Review article

Under five causes of death in Ethiopia between 1990 and 2016: Systematic review with meta-analysis

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Abstract

Background: Under-five, infant and neonatal mortality rates for Ethiopia were 67, 48 and 29 per 1,000 live births, respectively, based on the 2016 Ethiopia Demographic and Health Survey. Although under-five mortality is substantially improving in Ethiopia, about 190,000 deaths still occur every year. Although various studies have been conducted on the causes of neonatal and under-five deaths in different parts of the country, none of them document pooled analytic results for the causes of death.

Objective: To identify neonatal, post-neonatal, infant and under-five causes of death in Ethiopia.

Methods: A Cochrane systematic review and meta-analysis was carried out on published and grey literature relating to the causes of death for different categories of children under the age of five in Ethiopia between 1990 and 2016. Abstracts were initially reviewed using databases such as MEDLINE/PubMed, Embase, Google Scholar, Google and HINARI, as well as university databases, and conference compendiums of the Federal Ministry of Health and Ethiopian Public Health Association. A total of 220 online and grey literature documents were collected on the basis of their titles and abstracts. However, only 13 were found to be suitable for systematic review. Furthermore, meta-analysis was carried out on 12 of them using an inverse variance heterogeneity effect model. The effect sizes and 95% confidence intervals (CI) are presented in forest plot diagrams, alongside heterogeneity. Publication bias was also examined.

Results: The major causes of neonatal deaths in Ethiopia were bacterial sepsis 28.3% (95% CI: 18.3, 38.8), birth asphyxia 26.7% (95% CI: 14.5, 39.8), prematurity 17.6% (95% CI: 11.6, 24.1), congenital malformation 5% (95% CI: 0.7, 11.3), acute lower respiratory infection 4.4% (95% CI: 0.0, 16.0), and diarrheal diseases 3.6% (95% CI: 1.6, 5.7). The leading causes of death for post-neonates and infants were acute lower respiratory infection 28% (95% CI: 17.8, 39.0), intestinal infections with diarrhea 21% (95% CI: 13.7, 28.9), severe acute malnutrition 9.4% (95% CI: 5.7, 13.8), malaria 10.7% (95% CI: 11.0, 58.9), and bacterial sepsis 6.7% (95% CI: 0.0, 18.6). The leading causes of child (1-4 years) and under-five deaths were sepsis 14.1% (95% CI: 12.0, 16.3), prematurity 13.1% (95% CI: 6.4, 20.6), acute lower respiratory infection, including pneumonia 12.5% (95% CI: 6.2, 19.5), birth asphyxia 11.3% (95% CI: 5.2, 18.2), severe acute malnutrition 9.4% (95% CI: 5.0, 14.0), diarrheal diseases 2.6% (95% CI: 0.0, 7.1), meningitis 2.2% (95% CI: 0.0, 10.8), measles 1.4% (95% CI: 0.0, 23.4), and malaria 1.4% (95% CI: 0.0, 19.9).

Conclusions and recommendations: The major causes of death for under-five children in Ethiopia are easily preventable and treatable. Almost all of the causes could be addressed through high-quality primary health care services by strengthening the health extension program. Cause-targeted obstetric and child health care interventions will remarkably reduce mortality, which requires improving primary health care units in Ethiopia. [*Ethiop. J. Health Dev.* 2020; 34(2):141-160]

Key words: Under five mortality, Causes of death, systematic review and meta-analysis, Ethiopia

Introduction

Globally, significant progress has been witnessed in reducing childhood deaths since 1990. The under-five mortality rate dropped by 53%, from 91 deaths per 1,000 live births in 1990 to 43 in 2015; the neonatal mortality rate fell from 36 deaths per 1,000 live births in 1990 to 19 in 2015; and the number of neonatal deaths declined from 5.1 million to 2.7 million in the same period. However, the decline in neonatal mortality from 1990 to 2015 has been slower than that of post-neonatal and under-five mortality rates (47% compared with 58% and 53%) (1).

Despite the good progress in child survival in sub-Saharan Africa, one in 12 children die before their fifth birthday, which is far more prevalent than the average ratio of 1 in 147 in high-income countries. Accelerated progress is required to achieve the Sustainable Development Goal (SDG) target of an under-five mortality rate of 25 or fewer deaths per 1,000 live births by 2030 (1).

According to the 2015 World Health Statistics report, Ethiopia achieved the Millennium Development Goal (MDG) 4 target by reducing under-five mortality by 69% from the 1990 estimate (2). The 2016 Ethiopia Demographic and Health Survey (EDHS) documented neonatal (dying within the first month of life), infant (dying between birth and the first birthday) and under-five mortality (dying between birth and the fifth birthday) rates of 29, 48 and 67 childhood deaths per 1,000 live births, respectively (3). Notwithstanding the achievement observed in the reduction of under-five mortality rates, about 190,000 children are still dying each year. (4).

Globally, most childhood deaths are caused by diseases that are preventable or treatable with proven, cost-

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effective and quality-enhanced interventions. Infectious diseases and neonatal complications are responsible for the vast majority of under-five deaths globally (1). In Ethiopia, based on a WHO Africa report, the major causes of under-five mortality are: acute respiratory infection (ARI) (18%), diarrhea (13%), prematurity (12%), newborn infection (10%), asphyxia (9%), meningitis (6%), injury (6%), measles (4%), malaria (2%), tuberculosis (TB) (3%), congenital anomalies (2%), HIV (2%), pertussis (1%), and others (17%) (5).

Moreover, in 2011 the EDHS showed there are wide geographic and socio-economic variations in under-five mortality rates. For example, the rate in Addis Ababa was 53 per 1,000 live births compared with 169 per 1,000 live births in Benishangul-Gumuz region. Sporadic studies conducted in different parts of Ethiopia also show that the magnitude of under-five, infant and neonatal mortality vary in different localities. For example, in the Kersa Health and Demographic Surveillance System (HDSS), the under-five, infant and neonatal mortality rates were 77.4, 46.9 and 27 per 1,000 live births, respectively, during the period 2008 to 2013. More than four-fifths (82.4%) of the deaths occurred in the first week of life and malnutrition is the major cause of death among children (6, 7). By contrast, in the Butajira HDSS, the neonatal mortality incidence rate was 1.3 per 1,000 live births in the period 1987 to 2008. A higher level of early neonatal mortality rate compared with late neonatal mortality rate was observed (8). Meanwhile in a cross-sectional study conducted in North Gondar, among women who gave live births between 2005 and 2009, the neonatal mortality rate was 43.8 per 1,000 live births (9).

The studies referred to above didn't summarize causes of death for under five children in Ethiopia and focus on different categories of children under-five children. Accordingly, there is paucity of systematically organized information on the causes of under-five deaths in the country, requiring studies such as the present one to inform policies and programs. This study, therefore, is a systematic review and meta-analysis of studies on the causes of neonatal, post-neonatal, infant, child and under-five deaths in Ethiopia in the period 1990 to 2016.

Methods
Different descriptive and analytical studies, including cross-sectional, case-control and cohort designs from 1990 and 2016, were included. These studies examined the causes of death among the different categories of children under five in Ethiopia, namely neonates, post-neonates and infants, children (1-4 years), and under-fives (0-4 years).

Eligibility criteria: Published and grey literature written in English, whose study subjects were children under the age of five who had died and where the cause of death was documented, were consulted. These studies employed cross-sectional, cohort or case-control designs.

Search strategies: Electronic databases were searched, including MEDLINE/PubMed, HINARI, Google Scholar and Google, as well as the databases of universities in Ethiopia. Manual literature searches were also carried out of the libraries belonging to the Federal Ministry of Health (FMOH), Regional Health Bureaus, Ethiopian Public Health Association (EPHA) and Ethiopian Public Health Institute (EPHI). Also included were unpublished research reports by students or academic staff from five local public universities that teach public health and population studies. Medical subject heading (MeSH) terms and key terms using a Boolean operator – including 'child or neonate or post-neonate', 'infant deaths and death or mortality', 'causes of child or neonate or post-neonate or infant and mortality or death', 'child or under-five death', 'causes of child or causes of under-five death', and 'Ethiopia' – were used to search the literature. Reference lists of searched literature were also reviewed to minimize the omission of relevant articles. Based on the inclusion criteria, two authors screened the articles and cross-checked them for consistency.

