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

Wubet Alebachew Bayih, Metadel Yibeltal Ayalew, Ermias Sisay Chanie, Biruk Beletew Abate, Sintayehu Asnakew Alemayehu, Demeke Mesfin Belay, Yared Asmare Aynalem, Dagne Addisu Sewyew, Solomon Demis Kebede, Asmamaw Demis, Getachew Yideg Yitbarek, Misganaw Abie Tassew, Binyam Minuye Birhan, Abebaw Yeshambel Alemu

Department of Pediatrics and Neonatal Health Nursing, College of Health Sciences, Debre Tabor University, PO.BOX: 272, Debre Tabor, 6300, Ethiopia
Debre Berhan University, Ethiopia
Woldia University, Ethiopia
Bahir Dar University, Ethiopia

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 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 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 compared to those born to mothers who were febrile 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.

* Corresponding author. E-mail address: wubeale@dtu.edu.et (W.A. Bayih).

https://doi.org/10.1016/j.heliyon.2021.e06121
Received 16 September 2020; Received in revised form 24 December 2020; Accepted 25 January 2021
2405-8440/© 2021 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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
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:

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 | Crosssectional | 169 | 39.6 | high quality |
| 2  | Gudeta et al. 2017 [50] | Addis Ababa | Crosssectional | 356 | 18.8 | high quality |
| 3  | Bayana et al. 2018 [51] | Oromiya | Crosssectional | 341 | 19.9 | high quality |
| 4  | Alemu et al. 2017 [52] | Addis Ababa | Crosssectional | 304 | 90 | high quality |
| 5  | Getabelew et al. 2018 [53] | Oromiya | Crosssectional | 244 | 77.9 | high quality |
| 6  | Woldu et al. 2014 [54] | Oromiya | Crosssectional | 306 | 72.20 | high quality |
| 7  | Serbesa and Iffa, 2019 [55] | Tigray | Crosssectional | 301 | 34.7 | high quality |
| 8  | Mersha et al. 2019 [56] | SNNPR | Crosssectional | 275 | 33.8 | high quality |
| 9  | Roba and Diro, 2017 [57] | Other | Crosssectional | 3418 | 22.4 | high quality |
| 10 | Farah et al. 2018 [58] | Other | Crosssectional | 792 | 75 | high quality |
| 11 | Woldehanna and Idejene, 2005 [59] | Amhara | Crosssectional | 304 | 11.70 | high quality |
| 12 | Tewabe et al. 2018 [60] | Amhara | Crosssectional | 391 | 23.8 | high quality |
| 13 | Kokeb and Desta, 2016 [61] | Amhara | Crosssectional | 325 | 77.8 | high quality |
| 14 | Yismaw et al. 2019 [62] | Amhara | Crosssectional | 423 | 11.70 | high quality |
| 15 | Sorsa Abebe, 2019 [63] | Oromiya | Crosssectional | 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 Gebreyohannes, 2016 [69] | Addis Ababa | Crosssectional | 570 | 14.4 | high quality |
| 22 | Gidayu et al. 2019 [70] | Amhara | Crosssectional | 504 | 62.7 | high quality |
| 23 | Checkawa and Aga, 2016 [71] | Addis Ababa | Crosssectional | 561 | 26.97 | high quality |
| 24 | Gerensea 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.

Funnel plot with pseudo 95% confidence limits

Figure 2. Funnel plot to test publication bias of the 27 studies, In proportion (x-axis) with standard error of ln proportion (y-axis).
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/mm³), absolute neutrophil count (<2000/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

| 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 |
| Getabew et al. [2018] | 77.900 | 72.694 | 83.106 | 4.13 |
| Wolde et al. [2014] | 72.200 | 67.180 | 77.220 | 4.13 |
| Serbasa 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 |
| Tewabate 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 | 8.657 | 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 Gebreyohgan [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 |
| Gerenesesea 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%.
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 ≤3, 4–5, and ≥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 ≥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™ software.

