Heliyon 7 (2021) e06121

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

The burden of neonatal sepsis and its association with antenatal urinary tract infection and intra-partum fever among admitted neonates in Ethiopia: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Ethiopia
Antenatal urinary tract infection
Intra-partum fever
Neonatal sepsis
Meta-Analysis
Burden

ABSTRACT

Background: More than one-third of the neonatal death in Ethiopia has been attributed to neonatal sepsis. However, there is no recent national evidence about the burden of neonatal sepsis and its association with antenatal urinary tract infection and intra-partum fever, which are commonly reported maternal morbidities in Ethiopia. Therefore, the aim of this systematic review and meta-analysis was to assess the pooled burden of neonatal sepsis and its association with antenatal urinary tract infection as well as intra-partum fever in the country.

Methods: Primary studies were accessed through Google scholar, HINARI, SCOPUS and PubMed databases. The methodological and evidence quality of the included studies were critically appraised by the modified Newcastle-Ottawa quality assessment tool scale adapted for observational studies. From eligible studies, two authors extracted author/year, study region, study design, sample size, reported prevalence of neonatal sepsis, antenatal urinary tract infection and intrapartum fever on an excel spreadsheet. During critical appraisal and data extraction, disagreements between the two authors were resolved by the involvement of a third author. The extracted data were then exported to stata version 14. Effect sizes were pooled using the random inverse varience-effects model due to significant heterogeneity between studies (I^2= 99.2%). Subgroup analysis was performed for evidence of heterogeneity. Sensitivity analyses were performed. Absence of publication bias was declared from symmetry of funnel plot and Egger's test (p = 0.244).

Results: In this systematic review and meta-analysis, a total of 36,016 admitted neonates were included from 27 studies. Of these 27 studies, 23 employed cross-sectional design whereas 3 studies had case control type and only one study had cohort design. The prevalence of neonatal sepsis among admitted Ethiopian neonates at different regions of the country ranged from 11.7%–77.9%. However, the pooled prevalence of neonatal sepsis was 40.25% [95% CI: 34.00%, 46.50%; I^2 = 99.2%]. From regional subgroup analysis, the highest prevalence was observed in the Oromiya region. Neonates born to mothers who had antenatal urinary tract infection were at 3.55 times (95% CI: 2.04, 5.06) higher risk of developing neonatal sepsis as compared to those neonates born to mothers who didn't have antenatal urinary tract infection. Moreover, neonates born to mothers having intra-partum fever were 3.63 times (95% CI: 1.64, 5.62) more likely to develop neonatal sepsis as compared to those born to mothers who were nonfebrile during intrapartum.

Conclusion: Neonatal sepsis has remained a problem of public health importance in Ethiopia. Both antenatal urinary tract infection and intra-partum fever were positively associated with neonatal sepsis. Therefore, preventing maternal urinary tract infection during pregnancy and optimizing the intra-partum care are recommended to mitigate the burden of neonatal sepsis in Ethiopia.

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https://doi.org/10.1016/j.heliyon.2021.e06121
Received 16 September 2020; Received in revised form 24 December 2020; Accepted 25 January 2021

1. Introduction

Neonatal sepsis is a clinical syndrome with non-specific systemic signs and symptoms of infection within the first 4 weeks of life [1, 2, 3, 4]. It is a composite of six systemic infections namely septicemia, pneumonia, meningitis, osteomyelitis, arthritis and urinary tract infections [2, 4]. Neonatal sepsis is categorized as early onset neonatal sepsis [EONS] and late onset neonatal sepsis (LONS) [1, 2]. Early onset neonatal sepsis occurs within seven days of neonatal life whereas LONS from the seventh day and onwards [4, 5, 6, 7, 8]. Neonates are at high risk of EONS, which can occur as a result of direct transmission of the maternal colonizers (e.g. bacteria in the maternal vaginal tract) to the newborns during delivery [1, 3]. Of newborns with early onset sepsis, 85% present within 24 h, 5% present at 24–48 h, and a smaller percentage present within 48–72 h. Onset is most rapid in premature neonates [4].

Neonatal sepsis has considerable contribution to the worldwide burden of neonatal morbidity and mortality, thereby continuing as a major global public health challenge [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. It is highly prevalent in sub- Saharan Africa, South Asia and Latin America accompanied with a mortality risk of 9.8% of the septic neonates [21]. Neonatal sepsis has also been claimed for contributing more than one-third of the neonatal deaths in Ethiopia [19]. Therefore, better prevention and management of severe neonatal infections including intra-partum antibiotic prophylaxis for at-risk mothers [18, 20, 22, 23] is required to achieve the sustainable development goal (SDG) of reducing neonatal mortality rate to the desired target by 2030 [15].

Various literatures acknowledge the significance of intra-partum fever [25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38] and antenatal urinary tract infections [39, 40, 41, 42, 43, 44, 45, 46] in increasing the risk of pregnant mothers to have a newborn with clinical EONS [24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46]. It is so because EONS is associated with the acquisition of microorganisms from the mother during pregnancy and delivery [33, 47, 48]. For example, in America [34], the risk of neonatal sepsis among newborns delivered of mothers with intra-partum fever is 0.24%. Initial colonization of the neonate usually takes place after rupture of the chorio-amnionic layers of the amniotic fluid [28]. In most cases, the infant is colonized with the microflora of the birth canal during delivery. However, particularly if the rupture of membranes lasts longer than 24 h, vaginal bacteria may ascend and in some cases produce inflammation of the fetal membranes, umbilical cord, and placenta [30]. Fetal infection can result from aspiration of infected amniotic fluid [31], leading to stillbirth, premature delivery, or neonatal sepsis [27, 29, 30]. Besides, women with urinary tract infection during pregnancy are more likely to deliver premature or low birth weight neonates, who have higher risk of developing neonatal sepsis [36, 37]. Urinary tract infection during pregnancy may also be associated with an increase in neonatal mortality and a source for Gram negative septicemia [38]. Furthermore, other studies in Saudi Arabia [40], Iran [41], Iraq [42], Malaysia [44], Uganda [45] and Israel [46] witnessed that changes in the physiologic-anatomy of the urinary tract and immune system during pregnancy increase the prevalence of urinary tract infection, thereby leading to unfavorable