Study selection: The study selection procedure is depicted below in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. A total of 220 published and unpublished articles were identified through database searches and other sources. After removing duplicates and abstracts that did not include search terms, 35 studies were included in the review (see Figure 1).
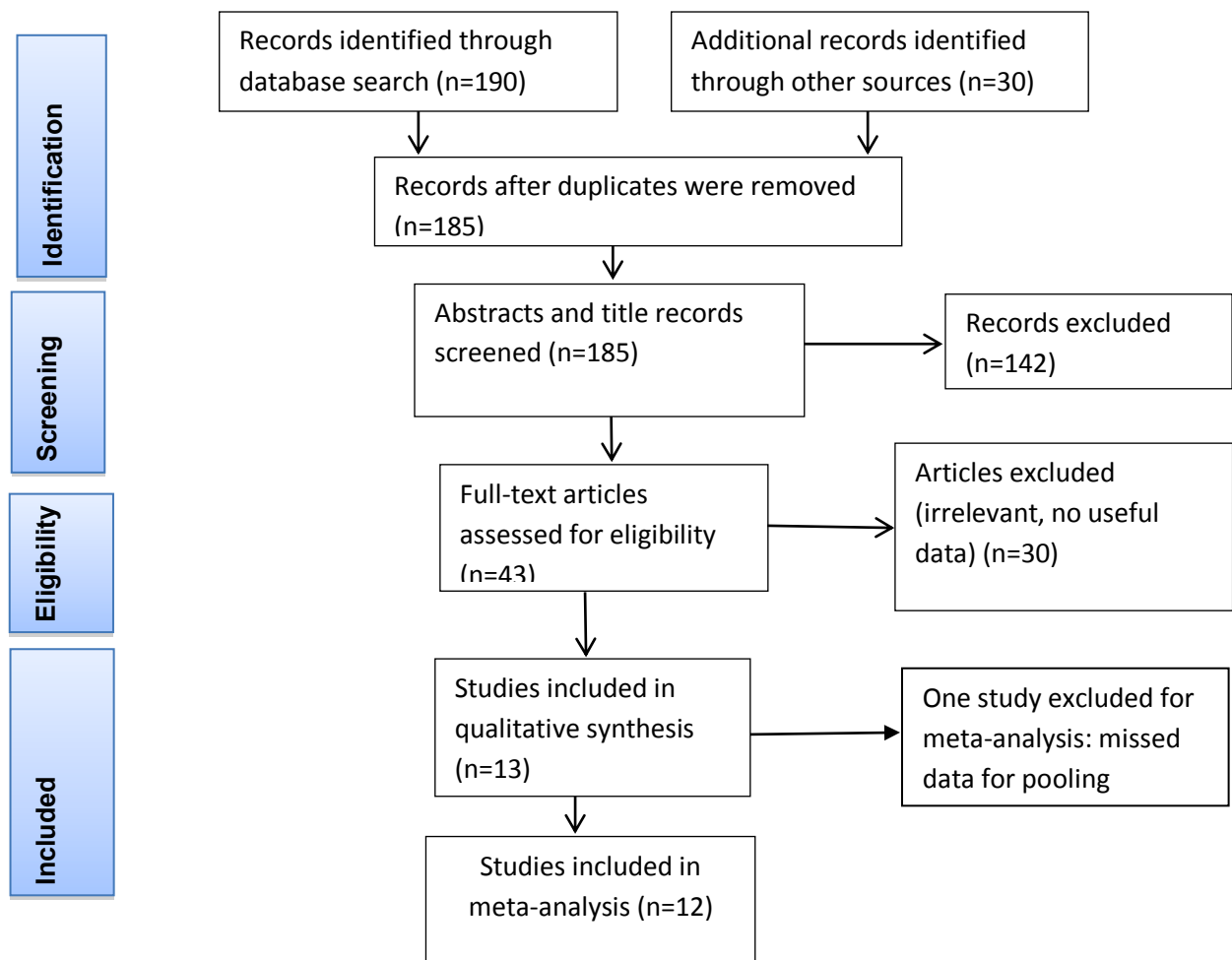
Figure 1: **PRISMA flow chart showing systematic selection of studies on the causes of under-five death in Ethiopia, 1990-2016**

Data extraction:
A form was developed to extract information from the reviewed literature. The data collection included author details, age groups, sample size, number of events, findings related to causes of death, and proportion for each cause of death. Two authors independently read and extracted data using the abstraction form. The reviewers checked their findings for consistency, and any disagreements or inconsistencies were resolved by consensus. Data were collated by age group, namely neonates (0-28 days), post-neonates (29 days-11 months) and infants (0-11 months), child (1-4 years) and under-five (0-4 years). Data extraction was done on 13 studies. However, meta-analysis was done on only 12 studies. Data extraction was done on 13 studies. However, meta-analysis was done on 12 studies, as one study used different age categories. The total number of studies examined for systematic review or meta-analysis may not be equal to the sum of total reviewed literature, since an article might be used for different age categories of children.

Quality assessment: The quality of the reviewed literature was assessed using the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analysis (10). The assessment criteria included the selection of study participants, comparability of study groups, methods for outcome or exposure ascertainment, and adequacy of follow-up. Separate criteria were included for cross-sectional, case-control, and cohort studies: cohort and case-control studies were given a maximum of 4, 2, and 3 scores on the selection, comparability and outcome/exposure criteria, respectively; cross-sectional studies were awarded a maximum of 4, 2, and 2 scores for the selection, comparability and outcome criteria, respectively. The overall quality assessment was classified as "high ($\geq$ 6 score)," "medium (4-5 score)," or "low ($\leq$ 3 score)." No reviewed study was excluded because of its poor performance in the quality assessment (see Table 1).

Table 1: **Quality assessment of reviewed literature on the causes of under-five death in Ethiopia, 1990-2016**

Author (year)	Design	Selection	Comparability	Exposure	Total score
Deribew, *et al.* (2007)	Case-control	****	**	***	9
Shamebo, *et al.* (1993)	Case-control	****	**	**	8
Assefa, *et al.* (2016)	Cohort	**	*	***	6
Weldearegawi, *et al.* (2015)	Cohort	**	**	***	7
Mengesha, *et al.* (2016)	Cohort	**	**	***	7
Fantahun (2008)	Cohort	**	**	***	7
Debelew, *et al.* (2014)	Cohort	***	**	***	8
Weldearegawi, *et al.* (2013)	Cohort	**	*	***	6
EPHA & CDC (2013)	HDSS data analysis	***	**	*	6
Abejew, *et al.* (2014)	Cross-sectional	***	**	*	6
EURCN, EPHA & CDC (2015) unpublished)	HDSS data analysis	***	**	*	6
Federal Ministry of Health (2016). unpublished	Report	****	**	**	8
Federal Ministry of Health (2015), unpublished	Report	****	**	**	8

Data analysis and synthesis: The main outcome of this study was to identify the main causes of death among children under-five using different age categories. The results are presented in a systematic narration, and include meta-analysis with the pooled proportion for each cause of death. The data extraction and analysis were done independently for three different age groups: neonates, post-neonates and infants, and children aged 1-4 years and under-fives. An attempt was made to rank each of the causes according to the magnitude they have in each of the studies.

In order to compute the pooled proportion of major causes of death among neonates, post-neonates and infants, and children aged 1-4 years and under-fives, a meta-analysis using the inverse variance heterogeneity (IVhet) effect model was carried out. The IVhet effect model uses metaXL version 5.3 software. The model is a recent statistical model available only in metaXL software.

The advantage of using the IVhet model over the random-effects model is that although both models used for heterogeneous studies to account for study variabilities, the latter underestimates the error of the effects size and may produce spurious results. The IVhet effect model omits errors through the use of an estimator under the fixed effect model assumption with a quasi-likelihood-based variance structure. In addition, the IVhet model has a novel feature to detect publication bias, the Doi plot, more sensitively than funnel plots (11). However, in this study we produced both graphs.

The effect size, i.e. the proportion of cause-specific death of the meta-analysis was ascribed individually to the main causes of neonatal, post-neonatal and under-five age groups. Summary proportions were presented in forest plots with 95% confidence intervals (CIs). Heterogeneity test that employed Q-statistic and tau-squared calculations were conducted. The IVhet model estimator retained a correct coverage probability and a lower observed variance regardless of the heterogeneity, unlike the other model (11). Sensitivity analysis was also performed. The entire statistical analysis results are annexed (see supplementary file_1-3).

Results
Characteristics of the studies: A total of 220 published and unpublished articles were identified through database searches and other sources. Of the 220 articles, 43 articles (30 published articles, two national health and health-related indicator reports and 11 unpublished theses) were selected for full-text review after reading the titles and abstracts. Thirteen of these were selected for data extraction after reviewing the entire documents. Thirty articles were excluded for methodological reasons or because the studies did not document causes of childhood death. One more study was excluded from the meta-analysis as it did not report the event number. Thus, 13 (seven of which referred to neonatal deaths, five of which referred to post-neonatal and infant deaths, and nine of which referred to child and under-five death) studies were selected for systematic review and 12 (six of which referred to neonatal deaths, four of which referred to post-neonatal and infant deaths, and six of which referred to child and under-five deaths) studies were selected for meta-analysis. From these studies selected for both the systematic review and meta-analysis, a total of 2,287 under-five children deaths in their different age categories with all the required variables were analyzed.

Of the 13 studies enlisted for systematic review, 10 were published and the rest were unpublished; 10 of them were community-based studies and the rest were facility-based studies (see Table 2). In terms of study designs, six employed cohort designs, two case-control reviews, three cross-sectional studies and two national FMOH reports (see Table 2).

Table 2: **Summary of studies included in the systematic literature review of under-five causes of death in Ethiopia, 1990-2016**

Author (Year)	Study design	Study setting	Place of study	No. of under-five deaths
Nega, *et al.* (2016)	Cohort study	Community based	Kersa HDSS	301 neonatal deaths
EPHA & CDC (2013)	HDSS data analysis	Community based	Six HDSS sites	–
Deribew, *et al.* (2007)	Case-control	Community based	Gilgel Gibe	171 under-five deaths
Weldearegawi, *et al.* (2015)	Cohort study	Community based	Kilite Awlalo HDSS	174 infant deaths
Mengesha, *et al.* (2016)	Prospective cohort study	Community based	Tigray Region	68 neonatal deaths
Shamebo, *et al.* (1993)	Matched case-control study	Community based	Butajira HDSS	306 under-five deaths
Fantahun (2008)	Cohort study and prospective case referent study	Community based	Butajira HDSS	142 under-five deaths
Debelew, *et al.* (2014)	Prospective cohort study	Community based	Jimma Zone	110 neonatal deaths
Abejew, *et al.* (2014)	Retrospective cross-sectional study	Facility based	Dessie	443 under-five mortality
Federal Ministry of Health (FMOH) (2016), Unpublished	Report	Facility based	Ethiopia	8,410 under-five deaths
Federal Ministry of Health (2015), Unpublished	Report	Facility based	Ethiopia	6,617 under-five deaths
EURCN, EPHA & CDC (2015, unpublished)	HDSS data analysis	Community based	Six HDSS sites	486 under-five deaths

Neonates: causes of death

As depicted in Table 3, seven reviewed articles (6,12-17) indicated the main causes of neonatal death. Bacterial sepsis was stated as a cause of death in the range 7.5% to 34.3%. The other major causes of death for neonates were birth asphyxia, with a proportion ranging from 5.7% to 47.5%, and prematurity, including respiratory distress, with a proportion of 11.1% to 34%. Bacterial sepsis, birth asphyxia and prematurity were the three major causes of neonatal deaths, claiming the lives of 70% to 92.9% of neonates. However, the rank of the causes of neonatal deaths varied among the reviewed studies. Bacterial sepsis was reported as the first major cause of death in three of the seven studies (6, 12, 13), as the second leading cause in two studies (14, 15), and as third leading cause in one study (16). On the other hand, birth asphyxia was reported as the first cause of death in two studies (14, 15), the second leading cause in three studies (6, 13, 16), and the third leading cause in one study (12). Prematurity was reported as the first leading cause of death in two studies (16, 17), as the second leading cause in one study (12), and the third leading cause in three studies (13-15). One study (17), carried out at Gilgel Gibe, mentioned that prematurity, acute lower respiratory infection (ALRI) and neonatal tetanus were the three major causes of neonatal death.

