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A SYSTEMATIC REVIEWON THE DETERMINANTS OF NEONATAL MORTALITY IN ETHIOPIA

By:

Mr. FantahunKibret (BSC)

Advisors:

Mulugeta Betre (MD, Associate Professor)

Gebretsadik Shibre (MPH)

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List of abbreviations

AIM - African Index Medicus

ANC- Antenatal Care

AOR- Adjusted odd ratio

ARR – Absolute Risk Reduction

C/S – Cesarean Section

EMBASE- Excerpta Medica + base

CASP - Critical Appraisal Skill Program

COD- Cause of Death

EDHS - Ethiopian Demographic and Health Survey

GDP - Gross Domestic Product

GHO – Global Health Observatory

UGH –University of Gondar Hospital

HF - Health Facility

IQR -Inter Quartile Range

LBW - Low Birth Weight

MEDLINE –Medical Literature Analysis and Retrieval System Online

MeSH-Medical Subject Headings

MLCC- Midwife-Led Continuity of Care

MPH – Master of Public Health

NICU - Neonatal Intensive Care Unit

ND - Neonatal Death

NMR- Neonatal Mortality Rate

OR – Odd Ratio

PICO - Population Intervention Comparator Outcomes

PICOS - Population Intervention Comparator Outcomes and Study design

PNC – Post-natal Care

PRISMA - Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

PubMed - Public/Publisher MEDLINE

QIQQA –pronounced ("Quicker") is freeware and freemium reference management software

RCT – Randomized Control Trial

Rh – Rhesus factor

SA- Social Autopsy

SDGs – Sustainable Development Goals

SVD – Spontaneous Vaginal Delivery

TT – Tetanus Toxoid

UNICEF - United Nations Children's Fund

WHO – World Health Organization

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Abstract

Background: Neonatal period is the age of child's first 28 days from birth to 27compeleted days of life. The neonatal period represents the most vulnerable time for a child's survival. Nearly halfof under-five death globally was occurred during neonatal period.Neonatal mortality rate in Ethiopia is 29 deaths per 1000 live births in 2016.

Objective: Theobjective of this study is to identifyand summarize the common determinants of neonatal mortality in Ethiopia, in the periods of from 1 January, 2014 until 30 April, 2019.

Methods: Atotal of six studies were included in this study, and these studies were selected based on a predefined protocol that contains clear criteria for eligibility. Major bibliographic database Pub Med-Medline, Google scholar, Cochrane, EMBASE, was used to collect study articles. Data were analyzed by narrative synthesis.

Results: The most common important determinants of neonatal death identified in this review were early age of neonatal period especially in the first 24 hours, prematurity, asphyxia, and sepsis. And home delivery, lack of antenatal and postnatal care, delayed initiation of breast feeding and delay in seeking of treatment or health service (delay one) were also among the leading socio economicdeterminants of neonatal deaths.

Conclusion;This study revealed thatthe determinants of neonatal mortality are largely preventable by addressing essentialneonatal careand case management service around labor, delivery and the immediate postpartum periodalong with health education and community awareness creation.

1. INTRODUCTION

1.1 Background

Neonatal period is the age of child's first 28 days from birth to 27completed days of life. The neonatal period represents the most vulnerable time for a child's survival [1]. In 2016, 2.6 million deaths, or roughly 46% of all under-five deaths, occur during this period, this means that 7000 newborn deaths every day. The majority of the neonatal deaths are concentrated in the first day and week, with about 1 million dying on the first day and close to one million dying within the next six days [1].

The global neonatal mortality rate fell from 37 deaths per 1,000 live births in 1990 to 19 per 1,000 in 2016; however, the decline in the neonatal mortality rate from 1990 to 2016 was slower than the decline in mortality among children aged 1–59 months: 49 per cent, compared with 62 per cent, a pattern consistent across all regions. [2]. Across region and countries there is a marked disparity in neonatal mortality and among the regions, neonatal mortality was highest in sub-Saharan Africa and South Asia, which each reported 28 deaths per 1,000 live births [2]. When we see the level of neonatal mortality (death per 1,000 live births) in some highest magnitude sub-Saharan country; Mauritania 33.8, Mali 35.4, Coted'lvoire 33.5, Sierra Leone 33.5, Senegal 20.5, Nigeria 32.9, Chad 34.8, Central Africa Republic 41.5, South Sudan 39.6, Sudan 29.5, Somalia 38.5, and Ethiopia 28.9etc. [2]. A child in sub-Saharan Africa or in South Asia is nine times more likely to die in the first month than a child in a high-income country. The risk of dying for a newborn in the first month of life is about 50 times higher in Pakistan than in Japan [2].

According to United Nations children's fundreport the neonatal mortality rate in Ethiopia in 2015 and 2018 was 28 and 28.9 per thousands of live births respectively [3]. The 2016 Ethiopia Demographic and Health Survey (EDHS) results show that the neonatalmortality rates for the 5 years before the survey is still shows the highest figure which is 29 deaths per 1000 live birth [4]. In other words, in Ethiopia 1 in every 35 children dies within the first month. When we see the trends of under-5 mortalities it declined from 166 deaths per 1,000 live births in 2000 to 67 deaths per 1,000 live births in 2016. This represents a 60% decrease in under-5 mortalities over a period of 16 years (4). Infant mortality also declined from 97 deaths per 1,000 live births in 2000 to 48 deaths per 1,000 live births in 2016, which is about a 50% reduction in the last 16 years. Neonatal mortality declined from 49 deaths per 1,000 live births in 2000 to 29 deaths per 1,000 births in 2016, a reduction of41% over the past 16 years [4].

Globally the major known cause of neonatal death are preterm birth complications (34%), intra partum related events (24%), sepsis and meningitis (15%), congenital abnormalities (11%), pneumonia (6%), tetanus and diarrheal disease each account (1%), and other causes (6%) [2]. The next important things that one should know is that identifying of determinants that contribute to neonatal death in Ethiopia, once identified these determinants it is easy to develop corrective measures. Many studies had indicated that child mortality, in peculiar neonatal mortality, is closely associated with a variety of factors: poverty, place of residence and region, parental education, demographic factors like maternal age at birth and sex of child, birth order, birth weight and maternal health care services usage such as antenatal care (ANC), place of delivery and delivery assistance [5].Further result of another study shows that newborns with small birth size were at a greater risk of mortality compared to those with large birth size. Also, preceding birth interval of less than two years was significant risk factor for neonatal mortality [6].

1.2 Statement of the problem

According to World health organization (WHO) report globally 2.5 million children died in the first month of life in 2017. There are approximately 7000 newborn deaths every day, amounting to 47% of all child deaths under the age of 5-years, up from 40% in 1990.About the same number of babies were born stillbirth (in 2015) [1].

Without improving the survival of newborns, meaningful impact on child survival would not be possible [7]. This is because globally neonatal mortality contributes nearly half (45%) of the under-five deaths and is estimated to grow by more than half (52%) by 2030 [7].

Most cases of neonatal deaths i.e.99% occurred in low- and middle-income countries, and around half of the cases occurred among home deliveries, making the global rate of neonatal mortality 30 per 1000 live births [8].

Despite various efforts to curb the NMR in the country, neonatal deaths remain a concern in Ethiopia. The report of the WHO and UNICEF (2018) estimated that Ethiopia’s neonatal death rate stands at 28/1000 live births in the country [1-3]. Two years preceding this report the Ethiopia Demographic and Survey (EDHS) 2016 revealed that neonatal mortality rate of the country was 29 per 1000 live birth [4].

The number of neonatal death in the country varies in terms of sociodemographic and economic factors such as region, place of residence, geographic location, maternal educational status, and family wealth index [9].

The 2016 Ethiopia Demographic and Health Survey (EDHS) findings show that neonatal mortality rate was 29 deaths per 1,000 live births. The findings further indicate that all childhood mortality rates have declined over time. For example, the under-5 mortality rate has declined from 116 deaths per 1,000 live births 10-14 years prior to the survey (2002-2006) to 67 deaths per 1,000 live births in the 0-4 years prior to the survey (2012-2016) (4). The 2016 EDHS data also show that there has been a steady decline in infant, child, and under-5 mortalities over the last 16 years. For example, under-5 mortality rates for the 5 years preceding the survey declined from 166 deaths per 1,000 live births to 123 deaths per 1,000 live births in 2005, to reach 67 deaths per 1,000 live births in 2016. Similarly, infant mortality decreased from 97 deaths per 1,000 live births, to 77 deaths per 1,000 live births, and to 48 deaths per 1,000 live births in the same period [4].

In spite of many efforts by the government and other partners, non-significant decline has been achieved over the last 15 years in neonatal death in Ethiopia [10].Moreover, according to a study done on determinants and causes of neonatal mortality in JimmaZone, Southwest Ethiopia: about 63% of infant deaths in the study area occur during the first month of life, and the great majority of neonatal deaths occurred in the first week of life, in neonates born preterm, not started breastfeeding on time, not on exclusive breastfeeding and, in those mothers, did not have adequate antenatal care visit [11].

In general, according to the different studies and report [2 -4] the neonatal death in Ethiopia is one of among the sub-Saharan African countries in which they have high prevalence ofunder-five year's mortality. Even though the mortality rate trends show a decline in a number of deaths but still large numbers of children are dying before they celebrate their first year. And globally most of the determinants of neonatal death are preventable but the high numbers of neonates are suffering from morbidity and mortality, and it needs appropriate and timely intervention. But this intervention should be targeted specifically on the underlining masking determinants of death in order to be successful in reduction of neonatal death. Therefore, this systematic review is going to identify and summarize recent evidence on the determinants of neonatal death from a various eligible studies done in Ethiopia conducted over the last five years.

1.3 Rational of the study

Ethiopia has made remarkable progress through achieving many of the national and global health indicators as a result the neonatal mortality rate were impressively reduced. Even though this achievement was done, the ministry acknowledges that neonatal mortality rate is disproportionally high accounting to 44% of under-five deaths. In addition, neonatal mortality rates vary across income, gender, and geographical areas. Cognizant of this Ethiopia has envisioned to end all preventable newborn and child deaths by 2035.

So that the purpose of this study is aimed to synthesize recent evidences on current determinants of neonatal death in Ethiopia, and the result of this study might be used as an input for activities aimed at reducing of neonatal death in the country.

2. Literature review

2.1 Magnitude of neonatal death in Global context

Neonatal death is defined as the death of a live born infant, regardless of gestational age at birth, within the first 28 completed days of life. Each neonatal death can be further clarified into viable and non-viable deaths depending on the gestational age at which they were born, and where they were born. Although global neonatal mortality rates have declined, through time this rate of decline lags the progress made in decreasing mortality in children aged 1–59 months [12].

The first 28 days of life the neonatal period is the most vulnerable time for a child's survival. Children face the highest risk of dying in their first month of life at an average global rate of 18 deaths per 1,000 live births in 2017 [2]. Globally, 2.5 million children died in the first month of life in 2017 alone approximately 7,000 neonatal deaths every day most of which occurred in the first week, with about 1 million dying on the first day and close to 1 million dying within the next six days [2].

