evaluation is the societal perspective (131). The perspective includes both direct and indirect costs such as productivity loss and cost to the patient and family (cost of illness) (131). Both Debrabant and Orlewska's studies focused on the healthcare perspective and Debrabant included productivity loss as part of its sensitivity analysis. The method for measuring productivity loss described in the Debrabant study was similar to the human capital method in the SBU method handbook. There is a concern that this method overestimates the real productivity loss (131).

Perspective is one of the factors to determine if a health economics study's result is transferable to a Swedish setting. Another important factor is how well the study's setting corresponds to the Swedish setting, such as the health care system, epidemiological data and difference in cost (131).

Although there is a difference in health care system between Denmark, Poland and Sweden, for example, GP service in Denmark and Poland is free while in Sweden, there are out-of-pocket co-payments (132, 133), the report from the Global Burden of Disease Study 2015 shows a slight difference in Healthcare Access and Quality (HAQ) Index with Denmark at 90.9, Poland at 88.8 and Sweden at 90.2 (134). This shows these three countries provide similar levels of personal healthcare access and quality by location and over time (134).

Regarding epidemiological data, this is a major challenge to transfer the studies' results to the Swedish setting. Sweden had a higher incidence and mortality rate compared to its Nordic peer countries, such as Denmark (135, 136). While compared to Poland, based on WHO website accessed on 4 June 2023, Poland has higher registered Covid-19-related death rate and lower vaccination coverage compared to Sweden (78).

Population, Intervention and Control

Orlewska's study setting took place in Poland and was composed of 5 population groups: the general population and based on 4 age groups (30-39 years old, 40-49 years old, 60-69 years old and older than 80 years old). The same composition was applied to the control group.

Debrabant study setting is Denmark, and Debrabant divided the intervention groups based on the two age groups (18-60 years old and 60 years old and older) into 4 scenarios:

1. Vaccination to 25 per cent of the total Danish population who are 60 years old and older. This implies the whole total of Danish population aged 60 years old and older. The total population in Denmark at the time of Debrabant article was 6 million, and the number of person aged 60 years old and older was 1,5 million which is equivalent to 25% of the total Danish population (127).
2. Vaccination to 25 per cent of the total Danish population who are 18-60 years old.
3. Vaccination to 15 per cent of the total Danish population who are 18-60 years old and 25 per cent of the total Danish population who are 60 years old and older.
4. Vaccination to 40 per cent of the total Danish population who are 18-60 years old.

Contrary to Orlewska, the control group in Debrabant did not follow the intervention composition, instead, Debrabant compared the intervention with only one group which is the non-vaccinated Danish general population.

Orlewska's intervention was the Comirnaty vaccine (Pfizer BioNTech) which was the real-life case of a vaccine given in Poland's Covid-19 vaccination program, while Debrabant did not emulate the vaccine's name or the producer in the study. However, Debrabant elaborated that the effectiveness of the vaccine in the study was 95 per cent, which was similar to the effectiveness of the Pfizer BioNTech vaccine.

Resources identification, measurement, and valuation

Both reports calculated the resources in local currencies and considered the vaccine's price and the vaccine administration cost. Orlewska quoted the exact value for both the vaccine's price and administration cost, while Debrabant provided a range of values for the combination of the vaccine's price and administration cost. Debrabant further utilized this range value in three different scenarios for economic evaluation simulation (300 DKK, 400 DKK, and 500 DKK).

Both articles also calculated hospitalization costs. Debrabant further included the cost of Covid-19 tests and after-test follow-up by physicians in the total resources used, while Orlewska limited the identification of the resource until hospitalization.

The measurement unit (for example, length of hospitalization, and cost of Covid-19 tests) for both studies were collected from each national registry and each national statistical agency. The valuation was conducted by both studies by combining measurement units with the size of the population and the probability of disease progression stage. For example, Orlewska multiplied the length of hospitalization stay by hospitalization cost and the number of patients, while Debrabant calculated the cost of tests by combining data on the number of Covid-19 diagnoses with the cost of tests and after-test follow-up.

Debrabant added productivity loss in the resource cost calculation. Debrabant calculated productivity loss by multiplying the number of days of sick leave due to Covid-19 disease (data from a survey for another Covid-19 study) with earnings per hour, employment rate and the number of working hours per day (data from Statistics Denmark) (127). None of these studies conducted primary data collection. Neither study considered the inflation rate or discount rate for cost since the time horizon is within 1 year period.