Table 3: **Causes of neonatal mortality in Ethiopia, 1990-2016**

Author (Year) (Ref)	Causes of death								
	Prematurity, including respiratory distress	Bacterial sepsis	Birth asphyxia	Disease related to perinatal period	ALRI	Neonatal tetanus	Congenital malformation	Diarrhea	Others
Deribew, *et al.* (2007) (17)	26.4%	7.5%	5.7%		24.5%	9.4%	1.9%	7.5%	15%
EPHA & CDC (2013) (14)	14.8%	29%	32.3%		-	-	-	-	-
Debelew, *et al.* (2014) (15)	11.1%	34.3%	47.5%		-	-	-	-	-
Weldeare gawi, *et al.* (2015) (12)	23.7%	32.5%	13.8%		-	-	-	-	-
EURCN, EPHA & CDC (2015) (13)	15%	32.8%	25.6%	2%	3.5%				
Mengesh a, *et al.* (2016) (16)	34%	12%	31%		-	-	7%	-	16%
Aseffa, *et al.* (2016) (6)	17.3%	31.2%	28.2%		2.7%	-	-	-	5%

Note: In each study, red = first leading cause of death; blue = second leading cause of death; yellow = third leading cause of death

Meta-analysis followed the systematic review using six studies through an IVhet model (from Table 3, one study (12) excepted). The meta-analysis addressed the identification of the leading causes of neonatal deaths.

Figure 2 shows the forest plot for bacterial sepsis as a cause of neonatal death. The magnitude of bacterial sepsis ranged from about 7.5% to 34%. The overall pooled proportion of neonatal deaths attributed to bacterial sepsis was 28.3% (95% CI: 18.3, 38.8).
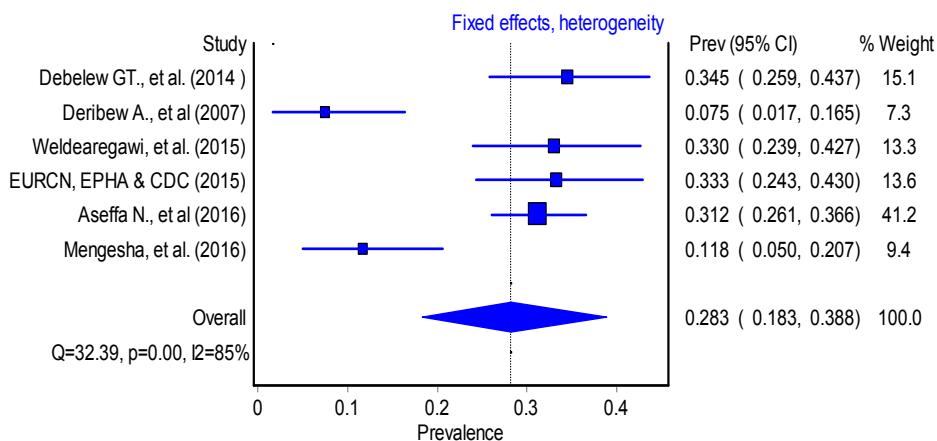
Figure 2: **Forest plot for the pooled proportion of neonatal deaths attributed to bacterial sepsis in Ethiopia, 1990-2016**

Birth asphyxia: The proportion of birth asphyxia as a cause of neonatal death ranged from 5.7% to 47.3%. The overall pooled proportion of neonatal deaths due to birth asphyxia was 26.7% (95% CI: 14.5%, 39.8%) (see Figure 3).
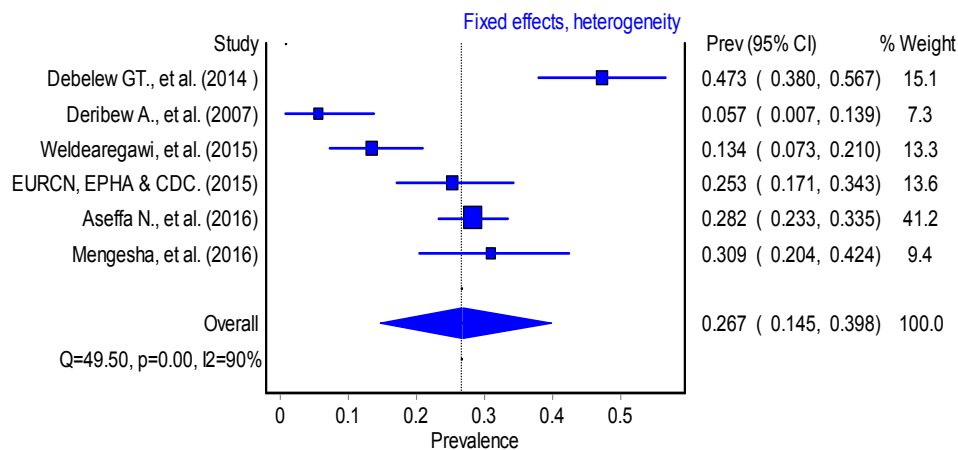

Figure 3: **Forest plot for proportion of neonatal deaths attributed to birth asphyxia in Ethiopia, 1990-2016**

Prematurity:

The proportion of prematurity as a cause of neonatal death ranged from 10.9% to 33.8%. The summary proportion of neonatal deaths attributed to prematurity was 17.6% (95% CI: 11.6, 24.1) (see Figure 4).
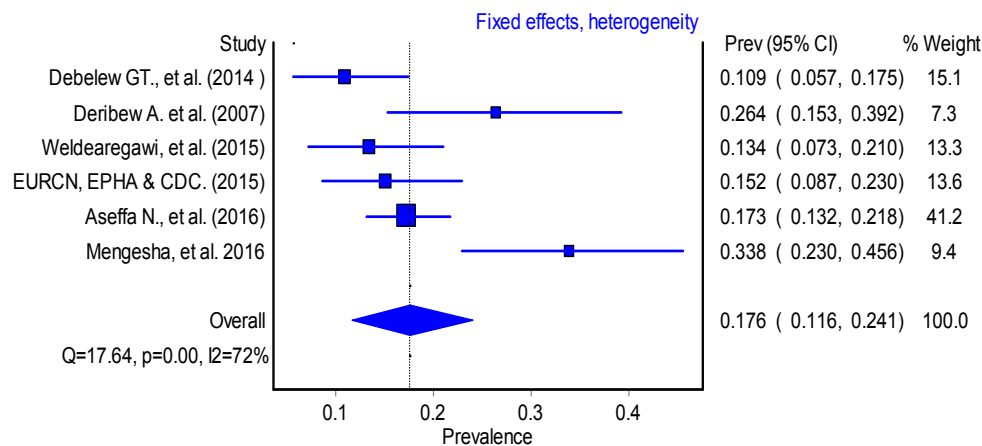
Figure 4: **Forest plot for proportion of neonatal deaths attributed to prematurity in Ethiopia, 1990-2016**

Diarrheal diseases:

Figure 5 shows that the diarrheal disease-related neonatal death rate ranged from 2% to 7.5% and the pooled proportion was 3.6% (95% CI: 1.6, 5.7).
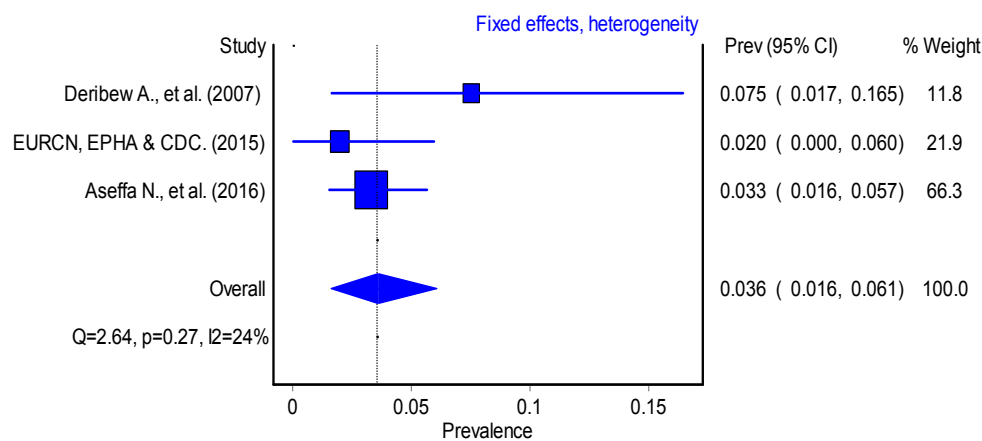
Figure 5: **Forest plot for proportion of neonatal deaths attributed to diarreal disease in Ethiopia, 1990-2016**