Despite a declining neonatal mortality rate globally, marked disparities in neonatal mortality exist across regions and countries. Regionally, neonatal mortality was highest in sub-Saharan Africa and South Asia, with each estimated at 27 deaths per 1,000 live births in 2017 [2].

In 2016, 2.6 million deaths, or roughly 46% of all under-five deaths, occur during neonatal period. This translates to 7000 newborn deaths every day. The majority of the neonatal deaths are concentrated in the first day and week, with about 1 million dying on the first day and close to one million dying within the next six days [1, 8]. Reducing neonatal mortality is increasingly important not only because the proportions of under-five deaths that occur during the neonatal period is increasing as under-five mortality declines but also because the health interventions needed to address the major causes of neonatal deaths generally differ from those needed to address other under-five deaths[1-2].On current trends, more than 60 countries will miss the SDG target of reducing neonatal mortality to at least as low as 12 deaths per 1000 live births by 2030. About half of them will not reach the target by 2050. These countries carry about 80 per cent of the burden of neonatal deaths in 2016 [1].

2.2 Neonatal death in the Ethiopian context

According to United Nations children's fund report in 2015 the neonatal mortality rate in Ethiopia was 28 per thousands of live births. [3] And 2018 World Bank data shows that neonatal death rate in Ethiopia are 28.9 per 1,000 live births [3], which is nearly similar to that of the 2016 Ethiopia Demographic and Health Survey (DHS) results that show the neonatal mortality rates for the 5 years before the survey is still shows the highest figure which is 29 deaths per 1000 live birth [4].

A prospective cohort study was conducted among neonates born between April 2014 and July 2014 in seven hospitals, in Tigray region, Ethiopia. Of the1152 live births, there were 68 deaths (63 per 1000 live births). Two thirds of deaths were attributable to prematurity 23 (34%) or asphyxia 21 (31%). Slight variance was seen between the morality patterns in early and late neonatal periods. In the early neonatal period, 37% were due to prematurity, while asphyxia (35%) was more common in the late neonatal period. All infection-related deaths occurred in neonate-mother dyads from rural areas [13].

Retrospective cross-sectional study was conducted to assess the proportion of death and its associated factors among preterm neonates admitted in NICU from January 2016 to March 2018 in University of Gondar comprehensive specialized hospital neonatal intensive care unit. Socio-demographic and obstetric characteristics of mothers of preterm neonates admitted in NICU at University of Gondar specialized Hospital from January 2016 to March 2018 ($n = 516$), and the proportion of death among preterm neonates admitted in University of Gondar Comprehensive Specialized Hospital NICU(Neonatal Intensive Care Unit)was 28.8% [95% CI (25.1, 32.9)] [14].

2.3 Cause and risk factors of neonatal death

According to 2018 Save the Children data among all children, newborns have the highest risk of death, more than 90 percent of newborn deaths occurs in sub-Saharan Africa and South Asia. More than 7,300 stillbirths occur each day, half of which happen during labor and birth.Three preventable and treatable conditions are responsible for an estimated 81 percent of newborn deaths (prematurity, complications during childbirth, and infections) (2). There is substantial evidence that up to two-thirds of these deaths could be prevented if mothers and newborns received cost effective, low-tech care [11].

According to WHO data, every year, an estimated 15 million babies are born preterm (before completing 37 weeks of gestation), and this number is rising continuously [15]. Preterm birth complications are the leading cause of death among children under five years of age and accounted for approximately 1 million deaths in 2015 [15]. Three-quarters of these deaths could have been prevented with current, cost-effective diagnosis, and treatment. The rising incidence of preterm birth and associated high death rate has augmented the demand for prenatal diagnosis, which is likely to drive the demand for neonatal and prenatal devices globally [15].

A hospital based study conducted in eastern part ofEthiopia show that suspected sepsis, prematurity, respiratory distress and perinatal asphyxia were the leading problems of neonates in which they constituted more than 82% of admission to Neonatal Intensive Care Unit (NICU). Sepsis was the top leading and anemia was the least for admission [16]. According to Study many neonatal deaths are preventable with existing low cost, low-tech interventions but to make effective use of limited resources, planners and policymakers require reliable cause of death information [15]. In Ethiopia, the main causes neonatal deaths in 2015 were birth asphyxia (31.6 percent) prematurity (21.8 percent) and sepsis (18.5 percent), followed by congenital anomalies (11.7percent), acute respiratory infections (8.4%) and others like neonatal tetanus (1.9%), diarrheal diseases (0.8%) and others not mentioned (4.5%) [16].

A study done in 2013 on cause and determinants of neonatal death study conducted in Ethiopia showed that excess neonatal mortality risk was associated with a number of proximate factors including being male, being born to younger mothers (< 18 years of age), and being born within 2 years of the last birth [17]. Neonates born in winter had an increased risk of dying compared with those born in other seasons. It also showed a protective role if mothers received two TTs before birth. Women's education remained the single most important socioeconomic factor associated with neonatal mortality in the multivariate analyses. This study confirms that male children have a 38% higher risk than females of dying during the neonatal period [17].

According to study done at North Shoa Zone, Amhara regional state, Ethiopia a total of 84 cases and 252 controls were enrolled to assess determinants of neonatal mortality. The results of the bivariate analysis revealed that household wealth, antenatal care visit, frequency of antenatal care visit, place of delivery, postnatal care visit, breast feeding within the first hour of delivery, feeding colostrum, tetanus toxoid injection before birth of last baby, child’s size at birth and child’s sex were significantly associated with neonatal mortality [18].

A study which had examined the factors associated with the risk of neonatal death with multivariate analyses showed that excess neonatal mortality risk was associated with a number of proximate factors including being male, being born to younger mothers (< 18 years of age), and being born within 2 years of the last birth. Neonates born in winter had an increased risk of dying compared with those born in other seasons [16].

According to a study done on examining social determinants of neonatal deaths in North West Ethiopia using the three-delay model approach, all of the deaths included in this study were associated to one of the three delay types. Delay in treatment seeking outside home (delay one) was associated with 81% (30/37) of the deaths. Of all the deaths investigated, 70 .31% (26 /37) of them did not take any treatment. The median time from recognition of illness to modern treatment seeking was 1 day (IQR 1 – 2.5 days). Similarly, the median time from recognition of illness to death of the newborn was 10 h (IQR 0.5 – 72 h). The major delays associated with earlyand late neonatal deaths were delay one followed by delay three [7].

Conceptual framework for Neonatal death

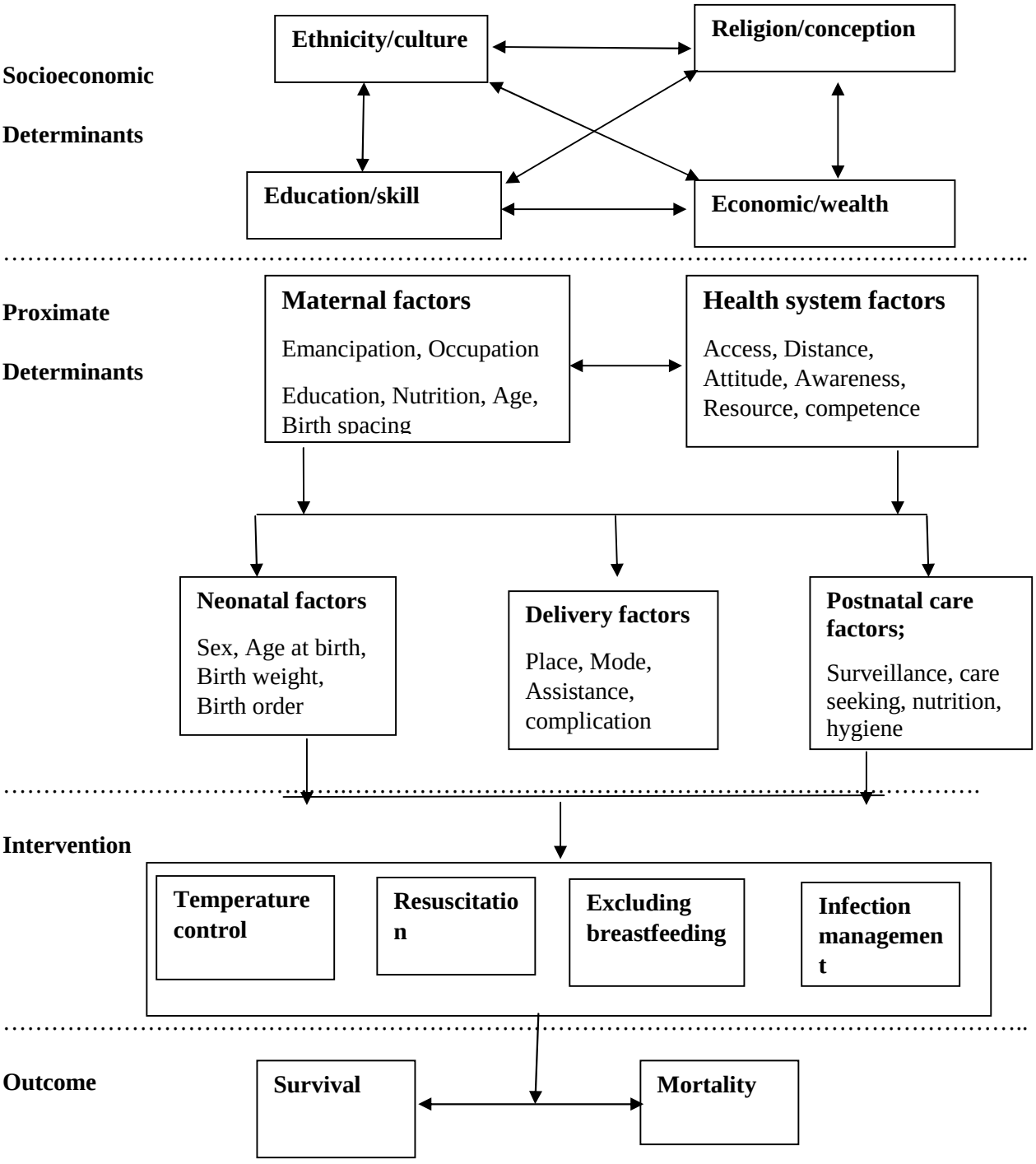

Figure 1 Conceptual framework linking determinants of mortality with neonatal death. Adapted and modified from UNICEF: state of the world's children maternal and newborn health 2009 [19].

2. Study objectives

The objective of this study is to identify and summarize the common proximate and socioeconomic determinants of neonatal death in Ethiopia, from a review of included studies done in a period of from January, 2014 up to April, 2019.

4. Methods

4.1. Study area and setting

“At 1,126,829 square kilometers (435,071 sq mi), Ethiopia is the world's 27th-largest country, comparable in size to Bolivia. It lies between the 3rd parallel north and the 15th parallel north and longitudes 33rd meridian east and48th meridian east. The Ethiopian highlands cover most of the country and have a climate which is generally considerably cooler than other regions at similar proximity to the Equator. The total population in 2016 was 102,403,000. Probability of dying under five (per 1 000 live births, 2017) was 58. In 2000 the country counted one hospital bed per 4,900 population and more than 27,000 people per primary health care facility. The physician to population ratio was 1:48,000, the nurse to population ratio, 1:12,000. Overall, there were 20 trained health providers per 100,000 inhabitants. Health care is disproportionately available in urban centers; in rural areas where the vast majority of the population resides, access to health care varied from limited to nonexistent. In 2007 (EFY) the number of hospitals, health centers and health post were 234, 3586, and 11446 respectively [20].

