SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS FOR PAEDIATRIC PULMONARY DISEASES

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PART 0: PREAMBLE

PLAGIARISM DECLARATION

I, Mutsawashe Chitando, hereby declare that the work on this dissertation/thesis is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION

I dedicate my thesis to my parents and siblings who have shown me love and unwavering support throughout this journey, to my friends and family for their encouragement, and above all to God in whom I trust.

ABSTRACT

Background

Pulmonary diseases are the leading causes of mortality globally amongst children under five years of age. Economic evaluations (EEs) guide decision-makers on which health care interventions to adopt to reduce the paediatric pulmonary disease burden.

Methods

We systematically reviewed EEs for paediatric pulmonary diseases published globally between 2010 and 2020. We searched PubMed, Web of Science, MEDLINE, Paediatric Economic Database Evaluation (PEDE), and the Cochrane library. EEs included were specific to paediatric pulmonary diseases in a hospital setting and for children aged from zero to six years old. We extracted data items guided by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. We collected qualitative and quantitative data which we analysed in Microsoft Excel and R Software.

Results

22 studies met the inclusion criteria. Seven of the articles were cost-effectiveness analyses, five cost-utility analyses, two cost-minimisation analyses, and eight cost analyses. Fourteen studies were conducted in high-income countries, and eight in low-middle-income countries (LMICs). Ten studies were on asthma, nine on pneumonia, two on asthma and pneumonia, and one on tuberculosis. Quality assessment of the articles revealed some methodological inconsistencies across the articles.

Conclusion

Fewer EEs were conducted in LMICs, yet children from these countries are disproportionately affected by pulmonary diseases. Developing standardised methods for EEs and conducting more EEs for paediatric pulmonary diseases in LMICs could allow for more evidence-based decision-making.

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TABLE OF CONTENTS

LIST OF TABLES

PART A: PROTOCOL

LIST OF FIGURES

PART A: PROTOCOL

LIST OF ABBREVIATIONS

Abbreviation	Description
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CMA	Cost-minimisation analysis
CBA	Cost-benefit analysis
BIA	Budget impact analysis
WHO	World Health Organisation
GAPP	Global Action Plan for Prevention and Control of Pneumonia
TB	Tuberculosis
HIC	High-income country
LMIC	Low-middle-income country
DALY	Disability-adjusted life year
QALY	Quality-adjusted life year
ICER	Incremental cost-effectiveness ratio
SDG	Sustainable Development Goals
CHEERS	Consolidated Health Economic Evaluation Reporting Standards

PART A: PROTOCOL

INTRODUCTION

The use of economic evaluations in informing decisions about health interventions by decision-makers is becoming more common as a response to the scarcity of resources in different societies (Weiss and Sullivan, 2001, Drummond et al., 2015). As health experts develop new strategies to combat disease burden, there is a growing need to ensure that the decisions they make are from an informed health economic perspective.

The proposed study seeks to systematically review economic evaluations for paediatric pulmonary diseases, which are the leading cause of morbidity and mortality amongst children (Nair et al., 2010). This study falls under a broader study, PediCAP, which is assessing the impact of oral step-down to amoxicillin or co-amoxiclav for children with severe community-acquired pneumonia, who have had intravenous antibiotics administered to them in a hospital setting. PediCAP is a randomised control trial which will be carried out in hospitals in South Africa, Uganda, Zimbabwe, and Zambia. The trial could potentially reduce the length of hospital stay (LOS) as well as have an impact on the clinical outcomes for the sick children. Across different groups, providers, payers and families, there is a common desire to reduce LOS for reasons which vary from cost-minimisation, reduction in loss of productive days and minimising exposure to antibiotic-resistant bacteria (Pati et al., 2012).

BACKGROUND TO THE STUDY

Children are considered a vulnerable group to research, and care needs to be taken so that their rights are not violated. There are also ethical considerations when dealing with this group, such as getting informed consent from the legal parent or guardian before any economic evaluation can take place. As the methods of conducting economic evaluations are continuously being improved, there is still a need to validate the use of standard methods in the paediatric population because of the vulnerability of children and other challenges that are presented when trying to conduct economic evaluations in children (Ungar and Santos, 2004, Ungar, 2011). Some of the cited deficiencies in economic evaluations for paediatric health have been the same as

those identified in adult economic evaluations which include; poor adherence to reporting standards, lack of transparency, failure to identify perspectives and incomplete costing amongst others (Ungar, 2011).

Understanding the methods and other aspects of economic evaluation in child health presents a unique opportunity to use evidence in informing policymakers, program administrators and other stakeholders who are at the forefront of making health care decisions for children. Since the inception of the Paediatric Economic Database Evaluation (PEDE), there has been an increase in promoting research in paediatric health economics (Ungar and Santos, 2004). Paediatric pulmonary diseases are a leading cause of morbidity and mortality in children, with pneumonia resulting in the largest number of childhood deaths globally (Nair et al., 2010). In the year 2013, 6.3 million deaths of under five-year-olds were caused by pneumonia, yet early diagnosis and treatment in that same time-frame could have averted as many as 600 000 deaths from pneumonia (Abrha et al., 2018). Pneumonia and bronchiolitis fall under acute lower respiratory infections and the group worst affected by lower respiratory infections are children under the age of five. The reported deaths amount to 704 000 each year and more than 6 million disability-adjusted life years (DALYs) worldwide (De Benedictis and Bush, 2018).

According to the United Nations (UN) commission on life-saving commodities for children and women, these deaths can be prevented or treated by simple and affordable medicines administered before, during and after birth (Abrha et al., 2018). Taking steps to control, prevent and cure respiratory diseases are considered as being amongst the most essential cost-effective health interventions available (FIRS. Forum of International Respiratory Societies, 2017). Respiratory diseases occur in all parts of the world, regardless of the level of development. The respiratory diseases held responsible for the highest levels of morbidity and mortality in children on a global scale are asthma, acute lower respiratory tract infections (pneumonia and bronchiolitis), and pulmonary tuberculosis (TB) (Mohammad et al., 2010, FIRS. Forum of International Respiratory Societies, 2017).

Below is a summary of three of the diseases that will be considered for purposes of the review. The focus will be on pneumonia; however, asthma and pulmonary TB will be searched for and included if any economic evaluations focusing on them are found.

Pneumonia

Pneumonia is the leading cause of mortality in children under the age of five globally (Ayieko and English, 2007). The main pathogens which cause pneumonia are the Streptococcus pneumonia (S.pneumoniae), non-typeable Haemophilus influenza and respiratory syncytial virus (Zhang et al., 2018, Wardlaw et al., 2006). It kills more children under the age of five than AIDS, measles and malaria combined (Wardlaw et al., 2006). Like the trend observable in most diseases where the brunt of the burden is borne by the world's poorest countries, half of the deaths from pneumonia are reported in the African continent (Bozzani et al., 2016). It is estimated that there are 156 million new episodes of pneumonia each year worldwide, where 151 million of these are found in the low-and middle-income countries (Rudan, 2008). The risk factors for pneumonia include being very young (or being very old), living in crowded housing, lack of breast-feeding in infants, low birth weight, HIV infection, lack of immunization and exposure to air pollutants (FIRS. Forum of International Respiratory Societies, 2017, Rudan, 2008). There is evidence that suggests that effective and appropriate management of clinical cases of pneumonia is possible in all settings (Niessen et al., 2009). The main challenge is that these interventions aimed at reducing pneumonia morbidity and mortality reach too few children (Wardlaw et al., 2006). In a report by the World Health Organisation (2019b), they estimated that only one-third of the children with pneumonia receive the antibiotics they need. According to the same report, most cases of pneumonia require oral antibiotics for their treatment except for instances when the pneumonia is severe, then hospitalization is recommended.

Community-acquired pneumonia is one of the most common paediatric inpatient diagnoses, yet also preventable (Pati et al., 2012). Several studies have been conducted to date to make meaningful contributions to child health. The "Pneumonia Etiology Research for Child Health" (PERCH) study, for instance, had the purpose of characterising the causes of severe pneumonia leading to hospital admissions (Grove et al., 2015).

Another study aimed at improving the understanding of child health was the "Aetiology of Neonatal Infection in South Asia" (ANISA) study where the objective was to provide a better understanding of causes of neonatal infections in resource constrained countries (Seale and Agarwal, 2018). There are also health economics studies that have been carried out which assess the cost-effectiveness of the different interventions to reduce pneumonia, such as the pneumococcal conjugate vaccine and other immunizations, reducing indoor pollution, nutritional interventions and case management, amongst others (Niessen et al., 2009). This study will systematically review the literature to identify which economic evaluations have been performed for pneumonia interventions, where have they been done, what still needs to be done, and what can be done differently to assist decision-makers in making evidence-based decisions about resource allocation and health service provision (Ram Jat and San Sebastian, 2013).

Asthma

Asthma is the most common chronic disease amongst children, the symptoms of which are more prevalent in children living in high-income countries (Asher and Pearce, 2014). It is defined as "a chronic inflammatory disorder of the airways that affects adults and children of all ages" (Braman, 2006). It is estimated that 334 million people worldwide are affected by asthma; however the actual number is unknown due to some unreported cases (FIRS. Forum of International Respiratory Societies, 2017). Despite the prominence of the disease in high-income countries, recent trends indicate that there is an increase in its prevalence in low-and middle-income countries (Lenney et al., 2018). According to (Asher et al., 2020, Asher, 2010), this can be attributed to environmental factors, and lifestyle changes as low-and middle-income countries become more urbanised, thus pointing to a reduction in disparities of global asthma prevalence. Genetic predisposition, exposure to allergens and air pollution, maternal smoking, and maternal stress, use of antibiotics and dietary factors have also been found to play a role in the development of asthma (FIRS. Forum of International Respiratory Societies, 2017, Lenney et al., 2018, Subbarao et al., 2009).

Fewer children die from asthma compared to other paediatric diseases such as pneumonia and tuberculosis, and consequently, the burden imposed by this disease is often overlooked (Asher and Pearce, 2014). However,

in the event of a child having asthma, certain cost implications arise. These include the time spent not involved in activities for the child (school and playtime), the cost of treatment and management of the disease (may include hospitalisation in severe cases), and the productivity loss for parents or guardian when taking care of the sick child (Lenney et al., 2018). From a provider's perspective, the costs may include; preventive and relieving medications, patient education, hospital care and ambulatory services amongst others (Asher and Pearce, 2014).

There is no known way of preventing asthma; however, adopting practices such as not smoking during pregnancy is effective in reducing childhood asthma (Subbarao et al., 2009). The use of controller medications (for acute relief of symptoms and long-term control of asthma) as a way of preventing attacks is considered one of the methods of asthma management (FIRS. Forum of International Respiratory Societies, 2017). Trigger avoidance, patient education, immunotherapy and monitoring of symptoms are some of the efforts that can be taken to manage asthma (Papadopoulos et al., 2012, Motala et al., 2009). Before the treatment of asthma, it needs to be accurately diagnosed. This process involves the identification of a characteristic pattern of respiratory symptoms (coughing, wheezing, chest tightening and shortness of breath) which can be achieved through; spirometry, bronchial hyper-activity test, peak flow monitoring and chest monitoring (Bush and Fleming, 2015, E.D. Bateman et al., 2018).

Despite having this understanding of the diagnosis and treatment of asthma, the elimination of asthma is still a distant vision. To date, studies have been conducted to assess the cost-effectiveness of the different aspects involved in the treatment and management of asthma. A scoping review of the literature in PEDE shows that asthma is second to pneumonia with regards to the number of economic evaluations that have been conducted to date.

Tuberculosis

Tuberculosis, caused by Mycobacterium Tuberculosis (TB), is one of the leading causes of death, yet it is a treatable infectious disease (Dye, 2006). It is estimated that approximately 15% of the global disease burden is carried by children, with Sub-Saharan Africa having the highest number of cases (Mandalakas et al., 2013b,

B et al., 2007). Children from low-and middle-income countries are said to have a twenty-fold risk of infection compared to those from high-income countries (Tsai et al., 2013). Studies have also shown that mortality from tuberculosis has a strong correlation with socio-economic status, nutritional status, and immunosuppression while the top five risk factors for the disease include; diabetes, smoking, HIV infection, harmful use of alcohol and undernourishment (Swaminathan and Rekha, 2010, WHO, 2019c).

According to the Global Impact of Disease report (2017), there are difficulties in diagnosing TB in children. As a result, the incidence of the disease in children is often understated. One of the reasons for it being difficult to diagnose is that the disease can mimic many of the common childhood diseases such as pneumonia and other bacterial infections (Tsai et al., 2013). To by-pass this challenge, diagnosis is often based on exposure history in addition to the clinical features presented by the patient (Tsai et al., 2013). Once the disease is confirmed, the patient is started on anti-TB medication. It is during the period of antibiotic treatment, where patients have a risk of poor medication adherence, that drug-resistant TB may develop (Nelson and Wells, 2004).

Some of the strategies that have been employed to date to control and eliminate the disease include integrated patient care policies, creating supportive systems, conducting intensified research and increasing coverage of the Bacille Calmette Guerin (BCG) vaccine (FIRS. Forum of International Respiratory Societies, 2017). The WHO guidelines also stipulate that all children who are below the age of five should be traced and screened if they have been in contact with a person who tested positive for TB (Swaminathan and Rekha, 2010). They are also put on isoniazid preventive therapy (IPT) for at least 6 months to reduce their risk of contracting tuberculosis (Tadesse et al., 2016).

Sustainable Development Goals (SDGs) and child health

It is worth mentioning that the WHO, which is prominent in child health, is not the only agency of the United Nations that seeks to improve the health and well-being of young children. The United Nations Children's Fund (UNICEF) is another agency of the United Nations that is responsible for the provision of humanitarian and

developmental aid to children around the world. In addition to these, the United Nations General Assembly is key in ensuring that the children's needs fall on the global agenda. See for example, the following section which discusses how child health falls under the sustainable development agenda.

In 2015, countries signed a commitment to achieve a set of goals to " end poverty, protect the planet and ensure prosperity for all" (Alfvén et al., 2019). Aimed at reducing infant mortality, sustainable development goal three (SDG 3) seeks to "ensure healthy lives and promote well-being for all at all ages" with countries being committed to "by 2030, end[ing] preventable deaths of new-borns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births" (WHO, 2020b, Saha et al., 2018, Grove et al., 2015). As the risk factors for different diseases change, so do the health strategies aimed at alleviating the disease burden worldwide. However, there are variations in the implications of disease burden with respect to the direct and indirect costs across various settings (Ehteshami-Afshar et al., 2016). There is still a dearth of studies that highlight the variation of these studies across different geographical regions and health care settings (Ehteshami-Afshar et al., 2016). There is also a scarcity of economic evaluations that have been conducted for paediatric diseases (Kwon et al., 2019). The implications for this could be a lack of evidence-based decision-making in terms of priority disease resource allocation which could negatively impact the progress towards achieving the SDGs.

Economic evaluations concepts and methods

In this study, we will be systematically reviewing economic evaluations of paediatric pulmonary diseases. We will include full economic evaluations (cost-benefit analysis (CBA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), cost-minimisation analysis (CMA)) and partial economic evaluations (cost analysis, and cost of illness (COI) studies). Economic evaluation is the comparison of alternative options in terms of costs and consequences (Drummond et al., 2015). In a CUA, the "outcomes of alternative procedures or programmes are expressed in terms of a single, utility-based unit of measurement" (Drummond et al., 2015). The unit is usually the quality-adjusted life-year (QALY) which is a generic health metric that allows

researchers to capture both the gains in health-related quality of life (HRQoL) and the increased life expectancy attributable to a healthcare intervention (Luyten et al., 2016). In calculating QALYs, a person's health state is valued relative to perfect health (value of 1) or death (value of 0), this health state is then weighted by the length of time a person spends in this state (O'Reilly et al., 2011). However, in other settings where it is difficult to measure the QALY such as in children, the disability-adjusted life year (DALY) is preferred. The DALY was developed by the WHO and the World Bank to quantify disease burden and injuries on the human population (Gao et al., 2015). DALYs seek to quantify 'the total years of life lost to premature death and the years of life lived with suboptimal health due to any condition that reduces functioning partially or fully for a short period or a long duration' (Chen et al., 2015). The multidimensional outcomes used within CUA enable comparisons across diseases, thereby overcoming the limitation of the CEA where outcomes are often 'natural' or disease specific (Kumar et al., 2006).