2.6. Heterogeneity and publication bias

The Cochran’s Q and the I² 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].
exclusion of 68 full text articles due to poor quality and whose text articles were further assessed for their quality resulting in the text, and only 95 of which had full text content. Then, all the 95 full text articles were considered for the presence of full text content. The remaining 245 articles were screened for their title and abstract based on which 141 articles were excluded. 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/or 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

| Author/year | ES (95% CI) | Weight |
|-------------|-------------|--------|
| Addis Ababa | 39.80 (32.23, 46.79) | 4.01 |
| Getachew et al. [2018] | 18.80 (14.74, 22.86) | 4.12 |
| Gudela et al. [2017] | 50.00 (44.38, 55.62) | 4.16 |
| Alemu et al. [2017] | 14.40 (11.52, 17.28) | 4.21 |
| Girma and Gebru [2016] | 26.97 (23.30, 30.64) | 4.19 |
| Cheyem [2016] | 29.72 (18.05, 41.39) | 20.69 |
| Subtotal (I-squared = 97.3%, p = 0.000) | 35.31 (33.71, 36.91) | 4.15 |
| Oromiya | 19.90 (15.66, 24.14) | 4.17 |
| Bayana et al. [2018] | 77.90 (72.69, 83.11) | 4.13 |
| Gelabelew et al. [2018] | 72.20 (67.18, 77.22) | 4.13 |
| Wolde et al. [2014] | 34.00 (30.91, 37.09) | 4.20 |
| Sena Abebe. [2019] | 34.30 (32.72, 35.88) | 4.24 |
| Debelew GT et al. [2014] | 29.70 (28.14, 31.26) | 4.24 |
| Seid et al. [2019] | 40.00 (33.60, 46.40) | 4.07 |
| Sime H et al. [2014] | 43.84 (33.35, 54.32) | 29.17 |
| Subtotal (I-squared = 98.9%, p = 0.000) | 77.80 (73.28, 82.32) | 4.12 |
| Tigray | 37.20 (29.32, 40.88) | 4.08 |
| Serbasa and Ifa [2019] | 47.00 (46.24, 47.76) | 4.25 |
| Gerenesea H et al. [2017] | 41.15 (29.11, 53.19) | 8.36 |
| Subtotal (I-squared = 94.9%, p = 0.000) | 75.00 (70.13, 79.87) | 4.19 |
| SNNPR | 33.80 (28.21, 39.39) | 4.11 |
| Mersha et al. [2019] | 16.90 (13.24, 20.56) | 4.19 |
| Ahmed et al. [2018] | 25.21 (8.65, 41.77) | 8.30 |
| Subtotal (I-squared = 95.9%, p = 0.000) | 50.00 (44.38, 55.62) | 4.19 |
| Other | 35.31 (33.71, 36.91) | 4.24 |
| Roba and Dino [2017] | 22.40 (19.50, 25.30) | 4.21 |
| Farah et al. [2018] | 28.91 (16.26, 41.57) | 8.45 |
| Subtotal (I-squared = 98.3%, p = 0.000) | 77.90 (72.69, 83.11) | 4.12 |
| Amhara | 75.00 (70.13, 78.78) | 4.14 |
| Woldehanna and Deskene [2005] | 23.80 (19.58, 28.02) | 4.17 |
| Tewabe et al. [2018] | 77.80 (72.69, 83.11) | 4.16 |
| Kokeb and Desta [2016] | 11.70 (8.64, 14.76) | 4.21 |
| Yisraw et al. [2019] | 67.90 (54.60, 71.20) | 4.20 |
| Demisse AG et al. [2017] | 63.70 (59.50, 67.90) | 4.17 |
| Gudayu et al. [2019] | 53.30 (48.14, 57.45) | 25.04 |
| Subtotal (I-squared = 96.6%, p = 0.000) | 40.25 (33.84, 46.50) | 100.00 |
| Overall (I-squared = 99.2%, p = 0.000) | 77.90 (72.69, 83.11) | 4.12 |

NOTE: Weights are from random effects analysis

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
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 across the studies. Therefore, given that the result of this meta-analysis revealed a statistically significant heterogeneity among studies (I² = 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 (I² 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%], I² = 99.6%) whereas the lowest estimated prevalence was reported from SNNPR 25.21% ([95%CI: 8.65%, 41.77%], I² = 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%,