The study was conducted in three regional states, namely Amhara, Somali and Tigray regional states.

4.2. Study design and period

A systematic review study design with narrative analysis was conducted in 2019 on studies that are done in a period of; from 1 January, 2014 until 30 April, 2019.

The aim of selection of this study period (from 2014 up to 2019) was to identify the recent findings on the common determinants of neonatal death in Ethiopia in the last five years from this 2019 year. A five-year gap for studies inclusion was taken to be satisfactory because most of the time within five years many studies can be published and trends and the course of changes in disease condition might be well determined.

4.3 Study population and sample size

This systematic review used a total of six studies and the study participants of these included studies are neonates. Study participants are recruited from a reference population of respective study area, in which all of these studypopulation aretaken from Ethiopia.The sample size, source population and other detailed characteristics of each studies included under this systematic review are presented in table 1.

4.4Information sources and scope

Searches for the studies were conducted in the following electronic databases: PubMed-Medline, Africa Index Medicus, and Web of Science, Cochrane library, Google scholar and Embase. A restriction on the date of publication and language was made. Additional searchesfor gray literature, conference abstracts and proceedings were not made.

4.5 Search strategy

This systemic review was designed to identify the determinants of neonatal death in Ethiopia. Initially narrative-analysis and systematic reviews, including registered protocols were searched to avoid duplications. It confirmed that there was no review and narrative-analysis conducted related to determinants of neonatal death in Ethiopia in this similar study period. Published research reports of neonatal death and its associated determinants factors of death were searched. The investigator systematically reviewed and analyzedpublished research articles to determine the major determinants of death of neonate in each study.

The searches in the aforementioned electronic databases were restricted to articles written in English and reporting data covering the period from 2014 to 2019. The search was conducted on their appropriate search fields of electronic databases, and with sensitive searches which combine text words with indexing terms. A broad range and wide variety of search terms are combined with “OR” within each concept. Various combinations of the following terms are used to identify papers on the determinants of neonatal death in Ethiopia: neonatal, neonate, death, mortality, determinant/s, cause/s, risk factor/s, proximate determinant/s, underlying cause/s, early neonatal death/mortality, socio-determinants, economical determinants, late neonatal death/mortality. Boolean search operations are applied to improve returns of electronic database searches.For example, (neonatal OR neonate) AND (death OR mortality) AND (cause OR causes OR determinant OR determinants OR proximate determinants ORsocio-economic determinant OR risk factor OR risk factors) AND Ethiopia. Both free-text words (including spelling variants, synonyms, related terms, opposites, plurals, acronyms, truncations, wildcards, and proximity operators) and appropriate subject headings were used[21].

4.6 Eligibility criteria for inclusion of studies in the review

A primary study witha topic are related to the term “determinant/s, cause, risk factors proximate determinant/s and socio-economic determinant/s” of neonatal death were selected for a full text review. An individual study which has taken source population from Ethiopia wasalso includedin this systematic review.The study participant of any study should be children at age of zero to twenty-eight days of life. And study was selected based on their study period that means this systematic review was planned to review studies conducted on last five years (from 1 January 2014 to 30 April 2019). Only published and freely accessed full text papers were included. And primary study designs like cross sectional, cohort and case control where their study design can identify the determinants of the outcome are included in review. And a study with an outcome variable of neonatal death was included for this systematic review study.

4.7 Exclusion criteria

- Non-published works,
- Study with abstract only, which doesn’t show the detail of its methods
- Study published in different language other than English
- Study that require subscription or not freely accessed
- Systematic review and meta-analysis data
- A study done before 2014.

4.8 Data collection

The search of primary studies was conducted after 30, April 2019 until the 09July 2019, from electronically searchable database of PubMed-MEDLINE, Google scholar, Embase, Cochrane library, Web of science and African Index Medicus. The results of search from database are presented in table1 below.

Table 1.Shows that the data collection profile from selected electronic databases in their respective advanced search fields with the key terms and filters.

1. PubMed search engine A. Search terms and Boolean	Number of articles found at each level of search	Remark
(((determinant* OR cause OR risk factor* OR proximal determinant* OR social determinants* OR economical determinant*) AND (neonatal OR neonate OR newborn) AND (death OR mortality) AND (Ethiopia))).	2141	
B. Filters applied on PubMed advanced search fields (note; filters are put in their order of search)		
Article type all	2141	
Text availability; free full text	1248	
Filter-date-publication from 2014 to 2019 year only	970	
Species; human	671	
Language; English	669	
Sex; female and male	599	

Table1. The data collection…continued.

Age; newborn, birth - 1 month	158	It is a final filtered result of the database and retained for furthertitle & abstract review
2. Google scholar search engine	Results of articles found	
Search with full words; determinants of neonatal death in Ethiopia	13400	
Filtered by Advanced search with a word; with all of the words, 'determinants of neonatal death in Ethiopia", with the exact phrase "Ethiopia", with at least one of the words " neonate", without words " death", where my words occur "anywhere in the article", reterurn articles dated between " 2014-2019".	6580	
Language ; English	5900	There is no longer filters after this and each data are screened manually
Manual search of the above number of articles for further review	11	It is a final filtered result of the database and retained for further title & abstract review
3. Cochrane library		
A. Search terms and Boolean		
(((determinant* OR causes OR risk factors AND neonate OR newborn AND death AND Ethiopia)))	7265	
B. Filters applied on Cochrane advanced search fields (note; filters are put in their order of search)		
Search field; all text	7265	
Date of publication, from 1/1/2014 to 4/30/2019.	3666	

Table1. The data collection…continued.

Topic; neonatal care	168	It is a final filtered result of the database and retained for further title & abstract review
4. **Embase search engine**		
A. Search terms and Boolean		
(((determinants AND neonatal AND death OR mortality AND Ethiopia)))	17375	
B. Results after filter was applied		
Availability of articles: Open access	13681	
Study period with in 01/01/2014 and 04/30/2019	10758	
Human species	598	
Language; English	596	
Sex; both male and female	533	
Participant; neonate	135	It is a final filtered result of the database and retained for further title & abstract review
A sum of total number of studies found in electronic search and retained for further refinement and full text review	472	

Searches are kept recorded to ensure reproducibility and the results of each search were exported to a Rayyan systematic review software and citation management program (Qiqqa, EndNote ver. 9.1.0 and Zotero ver. 5.0.0). Duplicates were removed and retained separately. At each step of the selection process, reasons for exclusion are recorded in the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) flowchart[21].

Based on key terms, searches were carried out and for those databases provided non-zero results,the above eligibility criteria and other additional filters were applied through their advanced search flied feature to prevent this search from inclusion of unnecessary data.The search was done by a single reviewer but repeated search and recheck were carried out to ensure to not missing of an important

data.A final data results found from each database are also stored to offline local disk and each record process was kept as snap shouted picture for sack of reproducibly. At each step of the selection process, reasons for exclusion are recorded in the PRISMA flowchart [22].A summary of data collection and search results of databases with a detailed description for retained and excluded data are illustrated in a figure 2 below.

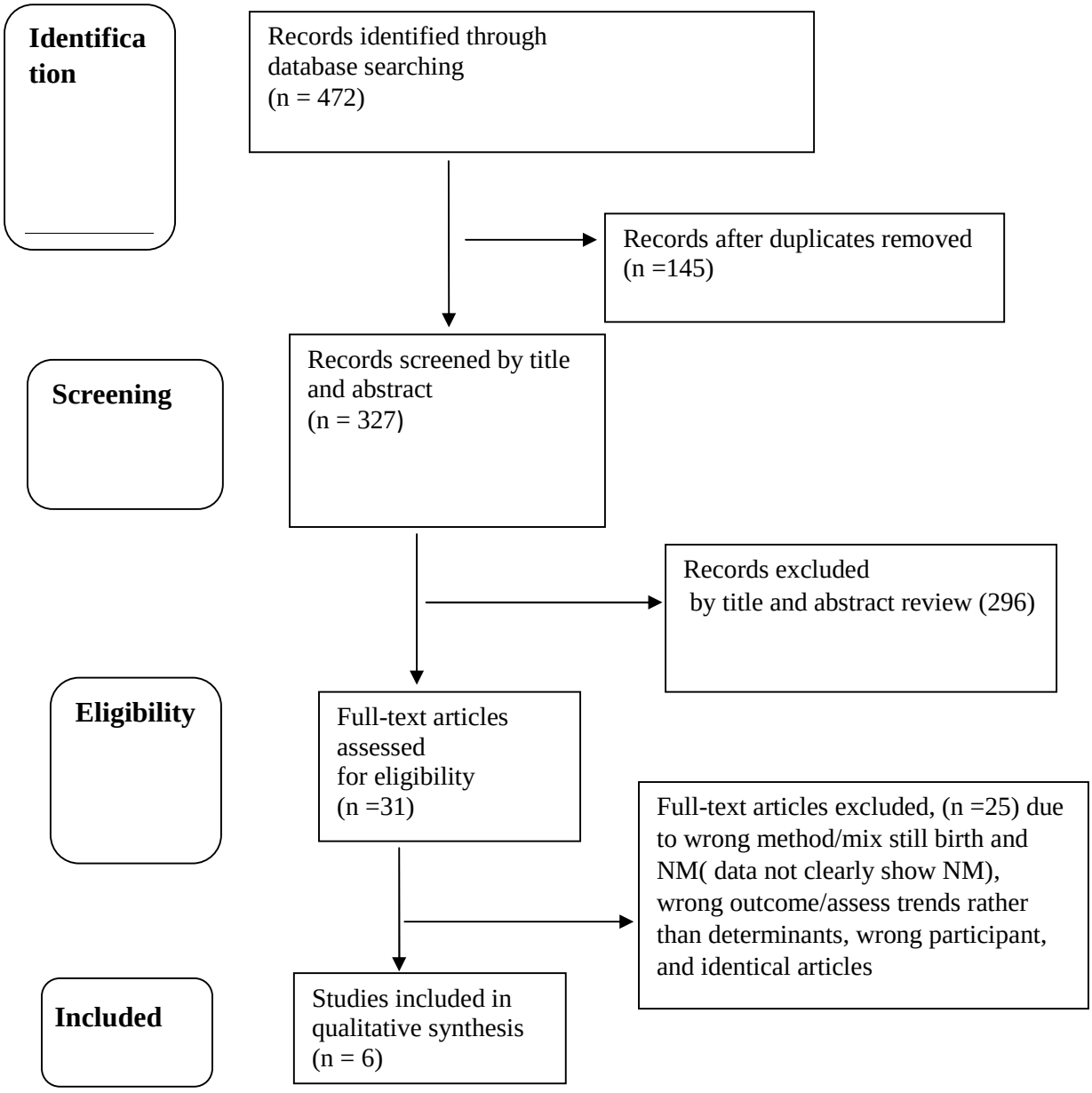

Figure 2.PRISMA flow diagram for extraction of data from an electronic databases engine. Adopted from the Moher D, Liberati, A, Tetzlaff J, Altman D. G, &the PRISMA Group. (2009) [23].