Acute lower respiratory infections (ALRI):
As shown in Figure 6, neonatal deaths caused by ALRI ranged from 2.7% to 24.5%. According to the IVhet effect model, the pooled proportion of neonatal deaths attributed to ALRI was 4.4% (95% CI: 0.0, 16.0).
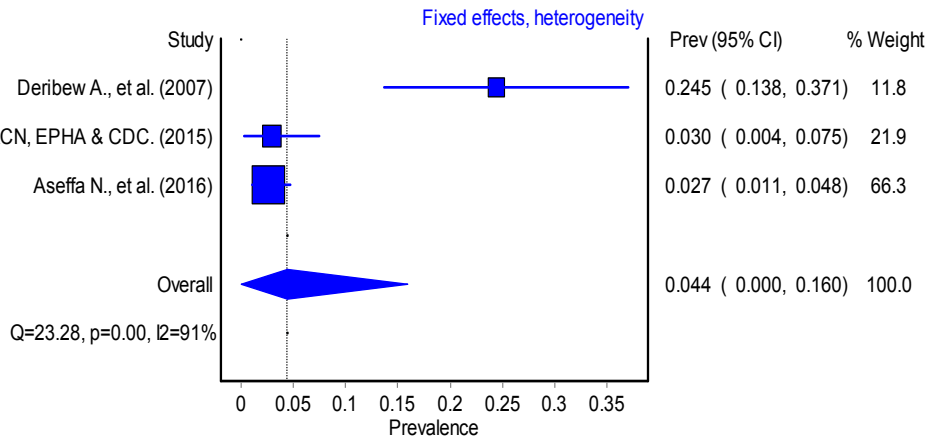

Figure 6: Forest plot for proportion of neonatal deaths attributed to ALRI in Ethiopia, 1990-2016

Congenital malformation:
Figure 7 is a forest plot drawn from the IVhet effect model to portray neonatal deaths attributed to congenital malformation. The pooled proportion of neonatal deaths caused by congenital malformation was 5% (95% CI: 0.7, 11.3).
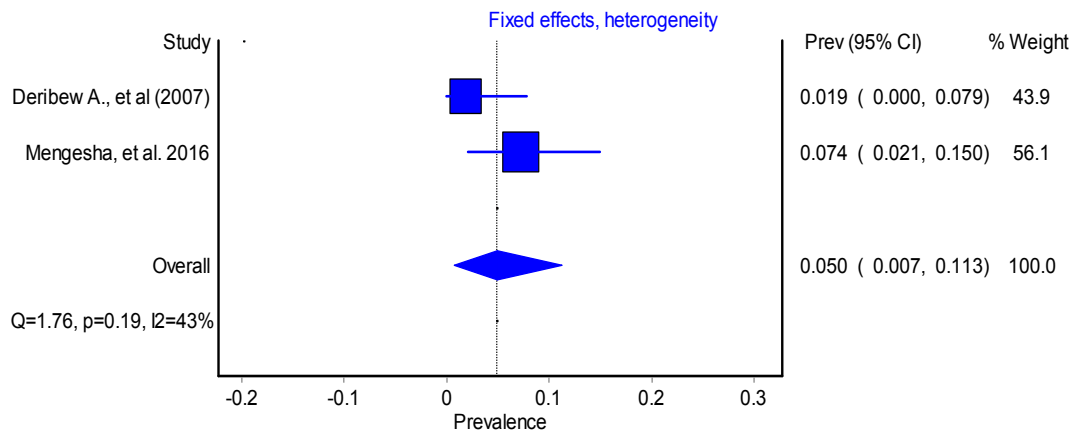
Figure 7: Forest plot for proportion of neonatal deaths attributed to congenital malformation in Ethiopia, 1990-2016

In summary, the leading causes of neonatal deaths in order of the pooled magnitudes are bacterial sepsis (28.3%), birth asphyxia (26.3%), prematurity (18%), congenital malformation (5%), ALRI (4.4%), and diarrheal diseases (3.6%).

Neonatal tetanus and "others" as a cause of death were not recruited for meta-analysis, as the former was reported by a single study and the latter had no relevant information for analysis.

Post-neonates and infants: causes of death
Five studies were reviewed for the causes of post-neonatal and infant deaths. All five studies (12-14, 17, 18) indicated that ALRI was the first leading cause of post-neonatal and infant deaths. Intestinal infection, including diarrhea (IID), was reported as the second cause of death in the three studies (13, 14) and as the third cause of death in one study (12). Malaria was reported as the second cause of death by one study (17). In two studies (13, 14), severe acute malnutrition (SAM) was reported as the third leading cause of post-neonatal and infant deaths. There was only one study each reported meningitis (17), measles (17), and tuberculosis (TB) (13) as a cause of post-neonatal and infants deaths (see Table 4).

Table 4: **Post-neonatal and infant causes of death in Ethiopia, 1990-2016**

Author (Year) (Ref)	Causes of death							
	ALRI	Intestinal infection, including diarrhea	Malaria	Meningitis	Measles	Bacterial sepsis	SAM	TB
Shamebo, *et al.* (1993) (18)	33%	23%*	-	-	-	-	-	-
Deribew, *et al.* (2007) (17)	47.8%	34.8%*	41.3%	13%	4.3%	-	10.9%	-
EPHA & CDC (2013) (14)	34.8%	19.7%	-	-	-	-	7.4%	-
Weldearegawi, *et al.* (2015) (12)	17.9%	11.9%	-	-	-	14.9%	- -	-
EURCN, EPHA & CDC (2015) (13)	24.0%	20.4%	5.2%	-	-	3.8%	8.8%	4.1%

* Studies reported diarrheal disease separately, without term intestinal infections.
Note: In each study, red = first leading cause of death; blue = second leading cause of death; yellow = third leading cause of death

Meta-analysis for causes of post-neonatal and infant deaths

Acute lower respiratory infection (ALRI):
The proportion of ALRI deaths ranged from 18.2% to 47.8%. In the IVhet model, the pooled proportion of deaths attributed to ALRI was about 28% (95% CI: 17.8, 39.0) (see Figure 8).
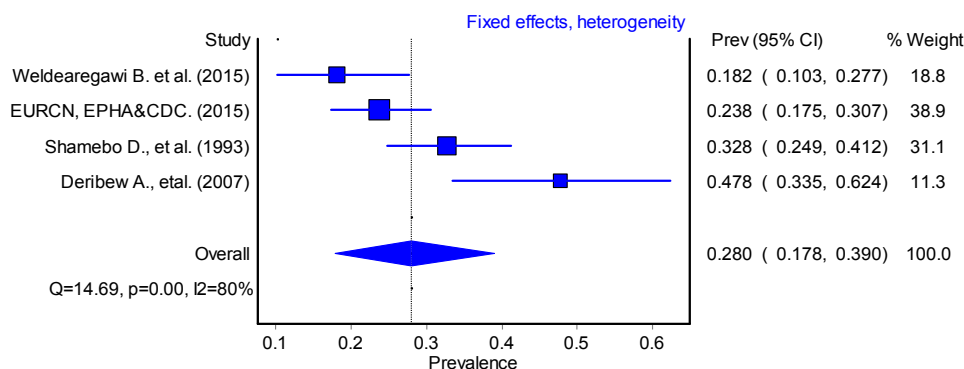

Figure 8: **Forest plot for proportion of post-neonatal and infant deaths attributed to ALRIs in Ethiopia, 1990-2016**

Intestinal infections, including diarrheal diseases:
Figure 9 depicts the forest plot of intestinal infections, including diarrheal diseases, as a cause of post-neonatal and infant deaths. The forest plot shows that the individual study proportion rate ranged from 11.7% to 34.8% and the pooled proportion was 21% (95% CI: 13.8, 28.9).
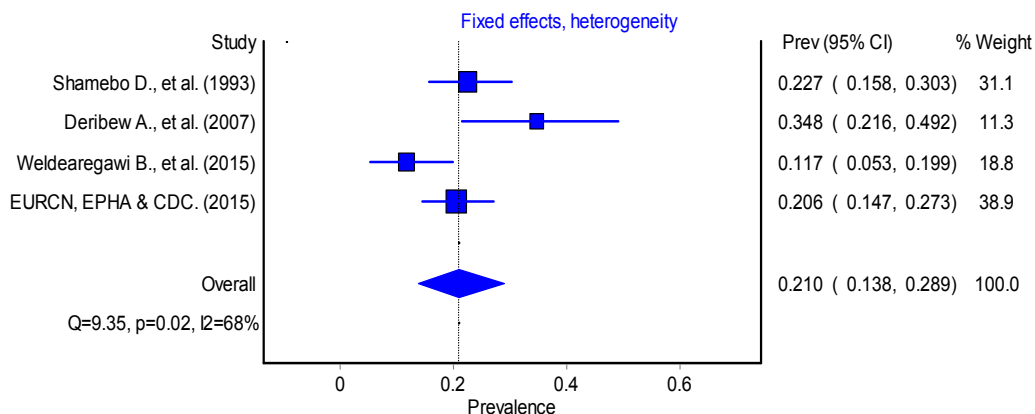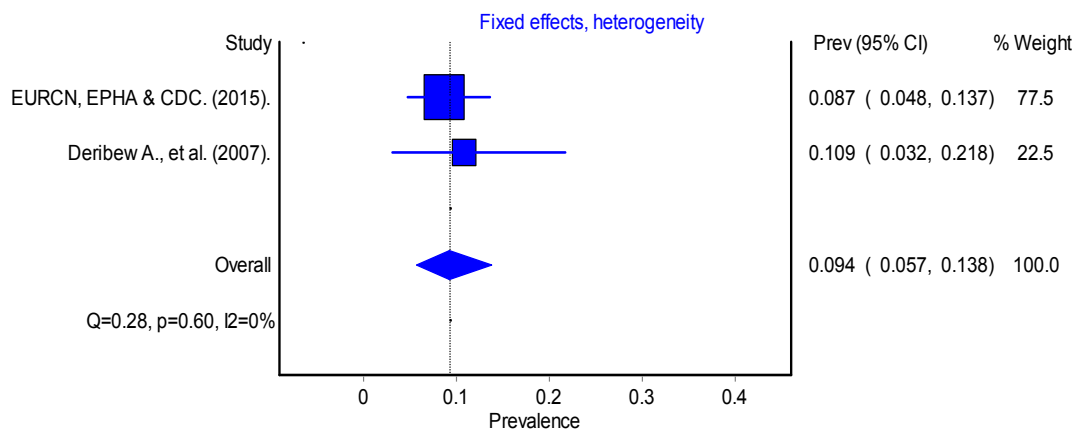