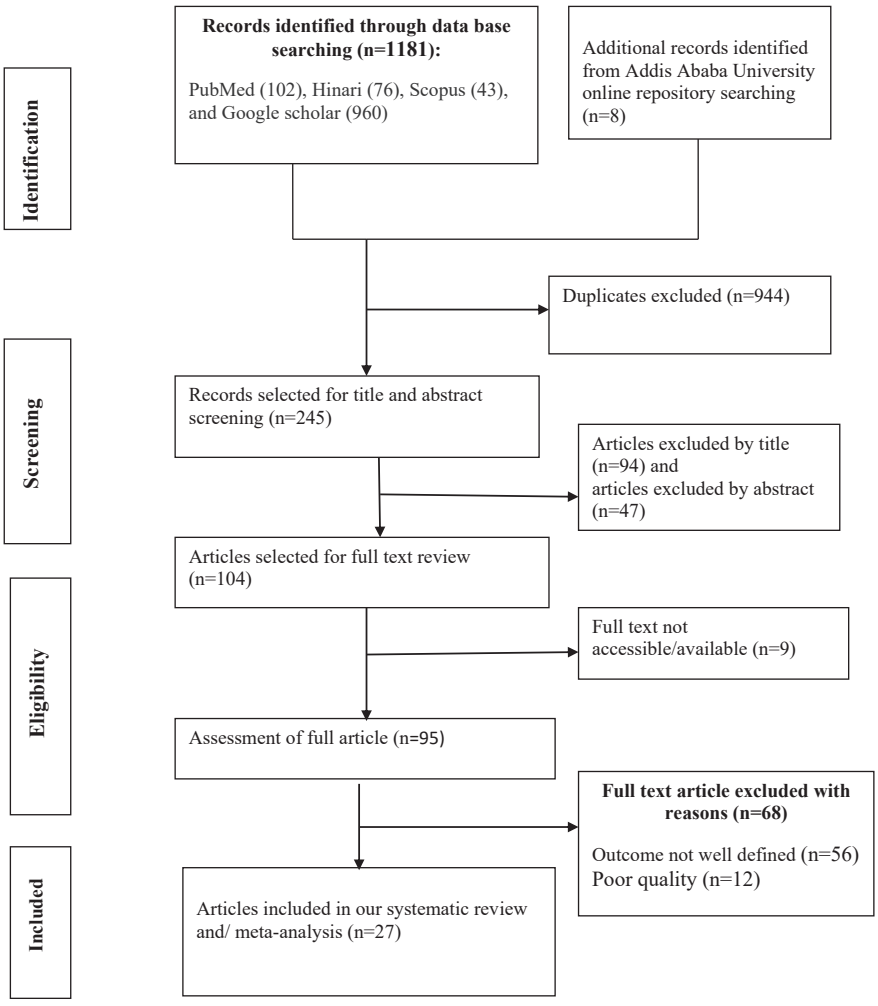

Figure 1. The PRISMA flow chart that shows the searching process.

Table 1. Characteristics of studies included in the systematic review and meta-analysis of neonatal sepsis in Ethiopia.

SN	First author/year	Study region	Design	Sample size	Neonatal sepsis (%)	Quality status
1	Getachew et al. 2018 [49]	Addis Ababa	Crossectional	169	39.6	high quality
2	Gudeta et al. 2017 [50]	Addis Ababa	Crossectional	356	18.8	high quality
3	Bayana et al. 2018 [51]	Oromiya	Crossectional	341	19.9	high quality
4	Alemu et al. 2017 [52]	Addis Ababa	Crossectional	304	50	high quality
5	Getabelew et al. 2018 [53]	Oromiya	Crossectional	244	77.9	high quality
6	Woldu et al. 2014 [54]	Oromiya	Crossectional	306	72.20	high quality
7	Serbesa and Iffa, 2019 [55]	Tigray	Crossectional	301	34.7	high quality
8	Mersha et al. 2019 [56]	SNNPR	Crossectional	275	33.8	high quality
9	Roba and Diro, 2017 [57]	Other	Crossectional	3418	35.31	high quality
10	Farah et al. 2018 [58]	Other	Crossectional	792	22.4	high quality
11	Woldehanna and Idejene, 2005 [59]	Amhara	Crossectional	304	75	high quality
12	Tewabe et al. 2018 [60]	Amhara	Crossectional	391	23.8	high quality
13	Kokeb and Desta, 2016 [61]	Amhara	Crossectional	325	77.8	high quality
14	Yismaw et al. 2019 [62]	Amhara	Crossectional	423	11.70	high quality
15	Sorsa Abebe. 2019 [63]	Oromiya	Crossectional	901	34	high quality
16	Ketema et al. 2018 [64]	SNNPR	case control	335	NA	high quality
17	Demisse AG et al. 2017 [65]	Amhara	crosssectional	769	67.9	high quality
18	Ahmed et al. 2018 [66]	SNNPR	cross-sectional	402	16.9	high quality
19	Gebremedhin et al. 2016 [67]	Tigray	case control	234	NA	high quality
20	Yirga et al. 2018 [68]	Amhara	case control	231	NA	high quality
21	Girma and Gebreyohanes, 2016 [69]	Addis Ababa	Crossectional	570	14.4	high quality
22	Gudayu *et al. 2019* [70]	Amhara	Crossectional	504	63.7	high quality
23	Chewaka and Aga, 2016 [71]	Addis Ababa	Crosssectional	561	26.97	high quality
24	Gerenesea H et al. 2017 [72]	Tigray	Crosssectional	16,596	47	high quality
25	Debelew GT et al. 2014 [73]	Oromiya	Cohort	3463	34.3	high quality
26	Seid et al [2019] [74]	Oromiya	Crosssectional	3,276	29.7	high quality
27	Sime H et al. 2014 [75]	Oromiya	Crosssectional	225	40	high quality

Other includes Somali and Dire Dawa; **NA** stands for 'Not Applicable', **SNNPR** refers to Southern Nations, Nationalities and Peoples Region.

neonatal outcomes such as bacteremia, toxic septicaemia, stillbirths, neonatal deaths, premature delivery and low birth weight [43]. Therefore, screening of pregnant women is essential to avoid the aforementioned complications through early diagnosis and treatment of urinary tract infection during pregnancy.

In Ethiopia, variety of studies [49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75] revealed the prevalence of neonatal sepsis with great inconsistencies across different geographical regions ranging from 11.7% in Amhara region [62] to 77.9% in Oromia region [53]. This inconsistence necessitates nationally pooled evidence about the burden of neonatal sepsis. Likewise, results of the effect of antenatal urinary tract infection and intra-partum fever on neonatal sepsis have been reported inconclusively. Therefore, the aim of this systematic review and meta-analysis was to determine the pooled national burden of neonatal sepsis and its association with antenatal urinary tract infection as well as intra-partum fever. This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Evidence from this review will be utilized to guide the development of guidelines for preventing neonatal sepsis attributable to antenatal urinary tract infection and intra-partum fever in Ethiopia, thereby enabling to optimize neonatal survival and achieve neonatal target of SDG by 2030.

2. Methods

2.1. Search strategy

Four international online databases (Google scholar, PUBMED, Hinari and Scopus) and Addis Ababa University online repository were searched for pocket studies on neonatal sepsis and associated factors in Ethiopia. A comprehensive search was conducted through the aforementioned databases using adapted PICO questions i.e. 'PEO' (Population, Exposure, Outcome) format was followed. These questions were developed from the following search key words and/or Medical Subject Headings (MeSH) which were combined using the "OR" and "AND" Boolean operators:

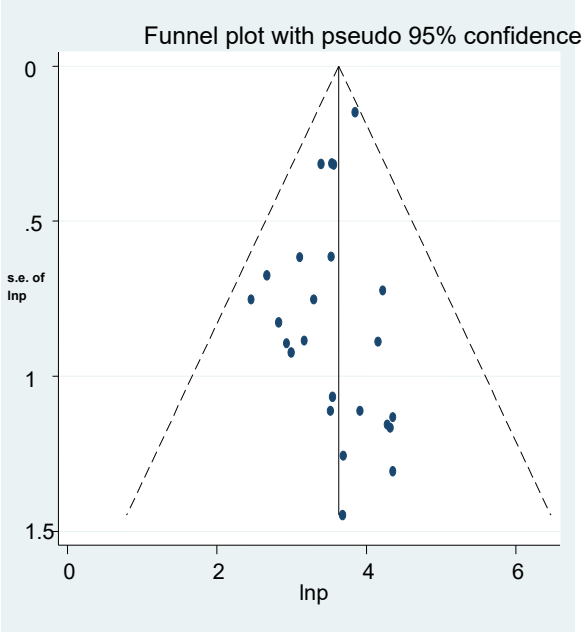

Figure 2. Funnel plot to test publication bias of the 27 studies, lnproportion (x-axis) with standard error of ln proportion (y-axis).

Table 2. Egger's test of the study involving 27 pocket studies about neonatal sepsis in Ethiopia.