4.9 Data processing and analysis

4.9.1 Data items extraction

This systematic review was aimed atidentifying the determinants of neonatal death based on selected published primary studies; relevant and important data information of studies that can satisfy the study questions and objectives of this review was extracted for eligiblestudies. These are: first author's name; study design; study area; outcome of the study; year of publication; number of live births; number of neonataldeaths; neonatal mortality rate (if reported, and by year); samplesize; major proximate determinants of neonatal death; socio-economic/demographic determinants of neonatal death and additional study characteristics.

Table 2. Shows that data extraction on major proximate determinants of neonatal death from an included studies.

Publication ID	Author	Design	region/study area	Period	sample size	case	Control	neonatal death	Death at early age (in 24 hours)	death in 1st 7day	Prematurity (freq %)	asphyxia	Sepsis	congenital abnormality	other causes	hypothermia	ALRTI
28077109	mengesha and sahele	prospective cohort	Tigray	2017	1152			68	73%		34%	31%	12%	7%	16%		
29282018	Bogale et al.	social autopsy	Amhara	2016	39			39	51.30 %		14%	32.50 %	32.50%		16.00%		5%
30216343	Elmi Farah et at.	retrospective cohort	Solmali	2017	792			45	96%		31.10 %	20%	24.40%				
26949319	Mehretie K. et al	Cross-sectional	Amhara	2014	325			75	36%		40.1 %	31%	26.9%	34.4 %		31. 6%	16%
30133527	Kolola et al.	mached case control	Amhara	2015		84	252	84									
29784060	Tewabe et al	Case control	Amhara	2016	410			54	AOR =0.39		34.69 %		5.30%		9.84%		

Table 3.Shows that data extraction on major socio-economic determinants of neonatal death from those included studies.

ID	Author	Design	region/ study area	period	sample size	ANC	PNC	1st 1 hr breast feeding	Colostrum feeding	Income	Maternal education	Tetanus toxoid injection	Child's size at birth	Sex of neonate	Distance
28077109	mengesha and sahele	prospective cohort	Tigray	2017	1152					P=0.09	P=0.16			No A. (p=0.943)	Has A. (p=0.043)
29282018	Bogale et al.	social autopsy	Amhara	2016	39										
30216343	Elmi Farah et at.	retrospective cohort	Somali	2017	792										
30133527	Kolola et al.	mached case control	Amhara	2015	84case+ 254 control	Has SA. AOR =3.47	Has SA. AOR= 3.09	Has SA. AOR= 23.48(P=0.000)	Has SA. AOR= 3.91	Low income (p= 0.017)	No (P=0.282), grade1-8 (P=0.064)	Single dose/no(p =0.011)	Small (p=0.001)		
29784060	Tewabe et al	cross-sectional	Amhara	2016	410	AOR =5.02		Has SA AOR= 2.89	34.69%		5.30%		9.84%		
26949319	Mehretie K. et al	cross-sectional	Amhara	2014	325	75									

The common similarities between these included studies were the population under which the study was carried for and primary outcome of interest which is neonatal death in five of six studies. But these included studies have shown difference in their many characteristics for example methodologically there is high heterogeneity between studies (includes qualitative and quantitative studies based on the eligible criteria). These studies also have wide exposures ranges from proximate and immediate exposure (e.g. prematurity, infection etc.) to distal one (culture, economic and other demographic). The outcome interest of the five included studies have shown similarities,but the remaining onestudyhas a different another major focused area of outcome of interest.

Keeping these differences of included studies in mind this systematic review cannot analyze data using meta- analysis; because it is difficult to pool the results of some of the included studies and/or data statistically. In fact,the include data from different study designs that are not suitable for lumping all together in analysis; or have captured a very wide range of interventions/exposure are not also suitable to conduct meta-analysis [24].Therefore, other ways of expressing and synthesizing the results of studies collected together for review are needed. So, this study describes these methods as ‘narrative’ analysis or synthesis.

4.9.2 Quality assessment in individual studies

A Cochrane critical appraisal check list and AXIS (critical appraisal check list for cross-sectional study) were used for assessment of quality of studies designed in cohort and case control, and in cross-sectional studies respectively[25].

Based on a critical appraisal tool to assess the quality of cross-sectional studies (AXIS) risk of bias assessment was performed for a cross-sectional study, and there was no significant bias was found, except the representativeness of study participants to the general population because these sample populations are taken from hospitalized clients (see under annex1).

In a selected case control study that was conducted at Felege Hiwot referral hospital, North West Ethiopia the aim of the study was clearly justified which was to assess the magnitude of neonatal mortality [26].And the sample size determination and the selection of study participants also clear, but they were recruited from patients admittedat referral hospital, in which most of the time such participants are rarely represent the target population because they are selected based on their particular health conditions where others are not having. So, this may raise questions on the representativeness of sample to the reference population. Since the study was planned to find out a hospital based neonatal mortality, and to generalize the results of neonatal mortality rate, first

adjustment of cofounders like hospital acquired infection is important, because not all neonatal death is caused by their initial admission cases only.And another limitation of this primary study that mentioned by authorsis the source of information for the study which was documented data and it could not display all factors that are not documented in the patient's files, representativeness, completeness and quality of the recorded information.More information about quality of the individual study shows at annex 2.

There are no hints mentioned to control cofounding in the study conducted at Felege Hiwot hospital. This is also true for the cross-sectional study done at Gondar University hospital and cohort study done at Karamara hospital [27].

A cross-sectional study which was done atGondar university hospital[28], and one of among the included study for this systematic review has no clear information about sample size determination and target population as well as the selection process of study participants.So that it might be arouse question on the representativeness of the target/reference population under investigation. Detailed information of the quality assessment of the study is as shown in annex 3.

For two case controlstudies and two cohort studies included in this systematic review Critical Appraisal Skill Program checklists (CASP) was used to judge the quality of these articles[25] (see annex 2).

In a prospective cohort study[13] a critical appraisal was performed based on CASP check list and it shows that the cofounding effect in the study result were not clearly mentioned and there were no measures taken to control it.

In a hospital based retrospective cohort study [27], the presence of known deep rooted culture of the society, which has some negative impact on their health seeking behavior was mentioned in the study. And the study was also conducted with in this community at a referral hospital, where critically ill and referred patients were admitted, so that the conclusion of result may be highly affected by selection bias if generalization to reference population is applied. And the authors of the study declared that they haven't received any fund from others and risk of bias regarding to this issue is null. (See annex 3).

According to CASP checklist a case-control study [18] included in this systematic review no detectable bias was seen by the reviewer (annex 1).

4.10 Summary of determinants of neonatal death through narrative synthesis

4.10.1 Theory in evidence synthesis

Narrative synthesis refers to an approach to the systematic review and synthesis of findings from multiple studies that relies primarily on the use of words and text to summaries and explains the findings of the synthesis. Narrative synthesis is one of a common approach to the synthesis of data in systematic review research methodology; however methodological guidance on the conduct of narrative syntheses is limited. As a result, in reviews where statistical or other formal methods of pooling of data is not possible or appropriate, approaches to summarising and presenting findings in narrative way is varied and often inadequate.Even though, narrative synthesis can involve the manipulation of statistical data, the basic feature is that it adopts a textual approach to the process of synthesis to 'tell the story' of the findings from the included studies. (28). Systematic reviews can contribute to developing and testing the limits of theories, by examining how contextual or temporal variables moderate outcomes. Theories themselves can also be the subject of systematic reviews [29].

In this systematic review the theory model of neonatal death was developed as shown at figure 3 below to elaborate the mechanisms how death during neonatal period ishappened. This theory model of neonatal death is also related to the conceptual frame work of the study as shown in figure 1 above.However this theory model used to present these determinants of death in a different way from the conceptual framework by categorizing them into other easily understandable major structural pillarsof determinant factors of death. Detailed description of the theory model is show in figure 3 below.

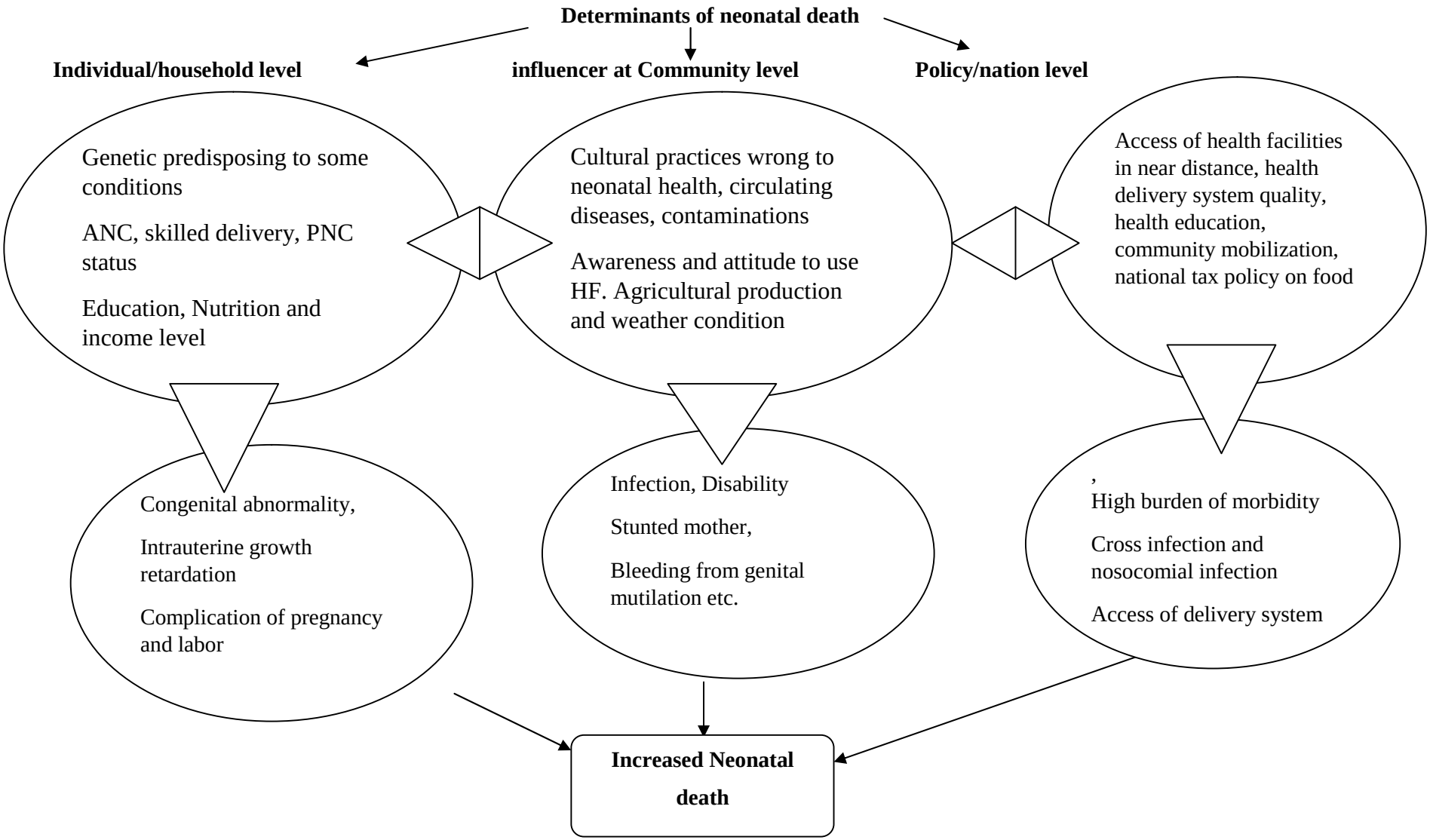

Figure 3. Example of a neonatal death Theory model: mechanisms how death occur in neonatal period. (It is adopted but modified in context of neonatal death from Weiss, 1998) [30].

