ECONOMIC EVALUATION OF VACCINATION PROGRAM AGAINST COVID-19 AMONG CHILDREN AND ELDERLY POPULATION IN EUROPEAN COUNTRIES:

A SYSTEMATIC LITERATURE REVIEW

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“Investing in vaccines is one of the most cost-effective ways to promote economic growth and reduce poverty”- Nobel Laureate Michael Kremer.

ABSTRACT

Background – The COVID-19 pandemic caused by the novel coronavirus, SARS-CoV-2, has had a significant global impact, with severe implications for public health and economies worldwide. As the virus spreads and new variants emerge, effective vaccination strategies are crucial in controlling the pandemic and mitigating its burden on healthcare systems. Understanding the cost-effectiveness of different vaccination approaches is essential for decision-makers to allocate limited resources efficiently and prioritize interventions for which a systematic literature review was used.

Objectives- In this systematic literature review, we aim to report and synthesize health economic evaluations of vaccination programs against Covid-19 in European countries among children compared with an elderly population.

Methods- According to Mandrik et al. (2021), a Systematic Literature Review consists of six stages, (i) planning and development, (ii) evidence search, (iii) study selection, (iv) quality assessment, (v) data extraction, and synthesis, (vi) presenting results. This SLR used CINAHL, MEDLINE, PsychInfo, and EMBASE databases. Use of health-economic databases and grey literature were also used.

Results- Through search identification, 6053 articles were found, of which 333 were removed because of duplication. Then after the title and abstract screening, 162 articles were selected for the full-text screening, and the rest were excluded for multiple reasons. No potentially relevant study was included in the final inclusion.

Conclusion- We did not find any relevant articles that reported an economic evaluation of covid-19 vaccination program among the children population compared to the elderly population in European countries. More evidence is required for the children population to evaluate the vaccination program economically.

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ABBREVIATIONS

CBA - Cost Benefit Analysis

CEA - Cost-Effectiveness Analysis

CUA - Cost-Utility Analysis

DALY - Disability Adjusted Life Years

HEED- Health Economic Evaluation Database

ICER - Incremental Cost-Effectiveness Ratio

INAHTA- International health technology assessment database

MIS-C – Multisystem Inflammatory Syndrome in Children

NMB - Net Monetary Benefit

QALY – Quality Adjusted Life Years

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus-2

SLR- Systematic Literature Review

WHO - World Health Organization

YLD- Years lived with disability

1 INTRODUCTION

Coronavirus is a large family of viruses that can cause respiratory illness in humans and animals (Cascella, 2023). The recent outbreak, known as COVID-19, is caused by a novel coronavirus that was first identified in Wuhan, China, in December 2019 (Zhu, 2020). The virus is highly infectious and spreads through respiratory droplets when an infected person talks, coughs, or sneezes.

Since the emergence of COVID-19, several variants of the SARS-CoV-2 virus that causes the disease have been identified. These variants have genetic material mutations that can change how the virus behaves. Some of these variants are of particular concern because they are more transmissible, virulent, or resistant to vaccines and treatments (Aleem et al., 2023). There are mainly three types of covid-19 variants, (i) Alpha Variant, (ii) Beta Variant, (iii) Gamma Variant, (iv) Delta Variant
The Alpha variant (B.1.1.7), first identified in the United Kingdom, is more transmissible than the original strain of the virus and has been associated with an increased risk of hospitalization and death (Aleem et al., 2023).

The Beta variant (B.1.351), first identified in South Africa, is also more transmissible and has mutations that may allow it to evade the immune system, potentially reducing the effectiveness of some COVID-19 vaccines (Zhou et al., 2021).

The Gamma variant (P.1), first identified in Brazil, is also more transmissible and has mutations that may increase its ability to re-infect people who have already had COVID-19 (Silva et al., 2021).
The Delta variant (B.1.617.2), first identified in India, is highly transmissible and associated with increased hospitalizations and deaths (Dhawan et al., 2022). There is also some evidence that it may be more resistant to vaccines than earlier strains of the virus.

Overall, the emergence of these variants highlights the importance of ongoing surveillance and research to understand how the virus is evolving and how to develop effective interventions to control its spread. It also underscores the importance of vaccination and other public health measures to reduce the impact of the pandemic.

According to World Health Organization (WHO covid-19 database), there have been around 660 million confirmed cases and 6.7 million deaths globally. The cost incurred to control the covid-19 and the overall burden of coronavirus on healthcare in every country is of great concern. Coronavirus is considered to be an important public health issue (Ayenigbara, 2020).

1.1 THE BURDEN OF COVID-19 IN EUROPE

The first covid-19 case in Europe was reported in France on 24th January 2020 (Spiteri et al., 2020). By 30th January, covid was declared a pandemic by WHO and was considered a public health emergency in the European Union. At the end of February 2020, Italy reported a high number of cases, after which there was a sudden rise in cases in European countries (Vicente & Suleman, 2022).

During the outbreak, European countries implemented various procedures to curb the spread of the coronavirus (Vicente & Suleman, 2022). The interventions ranged from pharmaceutical interventions to non-pharmaceutical interventions. Pharmaceutical measures included testing for covid virus and later vaccinations (Vicente & Suleman, 2022). Non-Pharmaceutical Interventions included lockdown strategy, closure of schools and other workplaces, and use of face masks outside in public surroundings (Vicente & Suleman, 2022). These strategies changed overtime of the pandemic period.
The total number of deaths in European countries differed from each other at the start of the pandemic year; countries were poorly hit by the pandemic with different intensities (Vicente & Suleman, 2022). On 31st December 2020, Belgium reported 1678.7 per million deaths, considered the highest at that time (Vicente & Suleman, 2022). At the same time, Norway had the lowest of 80 deaths per million. Several tests were done to determine how each country controlled the pandemic (Vicente & Suleman, 2022). By February 2022, Poland had reported conducting 817.2 tests per thousand inhabitants. Each country had different techniques to curb the pandemic (Vicente & Suleman, 2022).