In terms of resource cost, the author of this systematic review compared the cost of hospitalization and other relevant treatments as described in the studies from Debrabant and Orlewska with the cost in Sweden. The cost for hospitalization, vaccine administration and after-test follow-up by physicians in Sweden is taken from the official archive from Sveriges Kommuner och Regioner (SKR) website (https://skr.se/skr.25.html) (137) and the pricelist from the southern region of Sweden (Prislistor Södra sjukvårdsregionen - Vårdgivare Skåne (skane.se)) (138).

SKR is the organization for all municipalities and regions in Sweden and is tasked with signing central collective agreements on pay and general employment conditions (137). When only the daily price is provided in the Swedish price list, the total is calculated by multiplying it with the length of stay of hospitalization and ICU following the base case value data from Orlewska.

The cost for the Covid-19 test (139) and the vaccine price (140) was an estimation taken from newsletters as no information was provided in the price list in the year 2020. All cost was converted into Swedish kronor (SEK) based on the currency exchange rate in the year 2020 (121).

There were several notes related to the adaptation of the cost from Debrabant to the Swedish setting. There was no relevant price assigned specifically to Covid-19 in the Swedish price list year 2020, hence the price included in the table was adapted to the most similar description as in Debrabant. The major difference was a separation of hospitalization between patients aged 18-59 and patients aged 60 and older in Denmark which did not exist in the Swedish price list, thus the hospitalization price was similar for both groups in the Swedish setting.

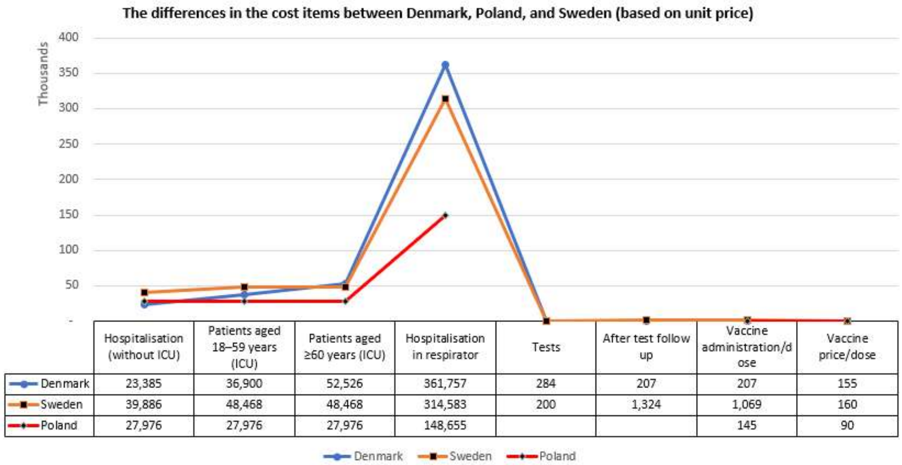
Table 2. Cost comparison between Denmark, Sweden, and Poland in 2020 (price is adapted in SEK)

Description	Denmark	Sweden	Poland
Hospitalisation outside the intensive care unit, patients 18 years old or older	23,385.01	(28,941-50,831)[1)]	27,976.09
Hospitalisation in an intensive care unit			
Patients aged 18–59 years	36,899.97	48,468[2)]	27,976.09
Patients aged ≥60 years	52,525.89	48,468[2)]	27,976.09
Hospitalisation in respirator	361,756.62	314,583.40[3)]	148,655
Corresponding after test follow up	207.34	1,324.00[4)]	
Tests	283.54	200.00[5)]	
Vaccine administration/dose	207.34	1,069.00[6)]	144.70
Vaccine price/dose	(26-155)	160.00[7)]	89.91

1) Retrospektiva DRG vikter somatisk vard 2012-2021_uppdaterad (DRG code: W29) (137)
2) Retrospektiva DRG vikter somatisk vard 2012-2021_uppdaterad (DRG code: X01O) (137)
3) Regionala priser och ersättningar för södra sjukvårdsregionen 2020, p. 59 (138)
4) Retrospektiva DRG vikter primärvård 2019-2021 (DRG code: Y90R) (137)
5) Carpman, A. Dagens Medicin 24 July 2020 (139)

6) Retrospektiva DRG vikter primärvård 2019-2021 (DRG code: X97R) (137)
7) Hedlund, F. Svensk Farmaci 14 January 2022 (140)