Std. Eff	Coef.	Std. Err.	T	P > t	[95% Conf.	Interval]
Slope	3.743415	0.1371499	27.29	0.000	3.458983	4.027846
Bias	-0.1338654	0.1119276	-1.20	0.244	-0.365989	0.0982582

Table 3. *Stata* output of the pooled 24 pocket studies on the prevalence of neonatal sepsis in Ethiopia, 2020.

Study	ES	[95% Conf. Interval]		% Weight
Getachew et al.[2018]	39.600	32.227	46.973	4.01
Gudeta et al.[2017]	18.800	14.741	22.859	4.17
Bayana et al. [2018]	19.900	15.662	24.138	4.17
Alemu et al. [2017]	50.000	44.379	55.621	4.11
Getabelew et al. [2018]	77.900	72.694	83.106	4.13
Woldu et al.[2014]	72.200	67.180	77.220	4.13
Serbesa and Iffa [2019]	34.700	29.322	40.078	4.12
Mersha et al. [2019]	33.800	28.209	39.391	4.11
Roba and Diro [2017]	35.310	33.708	36.912	4.24
Farah et al.[2018]	22.400	19.496	25.304	4.21
Woldehanna and Ideje [2005]	75.000	70.132	79.868	4.14
Tewabe et al. [2018]	23.800	19.579	28.021	4.17
Kokeb and Desta [2016]	77.800	73.282	82.318	4.16
Yismaw et al. [2019]	11.700	8.637	14.763	4.21
Sorsa Abebe. [2019]	34.000	30.907	37.093	4.20
Demisse AG et al. [2017]	67.900	64.600	71.200	4.20
Ahmed et al. [2018]	16.900	13.237	20.563	4.19
Girma and Gebreyohan [2016]	14.400	11.518	17.282	4.21
Gudayu et al.[2019]	63.700	59.502	67.898	4.17
Chewaka and Aga [2016]	26.970	23.298	30.642	4.19
Gerenesea H et al. [2017]	47.000	46.241	47.759	4.25
Debelew GT et al. [2014]	34.300	32.719	35.881	4.24
Seid et al. [2019]	29.700	28.135	31.265	4.24
Sime H et al. [2014]	40.000	33.599	46.401	4.07
D + L pooled ES	40.246	33.997	46.495	100.00

Heterogeneity chi-squared = 3056.85 (d.f. = 23) p = 0.000.
I-squared (variation in ES attributable to heterogeneity) = 99.2%.

a. **Population**: newborn, neonate
b. **Exposure**: Antenatal urinary tract infection, intrapartum fever
c. **Outcome**: Neonatal sepsis, neonatal infection, early onset neonatal sepsis, late onset neonatal sepsis
d. **Study design**: Observational studies, and
e. **Setting**: Ethiopia

We extended our search from systematic database searching to retrieving reference lists of eligible articles and hand searches for grey literature. Besides, the 'cited by' and 'related articles' functions of PubMed were considered for further literature searching. Finally, all studies which were in agreement with the review title were retrieved and screened for inclusion criteria. The last search was done on June 24/2020. The searches were restricted to free full text articles, human studies and English language publications. The search was done with the following medical subject headings (MeSH), and free-text terms: "Prevalence", "neonatal sepsis", "magnitude", "determinants", "associated factors", "Antenatal urinary tract infection", "intrapartum fever", "neonates", "newborn", and "Ethiopia". The literature search was performed by two independent researchers, with discrepancies resolved by discussion and consensus. A tie breaker (SAA) was invited when disagreements were not resolved by discussion and consensus.

Concerning PROSPERO registration, this review hasn't been registered yet, but entitled as 'review ongoing'.

2.2. Outcome measurement

The main outcome of interest was neonatal sepsis among admitted Ethiopian neonates as diagnosed by the diagnostic criteria of neonatal sepsis by the established Integrated Management of Neonatal and Childhood Illness (IMNCI) guideline. According to the guideline, a neonate was recorded as septic when it had two or more of the following clinical features along with ≥2 of the subsequent hematological criteria: persistent fever (≥37.5 °C) or persistent hypothermia (≤35.5 °C) for more than 1 h, fast breathing (≥60 breath per minute), severe chest in drawing, grunting, not feeding well, movement only when stimulated, bulged fontanel, convulsion, lethargic or unconsciousness along with ≥2 of the hematological criteria such as total leukocyte count (<4000 or >12,000 cells/mm3), absolute neutrophil count (<1500 cells/mm3 or >7500 cells/mm3), platelet count (<150 or >450 cells/mm3), and random blood sugar (<40 mg/dl or >125 mg/dl) [76].

2.3. Inclusion and exclusion criteria

Both published and unpublished observational studies that reported the prevalence and/associated factors of neonatal sepsis among Ethiopian neonates were included. However, studies whose study subjects were either adults or both adults and children were excluded. Besides, those studies that didn't report either the prevalence or associated factors

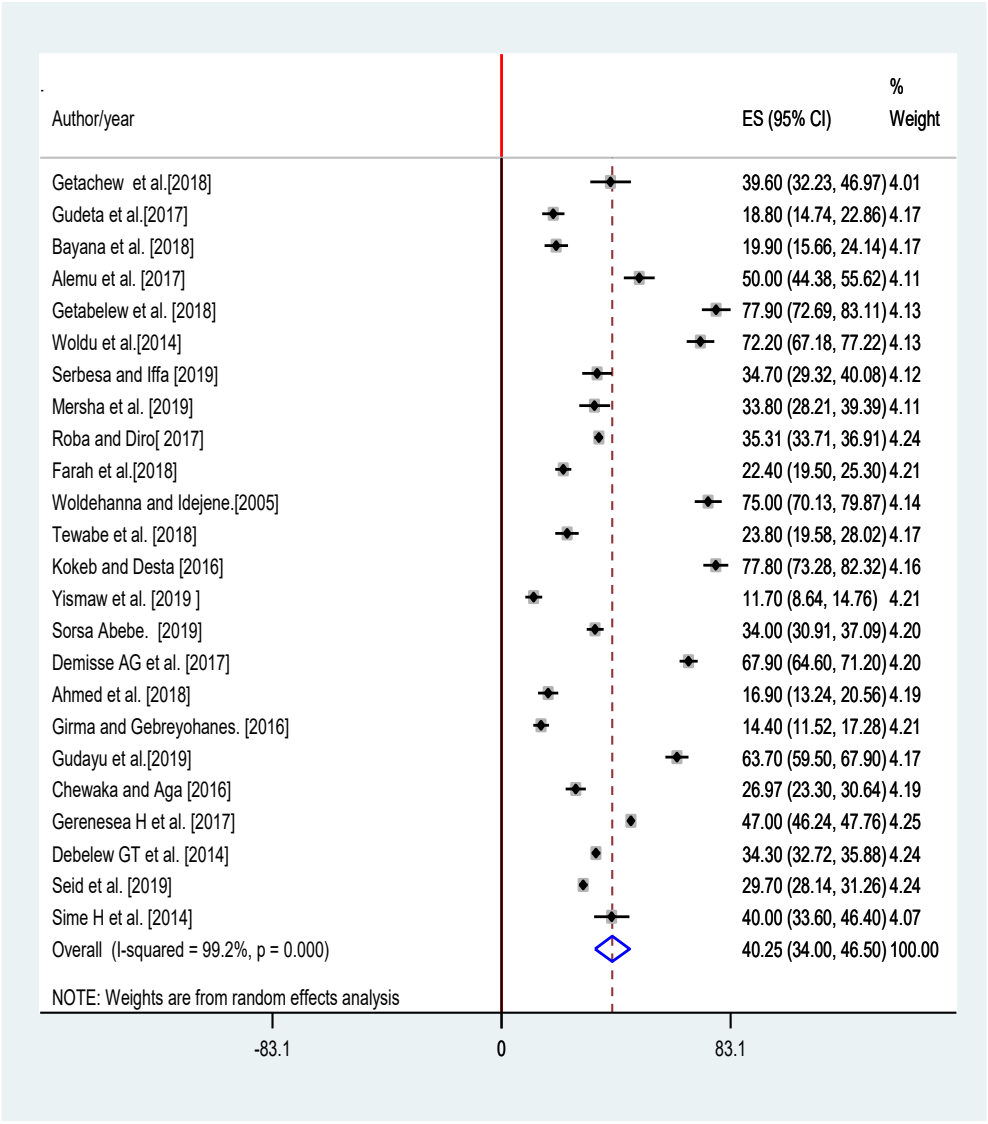

Figure 3. Forest plot showing the pooled estimate of neonatal sepsis.

of neonatal sepsis weren't eligible for inclusion. Studies whose full texts unavailable were also excluded from this meta-analysis.