Several measures are available to quantify the disease burden among a given population, and such a method is Disability-Adjusted Life Year (DALY) (Devleesschauwer et al., 2014). DALYs comprise estimates of population health loss due to living with the consequences of morbidity and premature mortality (Grosse et al., 2009). Years Lived with Disability (YLD) capture the morbidity (both the prevalence and severity of the disease) component of DALYs by estimating the number of years lost due to conditions diminishing the overall health status and are a valuable indicator to assess how impaired populations are due to living with the consequences of disease and injury (Wyper et al., 2020). DALYs have proven to effectively measure disease burden (Gianino et al., 2021). Whereas, if we compare the DALY, Scotland was found to have the highest DALY per 100,000 (1,770-1,980 DALY's/100,000) for the covid-19 cases, whereas Germany had the lowest DALY rate (368 DALY/100,000) for the covid-19 cases (Pires S et al., 2022). The difference between the DALYs was the significance that the pandemic hit each country in different intensities and magnitudes.

1.2 THE BURDEN OF COVID-19 IN SWEDEN

Regarding deaths with a COVID-19 diagnosis per million people, Sweden was one of the nations with the highest COVID-19 death rates. In contrast to several other nations, Sweden implemented a very distinct approach towards the covid-19 pandemic; while other Western nations-initiated lockdowns, we did not see any lockdowns in Sweden; instead, they kept the bars, restaurants, and schools operational (Pashakhanlau, 2021). The Swedish Public Health Agency (Folkhälsomyndigheten, FoHM) has documented 5,846 deaths since the COVID-19 pandemic in Sweden in late March 2020, with 2,580 cases requiring intensive care and 86,505 individuals with diagnoses as of September 14, 2020 (Westesson, 2021).

Persson et al. (2020) gave priority to covid-19 vaccination to elderly residents of nursing homes in Sweden. Following that, preference was given to elderly individuals who were 70 years of age or older and receiving medical care. Older adults were immunized in the third phase. Up until February 2021, Sweden made no recommendations on immunizations for kids (Persson et al. (2020). After that, Pfizer dosages were prioritized for youngsters 12 years of age and older who needed immunizations. Children aged five and older were given preference in January of the preceding year.

1.3 COVID-19 VACCINATION

According to Richard et al. (2022), there were significant economic burdens associated with covid-19, which included high medical costs and resource utilization. The population requiring mechanical ventilation or admitted to intensive care units had even higher costs. Apart from this, the pandemic had macroeconomic effects, as there were significant productivity losses/declines. Although non-pharmaceutical interventions like screening tests, social distancing, or medical treatments like Remdesivir and dexamethasone have been effective as well as cost-saving compared to the no-intervention strategy, vaccinations have been the most effective strategy in controlling the pandemic (Dye, 2022). It is considered that the vaccines have decreased hospitalization rates, risk of getting infected, and mortality rates. Among the Organization for economic corporation and development (OECD) countries, the United Kingdom, the United States, and Israel were one of the countries that rolled out the vaccine at an early stage (OECD,2021). The peak of covid-19 cases in these three countries occurred during the early week of January 2021, and since then, the infection rate has decreased.

One of the reports in Spain mentioned that mass vaccination had lowered the corona cases and the burden of hospitalization, such as no ICU days or deaths caused (López et al., 2021). A critical aspect of vaccination programs is the costs incurred in it. All costs, such as human resources, transportation, medical equipment, and syringes, should be considered (López et al., 2021). In the early stage of the vaccination program, most OECD countries rolled out vaccines for priority groups (OECD,2021).

Herd Immunity

According to Ma et al. (2022), Herd immunity refers to the indirect protection from infectious diseases that occurs when a significant proportion of the population becomes immune merely through vaccinations. According to them, herd immunity has a significant impact on the outcome as well as the cost-effectiveness of vaccination programs. Herd immunity benefits both directly and indirectly by protecting the non-vaccinated population who could not get the vaccine due to certain circumstances. According to Wolff. (2020), vaccination against infectious diseases would produce direct benefits by reducing the disease risk and indirect benefits by protecting the more vulnerable unvaccinated population. This phenomenon is called herd immunity. The effect of herd immunity needs a long-time horizon with multiple cohort models like the disease transmission model. This implies that herd immunity sheds light on vaccines' societal value and cost-effectiveness.

1.3.1 VACCINATION POLICIES

There have been different policies regarding the prioritization of vaccines in different countries of Europe. Vaccination policies to fight against covid-19 from four European countries (Sweden, Denmark, Poland, and the United Kingdom) have been mentioned as an example.

i. Sweden

According to Krisinformation.se (2021), the COVID-19 vaccination program is prioritized for the elderly population of the age group of 65 years old and above. In contrast, the vaccination program for children is limited to only particular groups of children only (such as children with comorbidities). Currently, Pfizer-BioNTech and Moderna are majorly used in Sweden.

ii. Denmark

According to Danish Health Authority (2023), the Covid-19 vaccination program is prioritized for the age group 50 and older population. However, the vaccination program for the children population from 1st July 2022 was stopped because of lower risks of this population getting severely ill from the covid-19 virus, although children with comorbidities can still get vaccinated. Currently in Denmark, the Pfizer-BioNTech vaccine is offered in Denmark.

iii. Poland

According to the Ministry of Health (2023), the Covid-19 Vaccination program was prioritized for the elderly population of the age group 70 years and above, whereas, for the children population, the vaccination program was prioritized for the age group of 12 and above. Currently, the Pfizer-BioNTech vaccine is offered in Poland.

iv. United Kingdom

According to National Health Service (2021), the COVID-19 vaccination program was prioritized for the population of age group 50 and above whereas, for the children population of age group 12-15 years old, children with comorbidities with a greater risk of having covid-19 were prioritized.

1.3.2 VACCINATION FOR THE ELDERLY

Vaccinating the elderly population has been the first most prioritization for all the countries since covid-19 tends to be a life-threatening disease, especially if the elderly population of 60 and above have other complications too (Wang et al., 2023). The vaccination program for the elderly population has been proven to be very effective as it has decreased the infection rate for every variant of the covid-19 (OECD,2021).

Higher vaccine efficacy is important among the elderly population as an effective vaccination among this age group would benefit them and reduce the burden on the healthcare systems (Sadarangani et al., 2021).

1.3.3 VACCINATION FOR CHILDREN

Rolling out vaccination programs for children, adolescents, and teenagers has been controversial (Kraaijeveld et al., 2022). Some studies have pointed out that there can be possible risks associated with vaccinating the younger population (children, adolescents, teenagers). The risk includes the development of myocarditis after mRNA vaccines; in one of the studies, it was reported that among 12-17 years of age group, after the second dose of the vaccine, there were around 6.3 to 6.7 cases per 100 000 doses (Zimmermann et al., et al., 2022). Whereas, in another study from the United Kingdom, it was estimated that for the age group between 12-17 years old, vaccination could avert 4590 hospitalizations, 310 ICU admissions, and 36 deaths, lowering the healthcare burden (Gurdasani et al., 2021).

