


Gram-Negative Bacteria Isolates and Their Antibiotic-Resistance Patterns in Patients with Wound Infection in Ethiopia: A Systematic Review and Meta-Analysis

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Background: Antibiotic resistance (ABR) restricts the armamentarium of health-care providers against infectious diseases due to the emergence of multidrug resistance (MDR), especially in Gram-negative bacteria. This study aimed to determine pooled estimates of Gram-negative bacteria, their resistance profiles, and rates of MDR in patients with wound infection in Ethiopia.

Methods: Electronic databases such as PubMed/MEDLINE, EMBASE, Science Direct, Web of Science, and Google Scholar were searched. Original articles, available online from 1988 to 2020, addressing the prevalence and resistance patterns of Gram-negative bacteria in patients with wound infection and written in English were screened. The data were extracted using a format prepared in Microsoft Excel and exported to STATA 14.0 for the outcome analyses.

Results: The data of 15,647 wound samples, from 36 studies conducted in 5 regions of the country, were pooled. The overall pooled estimate of Gram-negative bacteria was 59% [95% CI: 52–65%, $I^2 = 96.41\%$, $p < 0.001$]. The pooled estimate of *Escherichia coli* recovered from isolates of 5205 wound samples was 17% [95% CI: 14–20%], followed by *Pseudomonas aeruginosa*, 11% [95% CI: 9–14%], *Klebsiella pneumonia*, 11% [95% CI: 9–13%], *Proteus mirabilis*, 8% [95% CI: 6–10%], Acinetobacter species, 4% [95% CI: 2–6%], Enterobacter species, 4% [95% CI: 3–5%], and Citrobacter species, 3% [95% CI: 2–4%]. Multidrug resistance prevalence estimates of *E. coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, Citrobacter species, Enterobacter species and Acinetobacter species were 76% [95% CI: 66–86%], 84% [95% CI: 78–91%], 66% [95% CI: 43–88%], 83% [95% CI: 75–91%], 87% [95% CI: 78–96%], 68% [95% CI: 50–87%] and 71% [95% CI: 46–96%], respectively.

Conclusion: There was high resistance in Gram-negative bacteria from wound specimens to commonly used antibiotics in Ethiopia. The data warrant the need of regular epidemiological surveillance of antimicrobial resistance and implementation of an efficient infection control program.

Keywords: antibiotic resistance, Gram-negative bacteria, wound infection, meta-analysis, systematic review, Ethiopia

Introduction

Bacteriological isolation, identification, and antibiotic susceptibility testing of clinical specimens are essential tools for active surveillance of antibiotic resistance (ABR). They strongly support targeted antibiotic therapy and reduce exposure of

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non-involved bacterial pathogens to unnecessary antibiotics.¹ Globally, ABR restricts the armamentarium of the health care providers against infectious diseases. This is mainly related to the emergence of multidrug resistant Gram-negative bacteria.² Availability of less potent products, use of antibiotics for veterinary products, lack of standardized diagnostic facilities, and increased practice of antibiotic self-medication are directly related to the development of ABR.³⁻⁵ Worldwide, the prevalence and rate of antibiotic resistance is increasing at an

alarming rate.⁶⁻⁸ Resistant etiologies are common causes of community and health-care associated infections.^{9,10} These pathogens present a concerning therapeutic challenge to clinicians with few therapeutic options left.¹¹

To promote research and development of new antibiotics and advocate prudent use of the available ones, the World Health Organization (WHO) released a list of antibiotic-resistant priority pathogens, the majority being Gram-negative bacteria.¹² These microorganisms have become a major clinical and therapeutic dilemma in