3.7. Subgroup analysis of the magnitude of neonatal sepsis by study region

| Author/year          | Weight | %     | ES (95% CI)     |
|----------------------|--------|-------|-----------------|
| Getachew et al. [2018] | 100.00 | 100.00| 100.00          |
| Gudeta et al. [2017]  | 100.00 | 100.00| 100.00          |
| Bayana et al. [2018]  | 100.00 | 100.00| 100.00          |
| Alenu et al. [2017]   | 100.00 | 100.00| 100.00          |
| Getabew et al. [2018] | 100.00 | 100.00| 100.00          |
| Serbesa and Ifa [2019]| 100.00 | 100.00| 100.00          |
| Mensha et al. [2019]  | 100.00 | 100.00| 100.00          |
| Ronab and Dir [2017]  | 100.00 | 100.00| 100.00          |
| Farah et al. [2018]   | 100.00 | 100.00| 100.00          |
| Tewabe et al. [2018]  | 100.00 | 100.00| 100.00          |
| Kokeb and Desta [2016]| 100.00 | 100.00| 100.00          |
| Yismaw et al. [2019]  | 100.00 | 100.00| 100.00          |
| Sorsa Abebe. [2019]   | 100.00 | 100.00| 100.00          |
| Demisse AG et al. [2017]| 83.42 | 83.42 | 83.42           |
| Ahmed et al. [2018]   | 83.42  | 83.42 | 83.42           |
| Girma and Gerebeychanes. [2016]| 4.01 | 4.01 | 4.01|
| Gudayu et al.[2019]   | 4.01   | 4.01  | 4.01            |
| Chewaka and Aga [2016] | 4.01  | 4.01  | 4.01            |
| Genesesea H et al. [2017]| 4.01 | 4.01 | 4.01|
| Seid et al. [2019]    | 4.01   | 4.01  | 4.01            |
| Subtotal (I-squared = 99.3%, p = 0.000) | 4.01 | 4.01 | 4.01|
| Subtotal (I-squared = 99.3%, p = 0.000) | 4.01 | 4.01 | 4.01|
| Overall (I-squared = 99.2%, p = 0.000) | 4.01 | 4.01 | 4.01|
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%), I² = 99.3%] compared to those neonates born to mothers who didn't experience antenatal 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 and intra-partum fever [AOR = 3.55; 95% CI: 2.04, 5.06] [Figure 5].

3.9. Subgroup analysis by sample size

Pooled prevalence of neonatal sepsis among studies with primary source of data 39.98% [(26.34%, 53.61%), I² = 99.2%] was nearly equal to the pooled prevalence among studies whose data were sourced from chart review 40.40% [(32.89%, 47.90%), I² = 99.3%] [Figure 7].

3.10. Subgroup analysis by data source

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.

3.11. Sensitivity analysis

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] | Weight |
|--------------------------------|----------------|----------------------|--------|
| Getachew et al. [2018]         | 40.273678      | 33.873283            | 46.674072 |
| Gudeta et al. [2017]           | 41.179123      | 34.834961            | 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 |
| Gudeta et al. [2017]           | 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            | 47.287497 |
| Farah et al. [2018]            | 41.030075      | 34.655767            | 47.403374 |
| Woldehanna and Idejene [2005]  | 38.740791      | 32.524243            | 44.957336 |
| Tewabe et al. [2018]           | 40.961464      | 34.570347            | 47.352597 |
| Kokeb and Desta [2016]         | 38.611771      | 32.456485            | 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            | 45.210274 |
| Ahmed et al.[2018]             | 41.26403       | 34.95417             | 47.574833 |
| Girma and Gebreyohanes [2016]  | 41.37772       | 35.182724            | 47.572712 |
| Gudayu et al. [2019]           | 39.224251      | 32.998215            | 45.540921 |
| Chewaka and Aga [2016]         | 40.827126      | 34.405922            | 47.248333 |
| Gerenesha H et al. [2017]      | 39.961433      | 32.957886            | 46.964977 |
| Debelew GT et al. [2014]       | 40.518406      | 33.71212             | 47.324668 |
| Seid et al [2019]              | 40.718933      | 34.043983            | 47.393883 |
| Sime H et al.[2014]            | 40.257286      | 33.848122            | 46.66451 |
| Combined                       | 40.246112      | 33.997092            | 46.495132 |
### Author /year

| ES (95% CI) | Weight % |
|-------------|----------|
| 3.84 (0.58, 7.10) | 21.31 |
| 2.90 (0.90, 4.90) | 56.79 |
| 4.50 (0.70, 8.30) | 15.73 |
| 10.80 (-4.46, 26.06) | 0.97 |
| 5.23 (-1.38, 11.84) | 5.20 |
| 3.55 (2.04, 5.06) | 100.00 |

**NOTE:** Weights are from random effects analysis

---

**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.
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 >2015) showed that pooled estimate of neonatal sepsis among studies conducted during <2015 years (55.35%) was higher than during >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].