1.4 HEALTH ECONOMIC EVALUATION

Economic evaluation is defined as a "comparative analysis of alternative courses of action in terms of both their costs and consequences" (Drummond et al., 2015). Health economic evaluation requires comparing two different interventions in terms of their cost and benefits (Drummond et al., 2015). Since there are limited resources, priority has to be set, which allows the decision makers to decide which needs must be met and which needs must be traded off. Hence, health economic evaluation is an essential tool that could help decision-makers make well-informed decisions. Health Economic Evaluation is divided into different types of methods. There are four different types of health economic evaluation, i.e., Cost-Effectiveness Analysis, Cost Benefit Analysis, Cost Utility Analysis, and Cost Minimization Analysis. In this Master Thesis, we will focus on the Cost-Effectiveness Analysis and Cost Benefit Analysis.

Cost Effectiveness Analysis

Cost Effectiveness Analysis is a form of health economic evaluation that compares the cost of an intervention with the effectiveness or consequences. The consequences in this analysis are the natural units, e.g., life years saved or changes in blood pressure (Drummond et al., 2015). Cost Effectiveness Analysis of interventions is evaluated through ICER, i.e., Incremental cost-effective Ratios. ICER is calculated by dividing the difference between the cost of intervention A and the cost of intervention B by the difference in the consequences of intervention A to intervention B. Later, the ICER is also visualized through a cost-effectiveness plane divided into four quadrants.

Cost-Utility Analysis

Cost-Utility Analysis is a special type of cost-effectiveness analysis. In this method of analysis, the cost incurred in the intervention is measured against the utility related to health (Drummond et al., 2015). Utility relates to Quality Adjusted Life Years (QALY) and Disability Adjusted Life Years (DALY). This method is specially used when there are multiple objectives of the program and when both quality of life and quantity of life are important to determine. The quality-adjusted life year is a summary outcome measure used to quantify the effectiveness of a particular intervention (York, 2016).

QALY= Years of Life x Utility Value

Cost Benefit Analysis

Cost Benefit Analysis is another form of economic evaluation where the cost of an intervention is compared with the benefit of that intervention. Both cost and benefits are compared in monetary units (Drummond et al., 2015). An intervention is considered to result in a positive cost-benefit if the benefits from that intervention are greater than the cost incurred during the intervention.

Net Monetary Benefit Ratio

Net monetary benefit (NMB) is another way to represent the value of an intervention in monetary terms when a willingness to pay a threshold for a unit of benefit (for example, a measure of health outcome or QALY) is known (York, 2016).

Net monetary benefit = (E * WTP) – C

E = effectiveness; WTP = willingness-to-pay threshold; C = cost (Singh et al, 2011)

1.5 ROLE OF ECONOMIC EVALUATIONS IN THE VACCINATION PROGRAM

Economic Evaluation of vaccination programs is necessary as vaccine availability is already low. The cost to develop and distribute them is also high. However, the benefits of vaccinating the population, usually a decrease in hospitalization rate, diseases averted, and lives saved, could outweigh the cost associated with the vaccines (Bloom, 2011). According to them, vaccination can be cost-effective with long-term economic benefits. Decision-making for vaccines involves trade off's between different factors such as the effectiveness vaccine, the cost of the vaccine, the burden of disease, and available resources (Welte et al., 2005). Disease risk is also an essential factor that needs to be part of an economic evaluation of vaccination as it helps identify its benefits. The disease risk is closely linked with herd immunity (Wolff, 2020). It helps decision-makers understand the vaccine's effectiveness, for example, how much the vaccine's efficacy has helped in lowering the disease incidence and how much it has benefited in halting the transmission rate of disease. Moreover, the risk of disease would help understand the disease burden at the population level. Reduced disease risk through vaccination would ensure cost savings in reducing hospitalizations and medical expenditures.

Economic evaluation provides a framework for considering these factors and assessing the value of vaccines based on their cost-effectiveness. Economic evaluation helps provide a detailed understanding of the monetary value of the benefits of vaccination, the costs of implementing vaccination programs, and the budget impact of healthcare (Welte et al., 2005). In one of the studies based in Denmark, it was mentioned that the cost-effectiveness of vaccination among the elderly population would depend on several factors, such as the cost of the vaccine, the cost associated with administering it, as well as the cost associated with testing (Debrabant et al., 2021).

Health economic evaluations play an essential role in vaccinations by informing the decision makers about the value of vaccines, whether it is cost-effective, what the costs involved in it, what is the efficacy of vaccines, what are the targeted population, and what perspective to affect. According to Ericson et al. (2002), the choice of perspective is the most critical point to consider when evaluating the vaccination program. Decisions made for the choice of perspective help in determining what costs and benefits to include. Most commonly, a societal perspective is considered as it considers all costs and benefits that a vaccine could produce.

In evaluating a vaccination program, we also need to develop a model that could provide us with all information related to cost and benefits. Mauskoph et al. (2022) provided information about three different models; for example, Decision trees are a very simple and widely used modeling approach. However, one disadvantage of the decision tree modeling approach is that it cannot be used for complex problems. To overcome this approach, the Markov model is another approach widely used by decision-

makers considering complex and long-term outcomes. The dynamic Transmission model is another epidemiological modeling approach used by decision-makers. It is also considered one of the important models in the case of vaccination programs since they can calculate the disease transmission and highlight the herd immunity effects.

Moreover, the Economic Evaluation of vaccines helps provide relevant information to the decision-makers. This would help provide information decisions about prioritizing resources based on their value of money. They also provide details about vaccine efficacy, the impact of vaccination coverage rates on disease incidence, and healthcare costs (Calabro et al., 2022).

1.6 ROLE OF ECONOMIC EVALUATIONS IN COVID-19 VACCINATIONS

Economic evaluation for covid-19 vaccination is important because of numerous factors. Firstly, it helps to determine whether a particular vaccination would be cost-effective by comparing the costs against the benefits of a vaccine (Wang et al., 2021). It helps us compare different scenarios and find which scenario would give us the maximum results, especially when the evidence is limited. For example, in one of the studies in Israel, a Markov model was conducted for two different scenarios, one for the first wave of the epidemic and the other scenario if Israel never rolled out their vaccination program, both compared with no vaccination program (Wang et al.,2021). This helped in understanding resource allocation better and finding out how many benefits were gained when compared with the costs of the program.