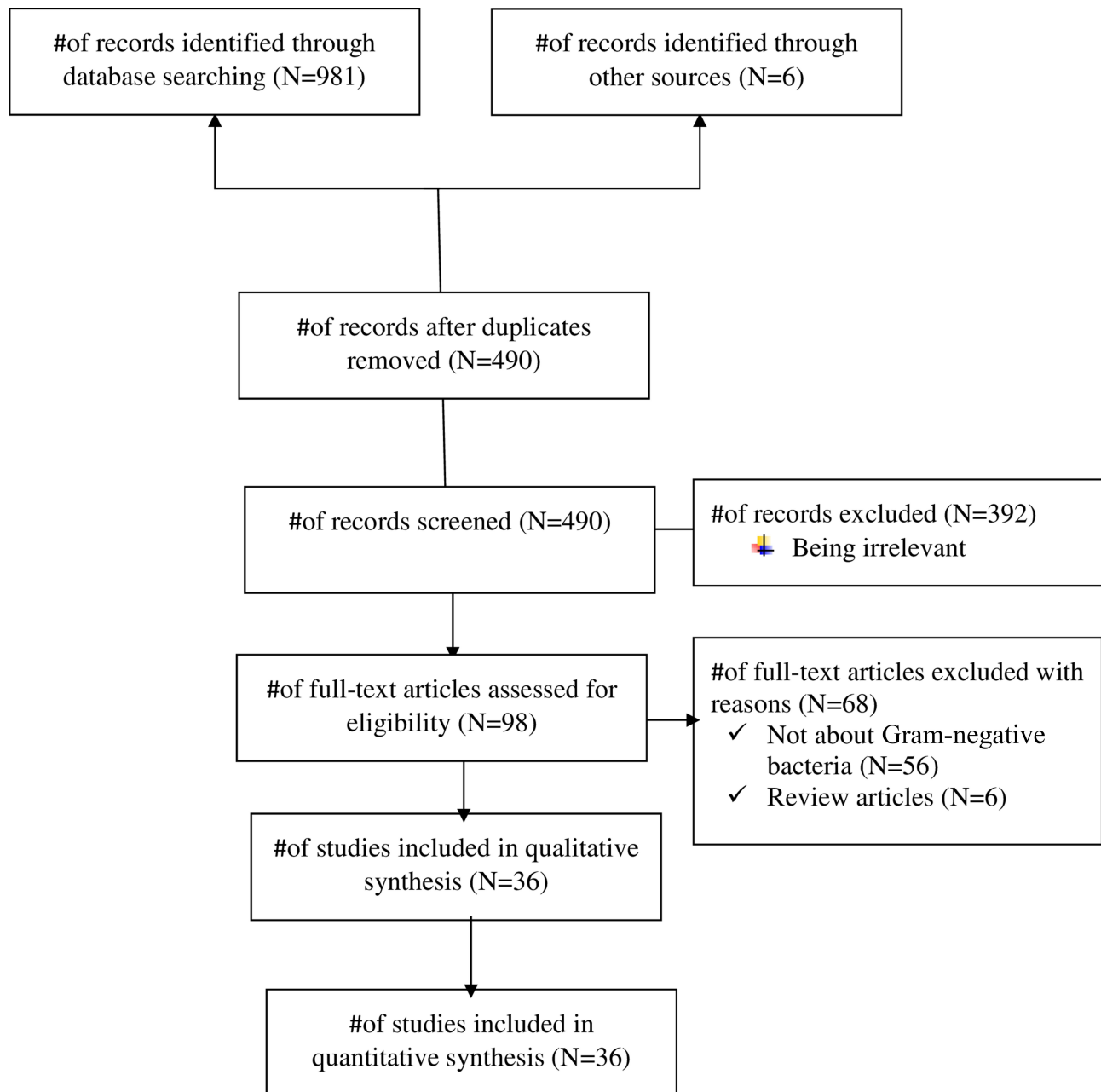


Figure 1 Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow chart for the included studies.

Table 1 The Study Characteristics, Quality, and the Number of Gram-Negative Isolates Recovered from Wound Samples