4.11Variables

Dependent Variable

Neonatal death

Independent variables

Socio demographic and other factors like:

- Age
- Sex
- Place of residence
- Time
- Parental educational status
- Distance from health facility
- Economic status and others like culturalpractice, family history (genetic factors), breast feeding status, whether condition, status of colostrums feeding, parity, maternal health, birth weight, place of delivery, birth spacing of parent, gestational age, etc.

Health service utilization status of mothers

- ANC visit, skilled delivery, tetanus toxoid immunization of mother before gave birth and PNC
- Quality of care given by health facility, access to health facility, clean and save delivery practice, facilities capacity on neonatal resuscitation and intensive care management practice.

4.12Ethical consideration

Ethical clearance was obtained from the Addis Ababa University College of Health Science School of Public Health Institutional Review Board. Collected data were used for study purpose only.

4.13 Operational definitions

Determinants: is referred to of an actor or something thatestablishesthenature of neonatal death.

Causes; is defined as something that produces an effect of neonatal death.

Neonatal death:means the death of child from birth to age of 27 completed days of life, irrespective of cause of death.

Neonatal mortality: indicate numbers of deaths of neonate by place, time and cause ora relative frequency of deaths in a neonatal period.

Newborn death; in this study the definition is similar to neonatal death definition so both may use interchangeably.

Infant mortality; refers to the death of child during the first year after live birth.

Narrative analysis; a study finding that is expressed and presented in the form of written as telling story instead of collection and processing of data numerically.is a genre of analytic frames whereby researchers interpret stories that are told within the context of research and/or are shared in everyday life.

Primary study; Defined as a methodology used by researchers to collect data directly, rather than depending on data collected from previously done research.

Published study; a study that is published from scientific research publishers within A period of from January 2014 up to April 2019.

Open access; is a mechanism by which *research* outputs are distributed online, free of cost or other access barriers.

Selected study; a primary study that fulfills the inclusion criteria of this systematic review and selected for study.

5. Results

5.1 Study characteristics of the included studies

A total of six articles that met the inclusion criteria for this systematic review were included for final review and synthesis of evidences. All the included studies were published in English from a range of year 2016 up to 2018. From the included studies two are cohort, one iscross-sectional,another one is also qualitative study design of social autopsy (SA) and the rest two arecase-control studies.

All studies that are included in this review identified the determinants of neonatal death in their respective study area. From the total of 6 articles, four studies were conducted in the Amhara regional state; one is from Tigray Regional State, and the remaining one study in the Somali Regional State.

The duration of across-sectional study included in this systematic review was last a total of threemonths of period (from January 1st to March 31st, 2014) of study.

A case control study that was included in this review and it took a total of five-month duration of study periods, and retrospective chart review method was conducted from July 2015 to June 2016. Another included study in this systematic review was a qualitative study which was conducted from March 16 to 24, 2016.

A prospective cross-sectional study conducted at University of Gondar Hospital (UGH) neonatal care unit, the primary outcome was to measure death and cause of death. This prospective cross-sectional study was designed to evaluate a 3 months' pattern of neonatal admissions at the neonatal unit of UGH.

The hospital based retrospective cohort study followed the neonates who were admitted in Neonatal Intensive Care Unit (NICU) for 34 months.Another cohort study included in this systematic review took three months of study.

The included studies involved a total sum of 3089 participants. The main inclusion criteria entailed neonates (age of 28 days or below) and most studies exclude stillbirth from their sample.

In most of the studies the primary outcome assessed was neonatal death. However,in a study done in Somali region, neonatal death was considered as secondary outcome, instead the primary outcome of this study was trends of admission of neonatein the study area.

Prevalence, pattern and predictors of neonatal death were among the study questions of individual studies. All of studies are measured the magnitude of neonatal death; some are expressed as rate, percent, others in numbers.

A narrative synthesis of the main results extracted from articles in full text is aimed to summarize and make conclusion on the recent five years status of records on determinants of neonatal death in Ethiopia.

5.2 Determinants of neonatal death from included studies

From the findings of a prospective cross-sectional study conducted at University of Gondar Hospital (UGH) neonatalmortality was found to be 23.1% out of the total 325 neonates included in the study. Ten variables were, found to have significant statistical association with neonatal mortality after adjusting for demographic covariates. Four variables:prematurity ($p < 0.001$, 95% CI), meningitis ($p < 0.001$, 95% CI), hemorrhagic diseases ($p < 0.001$, 95% CI), and hyaline membrane disease ($P < 0.001$, 95% CI) were having strong association. The other 6 variables: neonatal sepsis ($p < 0.05$, 95% CI),prenatal asphyxia ($p < 0.05$, 95% CI), neonatal seizure ($p < 0.05$, 95% CI), home delivery ($p < 0.05$, 95% CI) and meconium aspiration ($p < 0.05$, 95% CI) were also found to have significant statistical association. In this study thirty-six percent of neonatal deaths were found to happen before 24 hours of neonatal age. The socio-demographic characteristics with outcome variables of neonatal death in this study have unusual relationships, for example participants address from Gondar (study area) has mortality of 42(56.0%) when compared with those participant address where out of Gondar (which is expected to be far from those living at Gondar) has mortality of 33(44.0%. Similarly place of delivery at health facility 63(84.0%) and out of the health facility 12(16.0%) of died, antenatal care service those having at least once 67(89.3%) and those did not have ANC follow up 8(10.7%). And also, monthly income level having <500 has mortality of 2(2.7%), those having monthly income level of 500-1000 have mortality of 27(36.0%), 1000-1500 with died number of 25(33.3%) and monthly income level of >=1500 has mortality of 21(28. 0%) which means that economic empowerment did not show beneficiaries in protection of neonatal death in this study.

A study done on neonatal mortality at the Felege Hiwot referral hospital, Bahir Dar, Amhara Regional State, of the one-year retrospective chart review study it was designed to identify the determinants of neonatal death in that specified study area.This study used 391 patient charts for analysis of data and from this the identified independent determinants of neonatal mortality was: early age of the newborn, gestational age < 37 weeks or preterm, late initiation of breastfeeding, nonexclusive breastfeeding and inadequate antenatal care visit.Neonatal mortality was significantly

higher at early age (first week) of the neonates than at later age [AOR = 0.39 (0.16–0.97)].On the other hand, this studyidentified gestational age at delivery was also significantly associated with the neonatal mortality. The newborns who were preterm were two times higher to die than who were delivered term [AOR=2.14 (1.0–4.52)].Late initiation of breastfeeding was also identified as having associated with the occurrence of neonatal mortality. From the results of the study mothers who was initiated breastfeeding within 1 hour of birth of infant were almost three times higher to save their newborn than those who was delayed breastfeeding initiation [AOR = 2.89 (0.99–8.38)]. Other characteristic that is isolated to have association on neonatal death in this study was exclusive breastfeeding practice which is known to save the life of a newborn. An infant who was not on exclusive breastfeeding was almost seven times higher to die than a neonate who was on exclusive breast-feeding [AOR = 6.77 (3.04–15.07)]. And the number of antenatal visits was also associated with the prevalence of neonatal mortality. A neonate born from a mother with inadequate antenatal care visit less than four times were almost five times higher to die than an infant born from a mother having adequate antenatal care follow up [AOR=5.02 (1.02–24.70)]. Among the common diseases identified as a cause of neonatal mortality in this study were: pneumonia39 (10%), sepsis 93 (23.8%), congestive heart failure 9 (3%), jaundice 18 (3%), preterm/low birth weight 49 (17) and other unidentified causes 183 (1 8%). Neonatal mortality from all admitted neonate in the study area was 13.29%.

A result from the prospective cohort study which was conducted on Tigray Regional State, Northern Ethiopia; is designed to find the causes of neonatal death in the study area. From this cohort study out of the total included 1162 live births, 68 neonates died yielding an NMR of 63 per 1000 live births in the study area. The proximate causes of death in this study were identified and these are; prematurity [23 (34%)], and asphyxia [21 (31%)] which accounted for 2 of every 3 deaths. The remaining deaths were caused by infections 8 (12%), congenital abnormalities 5 (7%), and other causes 11 (16%). Three-fourths of the total deaths took place during the early neonatal period, primarily due to prematurity and asphyxia. Overall, prematurity was the highest reported cause of death in 20 per 1000 live birth whilst congenital abnormality was the least reported cause at 4 per 1000 live births in this study area of cohort study. The determinant effect of socio-demographic and economic factors on neonatal mortality were also assessed in this study and there was no significant difference in distribution of deaths between males and female neonates (P =0.943). Infection was higher among newborns from teenage mothers and all infection was occurred among mothers who lived in the rural areas. A substantial number of deaths [13 (43%)] in the urban areas were caused by asphyxia. Nearly half [12 (47%)] of premature infants were found in mothers of the lowest reported

monthly income category. In general, the cause of death in neonate from this cohort study report was that prematurity and asphyxia in early neonatal deaths; whereas, asphyxia, infection, and prematurity are the leading causes of late neonatal deaths, socio-demographic factors like residence (p=0.05, 95% CI), age at marriage (P =0.004, 95% CI), economic status (p=0.09, 95% CI) and distance (P =0.043, 95% CI) were found to be significantly associated.

Another cohort study included in this systematic review narrative analysis is a study done in hospital based retrospective cohort study in Somali region of Eastern Ethiopia. The aims of this study are identifying the trends of admission, specific causes and rate of neonatal mortality as well as predictors of neonatal mortality at a general hospital in Somali region of Ethiopia. This study reviewed a total of 792 newborns below the age of 28 days admitted in the NICU of Karamara hospital over a period of three years (August, 2014 to May, 2017). While all neonates were born in the hospital, 95 percent of them were below six days at the time of admission of which about three-fourth were first born. The number of neonatal deaths from this study were 45 (5.7%) in the course of hospitalization making a Neonatal Mortality Rate (NMR) of 0.057 (57 per 1000 live births). Ninety-six percent of these deaths were early neonatal that occurred in the first one week of life (<7 days). The results of this study show that, the leading causes of admissions and subsequent deaths in the NICU were found to be prematurity, sepsis, meconium aspiration syndrome and respiratory distress/perinatal asphyxia. In this study demographic and maternal factors have no association with neonatal death, ANC visit(p=0.158, 95% CI), mode of delivery [Assisted vaginal (p= 1, 95% CI), neonatal death followingC/S was 4 (6.9%) and survived neonates after C/S delivery was 54 (93.1%) with p value of 0.999 (95% CI),and death of neonate after SVD was 41(5.7%), survived 681(94.3%) (p=0.999, 95% CI), and there was no (0) neonatal death related to maternal multiple birthwhich means all of neonates were survived, 7 (100%) with(p=0.999, 95% CI).