Secondly, it helps in prioritizing the resources, whether to take productivity loss into account or not; for example, in the USA, not taking productivity loss into their covid-19 vaccination program evaluation was considered to be more cost-effective for the elderly population, i.e., 60 years and above, whereas in Denmark, accounting for productivity loss was helped in producing well-informed decisions for their cost-effectiveness result for people below 60 years (Utami et al., 2023).

Thirdly, it considers which type of costs to include; since resources are limited, cost plays a crucial part in an economic evaluation (Turner et al., 2021). It helps understand the trade-offs made when resources are used for one instance that become unavailable for another situation. It helps us understand the willingness to pay thresholds; decision-makers have to choose appropriate WTP thresholds to make accurate estimations which help in better resource allocation (Turner et al., 2021).

Moreover, di Frusco et al. (2023) emphasized taking a broader societal perspective which would allow the decision-makers to consider all the costs and benefits of the vaccine and make informed decisions. Vaccines have importance economically, socially, ethically, and also politically. It is important to look from the perspective of all the five domains mentioned in their article. This would allow reduced healthcare costs, equitable access to vaccines, and ensure that all policies made for the covid-19 vaccines are evidence-based.

1.7 WHY SYSTEMATIC LITERATURE REVIEW

A systematic literature review (SLR) is essential to health economic evaluations of vaccines. It involves a comprehensive and unbiased search of the literature to identify all relevant studies that have reported on vaccine effectiveness, safety, and cost-effectiveness (Vo & Riewpaiboon, 2016). The results of an SLR can be used to inform the development of a model to estimate the cost-effectiveness of a vaccine (Deogaonkar et al., 2016). A health economics perspective could help prioritize the vaccination program among different age groups, and economic evaluation could ensure sound decision-making. It can analyze whether the vaccination program for particular age groups could be cost-effective or result in a positive cost benefit. This systematic literature review will be helpful as it will pool all the health economic evaluations together, which could help further in future decision-making for the vaccination programs by analyzing different methods, models, cost analysis, and Effectiveness.

The advantages of conducting an SLR include the ability to identify all relevant studies, which reduces the risk of bias in estimating the effectiveness and cost-effectiveness of vaccines (Shamseer et al., 2015). Additionally, an SLR can help to identify data gaps and areas where further research is needed (Mengist et al., 2020). Finally, the results of an SLR can be used to inform decision-making by policymakers, healthcare providers, and patients.

However, there are also some limitations to conducting an SLR. For example, the quality of the studies included in the review can vary, affecting the validity of the results (Mohseni et al., 2022). Additionally, the search strategy used to identify studies may not be comprehensive, which can result in missing important studies (Mohseni et al., 2022). Finally, the results of an SLR may be subject to publication bias, where studies with positive results are more likely to be published than studies with negative results (Boutron et al., 2022).

1.8 THEORETICAL FRAMEWORK OF CONSTRAINED OPTIMIZATION AND PRIORITIZATION

Meltzer et al. (2016) proposed that constrained optimization and prioritization are crucial theoretical frameworks in public health resource allocation. These frameworks enable policymakers to systematically align available resources, associated costs, and budget constraints to maximize health outcomes. By evaluating the costs, benefits, and limitations of limited budgets, decision-makers can make informed trade-offs between different interventions. By incorporating both optimization and prioritization, this framework facilitates evidence-based decision-making in public health by providing a structured and comprehensive approach to resource allocation. It assists decision-makers in efficiently allocating resources, prioritizing interventions with the greatest impact, and accounting for specific contextual constraints and budget limitations. Ultimately, this framework enhances the effectiveness and efficiency of public health interventions, leading to improved health outcomes.

Moreover, this theoretical framework can be extended to the prioritization of vaccines. Considering factors such as vaccine efficacy, coverage, and cost-effectiveness enables the efficient allocation of vaccines. Additionally, by incorporating data on disease burden, transmission rates, and population characteristics (such as age), this framework can inform prioritization strategies tailored to different population groups' specific needs and vulnerabilities. Applying this conceptual framework promotes evidence-based decision-making, ensuring equitable and effective distribution of vaccines.

2 AIM

In this systematic literature review, we aim to report and synthesize health economic evaluations of vaccination programs against Covid-19 among the children population compared to the elderly population in European countries.

2.1 RESEARCH QUESTIONS

Q1) Is the vaccination program against COVID-19 among the children's population cost-effective or produces more benefits than costs in European countries?

Q2) What is the cost-effectiveness and cost-benefit of implementing COVID-19 vaccination programs for children compared with elderly populations in European countries? Is there any potential research gap identified?

3 METHODS

Ethical Consideration

A systematic literature review deals with previously published articles and does not involve any direct human participants, still when conducting a systematic literature review, several ethical considerations have to be followed, which would ensure the integrity and reliability of the research and also potentially minimize the bias of research work (Suri, 2019).

Objectivity and Transparency- Objectivity and transparency were balanced in this literature review. This was done by clearly addressing the risk of bias and limitations of this study. Transparency was ensured by documenting the search strategy, pre-defined inclusion and exclusion criteria, and decision-making process. This ensured that the review process became more transparent and reproducible. A common form of bias in the systematic literature review is publication bias, language bias, or selection bias. This was overcome by conducting a comprehensive search across many reliable databases.

Quality and Rigor- Systematic literature reviews should adhere to the highest standards of quality and rigor. Assessing the quality of the selected publication using the SBU checklist helped ensure the studies' reliability and validity.

Representation of Stakeholder's Interest- A systematic literature review should also clearly present the representation of stakeholders' interests. For this systematic literature review, multiple stakeholders can be identified, for example, policy-makers who would see from a perspective of evidence-based information. In contrast, public health workers might see it from a perspective of protecting the population's health and better resource allocation. Parents or guardians might see from a perspective the safety and effectiveness of vaccines for their children. A systematic literature review has to provide balanced and comprehensive information covering all these perspectives (for example, the societal value of vaccines or the economic or health implication of vaccines). Understanding their perspectives and incorporating their inputs can enhance the relevance and impact of research findings.

By adhering to the above-mentioned ethical principles, this systematic literature review will provide rigorous, transparent, and objective findings that can inform policymakers and other stakeholders regarding the covid-19 vaccination programs among children compared to the elderly population in European countries.