Figure 2. The differences in the cost items between Denmark, Poland, and Sweden (based on unit price)



	Hospitalisation (without ICU)	Patients aged 18–59 years (ICU)	Patients aged ≥60 years (ICU)	Hospitalisation in respirator	Tests	After test follow up	Vaccine administration/dose	Vaccine price/dose
Denmark	23,385	36,900	52,526	361,757	284	207	207	155
Sweden	39,886	48,468	48,468	314,583	200	1,324	1,069	160
Poland	27,976	27,976	27,976	148,655			145	90

Table 3. The weighted median of healthcare costs by vaccination scenario including test and follow-up and hospital cost specification according to Debrabant (table 5 in Debrabant article) for total Denmark population (price is adapted in SEK)

Scenario	Median (in thousand SEK)
Status quo: (0%; 0%)	810,849
1: (0%; 25%)	533,431
2: (25%; 0%)	399,187
3: (15%; 25%)	326,891
4: (40%; 0)	272,882

Table 4. Mean weighted cost per patient treated due to COVID-19 under base-case scenario assumptions according to Orlewska (table 3 in Orlewska article) for Poland (price is adapted in SEK)

Population	Cost/patient treated base-case (in SEK)
General population	3,239
Population aged 30–39	1,718
Population aged 40–49	2,061
Population aged 60–69	8,356
Population aged > 80	32,207

<u>Effect identification, measurement, and valuation</u>

While both studies utilized QALY as a unit to measure the effectiveness of the Covid-19 vaccination program, Debrabant also utilized LY (life-years) as an additional unit measurement. The purpose of adding LY was to compare with other Danish interventions and vaccine programs, while QALY was intended as a comparison tool with other healthcare interventions in general.

The calculation for effect was based on data collected by other studies (for QALY: EQ-5D-3L questionnaire) and secondary data from the national statistical agency of each country. Orlewska showed the biggest loss of QALY was in the age group 30-39 years old, while the least loss of QALY happened to the age group 80 and older if the groups were not vaccinated. Debrabant showed almost similar results in her study although there was a difference in perspective in how both studies calculated this.

Orlewska's study calculated QALY to the specific age group if the selected intervention group was not vaccinated. Further information can be seen in Table 2 and Table 3 in Orlewska's article. The QALY loss was specific to each age group when this age group was not vaccinated. Debrabant calculated QALY as a whole population when the selected groups as in scenarios were vaccinated. This can be further explained in Table 4 in Debrabant's article. The entire Denmark population's QALY was assessed when one scenario was implemented.

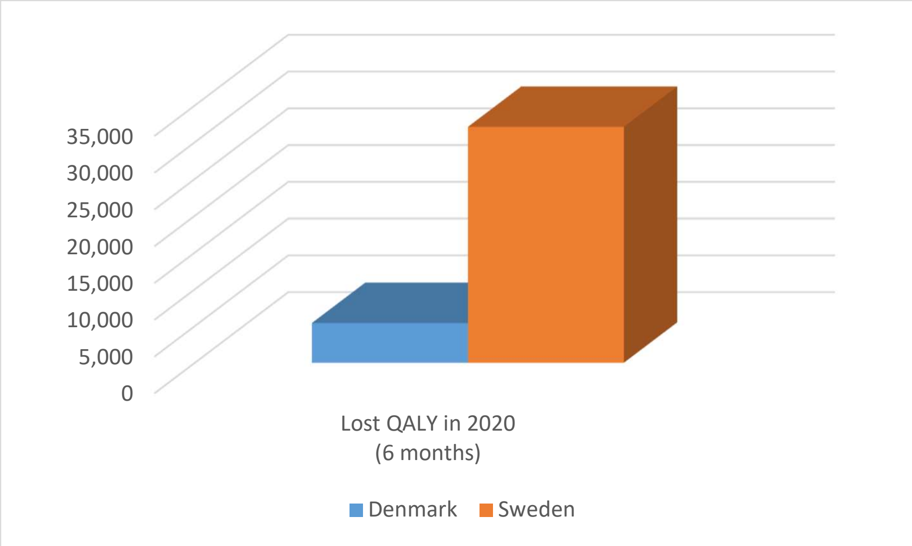
Debrabant also highlighted that scenario 3, where vaccination to 15 per cent of the total Danish population who were 18-60 years old and 25 per cent of the total Danish population who were 60 years old and older, was the group who lost QALY the least.