The CEA is defined as, "an economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (life-years gained, deaths avoided, heart attacks avoided or cases detected)" (Wonderling et al., 2011). The results for a CEA may be stated as, "either in terms of incremental cost per unit of effect or in terms of effects per unit of cost (life-years gained per dollar spent)" (Drummond et al., 2015). CEAs are used when comparing interventions with the same effects. This has been cited as one of their major limitations, the reason being, economic evaluations are often used to guide decision-makers in making informed decisions about resource allocation, which often requires comparing benefits of different programs and assessing the opportunity cost (Drummond et al., 2015). In such instances, the CUAs are more applicable because of their generic measure of benefit. The CUA also has limitations particularly in valuing utility of children (Kwon et al., 2019).

In this review, we will also include CBAs which have been performed for paediatric pulmonary diseases. CBAs are studies where, "both costs and benefits are measured in monetary values, making it suitable to evaluate interventions occurring inside or outside the health care sector…" (Zweifel and Telser, 2007). This allows for a relative comparison of the benefit of intervention(s)/ programme(s) to society. However, in children, this presents as a challenge as they are not economically productive.

There are also some instances where the decision to choose an intervention is solely based on the costs of each intervention, and the least costly intervention is adopted (Kumar et al., 2006). This usually occurs when the interventions are expected to have a similar outcome, and the deciding factor becomes the cost. This type of evaluation is the CMA, which is only possible in instances where prior research has been conducted that shows that the two programmes are equivalent in terms of effectiveness (Drummond et al., 2015).

Partial economic evaluations as earlier indicated include COIs, cost analysis, and cost description studies. A cost analysis "*compares the costs of two or more alternatives without examining their outcomes to find out which is of the alternatives is the least costly option*"(Drummond et al., 2015). the most basic type of economic evaluation as they provide only the costs of the interventions (Gunawardane, 2019).

With respect to COI, it is "the value of the resources that are expended or forgone as a result of a health problem" (Hessel, 2008). It includes health sector costs (direct costs), the value of decreased or lost productivity by the patient (indirect costs), and the cost of pain and suffering (intangible costs) (Jo, 2014). COIs also provide an estimation of the savings that could be made if the disease were to be eradicated (Costa et al., 2012). Whilst COI studies can demonstrate which diseases may require more allocation of treatment resources, they are limited in their determination of resource allocation as they do not measure health outcomes (Segel, 2006).

STUDY AIMS AND OBJECTIVES

The proposed study is a systematic review of economic evaluations on different interventions related to paediatric pulmonary diseases. These interventions will include different treatment regimens; promotive and curative measures; diagnostics and screening; medical devices and technology; and additional support such as supplemental oxygen. We are interested in identifying the health economic research that has been carried out in the past decade with regards to paediatric pulmonary diseases.

Research question

<u>The main research question is:</u>

- Which economic evaluations have been done to date on paediatric pulmonary diseases?

The sub-research questions are:

- Which type of economic evaluations have been done?
- When and where were they done?
- Which pulmonary diseases were assessed in the economic evaluations?
- At which level of care were these economic evaluations conducted?
- Has there been an increase or decrease over time in the number of paediatric economic evaluations?

Aim

To conduct a systematic review of economic evaluations on the interventions for paediatric pulmonary diseases conducted in a hospital setting.

Objectives

The proposed study seeks to:

- provide a qualitative and quantitative description of existing literature on economic evaluations for paediatric pulmonary diseases,
- categorise the methodologies used for the different economic evaluations,
- describe the health care and geographical settings of the studies included,
- highlight the timing of studies,
- describe the types of diseases and the different interventions covered in the economic evaluations,
- highlight any differences which might exist across the different study settings

Justification

The study will be carried out on the premise that the study findings will contribute towards a better understanding of the gaps that exist in the economic evaluations of childhood pulmonary diseases. It will also offer a description of methods used in the current literature to conceptualise methods for subsequent economic evaluations for paediatric diseases. The review will include economic evaluations from high-,

middle- and low-middle income countries to identify any differences which may occur across the various settings. The study should ultimately also inform policy from an angle of efficient and equitable resource allocation (Thielen et al., 2016). The study is a component of the PediCAP study aiding in the identification of some of the issues arising in the field of paediatric community-acquired pneumonia, to better inform the progression of the emerging study. The review will include different components of economic evaluations such as the costs, clinical effectiveness, cost-effectiveness, or cost-utility analysis for different paediatric pulmonary diseases. The diseases that will be considered in the review will include asthma, tuberculosis, and pneumonia. The review will only include inpatient-hospital based articles.

METHODOLOGY

This section provides details about the inclusion and exclusion criteria that will be used in the selection of the articles for the systematic review. It will also have sections on the information sources that will be used to identify the articles relevant to the systematic review, the search strategy that will be used, how the data will be managed throughout the process, and how the data will be synthesised. Ultimately, the data that will be analysed and synthesised in the systematic review should inform policy and most importantly, the PediCAP study. Figure 1 is a diagrammatic representation of the research plan showing the different phases of the research. The arrow on the far right of the diagram represents the continuous process of informing the PediCAP study and noting the policy implications across all the phases of the research.

Research diagram

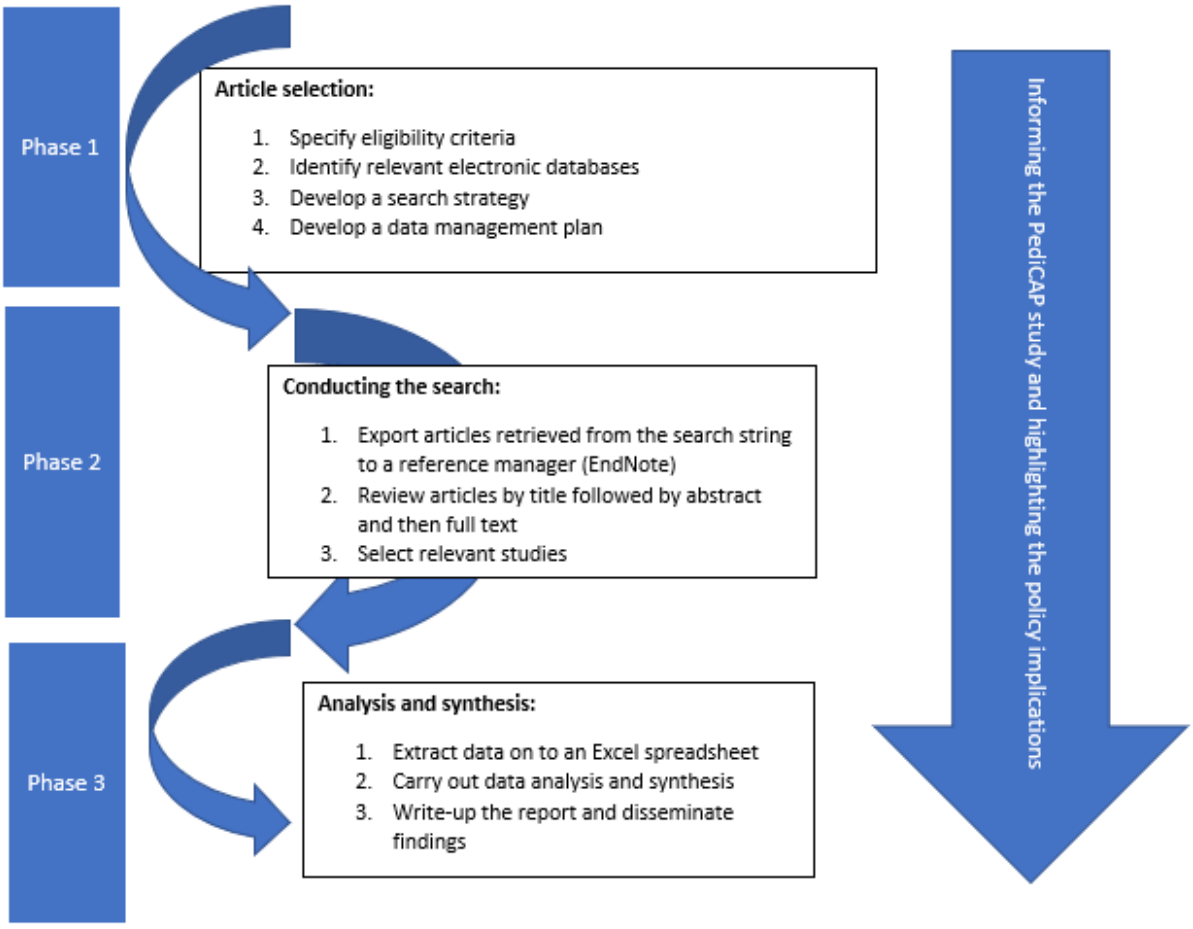

Figure 1: Research plan

Eligibility criteria

The study will include economic evaluations from high-, middle- and low-middle income countries, i.e. globally from any setting. The review will include studies of both full economic evaluations (CEA, CUA, CBA, CMA) and partial economic evaluations (cost descriptions, cost analysis studies and cost of illness studies) (Murthy et al., 2017). Only studies reported in the English language, specific to paediatric pulmonary diseases will be included in the review. The study will investigate the trends in paediatric health (disease focus and type of economic evaluation methodology used) and how these have changed over time. To meet this objective, the review will include studies published from 2010 to 2020. This review will not exclude studies based on their quality.

Study population

The review will include economic evaluations (EEs) that focus on paediatric or child health (0-6 years) in the field of pulmonary diseases. Therefore, the terms child, children, paediatric and neonates will be used interchangeably.

Study settings

The EEs that will be included will be those which are hospital-based, and of inpatients. That is, EEs conducted in non-hospital settings such as clinic-based, school-based, home-based, and other community-based interventions will be excluded from the systematic review.

Interventions

This systematic review will include economic evaluations that cover different aspects of paediatric pulmonary diseases. These aspects will be limited to those conducted in clinical settings, for example, different treatment regimens; curative measures; diagnostics and screening; medical devices and technology; and additional support such as supplemental oxygen. Different comparators will be considered in the review, such as placebos, alternative standards of care as well as do nothing scenarios (Murthy et al., 2017).

Outcomes

The outcome measures for this study will be those that are related to measures of cost-effectiveness and cost-utility. These will include; “Incremental cost per QALY”, “Incremental cost per DALY, “Incremental Cost-Effectiveness Ratio (ICER)” and natural units such as life years (Drummond et al., 2015).

Information sources

Electronic searches from different databases will be conducted to identify the studies which meet the pre-specified eligibility criteria. The searches will be conducted within PubMed, Web of Science, MEDLINE, PEDE, and the Cochrane library. The Cochrane library will be a useful resource in identifying systematic reviews related to the study which have previously been conducted.

Search strategy

The same search terms will be used for the different electronic databases listed above. The search terms will be guided by the following domains: population, intervention, comparator and outcomes (Thielen et al., 2016). Across all the electronic databases, there will be the use of keyword searches, MeSH terms, truncation, and Boolean operators. The initial step will include developing multiple search terms for each of the domains. Under the population domain the following search terms will be used; [“paediatric” OR “paediatrics” OR “pediatric” OR “child” OR “children” OR “infant” OR “infants” OR “neonate” OR “neonates”]. The next domain will be that of the condition, where the focus of this review is aligned to paediatric pulmonary diseases, with conditions such as; [“pneumonia” OR “asthma” OR “pulmonary TB” OR “ bronchiolitis” OR “bronchitis” OR “paediatric disease” OR “pediatric disease” OR “respiratory infections”] will be included. For the final domain, measures of the outcome will be searched for using the following terms; [“economic evaluation” OR “economic eval*” OR “economic*” OR “costs” OR “cost-effectiveness” OR “cost-utility analysis” OR “effectiveness” OR “cost-benefit” OR “cost*” OR “cost benefit” OR “cost effectiveness” OR “cost utility analysis” OR “CEA”OR “CUA” OR “CBA”]. The final step in developing the search strategy will be to make use of the Boolean operator “AND” to combine the multiple search terms for the domains.

The search string will include; [“paediatric” OR “paediatrics” OR “pediatric” OR “child” OR “children” OR “infant” OR “infants” OR “neonate” OR “neonates”] AND [“pneumonia” OR “asthma” OR “pulmonary TB” OR “ bronchiolitis” OR “bronchitis” OR “respiratory infections” OR “paediatric disease” OR “pediatric disease”] AND ; [“economic evaluation” OR “economic eval*” OR “economic*” OR “costs” OR “cost-effectiveness” OR “cost-utility analysis” OR “effectiveness” OR “cost-benefit” OR “cost*” OR “cost benefit” OR “cost effectiveness” OR “cost utility analysis” OR “CEA”OR “CUA” OR “CBA”].

Study records

One of the characteristics of a systematic review is the reproducibility of the methodology used (Moher et al., 2015a). Therefore, all the steps that will be taken in the study will be recorded properly.

Data management

The economic evaluations that will be included in the study will be managed using the reference manager, EndNote X9, Clarivate Analytics. The results from the searches will be exported to and stored in Endnote. A shareable library will be created to allow for any stakeholders interested in accessing the articles that were used in compiling the systematic review to do so. The search history from the different electronic databases utilised will be exported to Microsoft Excel as a mechanism to keep a record of the steps taken during the searching process.

Selection process

The selection process is a critical stage in the systematic review. It requires careful selection of the evidence to be collated to answer the research question. After the searches have been carried out in the different electronic databases and exported to EndNote, the studies will be screened for their appropriateness in meeting the research purpose according to the inclusion and exclusion criteria. The first stage of the screening process will be the removal of duplicates to be followed by the title review. After this will be an abstract review. Once the abstract review has been done, the articles will undergo full-text screening, and this will be the final step of the screening process. The articles that will be selected for inclusion in the study after the screening process will be stored in Endnote. The information that will be extracted from the selected articles will entered in a Microsoft Excel spreadsheet. This spreadsheet will be pretested before it is used for extraction purposes. Where inclusion or exclusion is unclear, a second researcher will be consulted.

Data items

The data items that will be extracted from the articles selected for inclusion in the systematic review are summarised in table 1 below.

Administrative information	Study characteristics	Methodological information	Quantitative data
Lead author	Geographical setting, healthcare setting.	Costing sources	Total costs (breakdown the costs into cost categories)
Journal name	Economic perspective (patient, societal or provider)	Effectiveness sources	Incremental cost per outcome measure: DALYs QALYs Natural units
Year of publication	Currency reported, currency year	Annuitisation	
Project title	Disease	Discounting	
Funding sources	Study population	Sensitivity analysis	
Database searched	Intervention and comparator	Modelling	Conversion rate ICER
	Type of economic evaluation (full or partial)	Ethical considerations arising	
	Discount rate	Costing approach	
	Study period	Timeframe	
	Follow-up period		

Table 1: Data items for extraction

Table 1 will be used as a tool to extract data from different selected articles. It will be pivotal in the synthesis and analysis of both qualitative and quantitative data on economic evaluations on interventions for paediatric pulmonary diseases.

Data analysis and synthesis

During the data analysis and synthesis, some relationships will be explored to answer the research questions. For the questions, "what economic evaluations have been done to date?" and "has there been an increase or decrease in the number of economic evaluations over time?", we will look at the volume of the publications conducted between 2010 and 2020 of economic evaluations for paediatric pulmonary diseases. For the other research questions, they will be addressed by studying the relationships that exist between the analytic technique (the type of economic evaluation) used and the variable of interest as indicated in figure 2. The statistical significance of the different relationships will be analysed using Microsoft Excel and R software (R Project, Vienna, Austria). Figure 2 below illustrates the different variables that will be analysed against the

choice of economic evaluation. These variables will include the geographical setting, age group, summary outcomes, healthcare setting, disease classification, and the intervention type.

Risk of bias

To minimise the risk of selection bias in the study, the study will be guided by the Cochrane guidelines on systematic reviews of economic evaluations (Higgins, 2019) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al., 2013, Drummond et al., 2015). All the articles that will be included in the review will be assessed by the researcher for their appropriateness in the study against the set of guidelines from the tools listed above.

Dissemination of findings

The plan for the dissemination involves the production of a manuscript for a named peer-reviewed journal that will be identified during the study. In addition, there will also be the development of a policy brief for different groups of key stakeholders. This might be an opportunity for those in decision-making spaces to use the evidence from the study to inform their decision-making. The full report will also be availed to individuals and other groups that might be interested in the study findings. The possible groups might include, PediCAP group, Ministries of Health, and some non-governmental organisations (NGOs) working in the hospital paediatric units.