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

References

[1] J.L. Wynn, et al., Time for a neonatal-specific consensus definition for sepsis, Pediatr. Crit. Care Med. 15 (6) (2014) 523.
[2] A.L. Shane, P.J. Sanchez, B.J. Stoll, Neonatal sepsis, Lancet (2017).
[3] L. Ana, Anderson Berry, Linda L. Belleg, Bryan L. Oehme, Neonatal Sepsis, 2015. Available at: https://med规模以上.gov/ency/article/007303.htm.
[4] K.A. Simonsen, A.L. Anderson-Berry, S.F. Delaite, H.D. Davies, Early-onset neonatal sepsis, Clin. Microbiol. Rev. 27 (1) (2014) 21–47. Available at: https://cmr.asm.org /content/cmrr/27/1/21.full.pdf.
[5] M.N. Cizmeci, S. Kara, M.K. Kanburugu, S. Simavi, C.I. Duvan, M.M. Tatli, Detection of cord blood hepcidin levels as a biomarker for early-onset neonatal sepsis, Med. Hypotheses 82 (3) (2014) 310–312.
[6] G.J. Chan, A.C. Lee, A.H. Baqui, J. Tan, R.E. Black, Prevalence of early-onset neonatal sepsis among newborns of mothers with bacterial infection or colonization: a systematic review and meta-analysis, BMC Infect. Dis. 15 (1) (2015) 118.
[7] A.C. Seale, M. Mwankisi, C.R. Newton, J.A. Berkley, Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa, Lancet Infect. Dis. 9 (7) (2009) 428–438.
[8] Grace J. Chan, A.C.L. Abdullah, H. Baqui, Jyngwen Tan, Robert E. Black, Prevalence of Early-Onset Neonatal Infection Among Newborns of Mothers with Bacterial Infection or Colonization: A Systematic Review and Meta-Analysis, 2015.
[9] J.E. Lawn, et al., USAID, Better Intrapartum Practices to Prevent Neonatal Infections, 2010.
[10] WHO, Preventative Maternal and Neonatal Sepsis A Critical Priority for WHO and Global Sepsis Alliance, 2017.
[11] UNICEF, Monitoring the Situation of Children and Women, 2017. https://data.unicef.org/.
[12] Bochen Cao, et al., Levels and trends in child mortality report: estimates developed by the UN inter-agency group for child mortality estimation, UNICEF, WHO, World Bank Group and United Nations, 2019.
[13] EDHS, 2019.
[14] Levels and Trends in Child Mortality, United Nations Children’s Fund, 2017.
[15] WHO, World Health Statistics 2016: Monitoring Health for the SDGs Sustainable Development Goals, World Health Organization, 2016.
[16] WHO, Neonatal Mortality. Global Health Observatory, World Health Organization, 2018. Available at: http://www.who.int/igo/child-health/mortality/neonatal/em/.
[17] L. Liu, S. Ota, D. Hogan, Y. Chu, J. Perin, J. Zhu, et al., Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals, Lancet 388 (10063) (2016) 3027–3035.
[18] WHO, Every Newborn: an Action Plan to End Preventable Deaths, World Health Organization, Geneva, 2014.
[19] UNICEF: committing to child survival: a promise renewed world health, Organ. Tech. Rep. Ser. 1–100 (2014).
[20] Federal Ministry of Health of Ethiopia, Neonatal Intensive Care Unit (NICU) Training Participants Manual, 2014.
[21] A.C. Seale, et al., Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, South Asia, and Latin America for 2012: a systematic review and meta-analysis, Lancet Infect. Dis. 14 (8) (2014) 731–741.
[22] K. Edmond, A. Zaidi, New approaches to preventing, diagnosing and treating neonatal sepsis, PLoS Med. 7 (3) (2010), e1000213.
[23] EMOH: Health Sector Transformation Plan (HSTP 2015/16 – 2019/20 (2008–2012)) October in, 2015, pp. 1–182.