Figure 9: **Forest plot for proportion of post-neonatal and infant deaths attributed to intestinal infections, including dirrheal diseases, in Ethiopia, 1990-2016**

Severe acute malnutrition (SAM):
The forest plot in Figure 10 shows that the proportion of post-neonatal and infant deaths ranged from 8.7% to 10.9%. The plot also reveals that 9.4% (95% CI: 5.7, 13.8) of the pooled proportion of deaths resulted from SAM.

Figure 10: **Forest plot for proportion of post-neonatal and infant deaths attributed to SAM in Ethiopia, 1990-2016**

Malaria:
The forest plot in Figure 11 indicates that the proportion of deaths due to malaria among post-neonates and infants ranged from 5% and 41.3%, and the pooled proportion rate was 10.7% (95% CI: 0.0, 58.9).
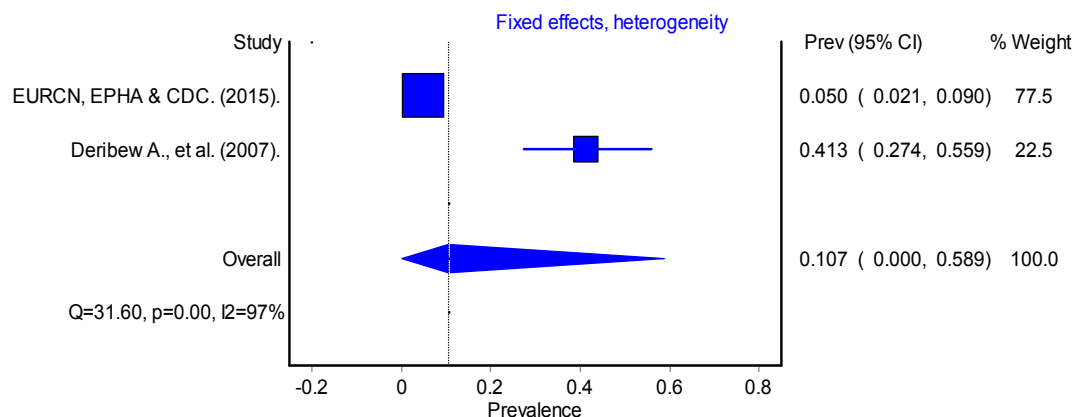
Figure 11: **Forest plot for proportion of post-neonatal and infant deaths attributed to malaria in Ethiopia, 1990-2016**

The forest plot in Figure 12, which draws on the IVhet effect model, shows bacterial sepsis claimed the lives of 3.7% to 14.3% of post-neonates and infants. The pooled proportion of deaths was 6.7% (95% CI: 0.0, 18.6).
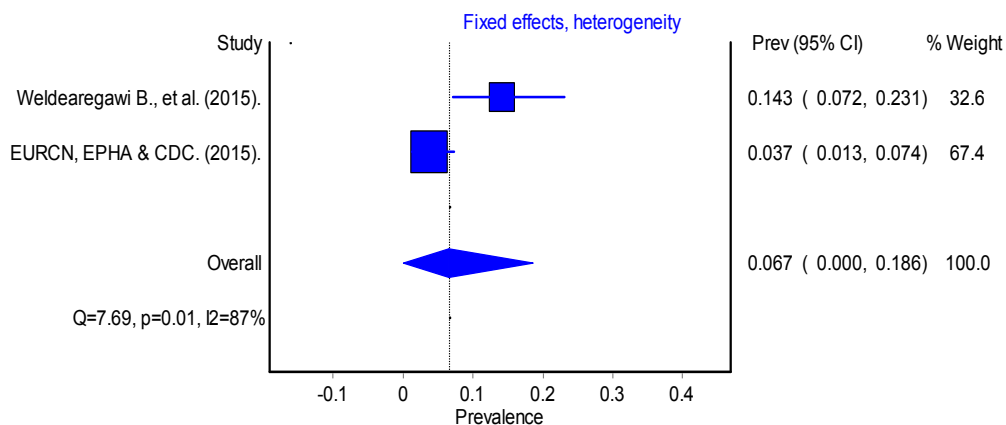
Figure 12: **Forest plot for proportion of post-neonatal and infant deaths attributed to bacterial sepsis in Ethiopia, 1990-2016**

In summary, for post-neonates and infants, the commonly reported cause of deaths by at least two or more studies were ALRI, malaria, intestinal infections (including diarrhea), SAM, and bacterial sepsis. The leading causes of death identified with the IVhet effect model were ALRI (28%), followed by intestinal infections with diarrhea (21%), malaria (11%), SAM (9%), and bacterial sepsis (7%).

Children aged 1-4 years and under-fives: causes of death
The causes of death for children aged 1-4 years and under-five are noted in Table 4. A total of nine studies were recruited for systematic review. Four (13,14,17,18) and five (19-23) of the studies reported a cause of death for age 1-4 years and under-five children, respectively. Of all of these studies, three studies (19,21,22), four studies (14,17,18,20), and two studies (13,23) informed that ALRI, including pneumonia, was the first, second and third leading cause of child and under-five deaths, respectively. However, ALRI, including pneumonia, was a first leading cause of death only among under-fives. The proportion of ALRI-related deaths ranged from 9% to 34.8%. Eight studies (13,14,17,19-23) reported SAM as a cause of death, and the proportion ranged from 7% to 31.8%. From all of these studies, SAM was reported in two (13,14) and three (20,22,23) studies as the first and third leading cause of mortality, respectively. In terms of age groups, three of the studies (13,14,17) focused on the age group of 1-4 years, and the rest focused on the under-five age group. However, the very large proportion were reported among 1-4-year-old groups (13%-31.8%), whereas among 0-4-year-old children it ranged from 7% to 16%. One study (19) reported sepsis as the first cause of death and three studies (20-22) reported it as the second cause of death for under-fives only. Overall, the proportion of under-five deaths attributed to sepsis ranged from 13% to 22%.

Diarrheal disease was the other cause of disease for children aged 1-4 years and under-fives. Four studies (17,18,22,23) indicated that diarrhea killed 2% to 50.7% of children aged 1-4 years and under-fives. Two of studies (17,18) mentioned it was the first leading cause of death (ranging from 32% to 50.7%) among children 1-4 years of age. Nevertheless, a nationwide report by FMOH (22,23) showed that diarrhea disease caused between 2% to 2.8% of under-five deaths. Prematurity, reported by four studies (13,20,22,23), was considered as a first leading cause (17%) of under-five deaths (23), and the third leading cause (8.4%) by another study (20). Three studies (20,22,23) reported birth asphyxia as a cause of under-five deaths, among which one of the studies (23) explained that it was a second leading cause of death (15%). Malaria was also a cause of deaths for about 4.6% to 29% (13,17,19,22) of children aged 1-4 years and under-fives. Among these studies reported malaria, one study (19) reported malaria, while another (17) reported as the second leading cause of death, respectively.

A number of causes of death, including measles, meningitis, injury, other perinatal disease, low birth weight, intestinal parasites and still births, were either reported as a leading cause of death in none of the studies or were mentioned by a single study only. Three studies (13,17,22) reported measles as a cause of death and the proportion ranged from 1.19% to 8.7%; two of the studies (13,17) reported measles as cause of death for children aged 1-4 years, while the third (22) mentioned measles as a cause of death among under-fives. Four studies (13,17,19,20) reported meningitis causing 2% to 23.2% of deaths among children aged 1-4 years and under-fives, and two studies (13,17) attributed meningitis as causes of death among children 1-4 years and the rest (19,20) were to under-fives. The remaining cause of death was categorized as "others", since it was reported by a single study, although the specific causes of death were known. "Others" referred to injury, other perinatal disease, low birth weight, intestinal parasites, and stillbirths. In this category, low birth weight (13) was the second leading cause of death, accountable for 16.7% of deaths among children aged 1-4 years; intestinal parasitic infections (8.4%) and stillbirths (6.3%) were the third leading cause of death among under-fives (20).