2.4. Quality assessment and data extraction

The methodological and evidence quality of the included studies were critically appraised by the modified Newcastle-Ottawa quality assessment tool scale adapted for observational studies [77]. The scale contains 9 major quality measure components. Originally, it was planned to grade the quality of the eligible studies as 'low quality', 'moderate quality' or 'high quality' when the numerical rating of the Newcastle-Ottawa quality assessment tool scale is $\leq$ 3, 4–5, and $\geq$6 respectively. However, quality of all the included 27 studies was graded as 'high quality' because their numerical rating for the 9 components in Newcastle-Ottawa quality assessment tool scale was $\geq$6. Quality appraisal was conducted by two authors (BBA and BMB) and disagreements were resolved by consulting a third author (DMB). Using Microsoft Excel spread sheet, two authors (WAB and YAA) independently extracted the following data from each included article: authors' name, year of publications, study region, sample size, study design, prevalence of neonatal sepsis and associated factors (i.e antenatal urinary tract infection and intra-partum fever). Disagreements in data extraction were resolved by the involvement of a third author (GYY).

2.5. Statistical analysis

The pooled prevalence of neonatal sepsis and its major predictors were weighted using Der Simonian random-effects model [78]. The pooled effect size (i.e. prevalence and associated factors) with a 95% confidence interval (CI) was produced and presented using a forest plot. Statistical analyses were performed using the STATA™ Version 14 software.

2.6. Heterogeneity and publication bias

The Cochran's Q and the I^2 statistic were evaluated to assess the presence of heterogeneity between studies [78]. Subgroup analyses were done to minimize heterogeneity. Sensitivity analysis was also conducted to assess the possible included outlier articles. The presence or absences of publication bias were evaluated with funnel plot and Egger test [79].

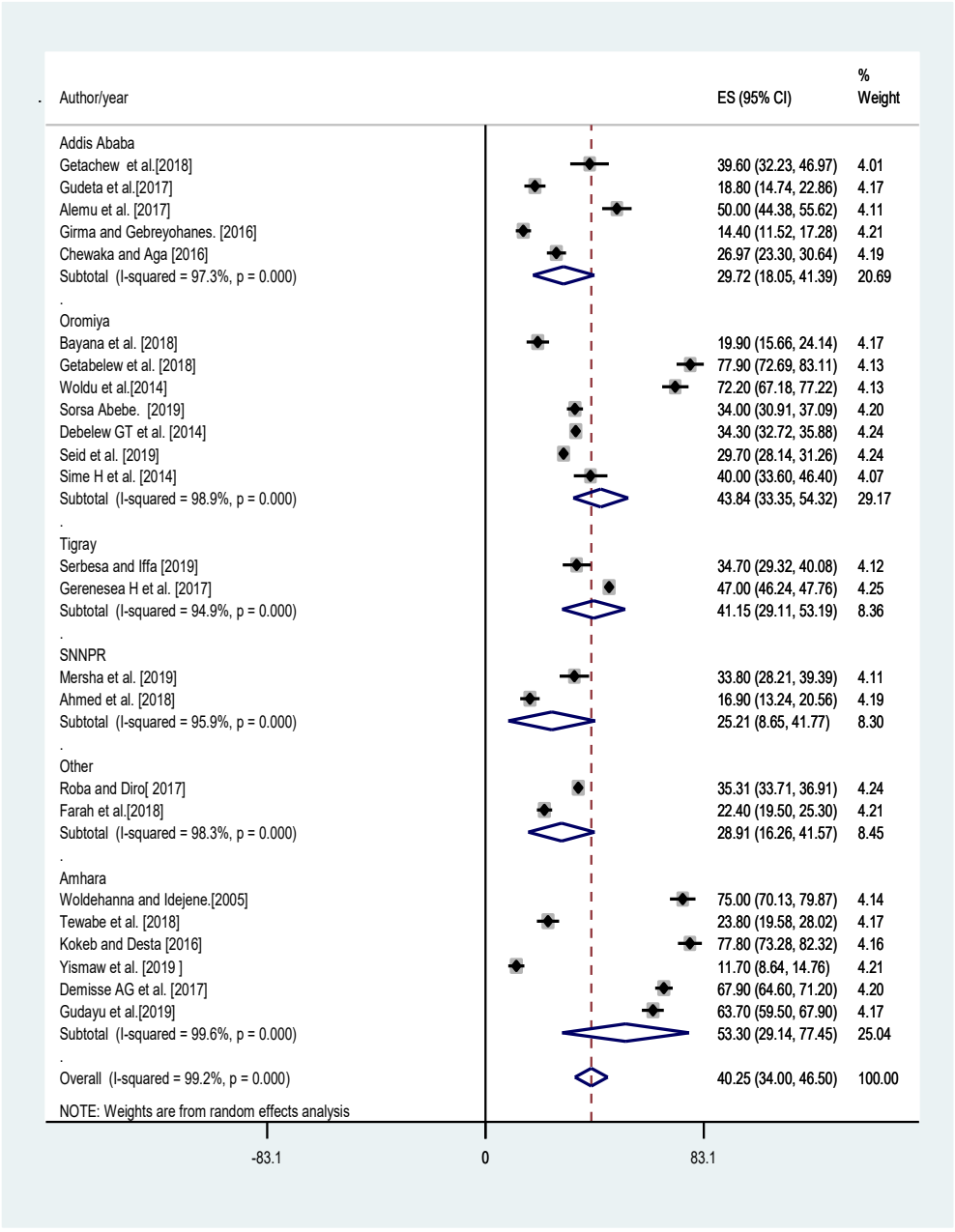

Figure 4. Subgroup analysis of the magnitude of neonatal sepsis by study region.

3. Results

3.1. Search process

We got a total of 1189 articles from our exhaustive searching of both published and unpublished sources. From these 1189 articles, 1181 articles were obtained through database searching whereas the rest 8 articles were retrieved from Addis Ababa University online repository. Then, among the 1181 database accessed articles, 960 articles were obtained using Google scholar, 102 articles were from PubMed, 76 from Hinari and 43 from SCOPUS. A total of 944 duplicate articles were excluded. The remaining 245 articles were screened for their title and abstract based on which 141 articles were excluded. Then, the rest 104 articles were considered for the presence of full text, and only 95 of which had full text content. Then, all the 95 full text articles were further assessed for their quality resulting in the exclusion of 68 full text articles due to poor quality and whose outcome not well defined. Finally, 27 articles were eligible for the final systematic review (qualitative synthesis) and/meta-analysis (quantitative synthesis) of the study. From these 27 studies, only 24 of which were utilized for estimating the pooled prevalence of neonatal sepsis [Figure 1].