Both Debrabant and Orlewska utilized QALY measurement from other studies in theirs, while in Sweden, there was no study yet, at the time this systematic review was composed, that compared QALY for Covid-19 vaccination against no vaccination in Sweden. The existing reports regarding Covid-19-related QALY in Sweden were provided by The Swedish Institute for Health Economics (141) and a journal article from Persson, U. et al. (142) which focused on QALY measurement during the Covid-19 pandemic in Sweden pre-vaccination. The transferability assessment of outcome results from Debrabant and Orlewska's studies was made against these two existing reports about Sweden.

The excess death in Sweden due to Covid-19 in the first 6 (six) months of the year 2020 was 5,310 deaths which translated to 32,082 total loss of QALYs (141). This equals with 6.04 QALY lost/death. The article by Persson, U., et al. suggested a similar number (6.07 QALY lost/death) (142).

Debrabant recorded a lost QALY of 5,410 for the non-vaccinated general population in Denmark (control group) for 6 months period of 2020. The voluntary Covid-19 policy in Sweden could be the factor that contribute to the higher lost QALYs in Sweden (6 times higher than in Denmark), however, Debrabant did not elaborate further regarding the calculation of QALYs in the study therefore it was unclear if 5,410 (median value) lost QALYs was due to excess mortality or other parameter(s). This posed a challenge to the transferability of Debrabant results to the Swedish setting.

Figure 3. The differences in the effect between Denmark and Sweden (Poland uses different parameter for effect, as shown in figure 3).

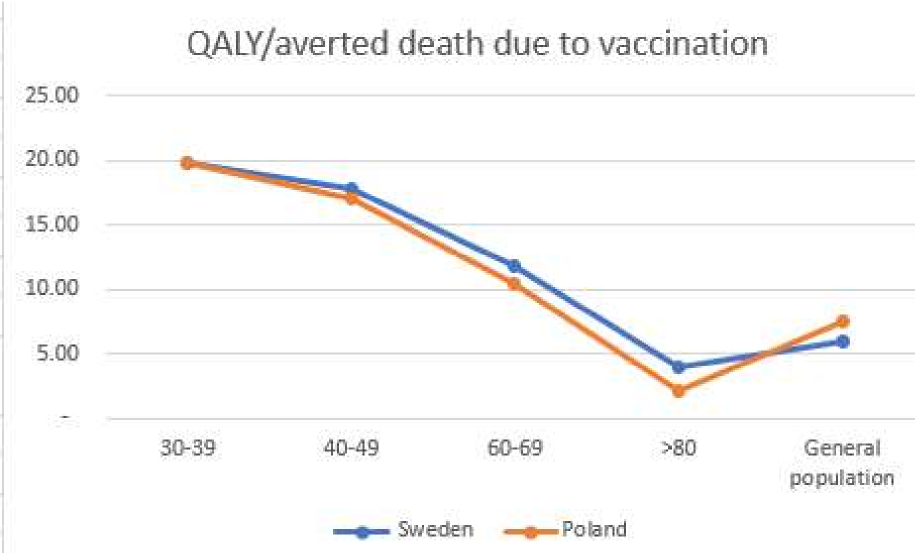


Orlewska's study provided information for the number of expected deaths if the population by age groups were vaccinated against those not vaccinated, and combined with information from Persson, U. et al., the QALY and averted death in Sweden in 2020 can be calculated (appendix 5).

Table 5. Estimation QALY lost/death in the Swedish population, based on Orlewska data.

Age	QALY lost/ averted death (vaccination)
30-39	19.81
40-49	17.84
60-69	11.91
>80	4.12
General population	6.07

Figure 4. The differences in the effect between Poland and Sweden



(Denmark uses different parameter for effect, as shown in figure 3). Calculation of figure 4 is in appendix 5.

The result in Table 5 showed a similar result to the Orlewska study for age groups 30-39, 40-49, and 46-69 while there were slight differences for the general population and age group 80 and older (compared with Table 2 and Table 3 in Orlewska). The result could provide an estimation of the effect when vaccination was implemented in Sweden which shows that age group 30-39 was the most beneficial age group if Covid-19 vaccination was decided only for the selected group. However, this did not imply that this decision was cost-effective. The incorporation of cost data was required to determine if this was cost-effective.