Purpose

The purpose of conducting a systematic literature review for economic evaluations of covid-19 vaccination programs among children compared with the elderly population is to gather and analyze existing research to assess the cost-effectiveness of vaccinating the two different age groups. A systematic Literature review would help identify all the relevant information regarding vaccines' cost, benefits, and value.

Protocol

The review followed the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement. The author and a colleague from the MPH program at the University of Gothenburg collaborated in the study's initial stages. To develop a research question and to screen study reports, we considered using the PICO framework (**P**opulation, **I**ntervention, **C**omparator, **O**utcome).

According to Mandrik et al. (2021), a Systematic Literature Review consists of six stages, (i) planning and development, (ii) evidence search, (iii) study selection, (iv) quality assessment, (v) data extraction, and synthesis, (vi) presenting results.

Inclusion Criteria

Population- We included studies that were related to Covid-19, age-specific, and were based in European countries. In this report, we included two age groups, (i) Children or Adolescent or Teenagers (5 years to 19 years old) and (ii) the Elderly population (60 or above). According to the Center for European Studies, the geographical definition of Europe extends from the Atlantic Ocean to the Ural Mountains and from the Arctic region to the Mediterranean Sea.

Intervention- We included studies that had covid-19 vaccination programs as their intervention. There were no criteria for the brand or dosage of vaccines.

Comparator- For the comparator, we included studies that reported no vaccination (unvaccinated) group as their comparator.

Outcome- Studies that reported cost per QALY or cost per DALY averted, net monetary benefit ratio, were included as cost per saved life years.

Type of Economic Evaluation- Studies that reported cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis were included.

Time Frame- Studies from December 2019 to the present year were included.

Exclusion Criteria

Studies were excluded because of the following reasons, (i) Systematic Literature Review or meta-analysis, (ii) not full economic evaluation, (iii) Wrong study design, (iv) Wrong population, (v) Wrong intervention, (vi) wrong comparator, (vii) wrong outcome, (viii) non-European country, (ix) no full text, (x) wrong year.

Search Strategies

We developed search strategies based on the search strings that were used by SBU (Swedish Agency for Health Technology Assessment and Assessment of social services) to retrieve relevant studies ("Effectiveness of Non-Invasive Ventilation," 2020.). We developed three different search blocks, (i) Population, (ii) Intervention, and (iii) Health economic aspects, to identify enough relevant publications. It was recommended not to change any search string as developing a new one is time-consuming and dependent on the researcher's experience (Ghislaine et al., 2016). The search strategy developed by SBU used synonyms and MeSH terms to be as relevant as possible (Appendix). Use of Boolean operators such as "OR," "AND," and "*" were also used to combine different search blocks. We selected four different databases for this thesis, (i) CINAHL, (ii) EMBASE, (iii) MEDLINE, and (iv) Psycinfo. The table for the search strategy can be found in the Appendix. After this, hand searching was also performed. We selected four health economics-specific databases, (i) Tuft's cost-effectiveness analysis (CEA) registry (Center for the Evaluation of Value and Risk in Health, n.d.), (ii) HEED, (iii) Cochrane database (Cochrane Library, n.d.) and (iv) INAHTA (International Network of Agencies for Health Technology Assessment [INAHTA], n.d.). However, it was found that the HEED database no longer exists (Glanville and Kaunelis (2022). Handsearching was also performed by searching the relevant reference list from the selected final publication list. We also selected three websites as the grey literature, (i) WHO (World Health Organization. (n.d.).,(ii)Folkhälsomyndigheten (Public Health Agency in Sweden (Folkhälsomyndigheten. (n.d.)., and (iii) EMA (European Medicines Agency. (n.d.).

Study Selection

After retrieving records from the four databases, all the results were imported to EndNote, a citation manager software. The next step was to remove all the duplicates that we found, which was done through EndNote (Ivey & Crum (2018). After removing the duplicates, all the results were imported to Rayyan.ai (Ouzzani M, Hammady H, Fedorowicz Z and Elmagarmid A, 2016), an AI-build application developed for screening titles and abstracts in collaboration with other reviewers. Through Rayyan, the title and abstract were screened with the help of inclusion and exclusion criteria. One advantage of using Rayyan was that it had a blind-on feature, through which we cannot see each other's results, that helped overcome the risk of selection bias. After title and abstract screening, all the selected publications were exported from Rayyan to EndNote. With the help of EndNote, we found all the full text of the articles, through which we did the full-text screening. The full-Text screening was also assessed through inclusion and

exclusion criteria. Throughout the Study Selection steps, two independent reviewers were involved. They screened the results by themselves and then compared them with each other, which led to reaching a consensus and helped in further including or excluding the final publications, shown in the form of a PRISMA flowchart (Figure 1).

Quality Assessment

Quality Assessments of the selected publications were analyzed using the SBU checklist for assessing the quality of health economic modeling studies (Appendix). This checklist assesses based on PICO-based research questions, Transferability of studies' economic results, potential conflicts of interests, model structure, costs and effects, interpretation of results, sensitivity analysis, and discounting. We assessed every selected publication based on four scales, (i) High, (ii) Moderate, (iii) Low, and (iv) Insufficient. Studies were included if they had high or moderate quality, whereas if the studies did not qualify for the quality assessment, they were rejected.

Data Extraction

Since no potential articles were found, no data extraction table was created.

4 RESULTS

Part A- Systematic Literature Review

Study Selection and Characteristics

Through search identification, 6053 articles were found, out of which 333 articles were removed because of duplication. Then after the title and abstract screening, 162 articles were selected for full-text screening, and the rest were excluded for multiple reasons (The exclusion Criteria table can be found in the appendix). However, no relevant articles were clear for the quality assessment step after the full-text screening. Although when the children population was discussed, no articles were found that analyzed the cost-effectiveness of vaccination programs against covid-19. However, two articles were found where data about the children's population was discussed and reported, also cited in Part B of Secondary Information that we retrieved from these papers.

The complete visual representation can be found in the PRISMA flowchart below (Page et al., 2021).

PRISMA

According to Page et al. (2021), PRISMA is defined as "The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, published in 2021, was designed to help systematic reviewers transparently report why the review was done, what the authors did, and what they found".