Possible difficulties and solutions

We anticipate facing difficulties in the identification of studies that match the pre-specified criteria. However, a second researcher will be enlisted for consultation. Going into the review, we also anticipate having to deal with many data collected through the database searches. We have proposed utilising the reference manager Endnote to address this challenge. In instances where an article is identified as relevant to the study, but the full text is unavailable, the researchers will request the full articles from the respective authors where possible.

Strengths and limitations

The main strength of the study methodology is in its inclusivity of studies from different geographical locations. This will provide an insight into the various issues regarding paediatric health by region. However, there is a limitation in the way that the review will include economic evaluations that fit the pre-specified inclusion criteria regardless of their quality. To address these drawbacks, the author will provide a section that will flag studies that do not meet the reporting standards of the CHEERS checklist. Another limitation is in the inclusion of studies that are reported only in English which might exclude some relevant studies; however, due to resource constraints research articles in other languages will not be included.

Figure 2: Framework for data analysis and synthesis

EXPECTED RESULTS

For this research, the results of the review will be reported in both tabular and non-tabular formats. The results will show the most recent studies to the least recent studies on economic evaluations for paediatric pulmonary diseases. It will identify which paediatric disease has received the most attention in terms of economic evaluations, the aspects which were covered, and get an overall understanding of where some gaps still exist. The review will provide a description of the health care settings where the economic evaluations took place, e.g., whether it was in a hospital setting (if reported) and the methodologies that were employed.

Regarding the PediCAP study, where costs and cost-effectiveness data of different strategies for community-acquired pneumonia will be collected at different hospitals in South Africa, Uganda, Zambia and Zimbabwe, this review will help establish the methods that have been used in previous studies to inform the work and methodology used in the economic evaluation component of the PediCAP study.

ETHICAL CONSIDERATIONS

Since the introduction of the Nuremberg Code and the Helsinki Declaration, there is an increasing awareness amongst researchers on the need to uphold ethical standards (Vergnes et al., 2010). Primary researchers who interact with human subjects and collect sensitive information need to be particularly aware of issues on obtaining consent from their participants, doing no harm and ensuring privacy and confidentiality (Suri, 2020). However, in systematic reviews, there are no explicit guidelines on the standard ethical considerations. In this section, the discussion will be around the steps that will be taken to ensure that the researchers will be reflexive and will adhere to good practices in conducting the review as a way of upholding ethical standards in the proposed study.

Study approval

The proposed review is a secondary analysis which does not involve human subjects; it does not require approval to be sought from the Ethics Committee. However, approval to conduct the proposed review will be

sought from the School of Public Health and Family Medicine (SPHFM) Departmental Research Committee at the University of Cape Town.

Selected studies

The proposed study is a systematic review of economic evaluations for paediatric pulmonary reviews. The authors of the included studies will be duly acknowledged in the references and the text. This also includes the different databases that will be used in identifying the different studies. It is also worth noting that any ethical insufficiencies, in reporting the ethical considerations in the studies included for the review, will be highlighted.

Good practices in systematic reviews

A way of upholding ethical standards in systematic reviews that has been cited is adherence to good practices in systematic reviews (Vergnes et al., 2010). These include:

- **Avoiding duplication**

To avoid redundancy, searches will be conducted through the Cochrane Library to identify similar reviews that have been carried out and areas where the proposed review can contribute towards or build on existing work (Wager and Wiffen, 2011). Where the need presents itself to contact authors that have worked on systematic reviews on economic evaluations for paediatric pulmonary diseases, then they will be contacted. A useful resource already uncovered to identify the existing literature on paediatric evaluations that will be used in the study is PEDE.

- **Author reflexivity**

Author reflexivity is a critical step in ensuring that results are unbiased. It will be the responsibility of the author throughout the study to understand their positionality in the study (Yin, 2002). The author throughout the study will be aware of the need to communicate the study findings to a broader audience as these findings will be disseminated to different groups of stakeholders. Yin's criteria for ensuring rigour and validity in studies will be used in the proposed study. Namely:

I. Confirmability, transferability, and dependability

The confirmability of studies will be ensured through providing the relevant information about the different articles that will be used in the review and a detailed process on how they will be retrieved in the results section of the systematic review. The steps that will be taken in this study will be recorded in such a way that whoever wants to conduct the same study can follow the same steps and come out with the same results (Wager and Wiffen, 2011). Also, the knowledge that will be generated from the proposed study could be used by future researchers who might be interested in conducting economic evaluations for the same age group (what to do or what not to do).

II. Credibility

The credibility of the study results will be ensured by following guidelines from different sources (triangulation) in terms of best practices in conducting a systematic review (Higgins, 2019), preferred methods for reporting systematic reviews (Moher et al., 2015a) and a thorough selection of studies that fit the pre-specified selection criteria.

Conflicts of interest

In the event of any sources of conflict arising, the author will be sure to highlight them. The sources of funding for this will also be reported as a means of ensuring transparency (Yin, 2002, Korstjens and Moser, 2018). Funding is provided for this work through the European Developing Countries Clinical Trials Partnership (EDCTP); no conflicts of interest are noted.

WORK PLAN

Activity	**Duration**
Protocol	2 months
Literature Review	2 months
Quality assessment of studies	2 months
Data extraction	2 months
Data analysis and synthesis	2 months
Writing up	2 months
Total	**12 months**

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PART B: STRUCTURED LITERATURE REVIEW

INTRODUCTION

Health has a central position in the United Nations 2030 Agenda for Sustainable Development through Sustainable Development Goal (SDG) 3 which seeks "to ensure healthy lives and promote well-being for all at all ages" (Barredo et al., 2015). Therefore, investing in children's health is critical as they constitute society's future human capital. It is from this premise that the health of children is enshrined in the Agenda for Sustainable Development (Alfvén et al., 2019). Having children at the centre of the SDGs provides them with the protection and the resilience they need to withstand emerging global challenges and a constantly evolving disease burden. Whilst significant progress has been made on many health fronts since the 2000s, to meet the SDG targets, there is a need to accelerate and expand this progress. Efforts to accelerate this progress include paying close attention to the death rates of children less than five, which is an essential indicator of child health globally (Barredo et al., 2015, Van Malderen et al., 2019). One of the SDG 3 targets is ending mortality from preventable causes in children below the age of five and new-borns by 2030. Achieving this target requires extensive efforts to ensure that effective interventions in reducing infant mortality are made accessible, affordable, and acceptable for all. Countries and the globe at large therefore require more robust evidence-based decision-making to inform resource allocation for such interventions. Economic evaluations provide an opportunity to inform evidence-based decisions.

Over the years, economic evaluations have increased in availability and have gained more acceptance as a tool for decision-making in health care. This has primarily been attributed to the scarcity of resources where decision-makers are increasingly seeking ways in which they can maximise the benefits from constrained resources (Kirigia and Asbu, 2013). The decision as to which health care intervention to adopt can be well informed by economic evaluations which help to determine the intervention which comparatively gives the best value for money (Lamsal and Zwicker, 2017). Economic evaluations to date have been conducted for different age-groups and across diverse settings. However, what remains scarce in literature is a consolidation of the health economic

evidence on paediatric pulmonary diseases. The interest in paediatric pulmonary diseases follows their emergence as the main causes of morbidity and mortality in the paediatric population (De Benedictis and Bush, 2018). Despite these diseases being the leading causes of morbidity and mortality of children, they are also often very preventable and manageable (FIRS. Forum of International Respiratory Societies, 2017).

This structured literature review serves as the precursor to a systematic review aimed at answering the question, "which economic evaluations have been done to date for paediatric pulmonary diseases?". It aims to inform a broader study, PediCAP. PediCAP has the overarching objective, "to optimise antibiotic treatment for children between the ages of 2 months to 6 years hospitalised with severe/very severe community-acquired pneumonia in South Africa, Uganda, Zambia and Zimbabwe" (Penta, 2020). PediCAP is a clinical trial that will investigate "the impact of oral step-down to amoxicillin or co-amoxiclav for children with severe community-acquired pneumonia (CAP), who have had intravenous antibiotics administered to them in a hospital setting" (Penta, 2020). Taking this approach could potentially reduce the length of hospital stay for children whilst also improving the clinical outcomes for the sick children.

Objectives of the literature review

This section will present a summary of the literature on economic evaluations, paediatric health, and pulmonary diseases. It will highlight some of the topical issues around paediatric pulmonary diseases. Also, it will provide a synopsis of the gaps that exist in economic evaluations for paediatric pulmonary diseases whilst also acknowledging the work that has been done to date in that field. This literature review will also provide an opportunity for the identification of other matters arising in child health (pulmonary health) whilst highlighting the policy implications of these issues.

Literature search strategy

The strategy involved using search engines (Semantic Scholar and Google Scholar) to identify relevant documents. Keyword searches were also conducted in different scientific databases, namely: PubMed,

Web of Science and Scopus, keeping in mind that this is a structured review (the systematic review is presented in the subsequent dissertation section – Part C). The keywords were "economic evaluations, paediatric pulmonary diseases, pneumonia, child health". Some of the keywords were combined during the search. The documents retrieved included policy documents, economic evaluations, qualitative and quantitative research, reports, conference proceedings and policy briefs. Documents that were included in this structured literature review were those that focused on child health and paediatric pulmonary diseases and economic evaluations. We excluded articles or studies reported in other languages besides English and those whose focus was not on paediatric pulmonary health.

SUMMARY AND INTERPRETATION OF LITERATURE

Economic evaluations: An overview

In making decisions, policymakers are often concerned with assessing the opportunity cost of the decisions they make. Opportunity cost refers to the value of the benefit foregone by taking a different course of action (Drummond et al., 2015). Decision-makers are interested in this value of the benefit foregone because its effects influence how health care resources are spent. In other words, the costs, and the benefits of different courses of action should be weighed before any decision can be made, and economic evaluation is a tool we can use to aid this process. An economic evaluation is referred to as "t*he comparative analysis of alternative courses of action in terms of both their costs and consequences"* (Drummond et al., 2015). Economic evaluations are divided into full economic evaluations, such as cost-benefit analysis (CBA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost minimisation analysis (CMA); and partial economic evaluations which encompass cost of illness studies, cost analysis and cost description studies (Higgins, 2019).

The evidence that is retrieved from these economic evaluations is referred to as economic evidence, and policy-makers across countries use this evidence. In addition to the economic evidence being used by policy-makers, the evidence is also relied upon by pharmaceutical companies, health care providers, and patients (Frick et al., 2012b). The audience for whom the economic evaluation is

intended influences the perspective taken (e.g. health care or societal perspective). Generally speaking, pharmaceutical companies require this economic evidence to make decisions on which drugs or devices to manufacture, health care facilities use this evidence to seek profit maximisation, and the patients are interested in this evidence to guide their decision on the utilisation of services to improve their health (Frick et al., 2012a). Economic evidence is particularly useful in health care decision-making, and it would be useful to consider the different techniques which are employed in economic evaluations and the value that each of them has. This will be covered in the following sections, including a discussion on the value of including evidence from economic evaluations into systematic reviews. This section will also illuminate some of the facilitators and barriers that exist in conducting economic evaluations across different age-groups and settings.

Systematic reviews of economic evaluations

In the sections leading to this one, the importance of economic evaluation in informed decision-making has been emphasised. In an article by Frick et al. (2012b), the importance of incorporating economic evaluation data into systematic reviews for health care interventions is explained. They also indicate that taking this route would be useful in strengthening evidence-based decision-making. The use of systematic reviews over the years has increased because they are considered as pillars for evidence-based health care (Selçuk, 2019). The methodological rigour of systematic reviews has been cited as one that facilitates their applicability in minimising bias, maximising contribution to science, providing a foundation for practice guidelines and use as a reference standard for getting clinical research into real-world practice (Munn et al., 2018, Moher et al., 2015b, Sutherland, 2004).

Systematic reviews are: *"a method/process/protocol in which a body of literature is aggregated, reviewed and assessed while utilising pre-specified and standardised techniques" (Selçuk, 2019).* Initially, systematic reviews were common for "*synthesising evidence from randomised controlled trials investigating health treatment efficacy*" (Gomersall et al., 2015). Over time, their methodology has evolved to allow reviewers to synthesise a large amount of evidence to answer specific research

questions and support evidence-informed decision-making. The evolving methodology resulted in different types of reviews which include methodological reviews, prognostic reviews, effectiveness reviews, aetiology reviews, prevalence reviews, diagnostic reviews, experiential reviews, psychometric reviews, expert reviews and cost/economic evaluation reviews (Munn et al., 2018). The choice of systematic review type is guided by the research question that the researcher seeks to answer. In this instance, the research question was one on economic evaluations performed for paediatric pulmonary diseases. This largely influenced our decision to select the cost/economic evaluation type of systematic review.

The Cochrane handbook for systematic reviews and other handbooks that provide guidelines for conducting systematic reviews have been adapted to include guidelines specific to systematic reviews for economic evaluations (SREEs) (Higgins et al., 2019). The guidelines differ in their presentation across the different handbooks, but what is consistent is their portrayal of economic evaluation reviews as tools for assessing the costs, processes, contexts, or procedures of different interventions (Munn et al., 2018, Higgins, 2019). More specifically, SREEs can be used with the aim of; quantifying the differences between competing interventions for the same condition; showing the effect of adjusting the delivery of an intervention at different intervals, different age-groups or risk groups; evaluating the effectiveness of new technologies; identifying conditions which need to be met to achieve optimum benefits of an intervention; and identifying patient, health service provider, or government preferences (Pignone et al., 2005, Tacconelli, 2010). SREEs have been cited as an efficient mechanism to synthesise evidence on cost-effectiveness which can help in avoiding research waste, enabling sponsors, governments, and investigators to maximise their efforts in meeting set targets (Jacobsen et al., 2020).

The ability of systematic reviews to synthesise large amounts of evidence is one of their strengths (Gomersall et al., 2015). What has been questioned is the synthesis of economic evidence in systematic reviews. This synthesis is made complex by the variability that exists across different health system contexts and very different methodologies used in the economic evaluation studies. These

variations can be observed in the different payment mechanisms for health care and in terms of health service delivery across country health systems (Jacobsen et al., 2020, Nixon et al., 2001). From this premise, one of the arguments against the value of SREEs is that the differences in the costs and utilisation of resources vary by country. This might translate to the same interventions producing different results across diverse settings (Gomersall et al., 2015). This variability could potentially undermine the transferability *("the extent to which the results of a study hold true for a different population or setting*") and generalisability ("*the extent to which the results of a study can be generalised to the population from which the sample was drawn"*) of the results obtained from the SREEs (Wijnen et al., 2016). SREE are also prone to confirmation bias. Confirmation bias in research is, "*when an individual looks for and uses the information to support their own ideas*" (Simundić, 2013). Whether it is unintentional or intentional, the effects of bias can diminish the value of SREEs to decision-makers and other users significantly (Wijnen et al., 2016, Liberati et al., 2009). It is therefore important to conduct SREEs with methodological rigour to minimise any potential bias. To date, tools such as PRISMA (preferred reporting items for systematic reviews and meta-analyses) have been developed to improve the quality and standardise the reporting of systematic reviews.

Standardising how systematic reviews are reported is of paramount importance, especially for the end-user. How systematic reviews are conducted differs from structured literature reviews. The critical differences between the two are observed in the methods of obtaining literature and the selection and extraction of material and data for the review (Okoli, 2015). Some of the defining features of systematic reviews and its conduct include; articulated objectives, predetermined inclusion and exclusion criteria to establish the eligibility of studies, predefined search strategy to identify all the eligible studies, a thorough process of screening and selecting relevant studies, appraisal or quality assessment of the selected studies, data extraction, analysis of the data extracted from the selected studies, presentation and interpretation of the results, and ensuring transparency in the reporting of the methodology used to conduct the review (Munn et al., 2018, Cronin et al., 2008). In comparison, structured literature reviews are influenced by the investigator's decisions in

selecting and evaluating the data. The criteria for literature selection in structured literature reviews are not always made known to the reader (Petticrew and Roberts, 2008).