3.2. Characteristics of the included studies

In this systematic review and meta-analysis, 27 studies have been considered from different regions of Ethiopia. In the current meta-analysis, a total of 36,016 admitted neonates were included from these 27 studies with sample size ranging from 169 [49] to 16,596 [72]. The prevalence of neonatal sepsis among the included studies varied from 11.7% [62] to 77.9% [53]. Regarding study design, 23 studies [49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 65, 66, 69, 70, 71, 72, 74, 75] employed cross-sectional design whereas 3 studies [64, 67, 68] had case control type, and only one study had

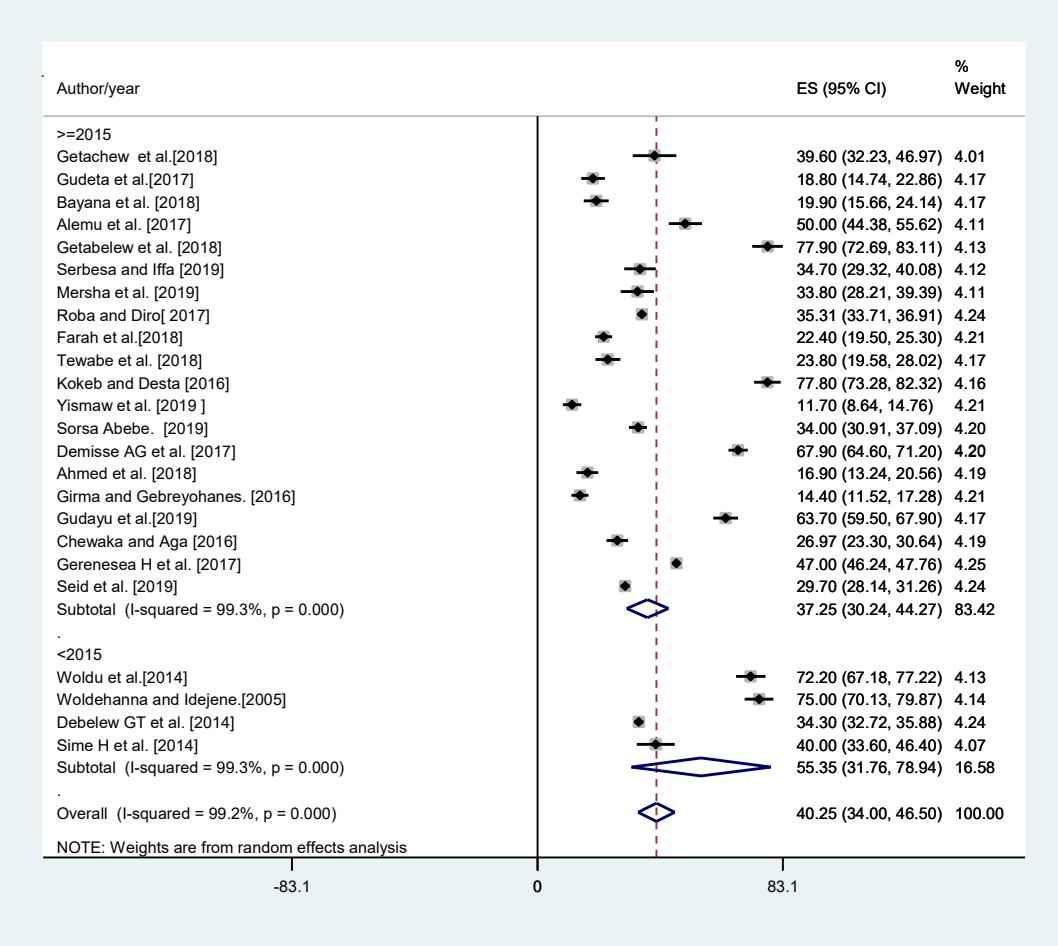

Figure 5. Subgroup analysis of the magnitude of neonatal sepsis by study year.

cohort design [73]. Furthermore, concerning study region, 7 studies [59, 60, 61, 62, 63, 65, 68, 70] were from Amhara region, another 7 studies [51, 53, 54, 63, 73, 74, 75] were from Oromiya region, five studies [49, 50, 52, 69, 71] from Addis Ababa, 3 studies from Tigray region [55, 67, 72], another 3 studies [56, 64, 66] from SNNPR and the rest 2 studies [57, 58] were from other regions in the country [Table 1].

3.3. Quality of studies

The modified Newcastle-Ottawa quality appraisal criteria established for cross-sectional, case control and cohort studies were used. The studies included in this systematic review and meta-analysis had no considerable risk of bias. Therefore, all the studies [49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75] were considered [Table 1].

3.4. Meta-analysis

3.4.1. Publication bias

Qualitatively, visual inspection of the funnel plot suggests symmetry (Figure 2). Moreover, the result of Egger's test is a statistically significant quantitative evidence for the absence of publication bias ($p = 0.244$) (Table 2).

3.5. Pooled prevalence of neonatal sepsis

Only 24 of the included 27 studies reported prevalence of neonatal sepsis. The pooled effect size of neonatal sepsis using the fixed effect model showed a significant heterogeneity across the studies. Therefore, we performed the analysis using a random effects model with 95% CI in order to adjust for the observed variability. Using random effects model, the overall pooled estimate of neonatal sepsis as reported by the 24 studies was 40.25% (95% CI: 34.00%, 46.50%) with significant heterogeneity between studies ($I^2 = 99.2\%$, $p = 0.000$) [Table 3]. Moreover, similar output can be noticed from the forest plot of pooled neonatal sepsis in Ethiopia (Figure 3).

3.6. Investigation of heterogeneity

Given that the result of this meta-analysis revealed a statistically significant heterogeneity among studies (I^2 statistics = 99.2%), we performed subgroup analysis by study region, year, data source and sample size in order to minimize heterogeneity.

3.7. Subgroup analysis by study region

From regional subgroup analysis, the highest prevalence of neonatal sepsis was observed in Amhara region 53.30% [(95%CI: 29.14%, 77.45%), $I^2 = 99.6\%$] whereas the lowest estimated prevalence was reported from SNNPR 25.21% [(95%CI: 8.65%, 41.77%), $I^2 = 95.9\%$] [Figure 4].

3.8. Subgroup analysis by study year

Subgroup analysis of the pooled studies by study year (i.e. study year <2015 and ≥2015) showed that pooled estimate of neonatal sepsis among studies conducted during <2015 years 55.35% [(31.76%,