Name of First Author	Year of Publication	Study Period	Study Design	Regional State	Age	Gender		Sample Size	E. coli (n)	K. pneumonia (n)	P. aeruginosa (n)	P. mirabilis (n)	EB. Species (n)	CB. Species (n)	Acinetobacter Species (n)	Overall JBI's Score
						M	F									
Godebo ⁵³	2013	June to Dec 2011	Cross sectional	Oromia	NR	NR	NR	NR	30	46	74	107		18	7	8
Mama ⁵⁴	2014	May to September 2013	Cross sectional	Oromia	6 months–90 years	107	43	150	29	14	11	23				9
Mengesha ⁵⁵	2014	January to June 2012	Cross sectional	Tigray	15–79 years	467	143	610	6	29	15	15		4		8
Feleke ⁵⁶	2018	February 1 to May 31, 2016	Cross sectional	Amhara	1–85 years	NR	NR	116	24	29	-	-				8
Ali ⁵⁷	2018	May to September, 2016	Cross sectional	Oromia	34.12 ± 16.86 years	168	282	450	14	5	-	-				8
Dessie ⁵⁸	2016	October 2013 to March 2014	Cross sectional	Addis Ababa	8–80 years	NR	NR	1088	22	10	6	1		3	23	6
Tesfahunegn ⁵⁹	2009	November 2005 and April 2006	Cross sectional	Tigray	35.5 years	134	112	246	14	7	1	1			1	7
Yallew ⁶⁰	2016	March to July 2015	Cross sectional	Amhara	16–40 years	NR	NR	908	22	30	25	8		6	6	6
Mullu ⁶¹	2012	October 2010 to January 2011	Cross sectional	Amhara	32.2 years	96	198	294	9	2	5	4				8
Kalayu ⁶²	2020	April 2016 to April 2017	Cross sectional	Addis Ababa	9 months–88 years	285	364	649	11	10	-	1		1	3	8
Asres ⁶³	2017	March to August 2015	Cross sectional	Addis Ababa	0–85 years	118	79	179	24	15	8	1		2	17	8
Sahile ⁶⁴	2016	June, 2012 to February, 2013	Cross sectional	Oromia	18–75 years	103	97	200	9	5	8	7		6	4	6
Amare ⁶⁵	2011	January 2010 and June 2010	Cross sectional	Amhara	7–75 years	NR	NR	1627	27	6	3	4				6
Endälatfer ⁶⁶	2010	2007 and April 2008	Cross sectional	Addis Ababa	17–79 years	130	85	215	16	12	12	-				7

(Continued)

Table 1 (Continued).

Name of First Author	Year of Publication	Study Period	Study Design	Regional State	Age	Gender		Sample Size	E. coli (n)	K. pneumonia (n)	P. aeruginosa (n)	P. mirabilis (n)	EB. Species (n)	CB. Species (n)	Acinetobacter Species (n)	Overall JBI's Score
						M	F									
Tekie ⁶⁷	2008	April 2006 to July 2006	Cross sectional	Addis Ababa	1-80 years	97	76	173	7	4	10	2	2	2		9
Kifile ⁶⁸	2019	January 2016 to May 2016	Cross sectional	Amhara	15-44 years	0	107	107	20	14	2	1	4	4		8
Dessalegn ⁶⁹	2013	November 2010 to March 2011	Cross sectional	SNINPR	12-100 years	116	78	194	45	24	12	18				7
Misha ⁷⁰	2020	April 20 to August 20, 2019	Cohort	Oromia	38 ± 16.30 years	125	126	251	8	5	7	6	4	4		8
Gelaw ⁷¹	2014	November 2010 to February 2011	Cross sectional	Amhara	NR	27	15	510	10	11	8	5	4	2		7
Ali ⁷²	2016	July 22 - October 25, 2016	Cross sectional	Amhara	16-76 years	87	251	338	9	7	2	1			3	8
Melaku ⁷³	2012	April-August 2009	Cohort	Amhara	NR	NR	NR	1383	49	36	26					6
Birew ⁷⁴	2019	January 1 to May 31, 2016	Cross sectional	Amhara	15-44 years	0	222	222	24	-	1	1	1	1		6
Badegne ⁷⁵	2009	September 2003 to June 2008	Cross sectional	Amhara	3 months-90 years	222	157	397	4	10	9	17	7	2		6
Birew ⁷⁶	2018	June 2016 to July 2017	Cross sectional	Addis Ababa	15-64 years	213	153	366	49	12	14	7	6	4	4	8
Hailu ⁷⁷	2016	1 January 2013 to 30 December 2015	Cross sectional	Amhara	4 months -76 years	195	185	380	33	20	26	22	5	5		7
Abraham ⁷⁸	2009	November, 2007 and May, 2008	Cross sectional	Addis Ababa	4-75 years	158	33	191	17	12	16	6				7
Mulu ⁷⁹	2006	-	Cross sectional	Amhara	NR	NR	NR	151	8	7	-	3				7
Lema ⁸⁰	2012	August 2006 to May 2007	Cross sectional	Addis Ababa	13 to 92 years	157	88	245	14	2	7	47				7
Ayalew ⁸¹	2014	December 2013 to May 2014	Cross sectional	Addis Ababa	10-68 years	268	32	300	19	21	53	24	9	8		9