SREEs can be time-consuming, costly, and are best conducted while working in teams (Tacconelli, 2010). The dearth of economic evaluations also raises concerns amongst reviewers interested in conducting SREEs that the outcome of their systematic review could be limited rather than producing quality evidence that could contribute in getting research into real-world practice (Gomersall et al., 2015). According to (Drummond et al., 2010), "*...the real contribution of a systematic review of economic evaluations may not be to produce a single authoritative result, but to help decision-makers understand the structure of the resource allocation problem that they are addressing and the impact, on the overall result of the main parameters".*

Economic evaluation concepts and methods

The value of economic evaluations in informing decision-makers on resource allocation in a manner that maximises the benefits and minimises waste have been emphasised in the earlier text. This section will summarise the different concepts and methods that characterise economic evaluations. Summaries will be provided for the different types of full economic evaluations (CUA, CMA, CBA, CEA). Full economic evaluation is not a single research method, but rather, "*a framework for structuring specific decision problems*" (Shemilt et al., 2008). Therefore, the choice of economic evaluation to be adopted is also determined by the economic question that the study seeks to answer. According to (Drummond et al., 2015), full economic evaluations studies aim to "*describe, measure and value all competing courses of action, including the respective resource inputs and outcomes*". In contrast, partial economic evaluations (cost of illness studies, cost analysis and cost description studies) do not "*provide explicit comparisons between different courses of action with regards to costs and consequences*" (Shemilt et al., 2008). However, they do provide some insights to help understand the economic aspects of interventions.

Cost-effectiveness analysis

Economists often use the term technical efficiency, which occurs when the minimum amount of input produces the maximum amount of output (Ahmed et al., 2019). Generally, this is the scenario that is ideal for policy-makers. The CEA allows policy-makers to compare different interventions to see how best they can achieve technical efficiency within a given budget (Miller and Trent, 2001, Perkins et al., 2015). A CEA measures the effect of an intervention in unidimensional units, also known as natural units (life-years gained, number of infections averted) (McIntosh and Luengo-Fernandez, 2006). Where one intervention costs less and is more effective, then the decision to adopt that intervention is straight forward (Clyne and Edwards, 2002). It often becomes difficult to decide on the appropriate course of action when one intervention is more effective, whilst also more costly.

To assist with the decision-making, costs per unit effect of the competing interventions are compared (Drummond et al., 2015). These are compared as a ratio known as the incremental cost-effectiveness ratio (ICER). The ICER is calculated by dividing the differences in the cost of the competing alternatives by the difference in their benefits. The ICER is then compared to an appropriate cost-effectiveness threshold (CET) or to results for similar interventions and contexts, to establish whether the intervention gives value for money. To look at the affordability of the intervention, a next step is required, which is assessing the budget for the given interventions. This is commonly referred to as the budget impact analysis (BIA). A BIA is carried out by taking "*the true unit cost of an intervention, multiplying it by the number of people for whom the intervention is for to provide a picture of the total budget required to fund the intervention*" (Yagudina et al., 2017). From this calculation, it can be determined whether high-value interventions are affordable.

To re-iterate, economic evaluations are a useful tool in guiding resource allocation. This often translates to decision-makers having to compare the benefits of different programs and assessing their opportunity cost. Unfortunately, the CEA does not fully accommodate this as it only measures interventions with the same outcome and does not allow for cross-sector comparisons. The CUA is more applicable for such comparisons (Wonderling et al., 2011, Drummond et al., 2015).

Cost-utility analysis

CUAs and CEAs are the same in many ways, with their main difference being how they measure outcomes/effects. In CEA, as already mentioned, the measurement of outcomes is in natural units. In contrast, in CUAs, the outcomes are utility adjusted, where utility refers to a "*patient's preference for a particular health outcome*" (Nancy et al., 2014). The multidimensional outcome is reported as either a disability-adjusted life year (DALY) or a quality-adjusted life-year (QALY). CUAs have gained popularity over the years in health care decision-making because they enable comparison of health benefits for different health care interventions by using a single measure of health benefit (the QALY and the DALY) (McIntosh and Luengo-Fernandez, 2006).

The DALY is a summary measure of health which combines morbidity and mortality into a single measure (Chen et al., 2015). DALYs quantify "*the total years of life lost to premature death and the years of life lived with suboptimal health due to any condition that reduces functioning partially or fully for a short time or a long duration*" (Chen et al., 2015). The QALY is a combination of the quantity and quality of life that a person can live in a given state (Goodacre, 2002). Put in other words, a QALY is, "*a generic health metric that allows researchers to capture both the gains in health-related quality of life (HRQoL) and the increased life expectancy attributable to a health care intervention*" (Luyten et al., 2016). To calculate the QALY, the quality of life is measured on a scale ranging from zero to one, where zero indicates death and one indicates perfect health (O'Reilly et al., 2011, Goodacre, 2002). The final stage in calculating the QALY involves multiplying the amount of time in years over which the quality assessment applies by its quality weighting (Drummond et al., 2015). The quality weighting is usually determined by generic preference-based measures such as the EuroQol 5 Dimension (EQ-5D) (Nancy et al., 2014).

Like CEA, CUA assesses relative efficiency using a ratio, which in this case is the incremental cost-utility ratio (ICUR) amounting to a cost per QALY gained or cost per DALY averted (Palmer et al., 1999). The ICUR also needs to be compared to an appropriate CET to assess whether the intervention gives value

for money. The CET describes the amount of money that, if removed from the health care system, would result in one less unit of health being generated (Woods et al., 2016). An intervention is considered as cost-effective if its ICUR or ICER is less than the CET. When the ICER is greater than the CET or to the results of similar studies where no country threshold exists, then the benefits are insufficient in comparison to the cost, thus the intervention cannot be cost effective (Woods et al., 2016).

To assist with the interpretation of an ICUR, a cost-effectiveness plane can be used as illustrated in the figure below. The comparator is plotted at the origin, the horizontal axis is the difference in outcomes between the interventions while the vertical axis represents the difference in total costs (Cleary et al., 2006). If the ICER falls in quadrant II and quadrant IV, the decision is straight forward, yes, and no respectively. In quadrant II the new intervention has lower costs and more benefits, unlike in quadrant IV where it has more costs and less benefits. Quadrants I and III are more difficult to decide from because they require the decision makers to make a trade off. In quadrant III the new intervention is less costly with lower outcomes and in quadrant I, the new intervention is more costly but with more outcomes (Cleary et al., 2006). Some countries have adopted the use of CETs to try and assist decision makers on dealing with ICURs falling in the quadrants in question (Klok and Postma, 2014).

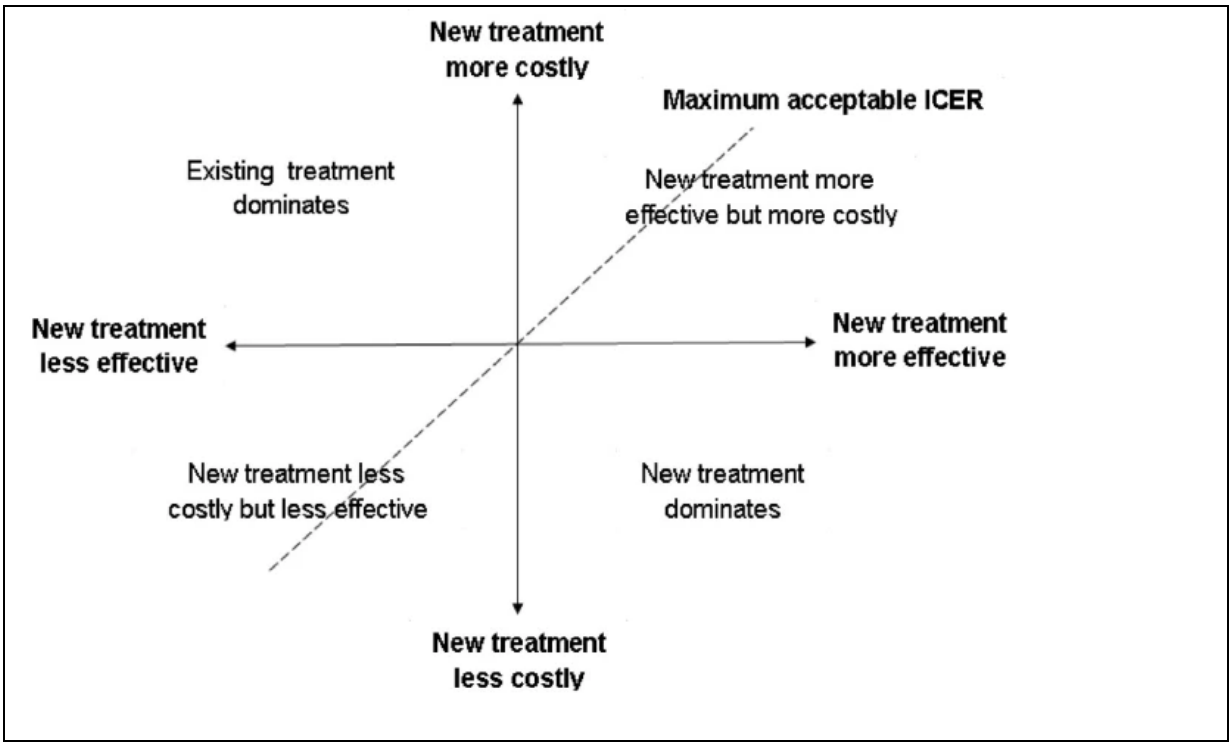

Figure 3: Cost-effectiveness plane (Hounton and Newlands, 2012)

Cost-benefit analysis

Following the definition by (Drummond et al., 2015), a CBA is, "*a type of economic evaluation where costs and benefits are both valued in monetary terms*". It is the broadest form of economic evaluation, where results are presented in terms of net benefit (Razzouk, 2017). The net benefit put in other words, is the benefit of an intervention (in monetary terms) minus the cost of an intervention (Perkins et al., 2015). The essence of a CBA therefore is, if the benefits of a project / programme / intervention outweigh the project / programme / intervention costs, then the project / programme / intervention is recommended (Johansson and Kriström, 2018). CBA is useful in measuring both allocative and technical efficiency in different sectors, including the health sector, where allocative efficiency relates to "*the distribution and mix of resources within the health sector in comparison with other sectors of the economy*" and technical efficiency is concerned with "*maximising the output produced from the given inputs/resources*" (Athanassopoulos and Gounaris, 2001).

Nonetheless, the applicability of CBAs in health care has been criticised due to the difficulties in converting benefits from health programmes into monetary values (Nancy et al., 2014, Robert, 2003).

The most common approach used in a CBA to quantify health in monetary units is the willingness to pay approach (WTP) which measures the degree to which patients value improvements in their health based on how much they would be willing to pay (Johansson and Kriström, 2018, Clyne and Edwards, 2002). Essentially, WTP estimates the "*monetary value of an outcome in the absence of an actual market for that outcome*" (Razzouk, 2017). It creates a measure by asking a sample, which aims to be representative of the population. However, as WTP is influenced by values, preferences, income, as well as state of health, this is not always a perfect fit (Nancy et al., 2014). Consequently, CBA is not as prominent in health care as the CEA and CUA. Another type of economic evaluation which is not so prominent is the CMA, which will be discussed in the subsequent section.

Cost minimisation analysis

A CMA is used in instances where clinical studies have shown the effectiveness of the competing alternatives to be broadly equivalent (Drummond et al., 2015). This is the simplest form of economic evaluation where the costs of two or more competing options under consideration are compared to establish the least costly intervention (Nancy et al., 2014, NICE, 2014). Essentially, the CMA can be described as cost analysis. The major drawback of CMAs is that they do not include the intended or unintended impacts from different health care interventions and only assume equivalent outcomes (Clyne and Edwards, 2002).

Partial economic evaluations

The previous sections described the uniqueness of the four main types of full economic evaluations (CUA, CMA, CBA, CEA). We shall now briefly describe the different types and characteristics of partial economic evaluations. Partial economic evaluations do not make explicit comparisons between alternative interventions in terms of both costs and consequences (Higgins, 2019). For example cost analyses are considered the most basic form of economic evaluation as they only offer comparisons on the costs of interventions and not on outcomes (Gunawardane, 2019, Segel, 2006). Similarly, cost of illness (COI) studies have been cited to have a limitation in their determination of resource

allocation as they do not measure health outcomes (Segel, 2006). The fundamental goal of COI studies is " to evaluate the economic burden that illness imposes on society as a whole health studies" (Jo, 2014). They provide an estimation of the savings that could be made if the disease were to be eradicated (Costa et al., 2012).

In addition to understanding the uniqueness of each type of economic evaluation, it also key to note the differences in methodological approaches of economic evaluations across age-groups, intervention settings and the type of intervention. Important to methodology is also noting whether the authors collected data on opportunity costs and include these to calculate the intervention cost, and how they did their discounting.

Concerns around economic evaluations

The growth in the use of economic evaluations in informing health care decisions has made difficulties in using standard methods for adults and children more relevant (Ungar, 2011). The observations made being that children are unique individuals, not just little adults, and as such, they require methods specific to them. The biological differences between the two groups mean that the results of economic evaluations of adults cannot be easily applied to children (Keren et al., 2004). Children differ from adults in their development, dependency, patterns of resource use and patterns of health and disease (Ungar and Gerber, 2010). These cognitive differences are relevant to economic evaluations as they affect how economic evaluations are conducted and what the results mean across different groups. Take for instance, in pharmaceuticals, the differences in medication dose and risk-benefit profiles between children and adults may produce different cost-effectiveness results (Keren et al., 2004). Children also have a high dependency on their parents and guardians, and often they stand in as proxies in valuing children's health (Oliveira et al., 2020). In a study by Ungar (2011), she argues that while parents may be reliable sources in reporting physical limitations on behalf of children, they might not be the best proxies in reporting more subjective outcomes such as the emotional status of children. The use of parents as proxies is more common in children under six years

old (Keren et al., 2004). For children over six years old, evidence shows that they can use the tools specifically developed for children to measure their health-related quality of life (HRQoL) (Stevens, 2010). However, questions have also been raised around these child-specific tools as to whether the dimensions of HRQoL for a 9-year-old are the same as those of a 16-year-old or if they differ.

Apart from the technical issues around economic evaluations for child health, there are also ethical considerations for this vulnerable group (Pitt et al., 2016). Since the Helsinki declaration in 1964, ethical guidelines in clinical research have been acknowledging the child's right as a research subject or patient to participate in their health care decision-making (Villena Sarmiento and Vieira Da Motta, 2013). Before minors can participate in any research, informed consent needs to be given by the parents or legal guardians of the children. In addition, children over six years of age are also expected to give their assent to participate in the research (Villena Sarmiento and Vieira Da Motta, 2013, Pitt et al., 2016). At this age, children are expected to have a degree of reflexive judgement, and as such, their views towards their health also matter (Stevens, 2010). The views of the children towards their health should be considered at all levels of decision-making. It is, therefore, of paramount importance that when using economic analyses to inform resource allocation, the interests and the rights of children should be safeguarded and protected.

Despite a plethora of considerations that are unique to child-related research, economic evaluations for children are not spared on some of the deficiencies that compromise the quality of adult economic evaluations. In a study by Ungar and Gerber ((2010), they summarised these deficiencies in economic evaluations to include; lack of clarity on study perspective, incomplete costing, difficulties in generalisability, reliance on intermediate outcomes and lack of sensitivity analyses. The study perspective in economic evaluations is essentially used to describe the decision-maker for whom the costs and consequences being measured in the economic evaluation is meant to inform (Drummond et al., 2015). Baharin et al. (2017) suggested that the societal and provider/health care sector perspective are the two perspectives most commonly used in economic evaluations.

The provider/health care perspective is inclusive of all health care expenditure by the provider, that is, private, or public (Carias et al., 2018). On the other hand, a societal perspective includes all the costs and health benefits, not considering who bears the costs or who receives the benefits (Sanders et al., 2016). The societal perspective includes costs and benefits which go beyond the health sector. The Second Panel on Cost-Effectiveness in Health and Medicine recommended this perspective, citing welfare economics principle (Carias et al., 2018). This scope goes beyond the one which was recommended by the first panel, which focused on family spill-over effects (Carias et al., 2018). Whilst the societal perspective is important, for it to be a useful reference case in CEAs, there is need to further efforts in developing standard measures of costs and outcomes (Sanders et al., 2016).

The lack of generalizability of economic evaluations poses a challenge for decision-makers. The main concern here being the difficulties in using the results of economic evaluations across different contexts and settings. A central challenge that is faced by those conducting or using economic evaluations in low-middle income countries (LMICs) is the lack of accessible high-quality data which can be attributed in part to fragmented health systems (Pitt et al., 2016). The unavailability of local data coupled with the differences in health care resources and practices raises questions about the relevance of informing health care decisions based on economic evaluations conducted elsewhere. For example, Hausler et al. (2006) conducted a study on cost-effective measures for controlling human immunodeficiency virus (HIV) and tuberculosis (TB) in South Africa. They highlighted that their findings could not be generalised to other parts of Africa because of the differences in salary costs of personnel in South Africa which are relatively high in comparison to other parts of Africa (Hausler et al., 2006).