Table 5: **Children aged 1-4 years and under-five causes of death in Ethiopia, 1990-2016**

Author (Year) (Ref)	Causes of death											
	Age	ALRI, including pneumonia	SAM	Sepsis	Diarrheal diseases	Measles	Meningitis	Malaria	Prematurity	Birth asphyxia	HIV/AIDS	Other
Shamebo, *et al.* (1993) (18)	1-4 yrs	20%	-	-	32%	-	-	-	-	-	-	-
Deribew, *et al.* (2007) (17)	1-4 yrs	34.8%	13%	-	50.7%	8.7%	23.2%	29%	-	-	2.9%	*4.3%
EPHA & CDC (2013) (14)	1-4 yrs	16%	31.7%	-	-	-	-	-	-	-	-	14%****
EURCN, EPHA & CDC (2015) (13)	1-4 yrs	12.7%	31.8%	-	-	4.3%	2.3%	4.6%	5.3%	-	-	16.7%****
Fantahun (2008) (19)	<5 yrs	29%	16%	-	-	-	10%	23%	-	-	-	18.0%**
Weldearegawi, *et al.* (2013) (20)	<5 yrs	12.6%	5.3%+++	22.1%	-	-	5.3%	-	8.4%	5.3%	-	8.4%**** 6.3%++
Abejew, *et al.* (2014) (21)	<5 yrs	21.2%	14.6%	17.3%	-	-	-	-	-	-	-	-
FMOH (2015) (22)	<5 yrs	15.4%	11.7%+	12.98%	2.8%	1.19%	-	1.16%	9.7%	8.16%	-	9.7%** 3.4%***
FMOH (2016) (23)	<5 yrs	9%	7%	15%	2%	-	2%	-	17%	15%	-	9%** 5%***

Others groups: * = injury; ** = other perinatal disease; *** = low birth weight; **** = intestinal parasitic infection; + = severe and moderate malnutrition; ++ = stillbirth; +++ = nutritional anemia and severe malnutrition.

Note: In each study, red = first leading cause of death; blue = second leading cause of death; yellow = third leading cause of death

In some cases a person may suffer from multiple causes of death.

Meta-analysis for proportion of causes of child (1-4 year) and under-five (0-59 months) deaths

The IVhet effect model was deployed for the meta-analysis. To examine the pooled effect size for the specific causes of death in each age group, child 1-4 years or under-five, we carried out a subgroup analysis, which was done when the studies had full information about the two age groups.

ALRI, including pneumonia, deaths for post-neonates and infants:

Figure 13 shows the forest plot for deaths caused by ALRI, including pneumonia. The proportion of ALRI-related deaths, including pneumonia, among children aged 1-4 years and under-fives ranged from 9% to 34.8%. The pooled proportion was 17.5% (95% CI: 6.2, 30.4) for children aged 1-4 years, 12.3% (95% CI: 6.1, 19.3) for under-fives, and the overall pooled proportion was 12.5% (95% CI: 6.2, 19.5).
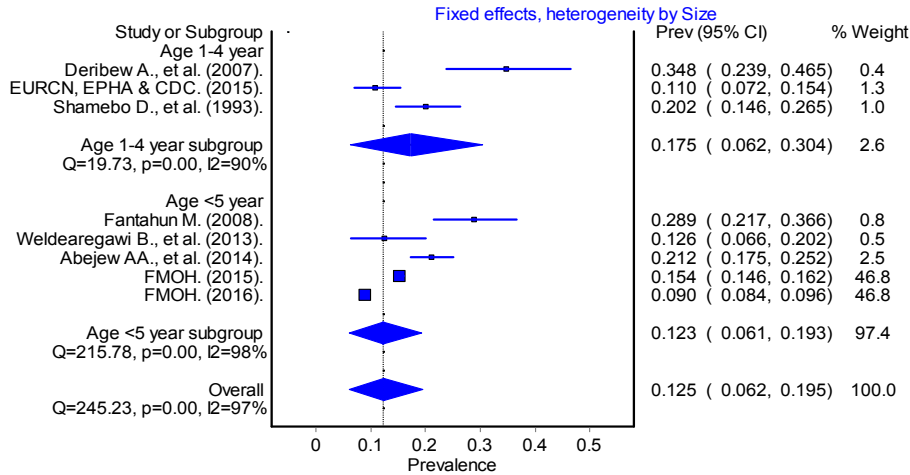
Figure 13: **Forest plot for proportion of under-five and child deaths attributed to ALRI, including pneumonia, in Ethiopia, 1990-2016**

Diarrheal diseases:
Using the IVhet effect model, the overall pooled proportion of child and under-five deaths attributed to diarrheal diseases was 2.6% (95% CI: 0.0, 7.1), whereas the pooled proportion for children 1-4 years and under-fives (0-4 year) was 37.2% (95% CI: 18.3, 57.2) and 2.4% (95% CI: 1.6, 3.2), respectively (see Figure 14).
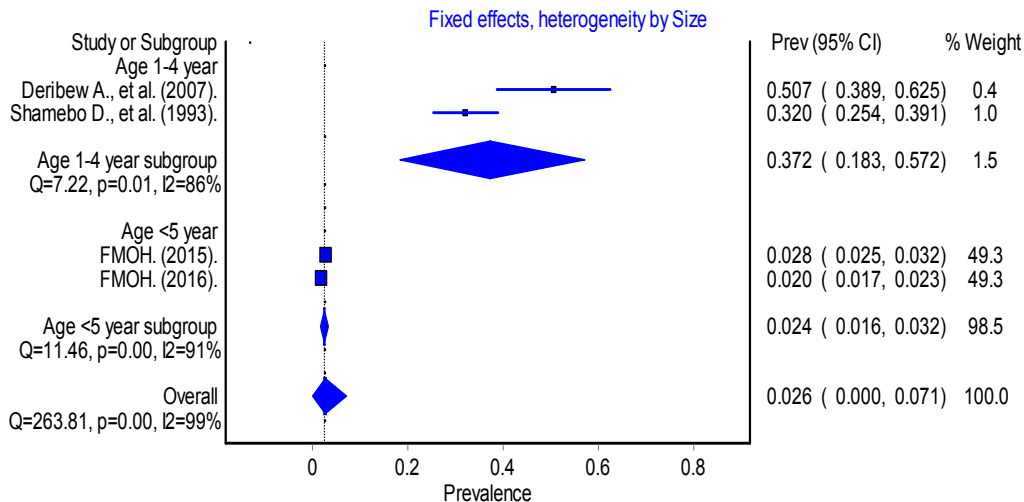

Figure 14: **Forest plot for proportion of under-five and child deaths attributed to diarrheal disease in Ethiopia, 1990-2016**
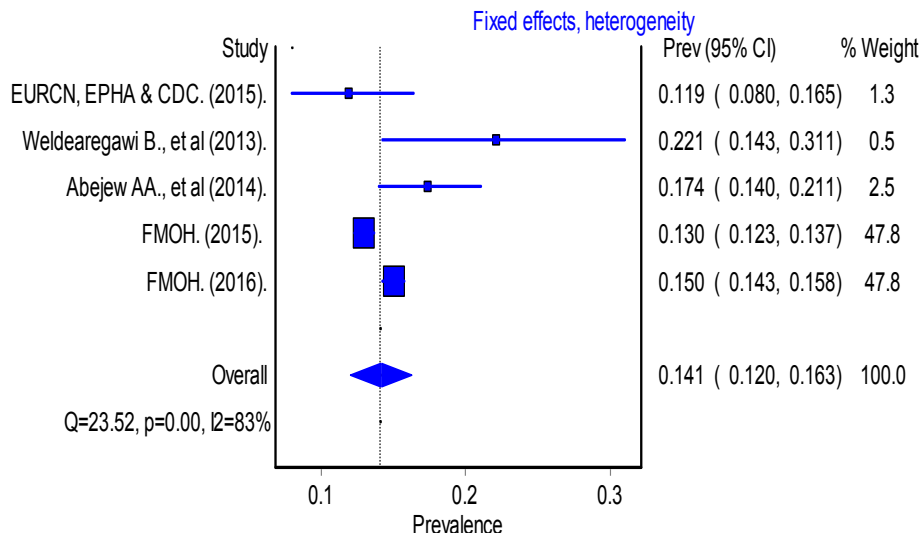
Figure 15: Forest plot for proportion of under-five and child deaths attributed to sepsis in Ethiopia, 1990-2016

Sepsis:
Sepsis was only reported as a cause of death among under-five age group, and ranged from 11.9% to 22.1%. The pooled prevalence was 14.1%% (95% CI: 12.0, 16.3) (see Figure 15).

Severe acute malnutrition (SAM):
SAM was a cause of death for children aged 1-4 years and 0-4 years. The overall proportion ranged from 7% to 15.4%. According to the IVhet effect model, the overall pooled proportion of sepsis-related deaths among children aged 1-4 and 0-4 was 9.4% (95% CI: 5.3, 14.0). However, the sub-group analysis showed that the pooled proportion was 12.1% (95% CI: 8.5, 15.9) for those aged 1-4 and 9.4% (CI: 5.1, 14.1) for those aged 0-4 (see Figure 16).
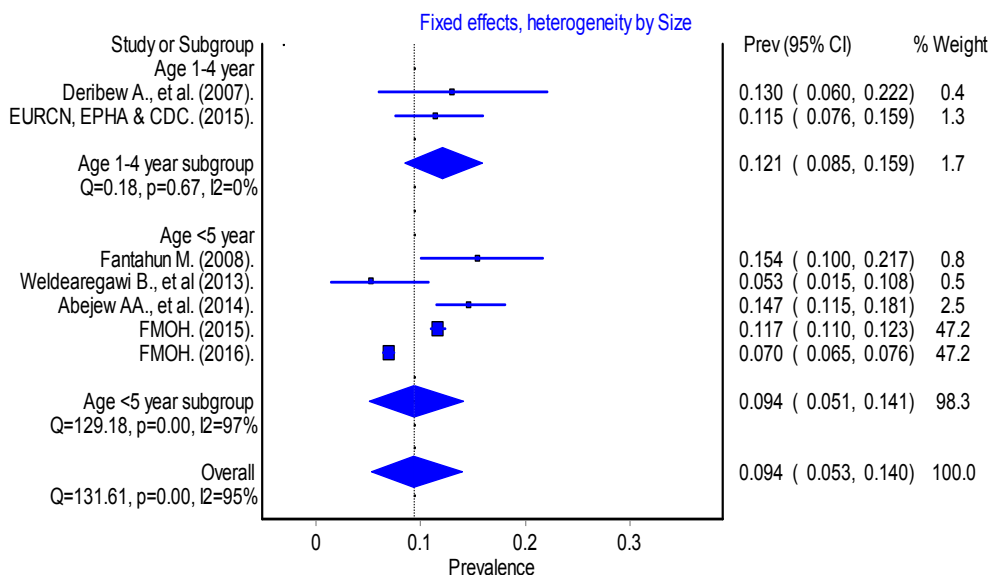