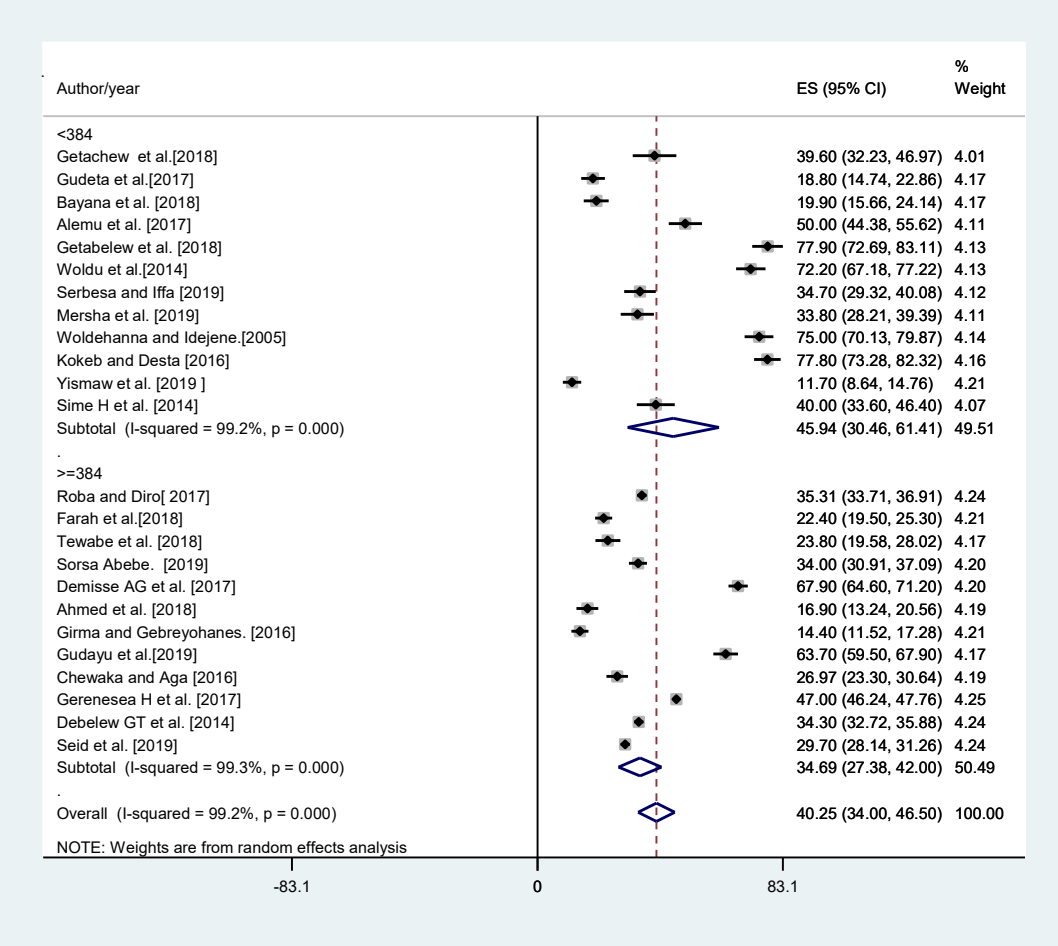

Figure 6. Subgroup analysis of the magnitude of neonatal sepsis by sample size.

78.94%), I^2 = 99.3%] was higher than during ≥2015 years 37.25% [(30.24%, 44.27%), I^2 = 99.3%] [Figure 5].

3.9. Subgroup analysis by sample size

The result of subgroup analysis based on sample size (i.e. sample size <384 and ≥384) revealed higher pooled magnitude of neonatal sepsis among studies whose sample size greater than or equal to 384, 45.94% [(30.46%, 61.41%), I^2 = 99.2%] than below 384, 34.69% (27.38%, 42.00%), I^2 = 99.3%] [Figure 6].

3.10. Subgroup analysis by data source

Pooled prevalence of neonatal sepsis among studies with primary source of data 39.98% [26.34%, 53.61%), I^2 = 99.2%] was nearly equal to the pooled prevalence among studies whose data were sourced from chart review 40.40% [(32.89%, 47.90%), I^2 = 99.3%] [Figure 7].

3.11. Sensitivity analysis

The result of sensitivity analyses using random effects model suggested that Kokeb and Desta [2016] and Getabelew et al. [2018] influenced the overall estimate significantly (Table 4). Besides, the aforementioned outlier articles can be diagrammatically appreciated from Figure 8.

3.12. The effect of antenatal urinary tract infection (UTI) on the pooled estimate of neonatal sepsis

Five of the overall 27 studies reported significance of antenatal urinary tract infection on neonatal sepsis. Besides, pooled effect sizes of these 5 different studies [51, 54, 64, 67, 68] showed that neonates delivered from mothers who experienced urinary tract infection during pregnancy were 3.55 times more likely to develop neonatal sepsis as compared to those neonates born to mothers who didn't experience antenatal urinary tract infection [AOR = 3.55; 95% CI: 2.04, 5.06] [Figure 9].

3.13. The effect of intra-partum fever on neonatal sepsis

Only 5 of the overall 27 studies reported significant effects of intra-partum fever on neonatal sepsis. Pooled analysis of these 5 different studies [62, 66, 67, 68, 70] revealed the presence of significant odds of association between intra-partum fever and neonatal sepsis [AOR = 3.63; 95% CI: 1.64, 5.62]. Thus, neonates born to mothers having intra-partum fever were 3.63 times more likely to develop neonatal sepsis as compared to those neonates born to fever free mothers during labor and/delivery [Figure 10].

4. Discussion

This systematic review and meta-analysis was aimed at estimating the pooled prevalence of neonatal sepsis and its association with antenatal urinary tract infection and intra-partum fever among neonates admitted in Ethiopia. Hence, the nationally pooled estimate of neonatal sepsis was found to be 40.25% (95% CI: 34.00%, 46.50%). Besides, both antenatal urinary tract infection and intra-partum fever were statistically significant factors having positive odds of association with neonatal sepsis.

The pooled prevalence of neonatal sepsis in Ethiopia (40.25%) was consistent with the report from Egypt, 45.9% [80]. However, it was lower

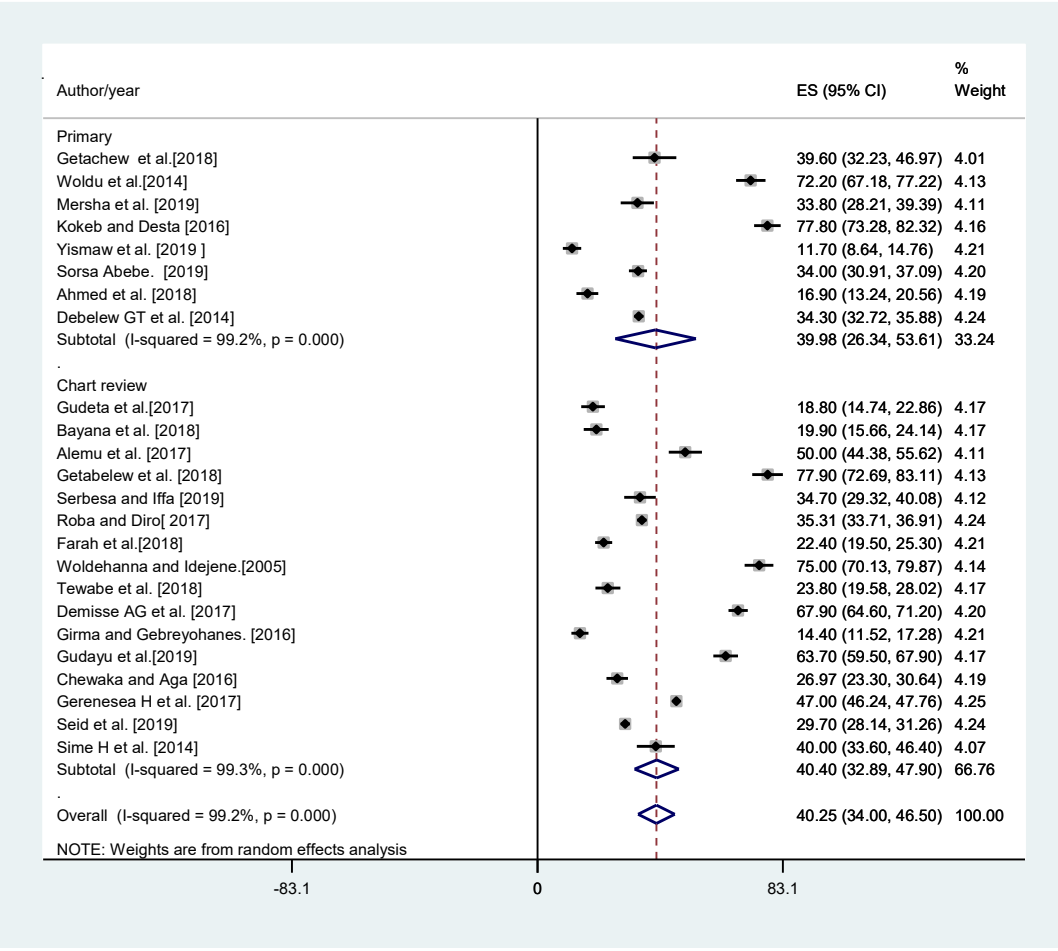

Figure 7. Subgroup analysis of the magnitude of neonatal sepsis by data source.