In addition to underscoring the importance of the different aspects of economic evaluations for child health (pulmonary health), it is also helpful to situate child health in a broader context, the global agenda for health.

Child Health: An overview

With countries world over having committed to the SDGs, good health is essential to meeting these global targets. The SDGs were adopted in 2015 by the United Nations to "promote healthy lives and well-being for all children" (WHO, 2019a). The SDG goal 3 is to end preventable deaths of new-borns and under-5 children by 2030 and its targets include, "*reducing new-born mortality to at least as low as 12 per 1 000 live births in every country*" and "*reducing under-five mortality to at least as low as 25 per 1,000 live births in every country*" (WHO, 2019a). Child mortality rates are key indicators for both global health and child health (Van Malderen et al., 2019). According to a report by the World Bank (2020), child mortality rates have halved from the year 1990 to 2020 with a notable decline in the under-five mortality rates. They dropped from 12.5 million per year to 5.3 million in 2018 alone (WorldBank, 2020).

Whilst this decline in mortality rate is commendable, with every region world-wide observing a decline in child mortality, the world is not on track to reach the SDG targets for child mortality (Max et al., 2019). Current evidence points to an estimated 15 000 children dying every day, which is an alarming statistic (World Bank(2020);(Max et al., 2019). The place where a child is born and resides plays a role in the survival of that child. Sub-Saharan Africa has the highest under-five mortality rates in the world, with one child in 13 dying before they reach their fifteenth birthday (Ester et al., 2011). This rate is more than sixteen times higher than the one in 199 average recorded in high-income countries. Meeting the SDG target on reducing under-five mortality by 2030 would reduce under-five mortality rates significantly. The World Health Organization (WHO) purported that meeting the under-five mortality target by 2030 would reduce the deaths by 10 million worldwide. However, efforts would need to be focused on Sub-Saharan Africa and South-East Asia to reduce 80% of these deaths (WHO, 2019a).

Paediatric pulmonary diseases are the leading cause of death and ill-health amongst children below the age of five, with pneumonia resulting in the largest number of deaths globally (Nair et al., 2010).

As paediatric health professionals and organisations seek ways to respond to the diseases that threaten the lives of children, they are sometimes faced with global situations that hinder their progress. The main challenge now which may hinder efforts to achieve the 2030 SDG targets for health is the COVID-19 pandemic. The available evidence thankfully points to COVID-19 having a limited impact on the mortality of children. Compared to the other age-groups, the direct impact of COVID-19 infection has been milder on children (UN, 2020). Drawing from the preliminary findings of studies conducted in China and the United States of America, the hospitalisation rates for symptomatic children are much lower (10 to 20 times less) than the middle-aged and even lower (25 to 100 times less) than the elderly (the most affected age-group) (UN, 2020).

Despite evidence pointing to children being less susceptible to COVID-19, the indirect effects of COVID-19 are most likely to affect the health and well-being of children. Whilst evidence shows that infants are not the face of the pandemic, they risk being amongst its biggest victims (UNICEF, 2020a). Child survival might be compromised stemming from weakened health systems, reduced household income, and disruptions in health-seeking behaviours such as not obtaining vaccines for children (which could lead to pneumonia in children in 2021) and other preventative medicines (UNICEF, 2020a). COVID-19 has caused a global economic recession and based on the historical correlation between global domestic product (GDP) growth and infant mortality in LMICs, a tragic number of deaths could occur in 2020 and 2021. Such an occurrence could potentially threaten the progress made in the last 2 to 3 years in reducing infant mortality within the space of a year (UN, 2020).

In crises, deep-seated inequalities and vulnerabilities of some population groups are exposed. The vulnerability of children is a subject that is often raised in paediatric research because of children's dependence on adults (Ungar and Gerber, 2010). The physical and psychological cognitive states of children often mean that their parents or guardians guide the health care decision-making for children (Petrou, 2003). When disasters strike, children need to be protected from these impacts. Some of the efforts in defending children amid a pandemic include ensuring the availability and accessibility of essential medicines and vaccines (UNICEF, 2020b). In such contexts, policymakers face having to make

difficult decisions about which interventions to implement and what the health and economic effects of these interventions are. Economic evaluations play an essential role in providing some of the guidance and intervention projections required by policy-makers. Policy-makers need to find a balance in realising COVID-19 specific gains whilst at the same time ensuring overall protection of global health.

As COVID-19 ravages the world, diseases that threaten the health of children still exist, even more so with the disruptions in health services caused by the pandemic. Reduced access to medicines, vaccines and other essential health services threatens efforts made in combating diseases such as pneumonia, asthma and tuberculosis, which are the leading causes of infant mortality globally (FIRS. Forum of International Respiratory Societies, 2017). The following sections discuss the aetiology, diagnosis, disease burden, treatment, prevention, and control of the diseases mentioned above (pneumonia, asthma, and tuberculosis). Gaining an understanding of the different aspects of these diseases is instrumental in the identification of gaps which may currently exist whilst also highlighting areas which might need further research.

Paediatric pulmonary diseases: An overview

The previous section mentioned that the place where a child is born is key in determining the survival of that child. In a report by the WHO, while significant progress has been made globally in lowering child mortality, some disparities still exist in under-five mortality across regions and countries (WHO, 2019a), with South Asia and Sub-Saharan Africa being the regions in the world with the highest under-five mortality rates as earlier mentioned. The mortality rates experienced in LMICs can be attributed to limited access to care, and fewer interventions in place to improve care compared to high-income countries (Izadnegahdar et al., 2013). Pneumonia is the leading cause of morbidity and mortality in children under the age of five globally despite the advances made in preventative and management strategies (FIRS. Forum of International Respiratory Societies, 2017). In 2018, approximately 802 000 children less than five years old died of pneumonia.

With less than a decade left to realise the global commitment (SDG3 targets) towards the health of children, a sense of urgency emerges. In a report by (UNICEF, 2020c), they estimated that if the current progress in scaling up pneumonia-related health interventions was maintained, up to 14.5 million children would be saved, including 5.9 million from pneumonia by 2030. Hence the concern for the COVID-19 pandemic derailing progress.

In this section we discussed why the focus on pneumonia is important globally and some of the strategies that have been employed and are still to come in ending preventable deaths from pneumonia by 2025 following Global Action Plan for the prevention and control of Pneumonia (GAPP). The goal for 2025 is "to reduce deaths from pneumonia to fewer than 3 children per 1000 live births" (WHO, 2020a). The importance of addressing the causes and effects of pneumonia for sustainable development cannot be understated. Additionally, attention should be paid to some of the other causes of morbidity and mortality in children under the age of five. Asthma and tuberculosis are some of the diseases which impede the lives of children under the age of five.

Asthma

Asthma is a chronic condition affecting between 1-18% of the population in different countries (GINA, 2018). It afflicts approximately 334 million people globally, with its prevalence being on the rise in the last three decades (FIRS. Forum of International Respiratory Societies, 2017, Asher and Pearce, 2014). Despite the disease being dominant in affluent countries, recent trends indicate that there has been an increase in its prevalence in LMICs (Lenney et al., 2018). In terms of the global ranking of DALYs in children, asthma is among the top 20 chronic conditions (Asher and Pearce, 2014). It disrupts daytime activities, sleep, school and leads to anxiety amongst parents, families, and other guardians (Lenney et al., 2018).

Asthma is an incurable lifelong disease. However, through the provision of quality-assured essential medicines, it can be effectively controlled (FIRS. Forum of International Respiratory Societies, 2017). Inhaled corticosteroids are on the WHO essential drug list because of their effectiveness in asthma

control (GINA, 2018). Inhaled bronchodilators are also on the list, though unfortunately, not everyone who has asthma can access these medicines due to their lack of availability or lack of affordability in certain countries (FIRS. Forum of International Respiratory Societies, 2017). Apart from the lack of available medicines, there are other predisposing factors which impede asthma patients from receiving effective treatment. Amongst these are the misconceptions about the disease which prevent people from using appropriate treatment.

Henceforth, making improvements in the knowledge and understanding of asthma amongst children and their families should be integral in the management of asthma. In so doing, patients and their families are better equipped to adopt lifestyles which allow for the improved management of the disease. Some of the strategies to control asthma include; trigger avoidance, minimising smoke exposure, immunotherapy, and monitoring of symptoms (Papadopoulos et al., 2012). Fewer children die from asthma compared to other paediatric diseases such as pneumonia and TB, and consequently, the burden imposed by this disease is sometimes overlooked (Asher and Pearce, 2014). In LMICs, there is a need for advocacy campaigns to increase governmental understanding of the long-term socio-economic burden caused by failure to diagnose asthma and the lack of effective treatment (Lenney et al., 2018). The outcome from this could be a change in attitude in addressing childhood asthma in the future.

This section on asthma highlighted the fact that fewer children die from asthma compared to pneumonia and TB. Whilst the section on pneumonia touched on the morbidity and mortality associated with the disease, it is also critical to highlight the burden imposed on children by TB.

Tuberculosis

TB remains a public health concern worldwide despite longstanding efforts to eliminate it as one (Cunnama et al., 2020). The burden of TB in children is understated because of the challenges in obtaining an accurate diagnosis for this group, particularly in LMIC settings (Perez-Velez and Marais, 2012). In 2015 alone, there were an estimated 10.4 million new TB cases. Of the 10.4 million, 1 million

were children, which was assumed to be an under-estimate because of the difficulties in diagnosing TB in children (FIRS. Forum of International Respiratory Societies, 2017). TB in children has not been a big public health priority despite it being a leading cause of morbidity and mortality amongst children globally (Nelson and Wells, 2004, Mandalakas et al., 2013a). A possible reason for this is that children contribute little to TB transmission compared to adults (Tsai et al., 2013).

TB incidence and prevalence vary by the WHO geographical regions. In 2017, the WHO regions of South East Asia, and Africa accounted for up to 70% of the global TB (MacNeil et al., 2019). However, the proportion of TB cases among persons living with HIV in Africa was higher than it was in South-East Asia (MacNeil et al., 2019). TB is prevalent in poor and marginalised populations, and HIV is often the key driver of the disease in these areas (Thomas, 2017). Children from LMICs are said to have a twenty-fold risk of infection in comparison to those from high-income countries (Tsai et al., 2013).

Some of the strategies employed to try and control and eliminate the disease include; integrated patient care policies, creating supportive systems, conducting intensified research and increasing coverage of the Bacille Calmette Guerin (BCG) vaccine (FIRS. Forum of International Respiratory Societies, 2017). The WHO guidelines also stipulate that all children who are below the age of five should be traced and screened if they have been in contact with a person who tested positive for TB (Swaminathan and Rekha, 2010). They are also put on isoniazid preventive therapy (IPT) for at least six months to reduce their risk of contracting tuberculosis (Tadesse et al., 2016). In countries with high TB burden, blanket IPT programmes were found to be cost-effective in TB prevention (Mandalakas et al., 2013a).

If the United Nations SDGs and WHO End TB Strategy targets for 2030 and 2035 are to be met, there is a growing need to intensify efforts to improve TB diagnosis, treatment, and prevention (MacNeil et al., 2019).

CONCLUSION

The role of economic evaluations in informing decisions is one that should not be understated. Throughout this discourse, their role in guiding resource allocation was emphasised. What also emerged were the difficulties in conducting economic evaluations in children due to their cognitive differences, among other reasons. The cognitive differences impact how economic evaluations are conducted as there is still no gold standard for conducting economic evaluations in children. The lack of standardised tools, the vulnerability of children, and ethical considerations when conducting research for children are some of the challenging issues which emerge when looking at paediatric health. Another facet in paediatric health is the burden of paediatric pulmonary diseases on children.

Paediatric pulmonary diseases are the leading cause of morbidity and mortality amongst children. Their burden on children is exacerbated based on where in the world the child is born and resides. These diseases disproportionately affect children from LMICs. There are some important questions which arise from this discourse, which if answered correctly, could make a significant contribution to the synthesis of previous work as well as economic evaluations for paediatric pulmonary diseases going forward. The questions are:

- Which economic evaluations have been done to date on paediatric pulmonary diseases?
- How have these economic evaluations been done?
- When and where were they done?
- Which diseases did the economic evaluations cover?
- At which level of care were these economic evaluations conducted?
- Has there been an increase or decrease over time in the number of paediatric economic evaluations?

By addressing the above questions, the findings could contribute towards a better understanding of the gaps that exist in the economic evaluations of childhood pulmonary diseases. Findings from these questions could also offer a description of methods used in the current literature to conceptualise

methods for subsequent economic evaluations for paediatric diseases. The consideration of economic evaluations from HICs and LMICs may aid in identifying any differences which may occur across the various settings. Against this background, the study findings could be used ultimately to inform policy from an angle of efficient and equitable resource allocation across various settings.

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PART C: MANUSCRIPT

Proposed Journal: International Journal of Tuberculosis and Lung Disease (IJTLD)

ABSTRACT

Background

Pulmonary diseases are the leading causes of mortality globally amongst children under five years of age. Economic evaluations (EEs) guide decision-makers on which health care intervention to adopt to reduce paediatric pulmonary disease burden.

Methods

We systematically reviewed EEs for paediatric pulmonary diseases published globally between 2010 and 2020. We searched PubMed, Web of Science, MEDLINE, Paediatric Economic Database Evaluation (PEDE), and the Cochrane library. EEs included were specific to paediatric pulmonary diseases in a hospital setting and of children aged from zero to six years old. We extracted data items guided by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. We collected qualitative and quantitative data which we analysed in Microsoft Excel and R Software.

Results

22 studies met the inclusion criteria. Seven of the articles were cost-effectiveness analyses, five cost-utility analyses, two cost-minimisation analyses, and eight cost analyses. Fourteen studies were conducted in high-income countries, eight in low-middle-income countries (LMICs). Ten studies were on asthma, nine on pneumonia, two on asthma and pneumonia, and one on tuberculosis. Quality assessment of the articles revealed some methodological inconsistencies across the articles.

Conclusion

Fewer EEs were conducted in LMICs, yet children from these countries are disproportionately affected by pulmonary diseases. Developing standardised methods for EEs and conducting more EEs and for paediatric pulmonary diseases in LMICs could allow for more evidence-based decision-making.

Keywords
Paediatric. Pulmonary disease; economic evaluation; systematic review.

BACKGROUND

Paediatric pulmonary diseases are the leading causes of morbidity and mortality amongst children under the age of five, particularly in low-and-middle-income countries (LMICs) [1, 2]. The burden of asthma is higher in high-income countries (HICs) than in LMICs, while the opposite is true for pneumonia and tuberculosis (TB) [3]. Decision-makers the world-over are constantly facing the challenge of resource constraints in their endeavours to curtail the burden of disease imposed on children by pulmonary diseases. Over the years, economic evaluations (EEs) have increased in availability and have gained more acceptance as tools to aid in decision-making in health care. EEs provide some guidance as to which health care intervention to adopt by comparing the interventions to assess which alternative provides the best value for money [4].

This systematic review is part of a broader study, PediCAP, which is looking into the impact of oral step-down to amoxicillin or co-amoxiclav for children with severe community-acquired pneumonia (CAP), who have had intravenous antibiotics administered to them in a hospital setting [5]. PediCAP is a randomised control trial which will be carried out in five hospitals in South Africa, Uganda, Zimbabwe, and Zambia. The trial could potentially reduce the length of hospital stay (LOS) as well as have an impact on the clinical outcomes for the sick children.

This study aimed to systematically review EEs for paediatric pulmonary diseases conducted globally from 2010 to 2020. Our objectives are to:

- Provide a qualitative and quantitative description of existing literature on EEs for paediatric pulmonary diseases,
- Categorise the methodologies used for the different EEs,
- Describe the health care and geographical settings of the articles included,
- Highlight the timing of articles,
- Describe the types of diseases and the different interventions covered in the EEs,
- Highlight any differences which might exist across the different study settings.