<u>ICER</u>

Debrabant had no specific threshold as the standard compared to the scenarios in its Covid-19 vaccination program, instead, Debrabant compared the result with the other public health interventions. The ICER for the base case in scenario 1 was between 53,000-118,000 DKK/QALY with a variance in vaccine price between 300-500 DKK (cost-effective) and for scenario 3 was between 319,000-803,000 DKK/QALY with a variance in vaccine price between 300-500 DKK (scenario 3 was cost-effective with vaccine price of 300 DKK, for vaccine price > 300 DKK, it was not cost-effective).

Debrabant study assigned 3 different scenarios for the vaccine prices and cost of administration, which were 300, 400 and 500 DKK. It was clear from Table 2 that real cost of combination of vaccine price and vaccine administration in Sweden exceeded 500 DKK. Therefore, this study utilized only the upper range value of ICER.

The author converted the ICER in Debrabant article into Swedish currency to have estimation of the ICER in SEK. Assuming the Swedish setting (if cost and effect data as described in Debrabant article) was similar to Denmark, the ICER:

1. to vaccinate 25% of the Swedish population aged 60 and older was 167,289 SEK/QALY
2. vaccinate 15% of the Swedish population aged 18-59 and 25% of the Swedish population aged 60 and older was 1,138,415 SEK/QALY
3. inclusion of productivity loss, the ICER to vaccinate 25% of the Swedish population aged 60 and older was 148,859 SEK/QALY
4. inclusion of productivity loss, the ICER to vaccinate 15% of the Swedish population aged 18-59 and 25% of Swedish population aged 60 and older was 783,990 SEK/QALY

Considering the threshold of 500,000 SEK/QALY for ICER in Sweden (131), vaccination to 25% of the Swedish population aged 60 and older was acceptable. If productivity loss was considered, the decision to vaccinate 15% of the Swedish population aged 18-59 and 25% of the Swedish population aged 60 and older was considered a high cost per QALY. Omitting productivity loss, the decision to vaccinate 15% of the Swedish population aged 18-59 and 25% of the Swedish population aged 60 and older was considered a very high cost per QALY.

Orlewska measured the effectiveness of the program to the threshold used in general in Poland which was three times GDP in 2020 or 147,024 PLN/QALY. The ICER for the general population was 6,249 PLN/QALY (cost-effective), the age group 30-39 was 67,823 PLN/QALY (cost-effective), the age group 40-49 was 28,135 PLN/QALY (cost-effective) and for 60 years and older was cost saving.

The ICER in Orlewska result was highest in the age group 30-39 at 67,823 PLN, which was equal to 160,254.75 SEK. This aligned with the conclusion of the Orlewska study that the decision to vaccinate any age group was cost-effective.

Sensitivity analysis

It was mentioned clearly in Orlewska that a deterministic sensitivity analysis was done with two sides of each parameter used, which were best- and worst-case scenarios. The parameters used were virus attack rate, case fatality rate, number of hospitalized patients, vaccine efficacy, treatment cost, length of hospitalization, vaccination cost and a combination of these parameters. The result of the sensitivity analysis concluded that ICER was sensitive to vaccine effectiveness, price, and attack rate only for the age group 30-39 years old.

Debrabant did not mention the type of sensitivity analysis used, however, the parameters used were simulation of vaccination for 70 per cent of the population, mortality rate, QALY parameters, vaccine efficacy, and cost of hospitalization. Debrabant included the productivity loss in the sensitivity analysis. The result showed that ICER was sensitive to mortality rate and vaccine efficacy, while the overall cost-effectiveness profile of the program was determined by vaccine price and if productivity loss was included in the cost.

Summary and interpretation of key findings from the authors

The article from Orlewska was a model-based economic evaluation to assess the economic value of the Comirnaty vaccine to the Polish population in general and in selected age groups from the healthcare perspective. Orlewska utilized the Markov model with transition probabilities and states based on the Comirnaty efficacy trial and Covid-19 disease progression and treatment, while the resource information was taken from real-world data in the Polish healthcare registry in the year 2020.

As a comparison, three times GDP per capita was used as a threshold to measure the cost-effectiveness of the program. The result was conclusive that the program was more cost-effective than no vaccination (status quo) for the Polish general population and all selected age groups. In the situation of scarce resources and choices needed to be made regarding which age group to be vaccinated first, Orlewska's study showed that prioritizing the most at-risk, which was 60 years old and older was a cost-effective decision.