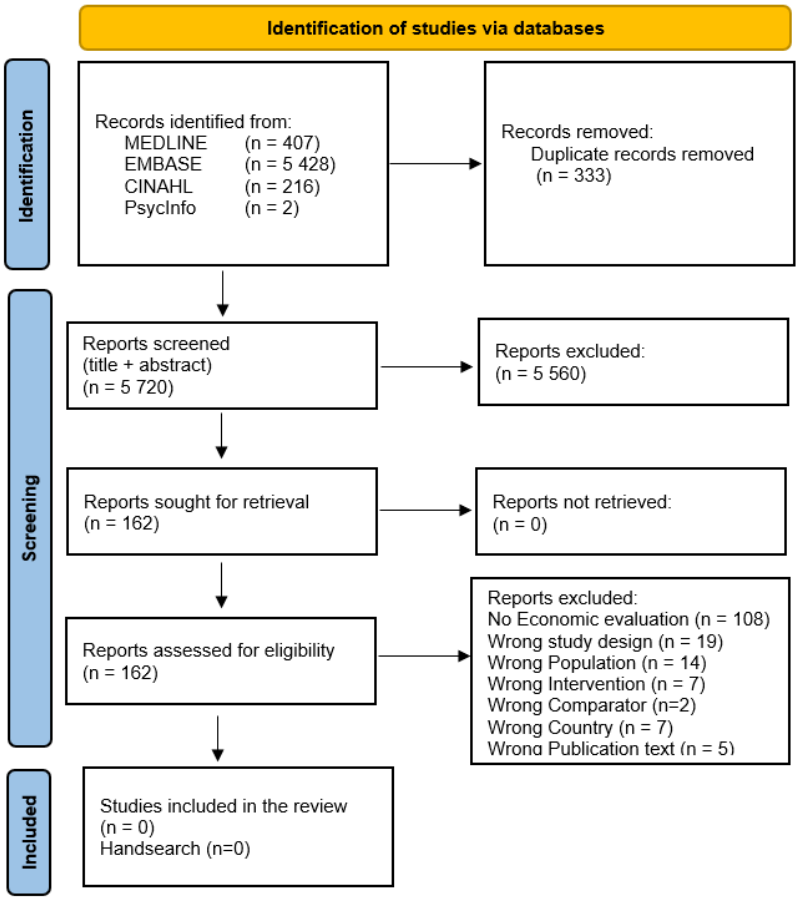

Figure 1. PRISMA FLOWCHART

Part B- Secondary Information

According to Volodymyrovych et al. (2021), the Vaccination program for the elderly population was cost-effective as they represent the high-risk group with the increase in age; rates of being hospitalized also increased because of the other comorbidities. Vaccination was also considered cost-effective for this age group because of more costs related to ICU and ventilation care, so there was more evidence that vaccination has improved the quality of life for this age group. This paper divided the vaccination program among six age groups (0-4 years, 5-12 years, 13-19 years, 20-39 years, 40-64 years, and 65+ years). They concluded that the cost-effectiveness of the vaccine depends on the covid-19 situation. They found that at the start of the vaccination role, vaccinating the elderly population was considered cost-effective, whereas vaccinating the adult population was considered cost-effective once the pandemic was known early in the pandemic since this group is considered a high transmitter group. They also used a disease transmission model, which is more of an epidemiological model, which was found to be a good model as it gave a better understanding of the burden of covid-19. In this model, they also studied the social contact patterns as it is linked with the high transmission rate. School-going children were found to have higher social contacts, so vaccination policy could also be targeted towards them. However, they did not report any economic evaluation information on children.

Whereas López et al. (2021) reported a cost-benefit analysis of covid-19 mass vaccination program in Catalonia, Spain. Although they did report various age groups ranging from 0-9 years to over 80 years, they did not target any specific age-related population, including the children population. According to López et al. (2021), the severity of coronavirus is lower among the age group of 0-9 years and 10-19 years old; however, they are still contacting the virus and may transmit this virus to the older age group (3695 cases out of 187,133 population of 0-9 years old age group which 5.5% of the population of this age group. Out of these, 26 cases were found to be hospitalized, and two were admitted to ICU. Similarly, there were 9346 cases among the population of 217,566 in the 10-19 years old age group, which is 14% of this population). Vaccinating the children will help lower the virus's transmission rate and also help contribute towards herd immunity.

Table 1: Percentage of Cases by age group without the effect of vaccine (Epidemiological Data 1 September- 31 December 2020), Catalonia

Group	Population	Cases	Hosp.	ICU	Deaths
0–9 years	187,133 (10.0%)	3695 (5.5%)	26 (0.4%)	2 (0.2%)	0 (0.0%)
10–19 years	217,566 (11.6%)	9346 (14.0%)	44 (0.7%)	4 (0.4%)	0 (0.0%)
20–29 years	192,940 (10.3%)	8850 (13.3%)	134 (2.2%)	7 (0.8%)	1 (0.1%)
30–39 years	240,411 (12.8%)	8493 (12.8%)	310 (5.1%)	38 (4.1%)	5 (0.5%)
40–49 years	330,845 (17.6%)	12,005 (18.0%)	604 (9.9%)	89 (9.7%)	11 (1.2%)
50–59 years	268,237 (14.3%)	10,137 (15.2%)	967 (15.8%)	188 (20.4%)	35 (3.7%)
60–69 years	202,241 (10.8%)	6072 (9.1%)	1126 (18.4%)	230 (25.0%)	72 (7.6%)
70–79 years	145,686 (7.8%)	3981 (6.0%)	1246 (20.3%)	260 (28.3%)	173 (18.3%)
over 80 years	93,861 (5.0%)	4009 (6.0%)	1674 (27.3%)	102 (11.1%)	647 (68.5%)

Source: *A Cost-Benefit Analysis of COVID-19 Vaccination in Catalonia cited by López et al. (2021)*

5 DISCUSSION

Economic evaluation is considered an essential tool for informed decision-making in the healthcare system. However, this was not the case during the covid-19 vaccination program, as it was not used to decide whom to prioritize the vaccine. Covid-19 suddenly appeared and disturbed the economy of many nations. The introduction of vaccines has helped minimize the effect of covid-19. However, because of limited resources, vaccine prioritization must be made, and hence such analysis helps in allocating such resources. The burden of covid-19 has certainly decreased after the rollout of vaccines (Reno et al., 2022).