Table 4. Sensitivity analysis of the pooled 24 pocket studies about neonatal sepsis among admitted neonates in Ethiopia.

Study omitted	Estimate	[95% Conf. Interval]	
Getachew et al. [2018]	40.273678	33.873283	46.674072
Gudeta et al. [2017]	41.179123	34.833496	47.524754
Bayana et al.[2018]	41.130093	34.770924	47.489265
Alemu et al.[2017]	39.828938	33.423527	46.234348
Getabelew et al.[2018]	38.62175	32.416565	44.826935
Woldu et al.[2014]	38.865112	32.607128	45.123096
Serbesa and Iffa [2019]	40.485317	34.066208	46.904423
Mersha et al.[2019]	40.523174	34.108387	46.937958
Roba and Diro [2017]	40.473946	33.660416	47.287479
Farah et al. [2018]	41.030075	34.656776	47.403374
Woldehanna and Idejene [2005]	38.740791	32.524242	44.957336
Tewabe et al. [2018]	40.961464	34.570347	47.352577
Kokeb and Desta [2016]	38.611771	32.465485	44.758053
Yismaw et al.[2019]	41.493816	35.341679	47.645954
Sorsa Abebe.[2019]	40.52285	34.030266	47.015438
Demisse AG et al.[2017]	39.028236	32.844398	45.212074
Ahmed et al.[2018]	41.264503	34.95417	47.574833
Girma and Gebreyohanes [2016]	41.37772	35.182724	47.572712
Gudayu et al. [2019]	39.224251	32.908215	45.540291
Chewaka and Aga [2016]	40.827126	34.405922	47.248333
Gerenesea H et al.[2017]	39.961433	32.957886	46.964977
Debelew GT et al. [2014]	40.518406	33.71212	47.324688
Seid et al [2019]	40.718933	34.043983	47.393883
Sime H et al.[2014]	40.257286	33.848122	46.666451
Combined	40.246112	33.997092	46.495132

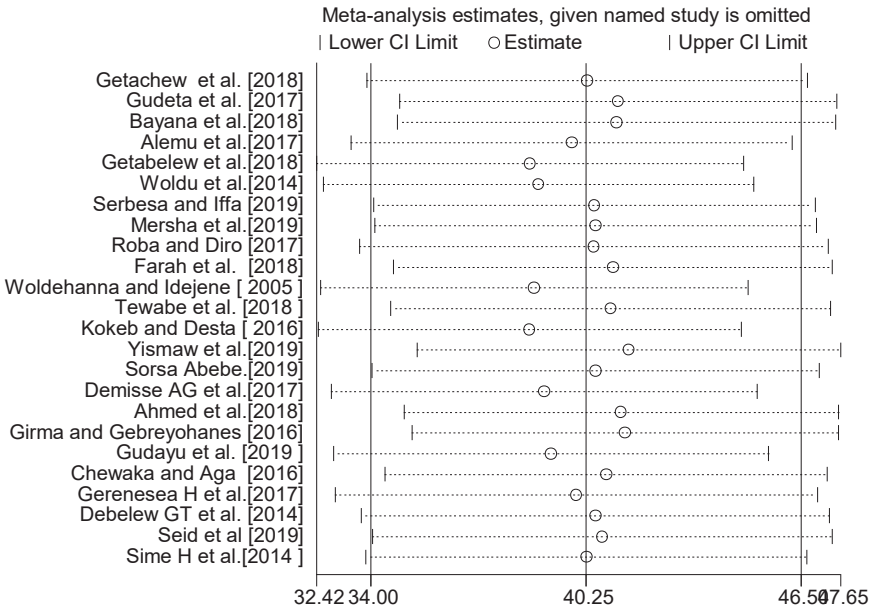

Figure 8. Sensitivity analysis of the 24 studies.

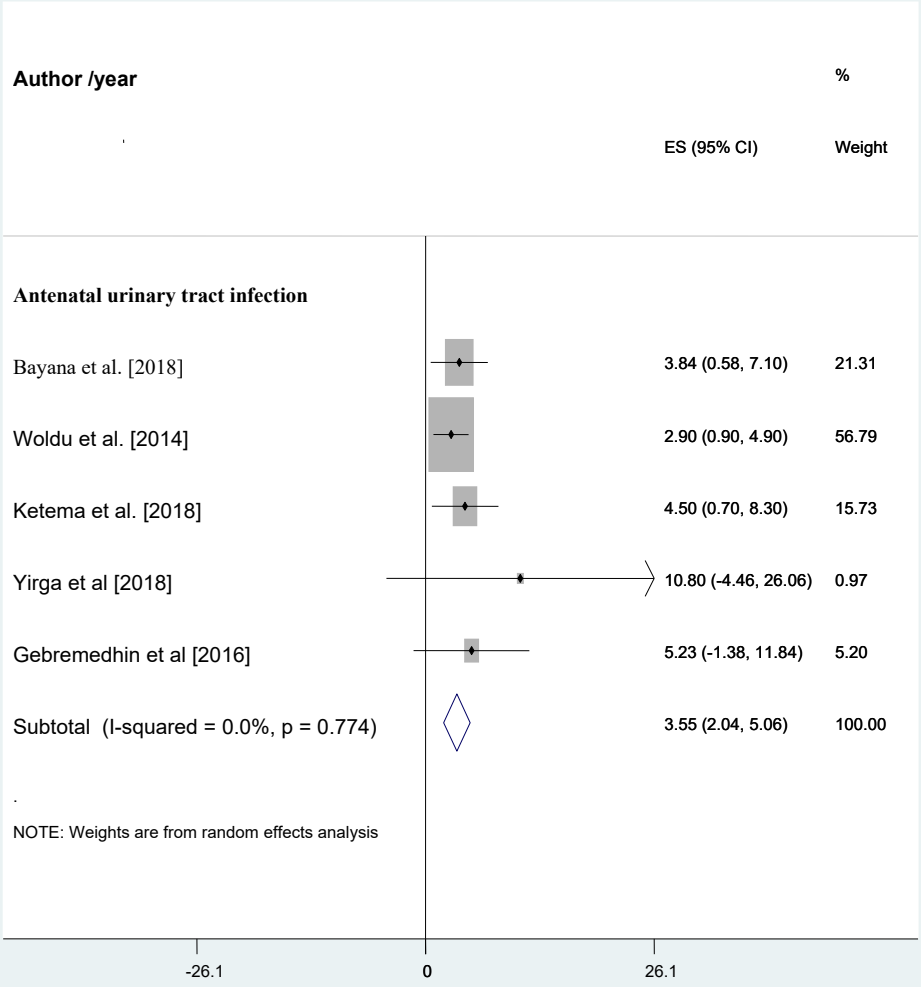

Figure 9. The pooled effect of antenatal urinary tract infection on the pooled estimate of neonatal sepsis in Ethiopia.