Figure 16: Forest plot for proportion of under-five and child deaths attributed to severe acute malnutrition in Ethiopia, 1990-2016

Birth asphyxia:
Birth asphyxia was a cause of death among under-five groups only. The proportion of deaths ranged from 5.3% to 15%. The pooled proportion of deaths attributed to birth asphyxia was 11.3% (95% CI: 5.2, 18.2) (see Figure 17).
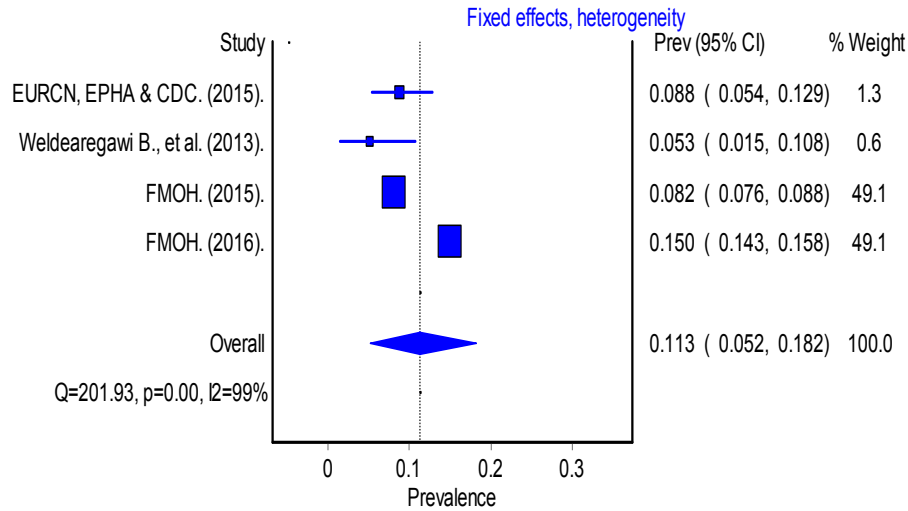
Figure 17: **Forest plot for proportion of under-five and child deaths attributed to birth asphyxia in Ethiopia, 1990-2016**

Measles:

Measles claimed the lives of 1.2% to 34.8% of children aged 1-4 years and under-fives. The IVhet effect model produced a pooled proportion of deaths of 1.4% (95% CI: 0.0, 23.4) among children aged 1-4 years and under-fives. A subgroup analysis showed that 15.8% (95% CI: 0.0, 43.9) of deaths among children aged 1-4 years were attributed to measles (see Figure 18).
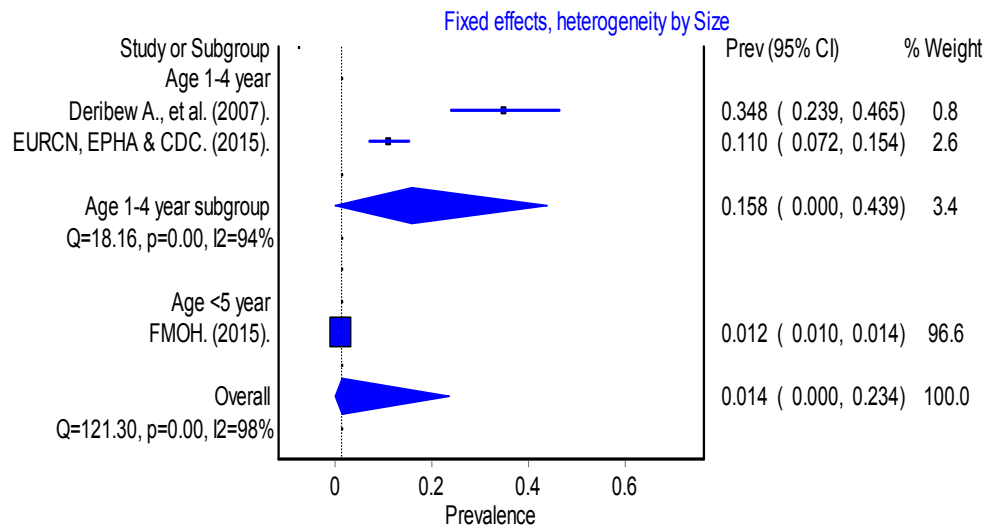

Figure 18: **Forest plot for proportion of under-five and child deaths attributed to measles in Ethiopia, 1990-2016**

Malaria:

Among children aged 1-4 years and under-fives, death due to malaria ranged from 1.26% to 29%. The pooled proportion of deaths was 7.3% (95% CI: 0.0, 40.3) for children aged 1-4 years and 1.3% (95% CI: 0.0, 33.5) for under-fives. The overall pooled proportion for both groups was 1.4% (95% CI: 0.0, 19.9) (see Figure 19).
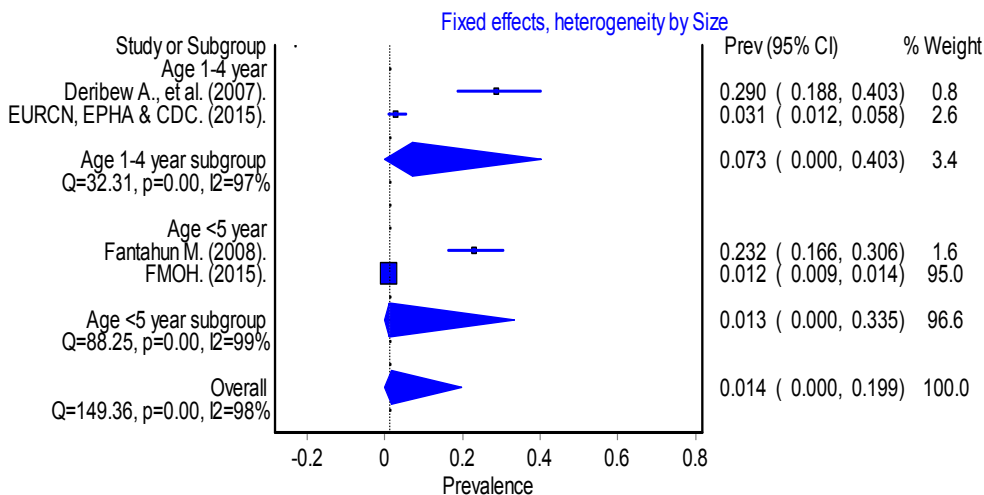
Figure 19: **Forest plot for proportion of under-five and child deaths attributed to malaria in Ethiopia, 1990-2016**

Meningitis: The proportion of deaths due to meningitis ranged from 2% to 23.2%. The overall pooled proportion of deaths caused by meningitis for children 1-4 years and under-fives was 2.2% (95% CI: 0.0, 10.8).

According to the subgroup analysis, the pooled proportion was 5.6% (95% CI: 0.0, 31.9) and 2.1% (95% CI: 0.0, 9.9) among children aged 1-4 years and under-fives, respectively (see Figure 20).
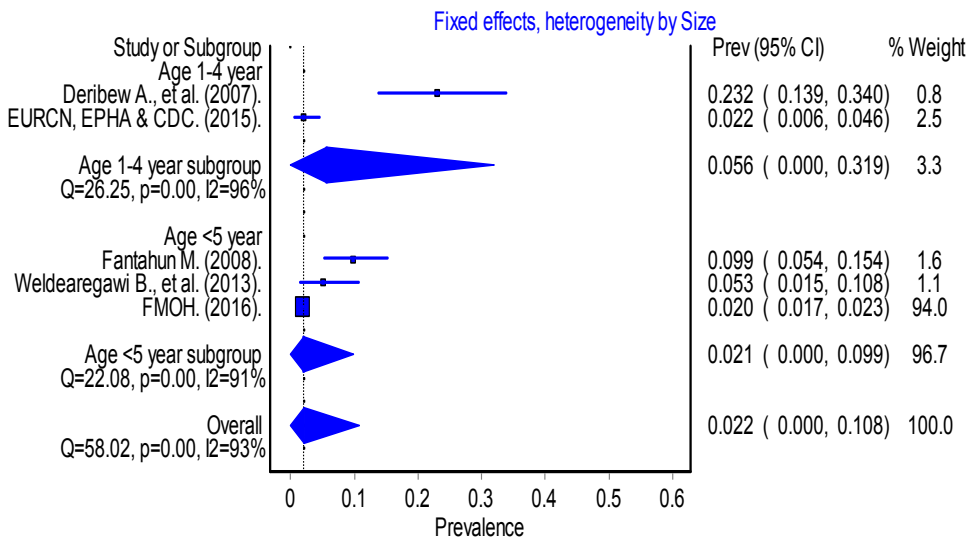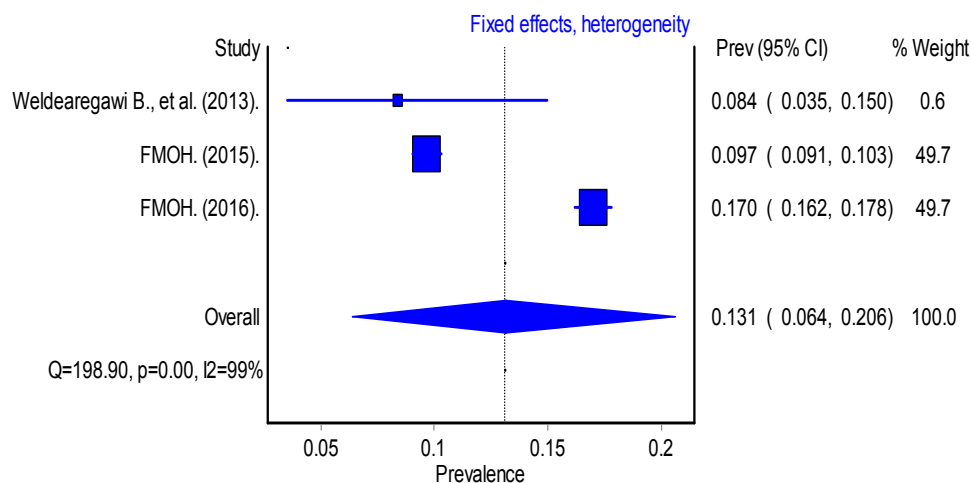