From the findings of Volodymyroych et al. (2021), it was found that school-going children had higher social contact patterns and were considered a high transmission group. Hence vaccination policy should also be targeted towards them. Covid-19 vaccination program among school-going children can be a cost-effective strategy as it would reduce the transmission of the virus, especially at the schools and the community. Also, vaccinating the school-going population can contribute towards the indirect benefits by reducing the transmission from them to the other vulnerable population like the elderly population. By looking at both the direct and indirect benefits, vaccinating the children and adolescent population could bring down the transmission rate of the disease and lower the rate of hospitalizations, ICU cases, and healthcare costs.

Whereas, from the findings of Lopez et al. (2020), the disease severity among children of the age group of 0-9 years and 10-19 years was generally lower when compared with the elderly population. The lower rates of hospitalization and ICU cases also suggest the same about the severity of covid-19 among children. However, the number of cases among this age group population, especially children between 10-19 years old, was even higher than the elderly population; this suggests that the children do contract the disease and also have the ability to transmit the disease. They can act as potential carriers and infect vulnerable populations such as elderly population adults with other comorbidities. Vaccinating children against covid-19 can help achieve herd immunity and reduce the transmission rate. Hence, the vaccination program against covid-19 among children could imply being cost-effective or producing more benefits than the cost.

There were other articles as well that discussed the effectiveness of vaccinating the children population as well as the disease transmission rate among this population. According to Orlewska et al. (2022), very little data are available for the children population. However, they mentioned that vaccinating the young population will lower disease transmission. Children and adolescents are considered to have a higher transmission rate for the covid-19 virus. Whereas, According to Pilz et al. (2021), the cost-benefit analysis would not be possible because of the lack of evidence about whether booster vaccine doses have

a positive benefit over the cost due to covid-19 for children as healthy young adults. So, for the children as well as young, healthy adults to be prioritized for the fourth dose, there needs to be enough evidence to get recommended in the health policy regarding covid-19 in Portugal.

The Iran Ministry of Health (ImOH) findings have given insights into the transmission rate of covid-19 virus from children to other vulnerable populations (Stein et al., 2022). They examined infectivity in different age groups at different phases or waves of the virus. During the first and second waves of the covid-19 virus, around 23-32% of the children and 15 % of adults caught covid-19 virus from children, whereas the numbers increased during the third wave. The numbers raised from 23-32% to 40-51% and 29%, respectively. During the fourth wave, i.e., during the delta variant phase, it was found that around one-third of all infected children aged 5 to 12 and adolescents under the age of 17 were the sole source of covid-19 infection for 49% of all infected individuals. This provides evidence that with each wave of the covid-19 virus, the transmission of disease from children has kept increasing, making it very important to vaccinate children as they have an important role in spreading SARS-CoV-2. Vaccinating children and adolescents would also produce more benefits through a decrease in hospitalization, which could eventually outweigh the costs linked with the vaccines or vaccination programs. With the adult vaccination becoming more widely used and available, it has become important to vaccinate children between the age group of 5 to 17, to stop the spread of the virus.

When evaluating the cost-effectiveness of the vaccination program among the children and adolescent population, we need to look for a few important points: the cost of the vaccine and potential harms or consequences produced by the vaccine. First, we need to assess whether the cost of the vaccine is high or low, how many cases are there among this population, and what is the availability of the vaccine because if the cost vaccine is relatively high, then this will impact our ICER, which would also imply that vaccination among this population would not be cost-effective. Hence, a vaccine's cost must be lower to be cost-effective. Similarly, we also need to assess whether there are any side effects of the vaccine because if the vaccine produces more side effects, then this might imply that the vaccination program among the children and adolescent population would not be cost-effective. Hence, to be cost-effective, a vaccine should produce no or very few adverse effects. Another thing that we need to remember while performing an economic evaluation of vaccines is that knowing the vaccine efficacy is important; it is important to know how effective the vaccine is for each age group or by how much percentage a particular vaccine is decreasing the risk of getting covid-19 virus.

According to Mauskoph et al. (2022), Transmission Dynamic Models are a type of epidemiological model widely used in economic evaluations, especially of vaccines. They simulate the spread of infectious diseases through a population over time. The transmission Model considers the disease's history, population characteristics such as age structure, social patterns, and the impact of interventions.

One of the advantages of this model is that it can capture the complex interactions between the infectious agent, the host population, and the environment, leading to more accurate predictions of disease transmission dynamics and the impact of interventions.

Strengths of the study

The strength of doing a systematic literature review is its comprehensive and rigorous approach. The search strategy involved four reliable databases (EMBASE, MEDLINE, CINAHL, and PsycINFO), ensuring no possible relevant literature was missed. Other than these four databases, hand searching from the references of papers, searching grey literature from reliable websites like the public health agency of Sweden, and searching through reliable health technology databases like the Tuft database. This comprehensive approach ensured that there were no studies that were missed. Moreover, collaborating with another colleague during the initial stages of the systematic literature review further enhanced the strength of this work. Collaboration with other colleagues ensured no potential bias in selecting or excluding studies which enhanced the reliability of findings as all the inclusion and exclusion were done with discussion and consensus, ensuring a more robust analysis. Also, the complementary search is the strength of this work as it helped highlight more insights on the vaccine efficacy and the impact of covid-19 among the children population, which helped analyze the current situation and provide more knowledge for future policies.

Limitations

According to Lang et al. (2007), an Empty Systematic Literature Review is a "systematic literature review that does not identify any eligible studies for inclusion in the analysis." Gray (2021) argued that empty systematic literature reviews could help identify the potential research gaps where there is a lack of evidence or research that could help in future research. However, Lang et al. (2007) and Gray (2021) mentioned that one needs to be careful in publishing an empty systematic literature review as this paper needs to be very transparent about the search methods used and the reporting of the results.

An empty systematic literature review can occur for several reasons, one of which may be the specificity of the research question. In our case, we were comparing the population of children with the elderly population regarding COVID-19 and vaccination. Since COVID-19 is a relatively new virus, there are still uncertainties about how the vaccine might affect the children population. Additionally, there is currently no consensus on the definition of long COVID, which may have impacted the number of relevant articles available for inclusion in our review.

Despite the absence of potentially eligible papers, conducting an empty systematic literature review is still valuable as it helps identify gaps in the existing literature and highlights areas for future research. It also provides transparency and accountability by demonstrating that a comprehensive search was conducted, and no relevant studies were identified.

Why vaccinate children or the adolescent population?