This conclusion was supported by sensitivity analysis, in which the age group 60 years and older remained insensitive to changes in parameters used in the study. While the age group 30-39's cost-effectiveness profile was the potential to be no longer cost-effective when vaccine efficacy, prices, and infection rate changed to the worst scenario.

The article from Debrabant was a model-based economic evaluation to assess if Covid-19 vaccination was cost-effective for Denmark from a healthcare perspective. Debrabant utilized a dynamic transition model and divided two age groups into four scenarios to determine which age group was the most favorable if choices need to be made.

While the vaccine price was simulative, the other resource information was taken from the national registry for the year 2020. Debrabant had three conclusions:

1. that vaccination age group 60 years and older only was cost-effective (it was the first choice in a resource-scarce situation).
2. that mixture of population age group < 60 years old (15%) and > 60 years old (25%) was more cost-effective than vaccination only age group < 60 years old (if resource allowed for the inclusion of more population in the program).
3. If productivity loss was included in the evaluation and if vaccine prices and administration cost 300 DKK or lower, starting vaccination in the age group < 60 years old, can also be a cost-effective choice.

Based on the result of this systematic review, it was concluded that the benefit outweighed the cost of vaccinating the elderly age group (60 and older) in Poland and Denmark. The result for the elderly group was insensitive to multiple parameter changes.

While in the adult age group, it was not considered cost-effective to vaccinate only the adult age group (18-59) in Denmark. This was in contrast with Poland, vaccinating the adult age group (30-49) fell under the threshold which meant this decision was also cost-effective in Poland. However, the result in Poland for the adult age group was sensitive to parameter changes, especially in the worst scenario, the policy of vaccinating the adult group became no longer cost-effective.

In resources constraint situation where a decision needed to be made between vaccinating the adult age group and the elderly age group, the decision to vaccinate the elderly age group was more favourable based on cost-effectiveness ground.

Summary for transferability

Even though the resources information (the unit price) in the Debrabant study was comparable to Sweden, more information regarding effect measurement was required to transfer the study's result to the Swedish setting. Further information was also required concerning the dynamic transmission model used since the article did not provide sufficient information about the model.

The complexity to apply Debrabant's result directly to the Swedish setting was also influenced by the health policy taken by Sweden during the Covid-19 pandemic. Voluntary non-pharmaceutical measures in Sweden such as voluntary testing procedures (143) while Denmark implemented a mass testing strategy (it is recorded that more than 8,000 citizens per 100,000 inhabitants per day were tested in the Spring 2021) (144)and a higher mortality rate due to Covid-19 infection in Sweden compared to Denmark could affect the higher gained QALY when vaccination was implemented, and in turn, lower the ICER.

In Orlewska's study, although the outcome information was comparable between Poland and Sweden, the difference in cost was contrast and could not justify the transferable of the study to a Swedish setting. Nevertheless, Orlewska's study provided adequate detail to replicate the study in other settings.

The result of this systematic review was not transferable to the Swedish setting. The resource and effect data between Denmark and Poland and Sweden were vastly different. The health policy taken by the Swedish government during the Covid-19 pandemic was assumed as the key factor that affected the outcome variances.

5 DISCUSSION

Summary of the results

The article from Orlewska was a model-based economic evaluation to assess the economic value of the Comirnaty vaccine to the Polish population in general and in selected age groups from the healthcare perspective. The result was conclusive that the program was more cost-effective than no vaccination (status quo) for the Polish general population and all selected age groups. In the situation of scarce resources and choices needed to be made regarding which age group to be vaccinated first, Orlewska's study showed that prioritizing the most at-risk, which was 60 years old and older was a cost-effective decision.

The article from Debrabant was a model-based economic evaluation to assess if Covid-19 vaccination was cost-effective for Denmark from a healthcare perspective. Debrabant utilized a dynamic transition and concluded that the vaccination age group 60 years and older only was cost-effective (it was the first choice in a resource-scarce situation).

The result of this systematic review was not transferable to the Swedish setting. The resource and effect data between Denmark and Poland with Sweden was vastly different. The health policy taken by the Swedish government during the Covid-19 pandemic was assumed as the key factor that affected the outcome variances.