METHODS

Search strategy

We conducted a systematic review of EEs (published literature) for paediatric pulmonary diseases within five electronic databases: PubMed, Web of Science, MEDLINE, Paediatric Economic Database Evaluation (PEDE), and the Cochrane library. We made use of keyword searches, MeSH terms, truncation, and Boolean operators. Our keywords were paediatrics, pulmonary disease, and EEs. The variations we used for paediatrics were, [“paediatric” OR “paediatrics” OR “pediatric” OR “child” OR “children” OR “infant” OR “infants” OR “neonate” OR “neonates”]. For pulmonary disease we used, [“pneumonia” OR “asthma” OR “pulmonary TB” OR “bronchiolitis” OR “bronchitis” OR “paediatric disease” OR “pediatric disease” OR “respiratory infections”]. Lastly, for economic evaluations, we used [“economic evaluation” OR “economic eval*” OR “economic*” OR “costs” OR “cost-effectiveness” OR “cost-utility analysis” OR “effectiveness” OR “cost-benefit” OR “cost*” OR “cost benefit” OR “cost effectiveness” OR “cost utility analysis” OR “CEA” OR “CUA” OR “CBA”].

The search string format was:

["paediatric" OR "paediatrics" OR "pediatric" OR "child" OR "children" OR "infant" OR "infants" OR "neonate" OR "neonates"] AND ["pneumonia" OR "asthma" OR "pulmonary TB" OR "bronchiolitis" OR "bronchitis" OR "respiratory infections" OR "paediatric disease" OR "pediatric disease"] AND ; ["economic evaluation" OR "economic eval*" OR "economic*" OR "costs" OR "cost-effectiveness" OR "cost-utility analysis" OR "effectiveness" OR "cost-benefit" OR "cost*" OR "cost benefit" OR "cost effectiveness" OR "cost utility analysis" OR "CEA" OR "CUA" OR "CBA"].

Inclusion criteria

We included both full EEs (cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-minimisation analysis (CMA)) and partial EEs (cost descriptions, cost analysis and cost of illness studies). We included articles reported in the English language, which were published

between the years 2010 and 2020. The EEs included in the review were specific to paediatric pulmonary diseases, comprising inpatients aged from zero to six years old. For study setting, we adopted a global standpoint and included EEs conducted in high-, middle- and low-income countries.

Also, only EEs conducted in inpatient hospital settings were included. We incorporated EEs that covered different aspects of paediatric pulmonary diseases such as different treatment regimens, curative measures, diagnostics and screening, medical devices, and additional support such as supplemental oxygen. We encompassed EEs reporting outcome measures relating to measures of cost-effectiveness, and these included the incremental cost per quality-adjusted life-year (QALY) gained, the incremental cost per disability-adjusted life year (DALY) averted, as well as incremental cost-effectiveness ratios (ICERs) reported in natural units.

Exclusion criteria

Articles excluded from the review were those reported in languages other than English. EEs which were conducted in outpatient hospital settings and in other settings such as clinic-based, school-based, home-based, or community-based were excluded. Furthermore, we excluded articles which did not meet the pre-defined age-group (i.e., those articles whose study population were exclusively above six years of age).

Selection process

In the first stage of the selection process, we removed duplicates in EndNote X9 Software (Clarivate Analytics). We did this both electronically and manually. The screening of the papers was done in three stages: title screening, abstract screening, and full-text screening. These stages are represented diagrammatically in the PRISMA diagram, Figure 1. The selection process was carried out by one reviewer who was in consultation with a second reviewer where study eligibility was unclear.

Data management

After the selection process, we stored the articles which met the eligibility criteria in a shareable folder in EndNote X9 Software, Clarivate Analytics.

Data extraction

We developed an extraction tool in Microsoft Excel using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist as a guide to identifying the data items to be extracted. The extraction tool was then pre-tested for its relevance and appropriateness to the study before being used. To do this, we tested out the data extraction template on five articles. The variables extracted were author, year, project title, journal name, funder, study perspective, duration, setting, intervention and comparator, currency reported and currency year, exchange rate, type of EE, discounting (whether there was discounting and the rate used), sensitivity analysis (if there was sensitivity analysis done and which type of analysis), ethics approval, informed consent, unit costs, outcome measures and ICERs.

Data synthesis and analysis

We adopted a convergent mixed-methods approach [(6)], combining both qualitative and quantitative data. For the qualitative assessment, we used a data analysis framework designed during the protocol development stage (Figure 2). The framework allowed for the comparison between the type of economic evaluation (outcome variable) and other variables of interest (geographical setting, summary outcome, healthcare setting, disease, type of intervention) by positioning the outcome variable at the centre of analysis. For the quality assessment, we utilised the CHEERS, 24-point checklist for assessing the reporting standards of the studies included in the review [(7)].

We conducted our quantitative data analysis in Microsoft Excel (2016) and R software (R Project, Vienna, Austria) using the user interface of RStudio. We analysed the volume of publications, the hospitalisation costs, and ICERS. All costs which were not reported in USD were converted to USD using the exchange rates for the study year [(8)]. We inflated the costs to 2019 USD using the World Bank Consumer Price Indices [(8)].

Study approval

The study is a secondary analysis which did not involve human subjects. It, therefore, did not require ethical approval. However, we obtained ethical approval from the Human Research Ethics Committee (HREC) at the University of Cape Town (UCT), reference number HREC 587/2020.

RESULTS

We retrieved 1470 articles from the searches conducted. Duplicates were removed both manually and electronically, and 1159 articles remained. Following the screening by title and by abstract, 945 of the 1159 articles were excluded. We then screened the full text of the remaining 214 articles and 22 articles met the full inclusion criteria (Figure 1). A description of the characteristics of each study included in the systematic review is found in Table 1. Of the 22 articles included, 14 were from HICs, and 8 were from LMICs. Amongst these, seven were CEAs, five were CUAs, two were CMAs, and eight were cost analyses (see table 2). Figure 2 shows the distribution of type of EE by the timing of publication.

Using our data analysis framework (Figure 3), we identified that there were 10 articles on asthma, nine on pneumonia, two on both asthma and pneumonia and one on tuberculosis (TB). Articles which covered asthma were predominantly from HICs, pneumonia articles were evenly distributed between HICs and LMICs, and the only TB study was from an LMIC (Table 2). The interventions for these diseases included diagnostic tests, operational guidelines, antibiotic use (oral vs intravenous), inhaled corticosteroids and supplementary oxygen.

We extracted hospitalisation costs and ICERs, where relevant, for all articles included in the systematic review. Table 3 summarises the methodological characteristics of the included articles. It shows the costing data, sensitivity analysis, informed consent, outcome measures, discount rate, hospitalisation costs (in USD) and ICERs (in USD). 77% (17/22) of the articles reported hospitalisation costs, and 71% (10/14) of the full EEs reported ICERs. The median hospitalisation cost per day for the articles reviewed was USD285. The median ICER was USD38.

For the methodology, three articles adopted a patient perspective, 14 a provider perspective and five a patient and provider perspective. The costing for 12 of the articles was done prospectively, and for the other 10, it was retrospective. We also assessed the reporting of informed consent in the included articles that reported a prospective record review and found that only 25% explicitly reported informed consent. With regards to sensitivity analysis, 64% (14/22) of the articles reported performing sensitivity analysis and the other 36% (8/22) did not. Of those that reported on sensitivity analysis, 11 specified the type of sensitivity analysis which was used; the most common being a one-way sensitivity analysis, reported by 55% (6/11) of these articles. Table 4 shows the results of the quality assessment of each study.

Our findings indicated that, of the six articles which span more than twelve months, only one study reported discounted costs. Articles which discounted their costs discounted at a 3% discount rate[16, 29] which is agreeable with the 0-5% standard in cost-effectiveness literature [37].We also used our data analysis framework to identify the outcome measures. These were reported in the articles as natural units, QALYs and DALYs. The natural units reported were, emergency department (ED) visits averted (5), life-years gained (1), complications avoided (1), and symptom-free days (1). Two articles reported QALYs gained and three reported DALYs averted.

We also used our data analysis framework (figure 3) in conjunction with the CHEERS checklist (table 4) to assess the quality of the articles we included in the review. Some of the methodological limitations that we identified in the included articles were the lack of country specific data, the variability of costs in diverse settings, heterogeneity limitations, and model assumption biases. Some articles considered only public provider profiles and not private provider profiles because of the unavailability of data from private providers. We had to make a subjective assessment of these findings as the articles were unclear about this. Some authors also reported lack of data on societal costs on TB in comparison to those from a healthcare perspective[6]. Regarding measures of health outcomes, in some instances, baseline health states were not valued using the same utility measure

as the study [30]. Also, some authors used utility measures collected for children over the age of five as estimates for those below the age of five [30].

Figure 1: PRISMA diagram

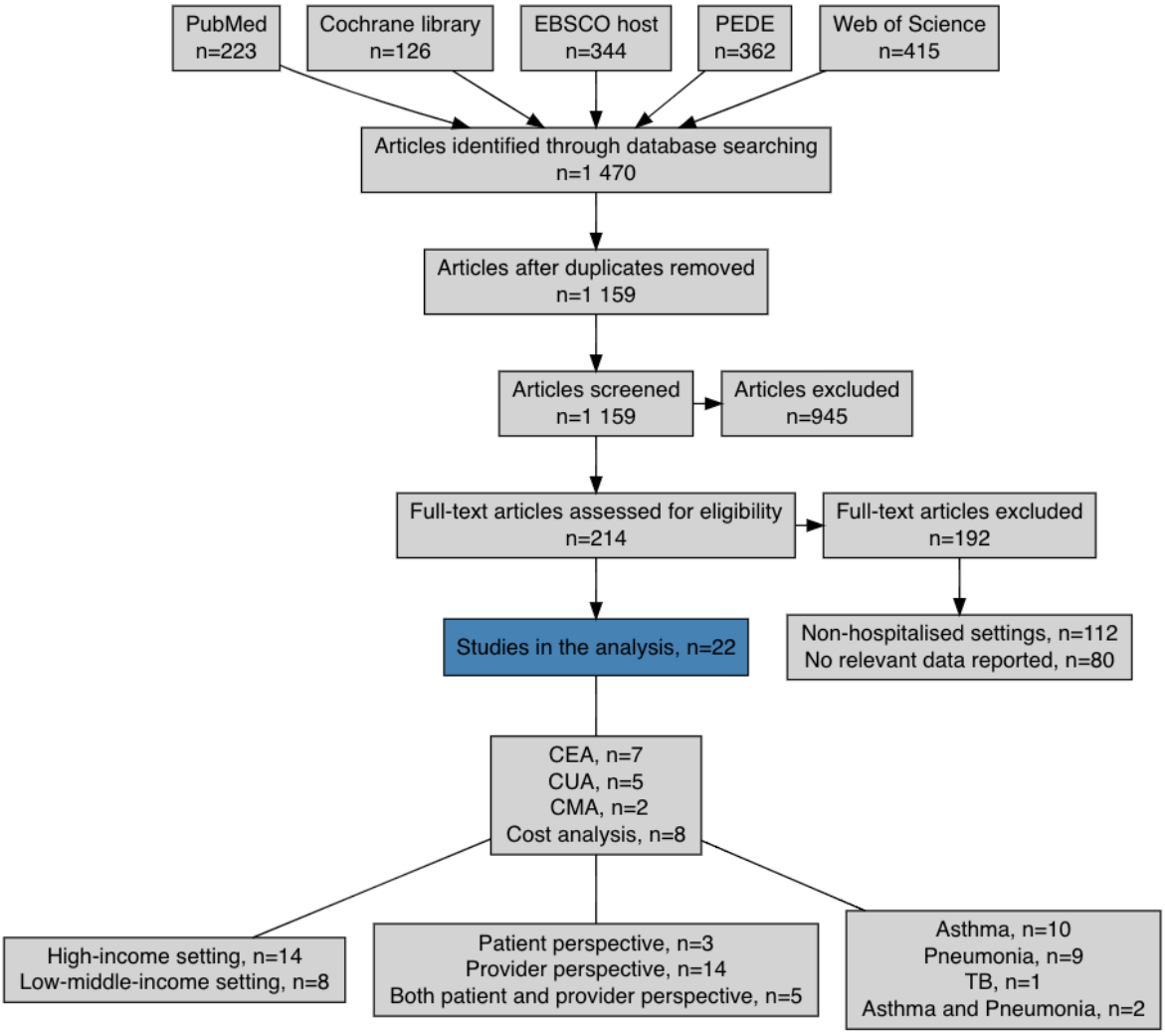

Table 1: Study characteristics

Lead Author	Reference year	Perspective	Country/ countries	Disease(s)	Intervention(s)	Comparator(s)
Kitano, T. [9]	2020	Provider and Patient	Japan	Asthma and Pneumonia	mPCR tests	Rapid Antigen Tests
Chen, H. H. [10]	2019	Patient	Ethiopia	Pneumonia	Oral antibiotics	Not reported
Krupp, N. L. [11]	2018	Provider	USA	Asthma	High-risk asthma clinic	Pre high-risk asthma clinic
von Schoen-Angerer, T. [21]	2018	Provider	Switzerland	Asthma and Pneumonia	Standard hospital care	Complementary treatment
Dor, A. [13]	2018	Provider and Patient	USA	Asthma	Community management of asthma	Management in health centres
Ceyhan, M. [14]	2018	Provider	Turkey	Pneumonia	In-patient treatment	Not reported
Zhang, S. [15]	2017	Provider	Uganda, South Africa, Zambia, Zimbabwe	Pneumonia	2013 WHO guidelines	2005 WHO guidelines
Debes, A. K. [16]	2017	Provider	Uganda	TB	MODS, Expert and Empirical	Standard treatment
Bozzani, F. M. [17]	2016	Provider	Malawi	Pneumonia	PCV 13	Pre-intervention
Razi, C. H [18]	2015	Provider	Turkey	Asthma	Nebulisation	Placebo
Andrews, A. L. [19]	2015	Provider	USA	Pneumonia	Targeted blood cultures	Universal blood cultures
Chu, S. M. [20]	2015	Provider	China	Pneumonia	Ventilator use (2 days)	Ventilator use (1 week)
Floyd, J. [21]	2015	Provider	Uganda	Pneumonia	PO1, PO2	IMCI
Petrou, S. [22]	2014	Provider and Patient	UK	Asthma	Nebulisation	Standard treatment
Krebs, S. E. [32]	2013	Provider	USA	Asthma	Nebulisation	Standard treatment
Char, D. S. [24]	2013	Provider	USA	Asthma	Volatile anaesthesia	Supplemental oxygen
Powell, C. [25]	2013	Patient	UK	Asthma	Nebulisation	Placebo
Andrews, A. L. [26]	2012	Provider and Patient	USA	Asthma	Prescribe and dispense ICS	Usual care
Andrews, A. L. [27]	2012	Provider and Patient	USA	Asthma	Oral antibiotics	Oral antibiotics
Doan, Q. [28]	2011	Provider	Canada	Asthma	Metered-dose inhaler	Nebulisation
Broughton, E. I. [29]	2011	Provider	Nicaragua	Pneumonia	Quality improvement	Pre-intervention
Lorgelly, P. K. [30]	2010	Patient	UK	Pneumonia	Oral antibiotics	Intravenous antibiotics

Table 2: Study setting by disease

	Asthma	Pneumonia	Asthma and Pneumonia	TB	Total
High-income	9	3	2	-	14
Low-middle-income	1	6	-	1	8
Total	**10**	**9**	**2**	**1**	**22**