This systematic review also includes a qualitative study design article in narrative data synthesis. And this qualitative study was done on examining social determinants of neonatal deaths in northwest Ethiopia using the three-delay model approach. Community based Social Autopsy(SA) was conducted from March 16 to 24, 2016. The SA included all neonatal deaths in the HDSS that occurred in the past 18 months prior to the survey.Social Autopsy was conducted for 37 (94.9%) of the 39 deaths. The families for two of the neonatal deaths had left the study area by the time the SA was conducted. Of all the deaths, 51.3% (19/37), 75.6% (28/37) and 24.3% (9/37) occurred in the first 24 h, 0–6 days and between 7 and 28 days of life, respectively. Birth asphyxia and bacterial sepsis were the leading causes of death contributing for 32.5% (12/37) of the deaths, followed by prematurity, which contributed 14% (5/37). The major cause of death in the first 24 h was birth

asphyxia, 52.6% (10/19), followed by unspecified illnesses, 21.1 % (4/19), and prematurity, 15.8% (3/19). For neonatal deaths between 1 and 6 and 7–28 days, the major cause of death (COD) was bacterial sepsis with increasing contribution, 44.4% (4/9), and 66.7% (6/9), respectively. Perceived causes of the deaths reported by caretakers included; fast breathing, excessive cord bleeding, cord tie around the neck of newborn during delivery, born too early to survive, intake of medications for treatment of illnesses during the indexed pregnancy, exposure of the newborn and the mother to sunlight and bewitchment or evil eyes. All of the deaths included in this study were associated to one of the three delay types. Delay in treatment seeking outside home (delay one) was associated with 81% (30/37) of the deaths. Of all the deaths investigate70.31% (26/37) of them did not take any treatment. The median time from recognition of illness to modern treatment seeking was 1 day (IQR 1–2.5 days). Similarly, the median time from recognition of illness to death of the newborn was 10 h (IQR 0.5–72 h). The major delays associated with early and late neonatal deaths were delay one (which is delay in treatment seeking outside home) followed by delay three (which is delay in receiving care at health facility). The major contributors of death for delay one was bacterial sepsis (33.3%), birth asphyxia (30%), unspecified illnesses (20%) and acute lower respiratory tract illnesses (6.7%). Bacterial sepsis was associated with all the death for delay two. For delay three, the major cause of death included birth asphyxia (50%), followed by prematurity (33.3%) and bacterial sepsis (16.7%).Nearly a third of the newborns, 30% (3/10), delivered at health facilities and more than half, 56% (14/25), of the newborns delivered at home died within the first 24 hours.

Acommunity based unmatched case-control study that was done at North Shoa Zone with study participants of a total of 84 cases and 252 controls were conducted with the primary goal to assess determinants of neonatal mortality. From this study the primary outcome was neonatal death. And the results of bivariate analysis confirmed that household wealth, antenatal care visit, frequency of antenatal care visit, place of delivery, postnatal care visit, breast feeding within the first hour of delivery, feeding colostrum, tetanus toxoid injection before birth of last baby, child's size at birth and child's sex were significantly associated with neonatal mortality.On the other hand, mother's age at birth, place of residence, maternal marital status, educational status of the mothers, history of previous neonatal death, preceding birth interval and birth order were not associated with neonatal mortality. From the multivariate analysis results of the study, the odds of dying during neonatal period were higher among neonates born to mothers who did not attend antenatal care (ANC) compared to neonates born to mothers who attended antenatal care (AOR: 3.47; 95%CI: 1.44-8.32). Neonates born at home were 2.86 as likely to die within the first 28 days of life compared with those born at health facility (AOR: 2.86; 95%CI: 1,56-5.26). The odds of neonatal death were three-

foldhigher among neonates whose mothers werenot received postnatal care (PNC) services than the mothers who werereceived postnatal care services (AOR: 3.09; 95%CI: 1, 73-5.51). The odds of neonatal death were much higher among those neonates who were not breastfed within the first hour of delivery than in those who were breastfed within the first hour of delivery (AOR: 23.48; 95%CI: 8.43-65.37). Likewise, neonates who were not fed colostrum were more likely to experience death during their first 28 days of life than that of who were fed colostrum (AOR: 3.91; 95%CI: 1.52-10.03).

In order to summarize the findings of these different included studies regarding to the determinants of death in the neonatal period, the major and leading proximate causes of neonatal death were; prematurity, the first week of life,low or very low birth weight, asphyxia, infections (like neonatal sepsis, lower respiratory diseases, meningitis, tetanus and others), hypothermia,hypoglycemia, neonatal seizure, and other causes like congenital abnormalities and unknown conditions.On the other hand,lack of antenatal care, skill institutional delivery and postnatal care service, age of the mother at birth, poor practice of early initiation of breastfeeding and colostrum feeding, multiple pregnancy, child's sizeat birth and child's sex, educational status of the mothers, and low house hold income were among the common socio-economic or demographic determinants of neonatal death.

5.3 Corrective measures that need to reduce neonatal mortality

The vast majority of newborn deaths take place in low- and middle- income countries, it is possible to improve survival and health of newborns and end preventable stillbirths by reaching high coverage of quality antenatal care, skilled care at birth, postnatal care for mother and baby, and care of small and sick newborns. In settings with well-functioning midwife programmes the provision of midwife-led continuity of care (MLCC) can reduce preterm births by up to 24%. MLCC is a model of care in which a midwife or a team of midwives provide care to the same woman throughout her pregnancy, childbirth and the postnatal period, calling upon medical support if necessary. With the increase in facility births (almost 80% globally), there is a great opportunity for providing essential newborn care and identifying and managing high risk newborns. However, few women and newborns stay in the facility for the recommended 24 hours after birth, which is the most critical time when complications can present. In addition, too many newborns die at home because of early discharge from the hospital, barriers to access and delays in seeking care. The four recommended postnatal care contacts delivered at health facility or through home visits play a key role to reach these newborns and their families [1].

The life course approach to health care recognizes the continuum from birth through childhood, adolescence and adulthood. This approach reflects the principle that care given to children at birth, or even that given to their mothers prior to their birth, will affect their immediate well being and will have an impact on their health and development in later years [16].

The good news is that proven and cost effective interventions, ranging from improved quality of antenatal care to skilled birth attendance to ensuring warmth and initiating breastfeeding at birth, have the potential to reduce the number of neonatal deaths and stillbirths, and many of these interventions can be taken to scale [11]. Since 2000, thanks to joint efforts by multiple national and global stakeholders, low income countries have recognized that focusing on newborn survival is critically important if they are to succeed in achieving the United Nations' ambitious goal of ending preventable deaths of newborns and children and reducing the neonatal mortality rate to 12 per 1,000 live births by 2030 the mandate of Sustainable Development Goal 3 [11].

Spacing children at least 36 months apart reduces the risk of infant death. The median birth interval in Ethiopia is 34.5 months. Infants born less than two years after a previous birth have high under-5 mortality rates. Under-5mortalitiesare dramatically higher among children born less than two years after a previous birth (114 deaths per 1,000 live births) than among children born three years after a previous birth (44 deaths per 1,000 live births). Overall, 22% of children are born less than two years after their siblings [4].

6. Discussion

Among the six studies included in this systematic review five of them (7, 12, 25-27) reported that prematurityand early age of neonatal period were considered as a potential major proximate determinant of neonatal death.Death caused by prematurity was found to be highly significant in this systematic review. Consistent findings were reported from previous studies that show preterm birth as the most common cause of death among infants worldwide (30). And about 15 million babies are preterm each year (5% to 18% of all deliveries) (31).Approximately 0.5% of births are extremely premature births, and these account for most of the deaths (32). The vast majority of deaths were occurred due to preventable complications of prematurity and at early neonatal period (particularly the first 24 hours to 7 days of life). This isalso similarin a systematic review done in Ethiopia (33) and China (34). And this also in line with findings in Pakistan,that shows around 70% of all neonatal deaths occurred in the early neonatal period(35).This may be due to inadequate birth preparedness and limited skill like essential newborn care and neonatal resuscitation to manage adaptation problems of newborn to extra uterine life.

Neonatal sepsis was the leading cause of neonatal death and admission to NICU. This finding was compatible with other similar studies (33, 36). From the study done in Ethiopia the finding shows that bacterial sepsis takes accounts of 36.7% of neonatal death (36).

Birth asphyxia was found to be among the big problems of neonatal health, and it is one of nearest or proximate determinants of neonatal death in this systematic review finding. And others like, hypothermia, hypoglycemia, meningitis, congenital abnormalities, acute lower respiratory infections, hyaline membrane disease, neonatal seizure were alsoamong the determinants of death during neonatal period. This is also similar to the study done in Ghana (37).

In this systematic review, reports confirmed that women who received antenatal care during pregnancy, skilled institutional delivery and postnatal care service were less likely to experience death of their offspring than the women who did not utilize this service. This finding was supported with similar results from a study (38)which has shown that a neonate born from a mother with inadequate antenatal care visit less than four times were almost five times higher to die than an infant born from a mother having adequate antenatal follow up [AOR=5.02 (1.02–24.70)]. This result also in line with a study(39), in which its result was as shown; receiving of antenatal care service during pregnancy and increased number of visit has significant importance in reduction of

neonatal loss. Newborn babies of mothers who attended fewer than four antenatal sessions during pregnancy had a risk of dying that was almost twice that of those whose mothers attended four or more times (39). Antenatal care has been recommended as one of the four main pillars of the safe motherhood initiative based on its effectiveness. It improves pregnancy outcomes by identifying and managing most pregnancy complications. With the identification and management of pregnancy complications, pregnant women receive counseling about the importance of safe delivery practices and early management of newborns' illness (39). Currently, the World Health Organization (WHO) recommends eight or more antenatal care visits for uncomplicated pregnancies ensuring these antenatal care visits is crucial for better survival of neonates (39).

This systematic review also reconfirmed that exclusive breast feeding until six months after birth and early initiation of breastfeeding with in the first hour of birth is known to have strong protective effect on neonatal mortality. A similar finding was also demonstrated in a study done in India, whichstates that if a woman did not breastfeed their newborn within 1 h after his/her birth then the odds of neonatal mortality is increasedfour (OR 3.54; 95% CI 2.34, 5.38) times compared to those neonates who have breastfed within 1 h of birth, and this is recommended by WHO (40).