Strengths and limitations of this study

This study's literature screening phase was done by a team of two members who worked individually to ensure independence and the results of each phase were reconciled to have a common consensus. This serves as the main strength of this study. This is important in reducing selection bias. The supervisor of this study is an experienced health economist who actively provided input and direction. This was proven valuable and an advantage for this study since the supervisor had working experience in Swedish HTA.

Most of the search was done through the university's library website which provides free full access to all articles found during literature screening. The support from the librarians was another strength of this study, especially during the creation of the search strategy and language check. This study was also conducted with systematic and structured approaches as mentioned in the guidelines for health-economic-specific systematic review (83, 145).

Usage of systematic review-related software such as Rayyan and End Note in this study is undeniably useful to ensure the systematic review process is structured and documented. It is desirable to include more databases to increase the possibility to find more relevant literature, however, due to the time limitation of this study, the team members and the supervisor agreed to select the above databases. It is also worth mentioning that based on the literature, the limitation of three databases is acceptable for a systematic review in an economic evaluation study, and it is concluded that a search in Medline and Embase is empirically enough to identify almost all references in the economic evaluation topic (83). This study engaged four general medical databases with an additional three health economic specific databases.

A further strength of this study was the hand search process into a reference list of selected studies. This process was repeated into new articles' reference lists until the reference list source was exhaustive from potentially relevant literature. This study utilized a checklist and search block developed by the Swedish HTA. This adds strength to this study in the specificity aspect of the transferability to the Swedish setting, as the evidence becomes relevant to decision-makers in Sweden.

The selected literature for this study was two articles. This could be the result of using too many search terms and limiters, and/or the PICO being too selective. This can be solved by adding more databases and grey literature searches. Nevertheless, this can also be viewed as normal consequences due to the period of Covid-19 itself. The time lapse between the beginning of the disease and this systematic review was only three years (2020-2022) which explained the limited number of publications available.

The resources data from Debrant and Orlewska use different parameters. Debrabant focuses on the cost for total population for each scenario while Orlewska uses cost per treated patient. This suggests the challenges in adapting it to Swedish setting. This information could be added to the future study.

Key factors of the cost-effectiveness of the vaccination program

Referencing from Orlewska and Debrabant, the vaccine price (including the administrative cost of the vaccine) is the main factor that determine if the

Covid-19 vaccination program is cost-effective. This was shown in Debrabant that the Covid-19 vaccination program in Denmark could be cost-effective for the adult age group if the vaccine price was 300 DKK or less. This finding aligns with the concept elaborated in the introduction section that the cost of the health intervention is a determinant factor in a program's cost-effectiveness profile (86).

Debrabant brought up productivity loss into the equation for Covid-19 vaccination economic evaluation. In its sensitivity analysis, Debrabant shows that by taking into account productivity loss, this could shift the balance of Covid-19 vaccination to cost effective for adult subgroup, with pre-condition of low vaccine price.

The risk of the disease (Covid-19) to the population is another main factor in assessing the benefit of the program. The high mortality and morbidity rate from Covid-19 is lower than some other infectious diseases such as Ebola and SARS, however, the high reproduction rate of the Covid-19 virus and increased human mobility globally catapulted Covid-19 to the forefront of public health emergencies (146). Vaccination is the solution to terminate the Covid-19 mitigation strategy, such as lockdown. This was highlighted in the introduction section from Debrabant.

There is no further information described in both Orlewska and Debrabant regarding factors affecting benefit cost balance of vaccination program. However, this information enriches the existing concept of benefit risk ratio of vaccination program as what Wolff, E. explained in her article in the year 2020 that the cost-effectiveness was heavily influenced by the vaccine price, the time horizon, and model choice of economic evaluation of vaccination program (88).

Comparison with previous studies

Based on the databases screening, as of March 2023, there was only one systematic review of economic evaluation for Covid-19 vaccination (147). The article focused on Covid-19 vaccination in low- and middle-income countries. There was no analysis regarding the cost-effectiveness of Covid-19 vaccination to different age groups neither analysis for transferability of the result. There is no overall estimation for the cost effectiveness value for Covid-19 vaccination program, instead this review provides specific information of value for each country of origin of the reports included in the review. The article concluded that vaccination shows high cost-effectiveness values in general compared to the status quo (no vaccination) in these countries.