Mohammed ⁸²	2017	March to May, 2014	Cross sectional	Amhara	2-80 years	81	56	137	15	17	16	13	13	15	2	7
Häbre-Gabir ⁸³	1988	April 1983 and January 1984	Cohort	Addis Ababa	NR	733	273	1006	54	46	40	94	14	14	1	6
Billoro ⁸⁴	2019	January 1 to September 1, 2017	Cohort	SNNPR	NR	147	108	355	5	25	5					7
Guta ⁸⁵	2014	November 2010 to June 2011	Cross sectional	SNNPR	NR	NR	NR	100	30	32	16	12	3	4		7
Azene ⁸⁶	2011	-	Cross sectional	Amhara	1-90 years	368	231	599	82	12	92	55	21	21		8
Sewunet ⁸⁷	2013	April to July 2010	Cross sectional	Addis Ababa	7-55 years	30	20	50	-	2	15	4				7
Motbainor ⁸⁸	2020	April 1 to July 31, 2018	Cross sectional	Amhara	-	129	109	238	-	-	11	-			9	

the health facilities of developing countries. They are responsible for increased health-care costs owing to protracted hospital stay, morbidity and mortality.¹² Multiple studies from Africa,¹³⁻¹⁵ Europe,¹⁶⁻¹⁹ USA,^{5,20-23} Australia,²⁴⁻²⁶ and Asia²⁷⁻³⁰ revealed that the huge increase of resistance in Gram-negative bacteria to available antibiotics is leading to a loss of efficacy for the treatment of many infections. Respiratory tract, urinary tract, bloodstream and wound infections are among the common conditions caused by these pathogens in health-care and community settings. Enterobacteriaceae (*Klebsiella pneumonia*, *Escherichia coli*, and *Enterobacter* species), *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Acinetobacter* species have been identified as the major resistant strains responsible for these and other infections.³¹⁻³⁴

Due to the nature of their outer layer envelope, Gram-negative bacteria are more resistant to a wide range of antibiotics than Gram-positive bacteria.^{35,36} A plethora of observational studies conducted across the regions of Ethiopia from various clinical settings showed increments in the prevalence of resistance patterns of Gram-negative bacteria isolates.³⁷⁻⁴³ However, there is a need of an updated pooled data set for the resistance burden of Gram-negative bacteria isolates among patients with wound infections. This might help to draw a national estimate of antibiotic resistance prevalence for these etiologies in such kinds of clinical specimens. Currently, there is one published review on the pattern of antibiotic resistance among bacteria isolated from wound samples in Ethiopia.⁴⁴ Although the review was informative, its search was not exhaustive and it included only limited original studies. Moreover, the review did not estimate pooled prevalence of MDR Gram-negative bacteria. Therefore, the current review was designed to synergize the prior work by determining the pooled estimates and the resistance pattern of Gram-negative bacteria in patients with infected wounds. It also computed the rates of MDR species of Gram-negative bacteria from the available studies conducted in the country.

Methods Reporting

This systematic review and meta-analysis was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 2 The Estimates of Common Gram-Negative Bacteria Isolated from Wound Samples

Bacteria	No. of Studies	Sample	Case	Estimate [95% CI]	χ^2	I ² (%)
<i>Escherichia coli</i>	34	5205	762	17[14–20]	380.24	91.32
<i>K. pneumoniae</i>	34	5281	539	11[9–13]	364.42	90.94
<i>P. aeruginosa</i>	32	6145	562	11[8–11]	557.33	94.44
<i>P. mirabilis</i>	30	4713	513	8[6–10]	369.37	92.15
Citrobacter species	20	3563	126	3[2–4]	39.81	52.27
Enterobacter species	16	2857	123	4[3–5]	29.41	49.00
Acinetobacter species	12	1786	80	4[2–6]	72.86	84.90

Abbreviation: CI, confidence interval.

(PRISMA) statement⁴⁵ and meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.⁴⁶

Literature Search

The electronic databases and indexing services PubMed/MEDLINE (<https://www.pubmed.ncbi.nlm.>