Initiating breastfeeding within the first hour of life is no easy feat: mothers cannot be expected to do it alone. They require adequate support and guidance on positioning and feeding their newborns (41). The appropriate care of both the newborn and mother in the moments after birth is critical to ensuring that breastfeeding not only begins but continues successfully (42).Children who are not put to the breast within the first hour of life also face a higher risk of common infections. This finding was compatible with study findings done in Tanzania (43).

Other studies confirmed that the benefits to the child of exclusive breastfeeding for the first six months are well established in terms of morbidity and mortality (44). In addition, evidence indicates that breastfeeding also promotes good health in mothers including reduced risk of breast and ovarian cancer, maternal obesity, diabetes, hypertension, and coronary heart disease (45).

The findings of this systematic review from the selected published primary studies (7, 17) show that a protective effect of institutional skilled delivery on neonatal survivals, where asother two included studies (12, 25) show no association between institutional delivery and neonatal survival. This gap may be due to the difference in study area that means the studies that show no association between institutional delivery and neonatal death are conducted in health facilities, where it was the place of the delivery of all study participants.

The best way to prevent newborn deaths is to ensure that essential care is provided around labor, delivery and the immediate postpartum period. Lack of appropriate care during neonatal period will result in significant ill health and even death(46).

Over all this systematic review identified that early age of neonatal period especially in the first 24hours, prematurity, asphyxia, and sepsis are crucial determinants of neonatal death. Other determinants and cause of neonatal death identified in this review were congenital abnormality, meningitis, hypothermia, low birth weight, neonatal seizure, and jaundice. So that an effort and appropriate care following delivery and postnatal care at this time of in age is critically important strategy in order to reduce the burden of neonatal mortality.

The leading contributing socio demographic factors for neonatal deaths in this study are home delivery, lack of ANC and PNC visits, and delayed initiation of breast feeding, not feeding colostrum, early age of mother at marriage,and delay in treatment seek. However distance to care, residence, income level of household index and sex of newborn on neonatal death are lacking consistency in the determinant effect of death across the study area of each included studies.

7. Limitation

This systematic review used studies conducted at a concentrated area which means four out of six included studies were selected from one region, Amhara regional state, and the included studies were conducted based on the documented data and could not display all factors that are not documented in the patient's files, representativeness, completeness and quality of the recorded information.

Due to financial and other constraints this systematic review was not used gray literature, other sources like conference abstract and governmental documents, and focused on freely accessed papers. So these may affect the conclusion of the study. And the search was also limited only to English papers.

Whereas there are many electronic database search engines, this study used a limited and only those databases that assumemore likely indexing of articles published from Ethiopia.

8. Conclusion:

The most critical time of neonatal deaths was in the first week of life. The common proximate determinants of neonatal death were prematurity, asphyxia, sepsis, hypothermia, pneumonia, jaundice. Late initiation of breastfeeding, not on exclusive breastfeeding, those mothers did not have adequate ante natal care visit, delayed in treatment seeking, home delivery, low house hold income and residence are among the socio-economic or demographic determinants of neonatal death.These determinants of neonatal death are largely preventable by addressing essential neonatal careand case management service around labor, delivery and the immediate postpartum periodalong with health education and community awareness creation.

9. Recommendation and dissemination of results

The focus of national neonatal care strategy shall be on first week of neonatal period. Because asphyxia and complication of prematurity were among the major determinants of mortality in neonatal period, basic trainings on essential newborn care and proper newborn resuscitation skills immediately after birth proved to reduce mortality among babies born with. Therefore, any responsible body from the Ministry of Health up to woreda Health office should strengthen their effort on human resource capacity building and health infrastructure development.

Inter-sectoral collaboration of governmental health facilities and organization with nongovernmental organizations and other stakeholders should be strengthenin order to build implementation capacity of health facilities.

Advocacy and Health education programs shouldintroduce to accelerate community awareness about health system.

The government should have a good system in allocating appropriate and fair budget distribution particularly to health system.

Since there is no enough amount of systematic review study conducted in Ethiopia on this topic, so that further study should be conducted to examine national level status of neonatal mortality.

The finding of this study will be disseminated as much as possible through publication or hard copy will availat Addis Ababa University library.

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11. Annexes

Annex. 1 the risk of bias analysis of two included cross-sectional studies. Critical appraisal tool for cross-sectional study (AXIS) adapted from (30).

		Included cross-sectional studies		
		Institution Based prospective Cross Sectional Study on Patterns of Neonatal Morbidity at Gondar University Hospital Neonatal Unit, North-West Ethiopia		
	Questions	Yes	no	Don't know/comment
	Introduction			
1	Were the aims/objectives of the study clear?	✓		
	Methods			
2	Was the study design appropriate for the stated aim/s?	✓		
3	Was the sample size justified?		✓	
4	Was the target/reference population clearly defied? (Is it clear who the research was about?		✓	
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?		✓	
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?		✓	
7	Were measures under taken to address and categorize non-responders?	✓		
8	Were the risk factors and outcome variables measured appropriate to the aims of the study?	✓		
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	✓		
10	Is it clear what was used to determined statistical significance and/or precision estimate? (e.g. p-values, confidence interval)	✓		
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	✓		
	Results			

Annex continued….

12	Were the basic data adequately described?	✓		
13	Does the response rate raise concern about the non-response bias?			Probably, yes because neonates who died on arrival with no documented diagnoses were excluded.
14	If appropriate, was the information about non-responders described?	✓		
15	Were the results internally consistent?	✓		
16	Were the results presented for all the analyses descried in the methods?	✓		
	Discussion			
17	Were the authors' discussions and conclusion justified by the results	✓		
18	Were the limitations of the study discussed?		✓	
	Others			
19	Were there any funding source or conflicts of interest that may affect the authors' interpretation of the result?			✓
20	Was ethical approval or consent of participants attained?	✓		

Annex 2. Critical Appraisal skill program check list for case-control and study design.

		Paper for appraisal and reference					
		Determinants of Neonatal Mortality in North Shoa Zone, Amhara Regional State, Ethiopia. **A Case control study**			Neonatal mortality in the case of FelegeHiwot referral hospital, Bahir Dar, Amhara Regional State, North West Ethiopia 2016:		
	Questions	Yes	No	can't tell	Yes	No	can't tell
	Section A: Are the results of the trial valid?						
1	. Did the study address clearly focused issue? HINT: An issue can be 'focused' In terms of • the population studied • Whether the study tried to detect beneficial or harmful effect • the risk factors studied	✓			✓		
	Comment						
2	Did the authors use anappropriate method to answer their question? HINT: consider • Is a case control study an appropriateway of answering the question underthe circumstances • Did it address the study question	✓			✓		
	Comment				But a cross-sectional study can also answer the question of this study		
….	Is it worth continuing?						
3	Were the cases recruited in an acceptable way? HINT: We are looking for selection biaswhich might compromise validity of the findings • are the cases defined precisely • were the cases representative of a defined population	✓				✓	

	(geographically and/or temporally) • was there an established reliable system for selecting all the cases • are they incident or prevalent • is there something special about the cases • is the time frame of the study relevant to disease/exposure • was there a sufficient number of cases selected • was there a power calculation						
	Comment				Cases and controls are not well defined		
4	Were the controls selected in an acceptable way?HINT: We are looking for selection biaswhich might compromise the Generalisability of the findings •were the controls representative of the defined population (geographically and/or temporally) • was there something special about the controls • was the non-response high, could non-respondents be different in any way • are they matched, population based or randomly selected • was there a sufficient number of controls selected	✓					✓
	Comment	Controls were selected randomly from respective case communities					

Annex continued….

5	Was the exposure accurately measured to minimize bias?HINT: We are looking for measurement,recall or classification bias • was the exposure clearly defined and accurately measured • did the authors use subjective or objective measurements • do the measures truly reflect what they are supposed to measure (have they been validated) • were the measurement methods similar in the cases and controls • did the study incorporate blinding where feasible • is the temporal relation correct (does the exposure of interest precede the outcome)	✓			✓		
	Comment				Exposures are clearly measured in AOR in both case and control groups		
6	(a) Aside from the experimental intervention, were the groups treated equally?HINT: List the ones you think might be important, that the author may have missed • genetic • environmental • socio-economic	✓					✓
.	Comment	Each case and controls have similar characteristics and drown from similar communities			No information about the control and case groups regarding to their basic characteristics.		

Annex continued….

	(b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis? HINT: Look for • Restriction in design, and techniques e.g. modeling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors	✓				✓	
	Comment						
Section B: What are the results?							
7	How large was the treatment effect? HINT: Consider • what are the bottom line results • is the analysis appropriate to the design • how strong is the association between exposure and outcome (look at the oddsratio) • are the results adjusted for confounding, and might confounding still explain the association • has adjustment made a big difference to the OR	✓			✓		
	Comment				The result shows a significant association between exposure and outcome		
8	How precise was the estimate of the treatment effect? HINT: Consider • size of the p-value • size of the confidence intervals • have the authors considered all the important variables • how was the effect of subjects refusing to participate evaluated	✓			✓		
	Comment	✓			P values of <0.005 and CI of 95%		

Annex continued….

9	Do you believe the results? HINT: Consider • Big effect is hard to ignore! • Can it be due to chance, bias, or confounding • are the design and methods of this study sufficiently flawed to make the results unreliable • consider Bradford Hills criteria (e.g. time sequence, does-response gradient, strength, biological plausibility)	✓		✓			
	Comment						
Section C: Will the results help locally?							
10	Can the results be applied to the local population?HINT: Consider whether • the subjects covered in the study could be sufficiently different from your population to cause concern • your local setting is likely to differ much from that of the study • can you quantify the local benefits and harms	✓				✓	
	Comment						
11	Do the results of this study fit with other available evidence? HINT: Consider • all the available evidence from RCT's Systematic Reviews, Cohort Studies, and Case Control Studies as well, for consistency	✓					✓
	Comment; Remember One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making. However, for certain questions observational studies provide the only evidence. Recommendations from observational studies are always stronger when supported by other evidence.						

Annex 3 Critical appraisal skill program check list for cohort study assessment

	Questions	Cause of neonatal deaths in Northern Ethiopia: a prospective cohort study			Trends of admission and predictors of neonatal mortality: A hospital based retrospective cohort study in Somali region of Ethiopia		
	SectionA: Are theresultsofthestudyvalid?	Yes	No	Can't tell	Yes	no	Can't tell
2	Did the study address a clearlyfocusedissue? HINT: A question canbe 'focused' in terms of •the populationstudied •the riskfactorsstudied •is it clear whether the study tried to detect beneficial or harmfuleffect •the outcomes considered	✓			✓		
	Comment						
2	Was the cohort recruited in an acceptable way? HINT: Look forselection bias which mightcompromise the generalisability of the findings: •was the cohort representative of a defined population •was there something specialaboutthecohort •was everybody included whoshouldhavebeen	✓				✓	
	Comment						
	Isitworthcontinuing?						
3	Was the exposureaccurately measured to minimize bias? HINT:Look formeasurementorclassificationbias: • did they use subjectiveorobjectivemeasurements •dothemeasurements truly reflect what you want them to (havetheybeenvalidated) • were allthe subjectsclassifiedintoexposure groups using the same procedure	✓			✓		
	Comment						

Annex continued….