Figure 2: Type of economic evaluation by year

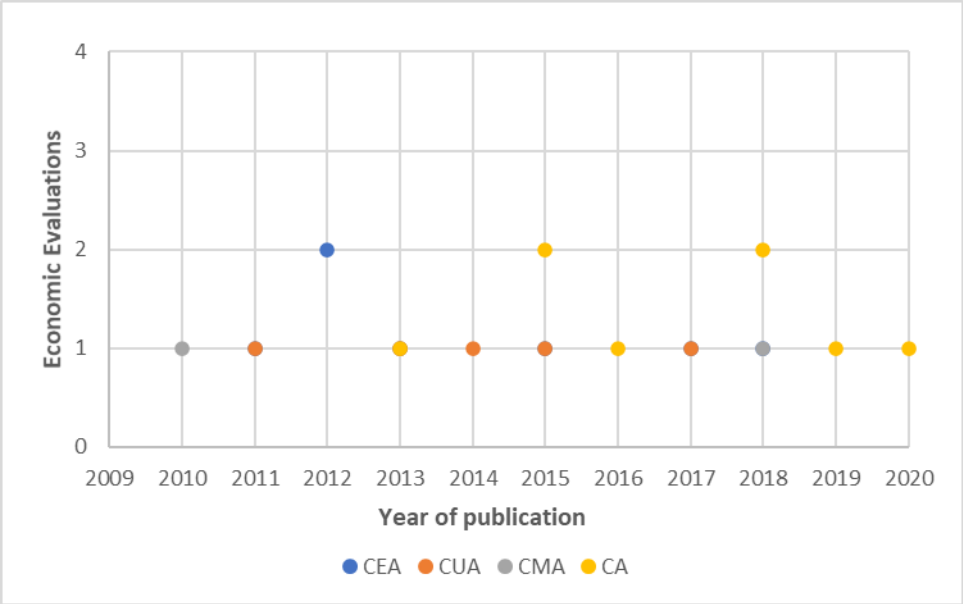

Figure 3: Framework for data analysis

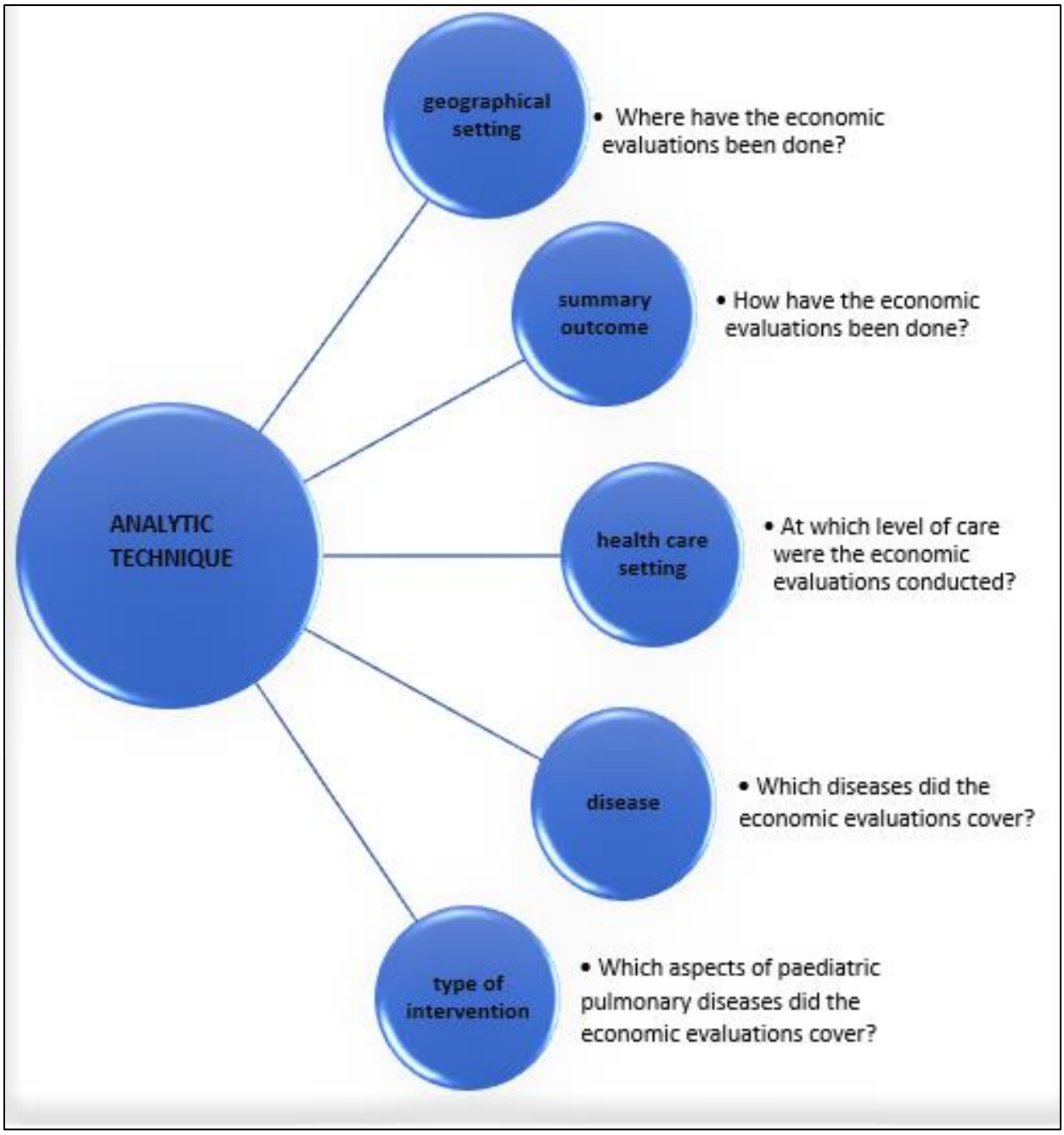

Table 3: Methodological characteristics

Lead author	Reference year	Type of economic evaluation	Costing data	Sensitivity Analysis	Informed consent	Outcome measures	Study duration (months)	Discount rate	Hospitalisation costs per day (USD)	ICERS (USD)
Kitano, T. [9]	2020	Cost analysis	Prospective	NR	Stated- no informed consent	NR	12	NR	1278,9	NR
Kitano, T. [9]	2020	Cost analysis	Prospective	NR	Stated- no informed consent	NR	12	NR	1158,3	NR
Chen, H. H. [10]	2019	Cost analysis	Retrospective	One-way	Not stated	NR	12	NR	13,92	NR
Chen, H. H. [10]	2019	Cost analysis	Retrospective	One-way	Not stated	NR	12	NR	55,68	NR
Chen, H. H. [10]	2019	Cost analysis	Retrospective	One-way	Not stated	NR	12	NR	162,4	NR
Krupp, N. L. [11]	2018	Cost analysis	Retrospective	NR	Not stated	NR	>48	NR	NR	NR
von Schoen-Angerer, T. [12]	2018	Cost minimisation analysis	Prospective	NR	Not stated	ED visits averted	18	NR	NR	-216,14
Dor, A. [13]	2018	Cost-effectiveness analysis	Prospective	NR	Stated- informed consent	Symptom free days	12	NR	1067,82	31,08
Dor, A. [13]	2018	Cost-effectiveness analysis	Prospective	NR	Stated- informed consent	Symptom free days	12	NR	1067,82	32,19
Ceyhan, M. [14]	2018	Cost analysis	Retrospective	Probabilistic	Not stated	NR	12	NR	1945,8	NR
Zhang, S. [15]	2017	Cost-utility analysis	Retrospective	One-way	Stated- no informed consent	DALY averted	12	NR	NR	43,18
Zhang, S. [15]	2017	Cost-utility analysis	Retrospective	One-way	Stated- no informed consent	DALY averted	12	NR	NR	211,95
Zhang, S. [15]	2017	Cost-utility analysis	Retrospective	One-way	Stated- no informed consent	DALY averted	12	NR	NR	45,5
Zhang, S. [15]	2017	Cost-utility analysis	Retrospective	One-way	Stated- no informed consent	DALY averted	12	NR	NR	11,55
Debes, A. K. [16]	2017	Cost-effectiveness analysis	Retrospective	Multi-way	Not stated	Life years gained	NR	3%	NR	131,44

Debes, A. K. [16]	2017	Cost-effectiveness analysis	Retrospective	Multi-way	Not stated	Life years gained	NR	3%	NR	156,24
Debes, A. K. [16]	2017	Cost-effectiveness analysis	Retrospective	Multi-way	Not stated	Life years gained	NR	3%	NR	228,16
Bozzani, F. M. [17]	2016	Cost analysis	Retrospective	One-way	Stated-informed consent	NR	3	NR	6,42	NR
Razi, C. H. [18]	2015	Cost analysis	Retrospective	NR	Stated-informed consent	NR	28	NR	299	NR
Andrews, A. L. [19]	2015	Cost-effectiveness analysis	Prospective	Probabilistic	Not stated	ED visits averted	12	NR	2030,4	NR
Chu, S. M. [20]	2015	Cost analysis	Retrospective	NR	Not stated	NR	30	NR	NR	NR
Floyd, J. [21]	2015	Cost-utility analysis	Prospective	NR	Not stated	DALY averted	NR	NR	196,3	18,12
Floyd, J. [21]	2015	Cost-utility analysis	Prospective	NR	Not stated	DALY averted	NR	NR	9,06	24,16
Petrou, S. [22]	2014	Cost utility analysis	Prospective	NR	Not stated	QALY gained	28	NR	285,36	337,02
Krebs, S. E. [23]	2013	Cost analysis	Prospective	NR	Not stated	NR	12	NR	123,76	NR
Char, D. S. [24]	2013	Cost-effectiveness analysis	Prospective	NR	Stated- no informed consent	Complications avoided	>48	NR	122,85	NR
Char, D. S. [24]	2013	Cost-effectiveness analysis	Prospective	NR	Stated- no informed consent	Complications avoided	>48	NR	58,05	NR
Powell, C. [25]	2013	Cost utility analysis	Prospective	NR	Stated-informed consent	QALY gained	NR	NR	1549,29	355637,52
Andrews, A. L. [26]	2012	Cost-effectiveness analysis	Prospective	Two-way	Not stated	ED visits averted	NR	NR	7244,64	NR
Andrews, A. L.[27]	2012	Cost-effectiveness analysis	Prospective	Two-way	Not stated	ED visits averted	NR	NR	7244,64	NR
Doan, Q. [28]	2011	Cost-effectiveness analysis	Retrospective	One-way	Stated- no informed consent	ED visits averted	NR	NR	2857,19	-3033,31
Broughton, E. I. [29]	2011	Cost utility analysis	Retrospective	One-way	Not stated	DALY averted	24	3%	280,17	-396
Lorgelly, P. K. [30]	2010	Cost minimisation analysis	Prospective	One-way	Not stated	ED visits averted	24	NR	870,46	NR

Table 4: Quality assessment using CHEERS checklist

Lead author	Reference year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Kitano, T.	2020	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	No
Chen, H. H.	2019	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No	No
Krupp, N. L.	2018	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	Yes	No	No
von Schoen-Angerer, T.	2018	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	Yes	No	No
Dor, A.	2018	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No
Ceyhan, M.	2018	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes	Yes	No	No	Yes	Yes	No
Zhang, S.	2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Debes, A. K.	2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Bozzani, F. M.	2016	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	No
Razi, C. H.	2015	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No
Andrews, A. L.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No
Chu, S. M.	2015	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	Yes	Yes	No	No	No	Yes	No	No
Floyd, J.	2015	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Petrou, S.	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Krebs, S. E.	2013	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No
Char, D. S.	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No
Powell, C.	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Andrews, A. L.	2012b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Andrews, A. L.	2012a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No
Doan, Q.	2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Broughton, E. I.	2011	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Lorgelly, P. K.	2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No

Key: *Yes = reported in full or partially; No = not reported.*

Checklist: *1. Title; 2. Abstract; 3. Introduction 4. Target Population; 5. Setting and Location; 6. Study Perspective; 7. Comparators; 8. Time Horizon; 9. Discount Rate; 10. Choice of health outcomes; 11a. Measurement of effectiveness (single study-based estimates); 11b. Measurement of effectiveness (synthesis-based estimates); 12. Measurement of performance-based outcomes; 13a. Estimating Resources and Costs (single study-based economic evaluation); 13b. Estimating Resources and Costs (model-based economic evaluation); 14. Currency, Price, Conversion; 15. Model Choice; 16. Assumptions; 17. Analytical Methods; 18. Study Parameters; 19. Incremental Costs and Outcomes; 20a. Characterizing Uncertainty (single study based economic evaluation); 20b. Characterizing Uncertainty (model-based economic evaluation); 21. Heterogeneity; 22. Study Findings; 23. Funding; 24. Conflicts of Interest.*

DISCUSSION

Our systematic review indicates that there were more partial EEs (cost-analysis) than there were full EEs. The cost analysis is the most basic form of (partial) EE as it assesses only the costs of the intervention and provides no information on the outcomes [31]. In terms of the full EEs, there were more CEAs than there were CUAs and more CUAs than there were CMAs. With regards to decision-making, the CEA has limitations in that it only allows for comparison within diseases and not between diseases due its uni-dimensional outcome measure. This makes it difficult to evaluate the benefits of an intervention across different diseases. The CUA on the other hand allows for cross-comparison because of its multi-dimensional outcome measure.

The findings from this study showed that there were more EEs conducted in HICs than there were in LMICs. These findings were consistent with those from a study by Ungar [32], where they noted that whilst there was an increase in the number of EEs globally, there were more EEs reported in HICs than there were in LMICs. We could attribute this to the resource-constraints in LMICs as economic evaluations require funding for them to be conducted.

For the distribution of EEs for asthma, pneumonia and TB, asthma articles were predominantly from HICs. This contrasted with pneumonia and TB which had more articles from LMICs. We could attribute the dominance of asthma articles in HICs to asthma being a disease of affluence [33]. In the case of pneumonia, it disproportionately affects less-affluent countries[3], which could explain the wider distribution of EEs for pneumonia inpatient interventions in LMICs.

Another interesting aspect of the review was that we only found one TB study for the zero to six age group, yet TB incidence is high in LMICs[3]. This could potentially be explained by the fact that TB is largely an outpatient disease, and our systematic review comprised only inpatient studies. Another explanation is that the economics of TB treatment in children has not been well researched [35].

We were also interested in understanding the different perspectives adopted in the articles. There were more articles which adopted the provider perspective, followed by the societal perspective (provider and patient perspective) and lastly, solely the patient perspective. This is despite the patient and provider perspective being recommended by the First and Second Panel on Cost-Effectiveness in Health and Medicine [36]. Part of this could be the cost of conducting EEs from both perspectives. The five articles which adopted both a provider and patient perspective were from HICs [9, 13, 22, 26, 27], those which adopted a patient perspective were from HICs[25, 30] and LMICs [10]. The provider perspective was the most common in all settings [11, 12, 14-24, 28, 29].

Our review also summarised the methodological approaches that were employed in the different articles included in the review. The notable differences in the reporting of discounting limits study comparability and the interpretation of study findings. Cost data were collected both prospectively and retrospectively with more articles reporting prospective cost data collection. In the CUA articles, more articles reported DALYs averted as outcome measures than they reported QALYs gained. This could be attributed in part to the difficulties in measuring utility in children for QALYs [32]. The DALYs averted reported were mostly in LMICs compared to HICs. We also identified a gap in the reporting of informed consent in the articles included in the review.

Concerns have been raised in the literature regarding methodological approaches in child-related research [31]. In this review, only a few of the articles reported informed consent. Our findings were also consistent with literature on the challenges that exist in health state valuation in paediatric economic evaluation [32]. Our review revealed that in the absence of a health utility measure validated across the childhood spectrum resulted, some authors had to use utility measures collected for those above the age of five as estimates for those below the ages of five [30]. Thus, making a case for the need to have validated health utility measures (child-specific questionnaires) across the childhood spectrum for more accurate results.

We also analysed our study findings as they relate to PediCAP. There was one study which was closely linked to PediCAP, assessing the impact of "oral versus IVV [intravenous] antibiotics for community-acquired pneumonia" [30] in children in a high-income setting. The results from this study indicated that the cost of in-patient stay made the greatest contribution to the total cost of care [30] . There were also some articles conducted in the countries where PediCAP will be run (Zambia, Uganda, Zimbabwe, and South Africa)[15, 16, 21]. In the study by Zhang et.al [15], they found child-pneumonia management as detailed in the standard World Health Organisation (WHO) guidelines to be cost-effective. Making a case on the importance of PediCAP.

It is worth mentioning the study limitations. The systematic review only EEs conducted in a hospital setting and of inpatients. Therefore, this data may not be generalizable to other service delivery platforms that are widely utilized and necessary to meet the Sustainable Development goals. There was also a missed opportunity to analyse the trends in methodological approaches over time as the review only included published literature between 2010-2020 due to practicality. The inclusion of published literature and excluding grey literature is also another limitation of this study.

CONCLUSION

The study set out to summarise EEs that have been conducted for paediatric pulmonary diseases globally. There were more partial EEs conducted than there were full EEs. The EEs were more prominent in HICs than they were in LMICs. Consequently, this meant that there were more articles for asthma than there were for pneumonia and TB.

Whilst there is a steady increase in the number of EEs conducted for paediatric health, there is still a dearth of studies for EEs conducted in hospital settings for paediatric pulmonary diseases. Meanwhile, these are the leading causes of under-five mortality globally. Also, there were fewer EEs published in LMICs compared to HICs. However, the evidence from EEs conducted in HICs cannot be used to inform decision-making in LMICs due to the variability of costs, yet children from LMICs are disproportionately

affected by pulmonary diseases. The differences in the reporting of methodological approaches also made the comparison across the studies difficult.