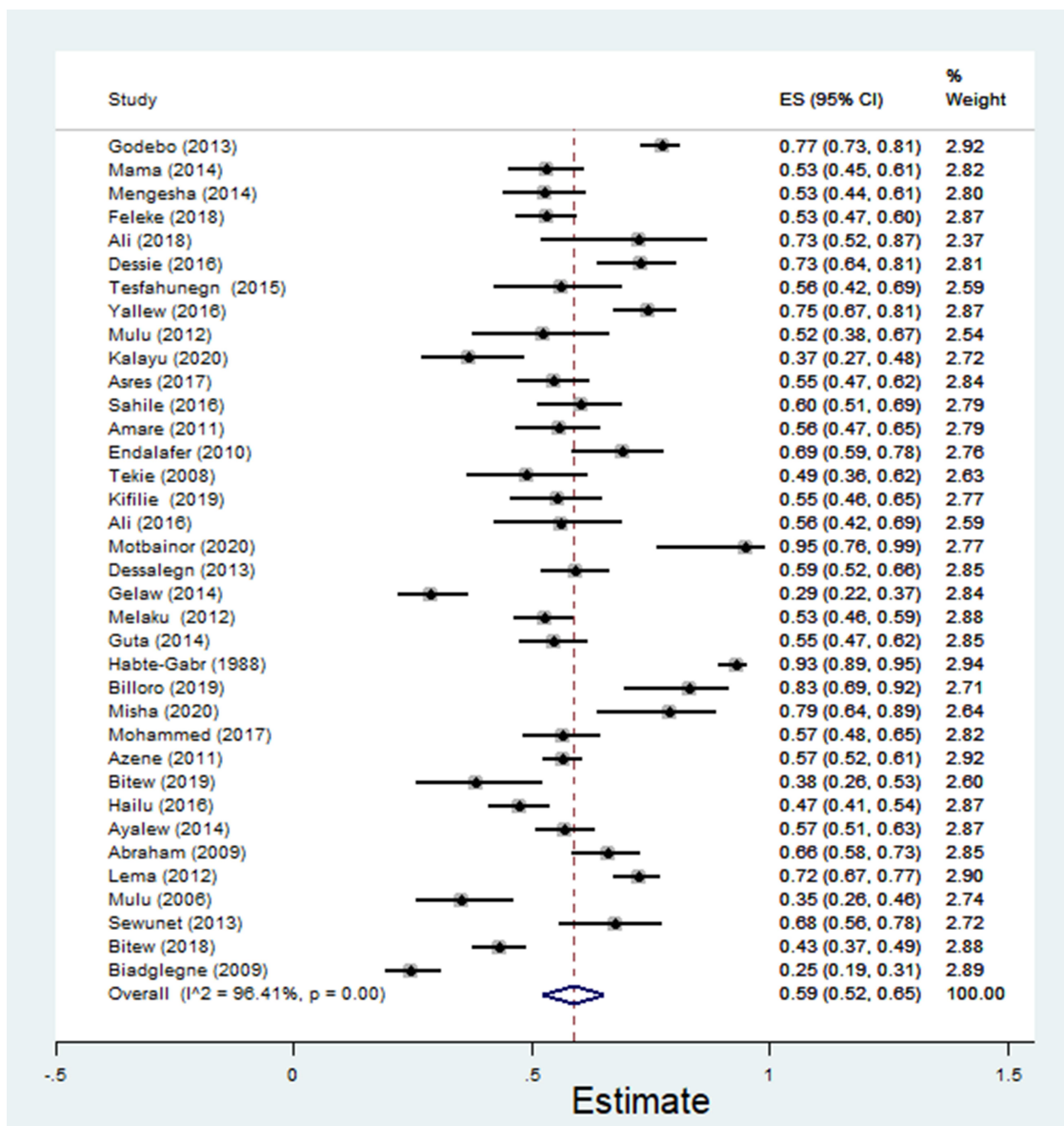


Figure 2 The pooled estimates of Gram-negative bacteria isolates from wound samples.

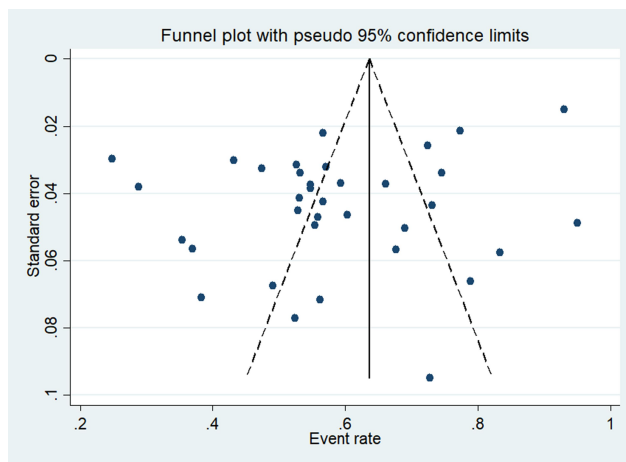


Figure 3 The funnel plot for the publication bias of the included studies for the prevalence of Gram-negative bacteria.