4	Was theoutcomeaccuratelymeasuredto minimize bias? HINT:Look for measurement orclassificationbias: • did they use subjectiveor objective measurements • do themeasurementstruly reflect what you wantthem to (have theybeenvalidated) • has a reliablesystembeenestablishedfordetectin gall the cases (formeasuringdiseaseoccurrence) • were the measurementmethodssimilarinthedifferen t groups ✓ Were the subject and/or the outcome assessor blinded to exposure (does the matter)	✓			✓		
	Comment						
5	(a) Have the authorsidentifiedallimportantconfo undingfactors? HINT: • list the onesyouthinkmightbeimportant, and ones the authormissed		✓		✓		
	Comment						
5	(b) Have they take account of the confounding factors in the design and/or analysis? HINT: •look forrestrictionin design,andtechniquese.g. modeling, stratified-,regression-,or sensitivity analysis to correct, control or adjustforconfoundingfactors		✓		✓		
	Comment						

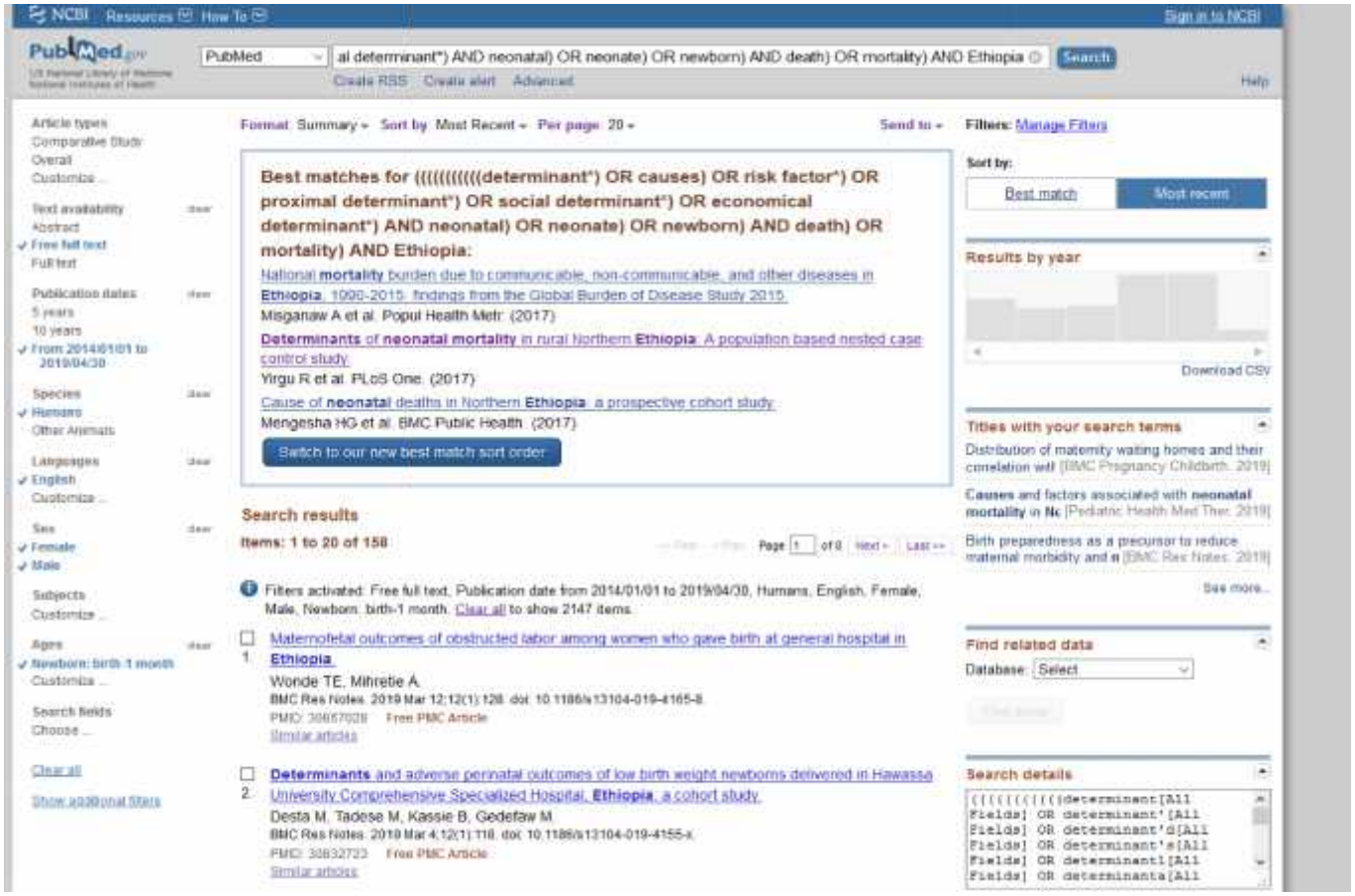
Annex continued….

6	(a) Wasthefollowup ofsubjectscompleteenough? HINT: Consider • thegoodorbadeffectsshouldhavehadlonge noughtoreveal themselves •the personsthatarelosttofollow-upmayhavedifferentoutcomesthanthoseav ailableforassessment •inanopenordynamiccohort,wasthereanyt hingspecialaboutthe outcome ofthe people leaving,ortheexposureofthepeopleenterin gthecohort	✓			✓		
6	(b) Was thefollowup ofsubjectslongenough	✓			✓		
	Comment						
	Section B: What are the results?						
7	What are theresultsofthisstudy? HINT:Consider • what arethebottom lineresults • have theyreportedtherateortheproportio nbetweenthe exposed/unexposed,the ratio/rate difference • how strongis the associationbetweenexposure and outcome(RR) • what istheabsoluteriskreduction (ARR)	✓			✓		
	Comment						
8	Howprecisearetheresults? HINT: • look fortherangeoftheconfidenceintervals, if given	✓			✓		
9	Do youbelievetheresults? HINT: Consider • big effect is hardto ignore • canitbedue to bias, chance orconfounding • are thedesign and methods ofthisstudysufficiently flawed tomaketheresultsunreliable • Bradford Hillscriteria(e.g.timessequence, dose-responsegradient,biologicalplausibility,co	✓		✓			

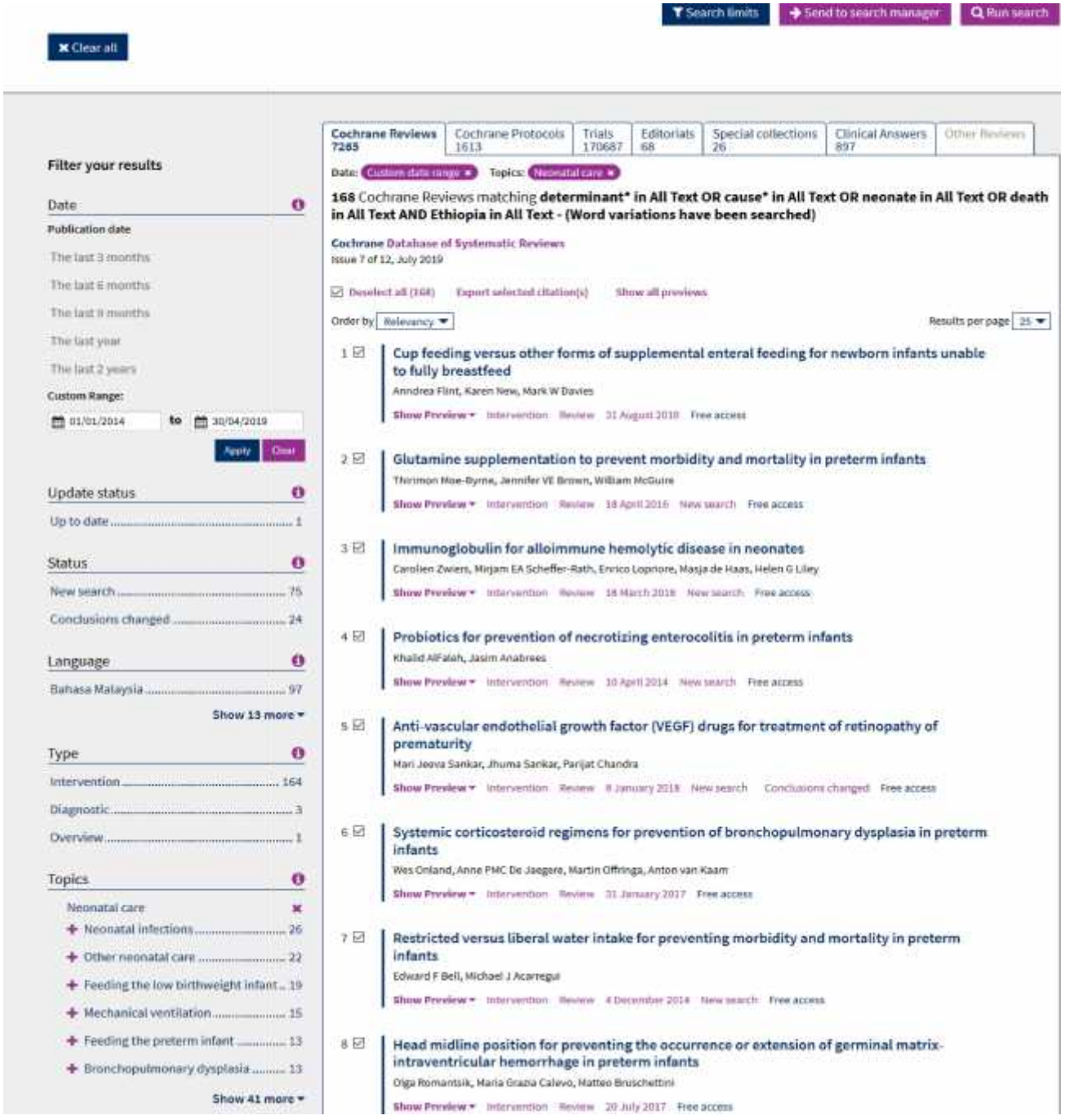
	nsistency)						
	Comment						
Section C: Will the results help locally?							
10	Can the results be applied to the local population?HINT: Consider whether • a cohortstudywastheappropriatemethod toanswer this question • the subjectscoveredinthis study couldbe sufficientlydifferentfrom your population causeconcern • your local setting is likelytodiffermuch from thatofthestudy • youcanquantifythelocalbenefits andharms	✓					✓
	Comment	This cohort applied on randomly selected 7 hospitals and participants were selected in a clear methods					
11	Do the results of this studyfitwithotheravailableevidence?	✓			✓		
	Comment						
12	Whataretheimplicationsofthisstudyforpractice? HINT:Consider • one observational study rarely provides sufficientlyrobust evidence torecommendchangestoclinical practice or within healthpolicy decision making • for certainquestions, observational studiesprovide the only evidence • recommendations from observationalstudiesare always stronger when supportedbyotherevidence	✓			✓		
	Comment s						

Annex 4. Snapshot picture of Data collection results of database.

A. The search results of studies from PubMed electronic database.



B. Results of Cochrane library search for a studies



C. Search results of data from Google scholar