The similar conclusion is also the result from Persson, U. et al., that calculated the cost effectiveness of Covid-19 vaccination program in Sweden (108). The article takes societal perspective and estimated that vaccination against Covid-19 provide a value of €744-€956 per dose (108). This is in line with Orlewska's result that in general, Covid-19 vaccination program is cost effective. However, Persson, U. et al. does not provide cost-effectiveness information at the sub-group level (108).

During database screening on 11 May 2023, the author of this study found one new systematic review of economic evaluation for Covid-19 vaccination (148). The article was published on 26 April 2023. The article screened reports from 1 January 2020 up to 1 August 2022, with language sources of English and Chinese. While for this systematic review, the authors screened databases specific for English reports only and the period was from December 2019 up to 28 February 2023.

There was no analysis of the transferability of the result in the new article. The article concluded that vaccination showed a cost-effectiveness profile of the Covid-19 vaccination program in general and if the supply of vaccines was inadequate, the conclusion of the article aligned with the result of this study which was to favor the high-risk and elderly group based on cost-effectiveness ground.

It is worth to highlight that in this systematic review, the scope is worldwide and includes all Covid-19 vaccination-related economic evaluation articles. In regard to articles with separation of age-group in European continent in its intervention criteria, the review takes in three articles. They are Debrabant (127), Orlewska (122) and article from Ukraine (129) (the article from Ukraine was excluded during quality assessment phase of this study, due to high risk of bias reason). The review does not provide in-depth analysis into the calculation of the economic evaluation for each report; however, the review provides summary for each report's conclusion.

6 CONCLUSION

Based on the result of this systematic review, it is concluded that the benefit outweighs the cost of vaccinating the elderly age group (60 and older) in Poland and Denmark. The result for the elderly group is insensitive to multiple parameter changes.

While in the adult age group, it is not considered cost-effective to vaccinate only the adult age group (18-59) in Denmark. This is in contrast with Poland, vaccinating the adult age group (30-49) falls under the threshold which means this decision is also cost-effective in Poland. However, the result in Poland for the adult age group is sensitive to parameter changes, especially in the worst scenario, the policy of vaccinating the adult group becomes no longer cost-effective.

In resources constraint situation where a decision needs to be made between vaccinating the adult age group and the elderly age group, the decision to vaccinate the elderly age group is more favorable based on cost-effectiveness ground.

The result of this systematic review is not transferable to the Swedish setting. The resource and effect data between Denmark and Poland with Sweden is vastly different. The health policy taken by the Swedish government during the Covid-19 pandemic is assumed as the key factor that affects the outcome variances.

7 PUBLIC HEALTH PERSPECTIVES

Implication to health policy and practice/clinical

There are three ethical principles in guiding priority setting in the health service (105). In some countries like Sweden, the early Covid-19 vaccination strategy was based only on 2 (two) of these principles which are the human dignity principle and the needs and solidarity principle.

It is clear from the studies conducted either within or outside Sweden that Covid-19 vaccination is cost effective in general population level. However, the cost-effectiveness profile with age-group prioritization strategy was not yet available.

This systematic review contributes to confirming that the Covid-19 vaccination policy in European continent which prioritizes the elderly age group population is valid based on cost-effectiveness ground. This is crucial since the initial consideration of this policy was not based on concrete economic evaluation.

The decision of this early policy was supported by clinical consideration that the elderly age group is at the highest risk due to Covid-19 infection. The result of this study encourages clinicians that the work they have done is ethically acceptable of all the three ethical principles.

Implication to research

In-house research to determine the cost-effectiveness profile of the Covid-19 vaccination prioritization policy in Sweden is encouraged, especially since Sweden adopted different non-pharmaceutical measures during the Covid-19 pandemic. This translates to the non-transferability of results from other countries to Swedish circumstances.

More detailed research can be done to determine specifically each phase of this policy for the effect and cost. The author concluded that in-house research is feasible due to the availability of the data in the Swedish registry that the author found during the composition of this study.

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Conflict of interest

The author of this study declares no conflict of interest.

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APPENDIX

Appendix 1

CINAHL search term and result.pdf

Cochrane via Wiley search history 2023(

Embase search history table 202302

Medline via Ovid search history table

PsycInfo search term and result.pdf

Appendix 2

full screening exclusion list.pdf

Appendix 3

SBU confirmation about quality checkl

SBU Checklist_modelbas

SBU Checklist_modelbas

SBU Checklist_modelbas

SBU Checklist_modelbas

Appendix 4

data extraction.pdf

Appendix 5

calculation outcome to poland