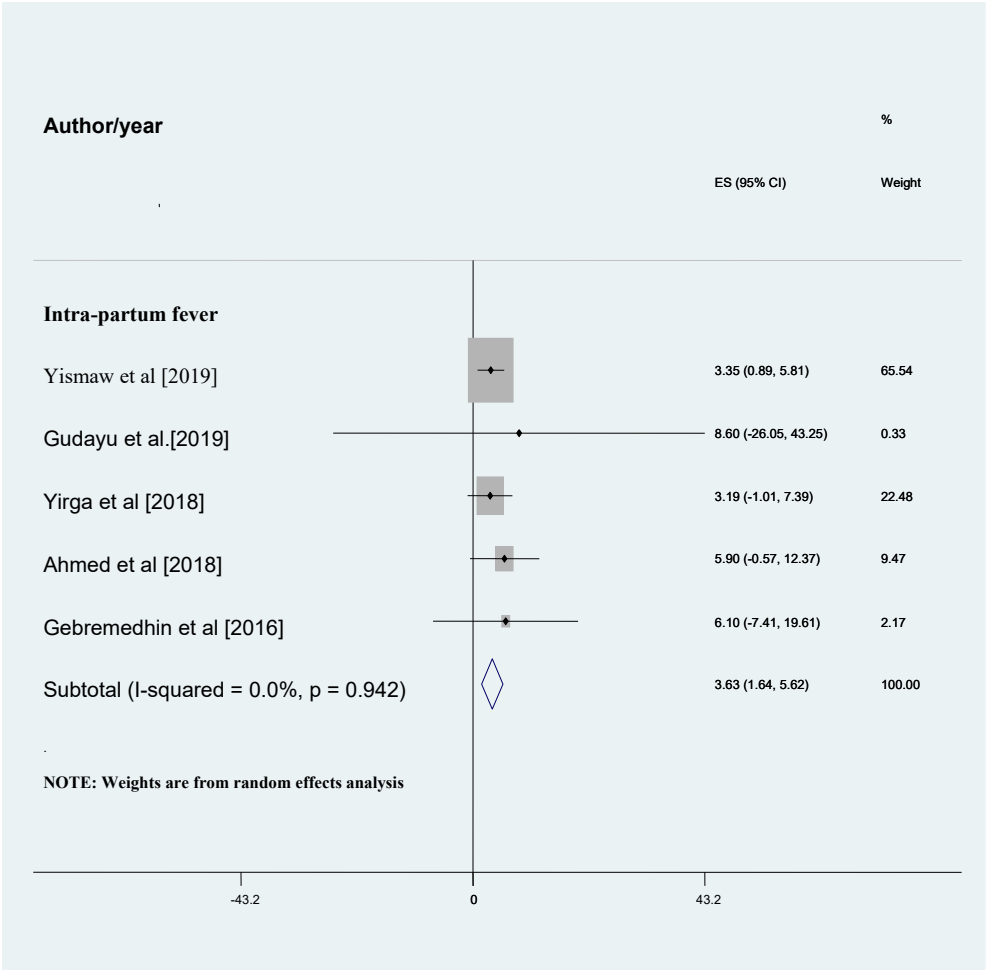

Figure 10. The pooled effects of intrapartum fever on the pooled estimate of neonatal sepsis in Ethiopia.

than the global burden of pediatric and neonatal sepsis, 48% [81], and higher than the prevalence among developing countries (29.92%) [82], East Africa (29.65%) [83], low and middle-income countries (LMICs), 17.2% [84], India, 7.6% [85], Kenya, 23.9% [86] and Tanzania, 31.4% [87]. The discrepancy may be due to differences in the respondents' socio-demographic characteristics and diagnostic modalities of neonatal sepsis in Ethiopia and other countries. Besides, in Ethiopia, there is low antenatal care visits, high home delivery rate [13], high prevalence of low birth weight [88], high perinatal asphyxia [89], greater prevalence of maternal Group B Streptococcus infection, high vertical and horizontal transmission of feto/neonatal and maternal infections and low intra-partum antibiotic prophylaxis rate [90] compared to other countries.

From regional subgroup analysis, the highest prevalence of neonatal sepsis was observed in Amhara region (53.30%) whereas the lowest estimated prevalence was reported from SNNPR (25.21%). This could be due to the highest prevalence of low birth weight delivery in Amhara region [91] and evidence showed that low birth weight neonates are quite prone to develop sepsis due to poor immunoglobulin and infection barriers [1, 2].

Subgroup analysis of the pooled studies by study year (i.e. study year $<$2015 and $\geq$2015) showed that pooled estimate of neonatal sepsis among studies conducted during $<$2015 years (55.35%) was higher than during $\geq$2015 years (37.25%). This could be due to the fact that different Sustainable Development Goal strategies have been planned and being implemented since 2015 to reach the reduction of neonatal mortality rate to as low as 12/1000 live births by 2030. Ethiopia is therefore striving to achieve this target of the health goal by implementing different preventive strategies including prevention of neonatal sepsis through effective implementation of the health sector transformation plan than before 2015 [15,18,23].

Neonates delivered from mothers who experienced antenatal urinary tract infection were 3.55 times more likely to develop neonatal sepsis as compared to those neonates born to mothers who did not experience antenatal urinary tract infection. Similarly, studies in Nigeria [92], rural Ghana [93] and Eastern Africa [83] asserted that neonates born to mothers who got UTI during pregnancy had higher likelihood of developing sepsis than those born to mothers without antenatal UTI. This may be due to the fact that mothers who suffer from untreated Urinary Tract Infection (UTI) even asymptomatic bacteriuria during pregnancy are more likely to have pre-term premature rupture of membrane, maternal chorioamnionitis and anemia [41, 43, 47]. The cascade of all these events results in adverse fetal outcomes such as low birth weight, preterm and Intrauterine Growth Retarded (IUGR) neonates, all of which are high risk groups for sepsis due to their low immune status and poorer infection barrier [47, 94]. This finding is supplemented by an Israeli study that showed independent association of UTI during pregnancy with pre-term delivery and IUGR [46]. Furthermore, untreated asymptomatic urinary tract infection in pregnancy can complicate to acute pyelonephritis thus leading to maternal septicemia contributing for fetoplacental transmission [42, 45].

Neonates born to mothers having intra-partum fever were 3.63 times more likely to develop neonatal sepsis as compared to those neonates born to mothers who were fever free during labor and/delivery. This finding is consistent with the study in Sweden [95] The consistency may

be due to the assertion that intra-partum fever is an already identified factor of statistical significance for vertical transmission of Group B Streptococcus (GBS), which is a gram-positive bacterium that can cause invasive newborn and fetal infection [47, 90]. Intra-partum fever mediates vertical transmission of GBS from maternal lower genital tract and rectum to the cervix, fetal membranes (chorio-amnionic layers), amniotic fluid and placenta mainly if accompanied with prolonged labor, multiple digital vaginal examinations and premature rupture of membrane [96]. Moreover, fever being among the inflammatory response manifestations increases the risk of feto-neonatal colonization by GBS [97, 98].

5. Conclusion

Neonatal sepsis has remained a problem of public health importance in Ethiopia thereby demanding the collaborative efforts of all concerned stakeholders. Furthermore, urinary tract infection during pregnancy and intra-partum fever are strongly associated with increased odds of neonatal sepsis in the country. Therefore, the existing efforts of early screening and treatment of pregnant mothers for possible urinary tract infection need to be strengthened during antenatal care. Moreover, measures like intra-partum antibiotic prophylaxis for at-risk mothers, limited digital vaginal examinations and shortening labor duration are of most useful to reduce the role of intra-partum fever in mediating vertical transmission of Group B Streptococcus (GBS) from maternal lower genital tract to the fetus during labor and/delivery. Most importantly, the maternal and child health service rendered by the Ethiopian Federal Ministry of Health should be at the reach of every pregnant mother in the community. This helps every pregnant mother to get quality antenatal care, deliver at health institution and attend postnatal care so that perinatal risks of neonatal sepsis including preterm delivery, low birth weight and perinatal asphyxia can be early mitigated.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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