The effect of covid-19 might be lower in the case of children and adolescent populations or groups. However, there has been a high range of evidence regarding the other complications that arise from the SARS-CoV-2 virus, for example, Long Covid and Multisystem Inflammatory Syndrome- Children (MIS-C). There have been hospital costs, antibiotics costs associated with each child affected by COVID-19. In one of the reports cited by Stein et al. (2022), it was found that vaccinating children, especially adolescents aged between 12-18 years in the USA, has benefited by lowering the risk of hospitalization due to COVID-19 by 93% and all of these children were unvaccinated. It was also cited that CDC has recommended vaccinating the children and adolescent group as early as possible after looking at the high efficacy of the Pfizer-BioNTech BNT162b2 vaccine in preventing the complications associated with covid-19 virus. Hence, it suggests that vaccinating children could produce more benefits than the cost incurred.

Whereas another study from the UK, cited by Shiri et al. (2021), emphasized that covid-19 vaccination program among the children population and adolescents has many potential benefits. They developed an age-structured dynamic transmission model and found that vaccinating this population can significantly reduce hospitalizations, deaths related to covid-19, and long-term effects covid-19 associated with the children population. Shiri et al. (2021) found that extending the vaccination programs to the adolescent population can reduce hospitalizations due to covid-19, covid related deaths, and the prevalence of long covid by 21 %, 18%, and 27 %, respectively. Whereas, for the children population aged five years and above, the model predicts that vaccination programs can result in a 60% reduction in hospitalization, a 57% reduction in deaths, and a 75% reduction in long covid cases. These findings suggest that including this population in vaccination programs can positively impact the disease burden. Even though there might be potential complications associated with vaccination, like myocarditis, the number of cases is significantly low, and the benefit of vaccination in preventing severe covid-19 outcomes far outweighs the risk of getting myocarditis or other rare complications.

Multisystem Inflammatory Syndrome in Children (MIS-C)

According to Sick-Samuels (2021), Multisystem inflammatory syndrome in children is a rare condition caused by the SARS-coV-2 virus. It causes an inflammatory reaction among the children after 4-5 weeks of getting infected by the virus. Symptoms usually vary from mild (e.g., fever, rashes, etc.) to fatal (e.g., inflammation in blood vessels or heart).

According to Buanseno et al. (2022), Vaccination could help prevent MIS-C, as suggested by the United States of America and France data. It was mentioned that there were no new MIS-C cases among the fully vaccinated children in France. In contrast, in the USA, children and adolescents diagnosed with MIS-C were unvaccinated, accounting for 95% of cases. These facts somehow do say that vaccinating

children against COVID-19 could have a direct impact on preventing MIS-C. According to CDC, MIS-C did impact children in the US, where around 5217 children between 5-11 years old were diagnosed with MIS-C, of which 46 mortality cases were recorded from October 2021. The average age was recorded to be nine years, and most children were admitted to ICU and needed mechanical ventilation.

Long-Covid among children and adolescent population

In one of the articles cited by Stein et al., 2022, it was reported that in Russia, around 25% of the 518 children experienced long covid symptoms after several months of being hospitalized. In contrast, another study conducted in the United Kingdom among the age group of 11-17 years old comparing 3065 covid-19 positive children with 3739 covid negative children found that the covid-19 positive children experienced symptoms of long covid after three months of being tested.

6 FUTURE RESEARCH

As the COVID-19 pandemic continues to evolve, it is becoming increasingly important to understand the impact of the disease on children and the potential benefits and risks of vaccinating them. While children are generally less likely to experience severe symptoms or require hospitalization than adults, there are emerging concerns regarding the potential long-term effects of COVID-19, including multisystem inflammatory syndrome in children (MIS-C) and long COVID.

To assess the potential benefits and risks of vaccinating children against COVID-19, more research is needed on the long-term health effects of the disease among children and the safety and efficacy of COVID-19 vaccines in this population. Once this evidence is generated, it will be important to perform an economic evaluation of COVID-19 vaccination among children to determine the cost-effectiveness of this intervention.

Economic evaluations can help assess whether the benefits of vaccinating children against COVID-19 outweigh the costs, including vaccine procurement, administration, and any potential adverse effects. Economic evaluations can help inform policy decisions and resource allocation to optimize public health outcomes by weighing the costs and benefits of vaccination.

In addition to assessing the cost-effectiveness of vaccination among children, economic evaluations can also help identify potential inequalities in vaccine access and uptake and inform strategies to address these disparities. This is particularly important given the potential long-term health impacts of COVID-19 on children and the need to ensure that all children have equitable access to COVID-19 vaccines.

Overall, generating more evidence on the long-term health effects of COVID-19 among children, as well as the safety and efficacy of COVID-19 vaccines in this population, and performing economic evaluations of vaccination among children will be crucial in guiding public health policies and resource allocation to ensure optimal health outcomes for all.

7 CONCLUSION

Until now, we did not find any relevant study that performed an economic evaluation for the covid-19 vaccination program among children compared with the elderly population in European countries. To compare the cost-effectiveness of vaccination programs between them, we would need more evidence about the economic evaluation of vaccination programs among the children population.

8 PUBLIC HEALTH PERSPECTIVES/IMPLICATIONS

Since we did not find any economic evaluations of covid-19 vaccination programs among the children population compared with the elderly population in European countries, a research gap in this topic may have certain implications for EU policies. First, a lack of evidence in the economic evaluation of the covid-19 vaccination program may address health inequalities among children. While including the elderly in the vaccination program and neglecting the children population from it raises a point of equitable vaccine distribution strategies, policies must ensure equal access to vaccination programs across different age groups. The findings retrieved from those articles mentioned earlier show children as a high transmission group, and the long-term effects of covid-19 associated with them can help provide evidence-based decision-making. As policymakers rely heavily on evidence to analyze a particular intervention, whether it is cost-effective, cost-benefit, or cost-saving, the lack of economic evaluation in this population can raise a point for also including this population group in future considerations. For a good resource allocation, economic evaluation is important. Lack of evidence among the children population would raise a point of undergoing economic evaluation among the children population to determine the most efficient use of resources. Hence, the lack of economic evaluation for the children population can raise a point to develop some policies that address the gap, which would eventually help decision-makers to prioritize and allocate resources for conducting economic evaluation in those populations.

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APPENDIX

Task	Link
1. Search Blocks	Click
2. Full-Text Screening	Click
3. Reason for Excluded Articles	Click
4. Quality Assessment	Click