[24] R. Kumar, A. Kumari, A. Kumari, N. Verma, Evaluation of perinatal factors in preterm birth, Int. J. Reprod. Contracept Obstet. Gynecol. 6 (2017) 1261–1264.
[25] M.A.G. Shrutji MurthyID, I.D. Vasudeva Guddattu, Edward Leslie, N.S.N. Simon Lewis, Risk Factors of Neonatal Sepsis in India: A Systematic Review and Meta-Analysis, 2019.
[26] R.S. Gibbs, P. Duff, Progress in pathogenesis and management of clinical intraamniotic infection, Am. J. Obstet. Gynecol. (1991) 1317–1326.
[27] S.L. Hillier, M.A. Krohn, N.B. Kiviat, D.H. Watts, D.A. Eschenbach, Microbiologic causes and neonatal outcomes associated with chorioamnion infection, Am. J. Obstet. Gynecol. 165 (919) 955–961.
[28] J.O. Klein, Bacterial Sepsis and Meningitis. Infectious Diseases of the Fetus and Newborn Infant, WB Saunders Philadelphia – 1991.
[29] R.S. Gibbs, P. Duff, Progress in pathogenesis and management of clinical intraamniotic infection, Am. J. Obstet. Gynecol. 164 (1991) 1317–1326.
[30] J.W. St Geme Jr., D.L. Murray, J. Carter, C.J. Hobel, B.D. Leake, B.F. Anthony, D.C. Thibeault, I.B. Ross, J.S. Drage, Perinatal bacterial infection after prolonged rupture of amniotic membranes: an analysis of risk and management, J. Pediatr. 104 (1984) 608–613.
[31] P.R. Yoder, R.S. Gibbs, J.D. Blanco, Y.S. Castaneda, P.J. St Clair, A prospective controlled study of maternal and perinatal outcome after intra-amniotic infection at term, Am. J. Obstet. Gynecol. 145 (1983) 695–701.
[32] L.A. Chan GJ1, A.H. Baqui, J. Tan, R.E. Black, Risk of Early-Onset Neonatal Infection with Maternal Infection or Colonization: a Global Systematic Review and Meta-analysis, 2013.
[33] L. Lorenz, et al., Sweden. Intrapartum Fever and Early Neonatal Sepsis, 2018.
[34] C.V. Towers, A. Yates, N. Zite, et al., Incidence of fever in labor and risk of neonatal sepsis, Am. J. Obstet. Gynecol. 216 (2017), 596.e 1–5.
[35] The American College of Obstetricians and Gynecologists 409 12th street, SW PO Box, 96920, Washington, DC, 20090-6920. Intrapartum management of intraamniotic infection. Committee Opinion No. 712, American college of obstetricians and gynecologists, Obstet. Gynecol. 130 (2017) e95–101.
[36] G.D. Wendel, K.J. Levin, P.J. Sanchez, G.L. Jackson, D.D. McIntire, J.D. Siegel, Prevention of neonatal group B streptococcal disease: a combined intrapartum and neonatal protocol, Am. J. Obstet. Gynecol. 186 (2002) 618–626.
[37] C.V. Towers, P.J. Runney, S.F. Minkiewicz, T. Arsat, Incidence of intrapartum maternal risk factors for identifying neonates at risk for early onset group B streptococcal sepsis: a prospective study, Am. J. Obstet. Gynecol. 181 (1999) 1197–1202.
[96] A. Berardi, C. Rossi, I. Guidotti, et al., Factors associated with intrapartum transmission of group B streptococcus, Pediatr. Infect. Dis. J. 33 (12) (2014) 1211–1215.

[97] D. Shah, S. Saxena, V.S. Randhawa, S. Nangia, R. Dutta, Prospective analysis of risk factors associated with group B streptococcal colonization in neonates born at a tertiary care centre in India, Paediatr. Int. Child Health 34 (3) (2014) 184–188.

[98] M. Kacerovsky, I. Musilova, C. Andrys, et al., Prelabor rupture of membranes between 34 and 37 weeks: the intraamniotic inflammatory response and neonatal outcomes, Am. J. Obstet. Gynecol. 210 (4) (2014) 325. E321–325.