Figure 20: **Forest plot for proportion of under-five and child deaths attributed to meningitis in Ethiopia, 1990-2016**

Prematurity: For under-fives, the proportion of deaths attributed to prematurity ranged from 8.4% to 17%. The overall pooled proportion of deaths was 13.1% (95% CI: 6.4, 20.6).

Figure 21: **Forest plot for proportion of under-five and child deaths attributed to prematurity in Ethiopia, 1990-2016**

In summary, the meta-analysis indicated the causes of death for children 1-4 years, under-fives, or both. Reported cause of deaths with estimated pooled proportion for children aged 1-4 years were diarrheal disease (37.2%), ALRI, including pneumonia (17.5%), measles (15.8%), SAM (12.1%), malaria (7.3%), and meningitis (5.6%).

Under-five child deaths were principally caused by prematurity (13.1%), ALRI, including pneumonia (12.3%), SAM (9.4%), diarrheal disease (2.4%), meningitis (2.1%), and malaria (1.3%). This was based on the pooled proportion of the subgroup analysis if at least two studies had reported.

The causes of death for children 1-4 years and under-fives, and the overall pooled proportions, were measles (15.1%), sepsis (14.1%), ALRI, including pneumonia (12.5%), birth asphyxia (11.3%), SAM (9.4%), diarrheal diseases (2.6%), meningitis (2.2%), and malaria (1.4%).

Discussion
Although progress in reducing neonatal and under-five mortality has been considerable in Ethiopia (2, 24), high numbers of children, particularly neonates, continue to die of easily preventable and treatable diseases (2, 4). As a result, Ethiopia has proposed to end all preventable newborn and child deaths and reduce the under-five mortality rate to less than 20 per 1,000 live births by 2035 (25). Thus, it is important to understand and synthesize the major causes of death among neonates, post neonates, children aged 1-4 and under-fives.

In this study, the most common cause of neonatal death, according to the pooled proportions from the IVhet model, were bacterial sepsis (28.3%), birth asphyxia (26.3%), prematurity (18%), congenital malformation (5%), ALRI (4.4%), and diarrheal diseases (3.6%). The major causes of neonatal death reported by UNICEF in 2015 were intra-partum-related complication (31.6%), preterm birth complication (21.6%), and sepsis (18.5%) (26). The reported causes

partially match those of the current study, since the UNICEF report combined different causes although the magnitude of the causes varied. The misclassification of causes in the original studies and cause category synthesis could be a source of difference in estimates. In addition, the publication biases in the meta-analysis might have led to under-estimation.

A systematic analysis of global, regional, and national causes of child mortality (27) noted that the leading causes neonatal deaths in Africa in 2010 were preterm birth complications (33.3%), intra-partum-related complications (26.7%), and sepsis or meningitis (13.3%). The same study (27) also reported that neonatal deaths in South-East Asia were mainly preterm birth complications (39%), intra-partum-related complications (20.7%), sepsis or meningitis (14.5%), pneumonia (14.5%), and congenital abnormalities (10.4%). The differences between South-East Asia and Africa could be due to variations among study settings, study participants, social, behavioral, or biological risk factors, and health care settings.

The findings from this study, in terms of the meta-analyzed causes of deaths among neonates, are similar to a 2015 WHO report (2) that defined prematurity, birth asphyxia, and neonatal sepsis as major causes of neonatal mortality. In terms of proportions, our study showed a little higher magnitude than the global results in relation to all these causes. The difference may be explained by lower health service coverage, meager service access with limited skilled personnel, and inadequate health technology use in Ethiopia compared to the rest of the world.

The meta-analyzed results in this study show that the most common causes of post-neonatal and infant deaths were ALRI (28%), intestinal infections, including diarrhea (21%), malaria (11%), SAM (9%), and bacterial sepsis (7%). In these age groups, UNICEF in 2015 reported pneumonia (13.1%) and diarrheal diseases (8.1%) as major causes of infectious disease in Ethiopia (26). The causes of death and the proportions were different from our study. We

generated evidence dating back to 1990, when infant mortality was much higher and with weak responses to interventions, which may account for the discrepancies. In addition, regional variations, cause cataloguing, and quality of studies included, may be the reason for the divergence.

Similar results to our review were reported by WHO member countries in 2015, in that pneumonia, malaria, and diarrhea were the leading causes of post-neonatal death (28). In the following year, 2016, WHO World Health Statistics reiterated more or less the same findings, namely that pneumonia, diarrhea, injuries and malaria were the main causes of post-neonatal deaths (29).

Eventually the causes of death among child and under-fives were examined. In the current study, the major causes of death among children aged 1-4 years and under-fives, based on the overall pooled proportions, were measles (15.1%), sepsis (14.1%), prematurity (13%), ALRI, including pneumonia (12.5%), birth asphyxia (11.3%), SAM (9.4%), diarrheal diseases (2.6%), meningitis (2.2%), and malaria (1.4%). Studies on global, regional and national causes of under-five mortality (30) report that preterm birth complications (17.8%), pneumonia (15.5%), and intra-partum-related events (11.6%) were at the top of the list. This study underscored that infectious diseases, such as pneumonia, diarrhea, malaria, and sepsis or meningitis, remained were the second group of causes of death for under five children. It also outlined the leading causes of under-five deaths in sub-Saharan Africa: pneumonia (16.6%), preterm birth complications (12.1%), and intra-partum-related events (11.5%) (30). Incongruously, a study from India (31) showed that half of under-five deaths were attributed to pneumonia and diarrheal diseases. In this case, cause of death misclassification and source of data may account for the variation.

According to Li *et al.* in 2012, the leading causes of under-five mortality across the globe were pneumonia (18%), diarrhea (11%), and malaria (7%); in Africa, the proportions were 17% for pneumonia, 12% for diarrhea, and 15% for malaria (27). In spite of the similarities in the list of causes, the proportion for each cause varied with our findings. The reasons for the divergence could be related to assigning causes, sampling variability and biases. Fundamentally, the greater prevalence of these causes in the current study could be due to the poor cost-effective intervention implementation, the low level of care services, and low coverage of vaccinations in the country.

In this systematic review, the causes of death for children 1-4 years and under-fives were meta-analyzed separately. The reported causes of death with pooled proportions for children aged 1-4 years were diarrheal disease (37.2%), ALRI, including pneumonia (17.5%), measles (15.8%), SAM (12.1%), malaria (7.3%), and meningitis (5.6%). In contrast, the causes of under-five deaths were prematurity (13.1%), ALRI, including pneumonia (12.3%), SAM (9.4%), diarrheal diseases (2.4%), meningitis (2.1%), and malaria (1.3%). This

was based on the pooled proportion of the sub-group analysis where there were reports from at least two studies. In comparison, the *Countdown to 2015* report recorded ALRI (18%), diarrhea (9%), prematurity (11%), sepsis (9%), birth asphyxia (14%), injuries (6%), measles (2%) and others (21%) (32) as major causes of under-five deaths in Ethiopia.

Limitations of the study
The results of this review should be interpreted with caution, since most of the reviewed studies had small sample sizes. Moreover, there are limited nationwide studies – limited in scope and coverage, and which do not include pastoralist areas. In some cases, we lacked access to relevant information, such as the standard deviation, confidence intervals, a measure of the effect size or the raw data, to estimate effect sizes. Besides, though optimal effort was made to access relevant literatures, yet a file drawer effect is unavoidable which may have an effect in the magnitude of the estimation. In addition, due to data incompleteness, misclassification of the causes of death may have been inevitable, leading to over- or under-estimation. Furthermore, issues of potential bias, sample variability and heterogeneity are inevitable, though the model applied took this into account.

Conclusions and recommendations
The main causes of death for neonates in Ethiopia were bacterial sepsis, birth asphyxia, prematurity, congenital malformation, ALRI, and diarrheal diseases; whereas the major causes for post-neonates and infants include ALRI, malaria, intestinal infections with diarrhea, SAM, and bacterial sepsis. The main causes of death for children 1-4 years and under-fives were diarrheal diseases, ALRI, including pneumonia, measles, SAM, malaria, and meningitis. All of the above are easily preventable and treatable infectious diseases.

These findings indicate that the country's child survival strategies should be geared towards the above-mentioned major causes of neonatal, post-neonatal, child and under-five deaths. Moreover, high-quality maternal health care is important to avert causes related to pregnancy and delivery complications. Continued efforts to generate evidence and enhance estimation methods are essential for the improvement of future estimates of comprehensive nationwide registration of the causes of maternal and childhood deaths in Ethiopia.

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