We, therefore, assert the need to develop standardised methods of conducting EEs for paediatric pulmonary diseases in LMICs to inform evidence-based decision-making. Potentially addressing the social and economic burden imposed by paediatric pulmonary diseases, particularly in less well-off groups.

ACKNOWLEDGEMENTS

Conflict of interest

No conflict of interest noted by the authors.

Funding

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PART D: POLICY BRIEF

SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS FOR PAEDIATRIC PULMONARY DISEASES

INTRODUCTION

The health of children has a central position in achieving sustainable development [(1)]. One of the Sustainable Development Goal 3 targets is ending mortality from preventable causes of newborns and children below the age of five by 2030. Achieving this target calls for ensuring the availability, affordability, and acceptability of interventions which are all essential to child health. Governments, therefore, require robust evidence to inform resource allocation for such interventions.

Economic evaluations (EEs) provide an opportunity to inform evidence-based decision making as they are, "t*he comparative analysis of alternative courses of action in terms of both their costs and consequences" [(2)].* EEs to date have been conducted for different age-groups and across diverse settings. However, what remains scarce in literature is a consolidation of the health economic evidence on paediatric pulmonary diseases. The interest in paediatric pulmonary diseases follows their emergence as the main causes of morbidity and mortality in the paediatric population [(3)].

ABOUT THE STUDY

The study systematically reviewed EEs for paediatric pulmonary diseases published globally between 2010 and 2020 and of in-patients in hospital settings. It provided a qualitative and quantitative description of existing literature on EEs for paediatric pulmonary diseases. Furthermore, it categorised the methodologies used for the different EEs and described the health care and geographical settings of the studies included. Also, it highlighted the timing of studies and described the types of diseases and the different interventions covered in the EEs. Finally, it highlighted the differences existing across the various study settings.

METHODS

We conducted our searches in five different databases, retrieving 1470 articles. We removed duplicates electronically and manually. We then screened these documents by title, by abstract and finally by full text using our pre-defined selection criteria. Only articles reported in the English language, conducted in hospitalised settings, published from 2010-2020 and of children between the ages of 0-6 years old were included in this systematic review. The selection process was carried out by one reviewer who was in consultation with a second reviewer for all the steps, including where study eligibility was unclear. The next stage was data extraction. We developed a tool in Microsoft Excel, which was pretested to assess its appropriateness before using it. To analyse the qualitative data we extracted, we used a data analysis framework which we developed during the protocol development stage. The quantitative data analysis was conducted in Microsoft Excel.

KEY FINDINGS

Which EEs have been conducted for paediatric pulmonary diseases?

> ***What is a systematic review?***
>
> *A systematic review is a method/process/protocol in which a body of literature is aggregated, reviewed, and assessed while utilising pre-specified and standardised techniques*

There were 22 articles included in our systematic review. Seven of the articles were cost-effectiveness analysis (CEA) studies, five were cost-utility analysis (CUA) studies, two were cost-minimisation analysis (CMA) studies, and eight were cost analyses.

What is a cost-effectiveness analysis?

A cost-effectiveness analysis compares the costs and effects associated with different treatment intervention options over a set period through the generation of incremental cost-effectiveness ratios (ICERs).

What is a cost-utility analysis?

A cost-utility analysis compares the costs and effects associated with different treatment interventions over a set period through the generation of incremental cost-utility ratios (ICURs).

What is a cost-minimisation analysis?

A cost-minimisation analysis compares two interventions which are assumed to have the same outcome or effects to find out which is of the two is the least costly option.

What is a cost-benefit analysis?

A cost benefit analysis is a type of economic evaluation where costs and benefits are both valued in monetary terms.

Where were these EEs conducted?

Fourteen studies were published in high-income countries (HICs) and eight in low-middle-income countries (LMICs)

How have these EEs been done?

Concerns have been raised in literature regarding methodological approaches in child-related research. In this systematic review, we found that only 25% of the studies that should have (e.g. randomised control trials) reported informed consent reported it. There were also some challenges identified in how health was valued in some of the included articles.

Which diseases did these EEs cover?

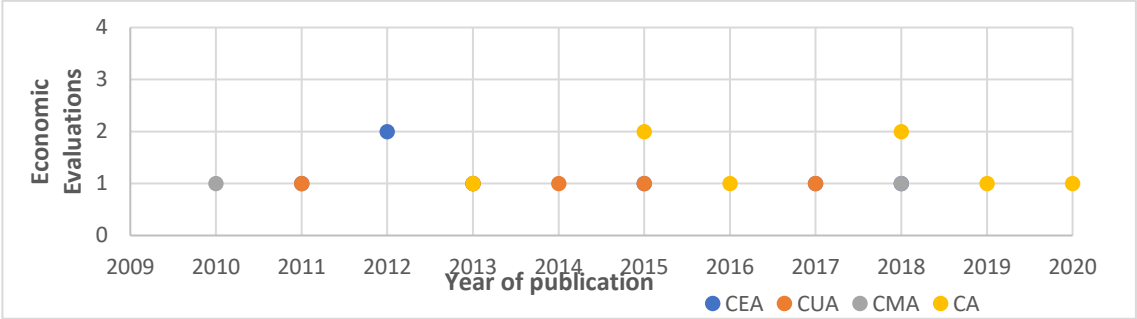
The diseases covered by the EEs were pneumonia, asthma, and TB.

	Asthma	Pneumonia	Asthma and Pneumonia	TB	Total
High-income	9	3	2	-	14
Middle-income	1	2	-	-	3
Low-income	-	4	-	1	5
Total	**10**	**9**	**2**	**1**	**22**

What is a cost analysis?

A cost analysis compares the costs of two or more alternatives without examining their outcomes to find out which is of the alternatives is the least costly option. It can also be the costing of a single intervention.

When were these EEs published?



CONCLUSION

There were more partial EEs conducted than there were full EEs. The EEs were more prominent in HICs than they were in LMICs. Yet, children from LMICs are disproportionately affected by pulmonary diseases. We also identified some inconsistencies in how health was valued in the articles we included. We, therefore, highlight the need to standardise methods for conducting economic evaluations. We also assert that having more EEs for paediatric pulmonary diseases in LMICs could aid in evidence-based decision-making. This could go a long way in informing resource allocation for paediatric pulmonary diseases. Thereby reducing the social and economic burden imposed by paediatric pulmonary diseases, particularly in less well-off groups.

POLICY RECOMMENDATIONS

- Formulate public health policies that support the uptake of EEs in child-health decision making.
- Facilitate improvements in paediatric pulmonary disease research in the under-five age group through strengthening the capacity of research institutions, particularly in low-income settings where pulmonary diseases are common.
- Equip health economists to conduct EEs in children through training and workshops.
- Develop standardised protocols for those intending to carry out EEs for children.

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PART E: APPENDICES

APPENDIX 1: Guide for authors in the International Journal of Tuberculosis and Lung Disease (IJTLD)

General:

- All compiled in the same Word file.
- All blue instruction text to be deleted before paper finalised
- Source: https://www.theunion.org/what-we-do/journals/ijtld/information-for-authors
- Give all files to be uploaded a short name of 15 letters maximum. File names should not include spaces, special characters, punctuation marks or symbols. Failure to do so may lead to difficulties in uploading your manuscript and prevent its conversion to pdf

AUTHORSHIP:

International Committee of Medical Journal Editors' criteria for authorship (http://www.icmje.org/recommendations/browse/roles-andresponsibilities/defining-the-role-of-authors-and-contributors.html) recommends that authorship be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

When a multicentre group has conducted the study, all individuals who accept direct responsibility for the manuscript should be identified. When submitting a group author manuscript, the corresponding author should clearly identify all individual authors, as well as the group name.

Title page (first page of document)

Title (110 characters and spaces):

Author names and affiliations (full names and surnames and where you are affiliated to i.e. University of …, National Tuberculosis Programme etc. Ensure that affiliations are clearly linked to authors):

Corresponding author name and address (usually the first author):

Running title (45 characters and spaces) this is the short/concise title:

Word count for text (limit 2500 words, excluding abstract, references, tables, and figure captions)

Number of references (maximum 35 references):

Number of Tables (Maximum of 7 tables or figures (combined not 7 of each)):

Number of Figures (Maximum of 7 tables or figures (combined not 7 of each)):

Abstract (this is the summary of 200 words): An informative structured abstract that can be understood without reference to the text should be included. Abstracts will be translated into French and Spanish on acceptance for publication (authors are welcome to provide their own translations).

Background

Methods

Results

Conclusion

Key words: (max 5) These should be placed beneath the summary

Manuscript

Main text headings: Three categories of heading are used.

Major headings (e.g. METHODS, RESULTS) are in Arial 12 bold caps.

Minor heading 1 (e.g. Study population and materials) in Arial 12 italics.

Minor heading 2 (e.g. Human subjects) in Times Roman 12 italics.

First section: BACKGROUND/ INTRODUCTION (does not require a heading): This should include the aim, objectives and/or hypotheses for the manuscript, preceded by their rationale.

Double spacing, continuous line numbering (1-∞), 12 point font (already selected for this template)

METHODS:

This should include a description of the study design, study population, intervention, exposures, outcomes, and other relevant variables, where applicable. Details of the statistical analysis plan and sample size and study power should also be included. Methods should be described in a manner that is conducive to replication. Details of ethics approval (or a statement as to why it was not required) should be provided in the Methods section of all research studies. All studies involving human subjects should include details of informed consent.

Study population (Minor heading)

Ethics statement and details of informed consent

RESULTS:

Present the results in logical sequence, referencing figures and tables (see information below on submitting figures and tables). For complex tables only highlight the most important results.

DISCUSSION:

Bring the reader back to your initial aims, objective, or hypothesis, showing how this study has improved our understanding of the topic.

CONCLUSIONS:

Optional, but if used, please briefly highlight the single most significant aspect of this study.

ACKNOWLEDGEMENTS:

A conflict of interest statement, author contributions and all funding information should all be included in the acknowledgements - here you can use the initial of all authors.

REFERENCES:

References in correct Journal style (Vancouver, superscript in text).

References cited consecutively throughout the text (references in tables/figures are numbered according to where the table/figure is cited in the text).

The accuracy of references is the responsibility of the author. They must be numbered in the order in which they are cited. References that are cited more than once retain the same number for each citation. The list of references at the end of an article should be arranged in numerical order. References to an article: should include the names of the authors, followed by their initials. List all authors when three or fewer - see the example below: Gordon JB, Bennett AM. Tuberculosis in reindeer. Scand Rev Respir Dis1978; 96 (Suppl): 217-219. When there are more than three authors, list only the first author and add 'et al.' References to a piece of work: (book/monograph) should include the names of the authors, the title of the piece of work, the ISSN number of the publication, the name of the Editor, the place and year of publication, the number of the volume and the first and last page numbers. References to a chapter in a book: should include the names of the authors, the title of the chapter with the word "In" preceding the reference of the work e.g. Girling DJ. The chemotherapy of tuberculosis. In: Ratledge C, Stanford J, Grange JM, eds. Biology of the mycobacteria. London, UK: Academic Press, 1989: pp 285-323. Electronic references should be given only when an original citation is unavailable; please provide as much information as possible, including html address. References to an article yet to be published: should give the name of the journal as '(In Press)' and only appear after having been accepted. Personal communications: should be given in the text with the name of the individual cited and with his/her consent.

TABLES:

Tables in correct format and at end of text (after references) on separate pages in the same document. Tables should not contain bolding or shading
Please see examples of table sizes that will fit this layout within the section 'Figures and Tables'. Large Tables which are not easy to accommodate into a printed journal page should be included as Supplementary Data

Tables and figures should be self-explanatory and easily understood as a standalone element. Numbering of tables/figures corresponds to where they are first cited in the text. All abbreviations included in the title or in the Table/Figure, even if explained in the text of the article, should be expanded in a footnote to be understandable without referring to the text. Tables: A short descriptive title should appear above the table. Each column should have a short or abbreviated heading. All abbreviations should be explained in a clear legend below the table. Tables should not have shading or bolding. Explanations of data should be included in the legend and linked to the respective element by a number (1, 2, 3 etc). Tables should be treated as a standalone item, so references should be included in their entirety in the legend and not added to the Reference list at the end of the article. Please note that the number and size of the tables need to be accommodated within the pages

allocated for each type of article. Examples of table sizes: Small table with 4-5 columns and 4-5 rows = 1/4 page in a typeset article Moderate table with 4-6 columns and 10-12 rows = 1/2 page in a typeset article Large table with 6-10 columns and 12-16 rows = 1 full page in a typeset article If there is the need to refer to very large datasets, the excess material can be included as Supplementary Data (please note there is a charge of €200 per 10 pp of Supplementary Data). The figures and tables in Supplementary Data should be numbered as Figure S1, Table S1 etc (to avoid confusion over labelling of the figures and tables in the main body of the article). Alternatively, the data can be hosted via a service such as Fig share (https://figshare.com) with a link embedded in the text.

FIGURES:

Figures after the tables on a new page. These should be referred to consecutively in the text. A brief explanatory legend should be provided for every figure to ensure it can be understood as a standalone item. Figures uploaded separately in image files (as .xls, .ppt, .jpg, .gif, .rtf, .tifor .ps files.) or embedded in the Word file. On acceptance, all figures must be supplied in editable format (Excel, Word, PPT) or in high resolution image files (PNG, TIFF, PDF). If they cannot be provided in editable format, they must be high resolution, with text in black (not grey) Arial 12 (or proportional to size), no bolding. Colour and half-tone figures should be at least 300 dpi (and preferably 500 dpi).

SUPPLEMENTARY DATA:

Other:

• Once the submission process is complete and the article has been checked, the corresponding author will receive a request to log on again to submit an electronic copyright form directly on the website
• On acceptance, all listed authors will be contacted to submit an electronic copyright form directly on the website. Note that all forms need to have been submitted before the article is sent to press.

Copyright:

After submission of the article the copyright e-form must be completed online by the submitting author.

In the event of acceptance, the copyright e-form must be submitted online by all authors. The article cannot be published until all authors have submitted their e-forms.

Open Access:

Abbreviations and units:

Avoid abbreviations in the title or summary. Abbreviations or unusual terms should be described the first time of use. Symbols and units of measure must conform to recognised scientific use, i.e. SI units. For more detailed recommendations, authors may consult the Royal Society of Medicine publication

Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors. Designation of diseases must conform to the International Classification of Diseases. Designation of micro-organisms must conform to the norms of biology. Proprietary names of drugs, instruments, etc. should be indicated using initial capital letters. Names of instruments should be accompanied by the manufacturer's name, city, state, and country

Requirements:

Manuscripts should conform to the Uniform Requirements for Manuscripts submitted to Biomedical Journals (http://www.icmje.org/index.html). Authors should ensure they follow the relevant recommendations and guidelines for reporting their findings (CONSORT, STARD, MOOSE, STROBE, PRISMA, STREGA). Articles on clinical research should conform to the standards defined in the Helsinki Declaration, as revised in 2013 (www.wma.net/en/30publications/10policies/b3/index.html).

Stigmatising language:

Authors are advised to avoid terms that may be perceived to be stigmatising, such as “TB suspect” or “defaulter”. Authors can refer to the following publications: Zachariah R. et al., Language in tuberculosis services: can we change to patient-centred terminology and stop the paradigm of blaming the patients? Int J Tuberc Lung Dis 2012; 16: 714–717.

Plagiarism: The Journal checks for plagiarism. If suspected, the IJTLD follows the guidelines set out by the Committee on Publications Ethics (COPE) (http://publicationethics.org/flowcharts).

APPENDIX 2: Human Research Ethics committee.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

25 September 2020

HREC REF: 587/2020

Ms Lucy Cunnama
Health Economics Unit
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7925
Email: Lucy.cunnama@uct.ac.za
Student email: chtmut001@myuct.ac.za

Dear Ms Cunnama

PROJECT TITLE: SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS FOR PAEDIATRIC PULMONARY DISEASES-MASTER'S CANDIDATE-MS MUTSAWASHE CHITANDO

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 and 06 July 2020, found on the following website link:
http://www.health.uct.ac.za/fhs/research/humanethics/about

Approval is granted for one year until the 30 September 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Ms Mutsawashe Chitando will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

HREC 355/2020 le

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 355/2020 le