nih.gov), EMBASE (<https://www.embase.com>), Science Direct (<https://www.sciencedirect.com>), Web of Science (<https://mjl.clarivate.com/search-results>), and Google Scholar (<https://scholar.google.com>) were searched. The institutional repositories of Jimma & Addis Ababa Universities; available in Ethiopia, were also explored for grey literature. The references of all retrieved articles were checked for additional relevant publications. All searches were limited to articles written in English. The databases were searched from 1988 to March, 2020. The search terms stemmed from the following key words: prevalence, magnitude, surgical site infection, wound infections, post-operative infection, resistance, multidrug resistance, bacterial profile,

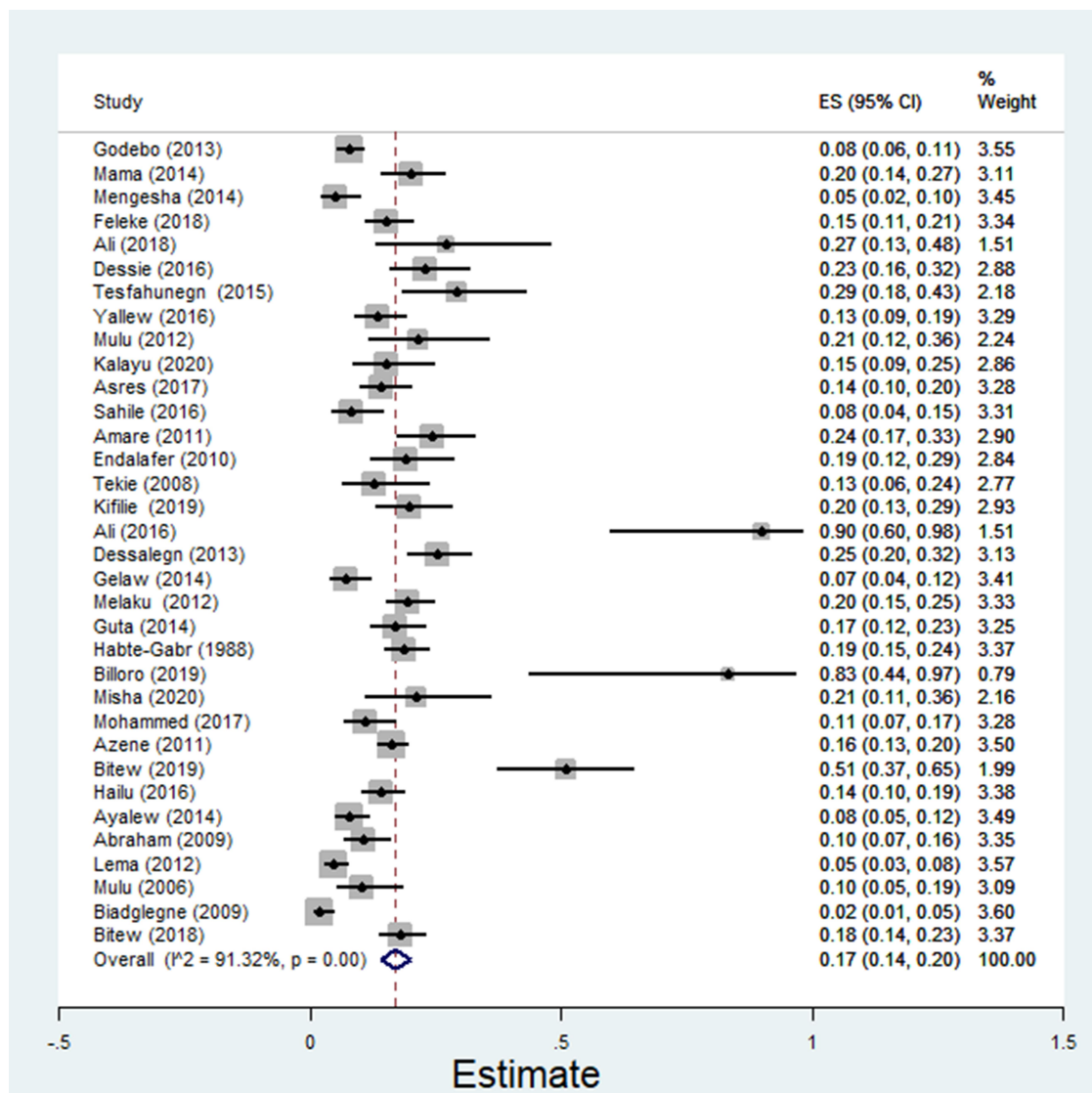


Figure 4 Forest plot showing pooled estimate of *E. coli* bacteria among patients with wound infection.

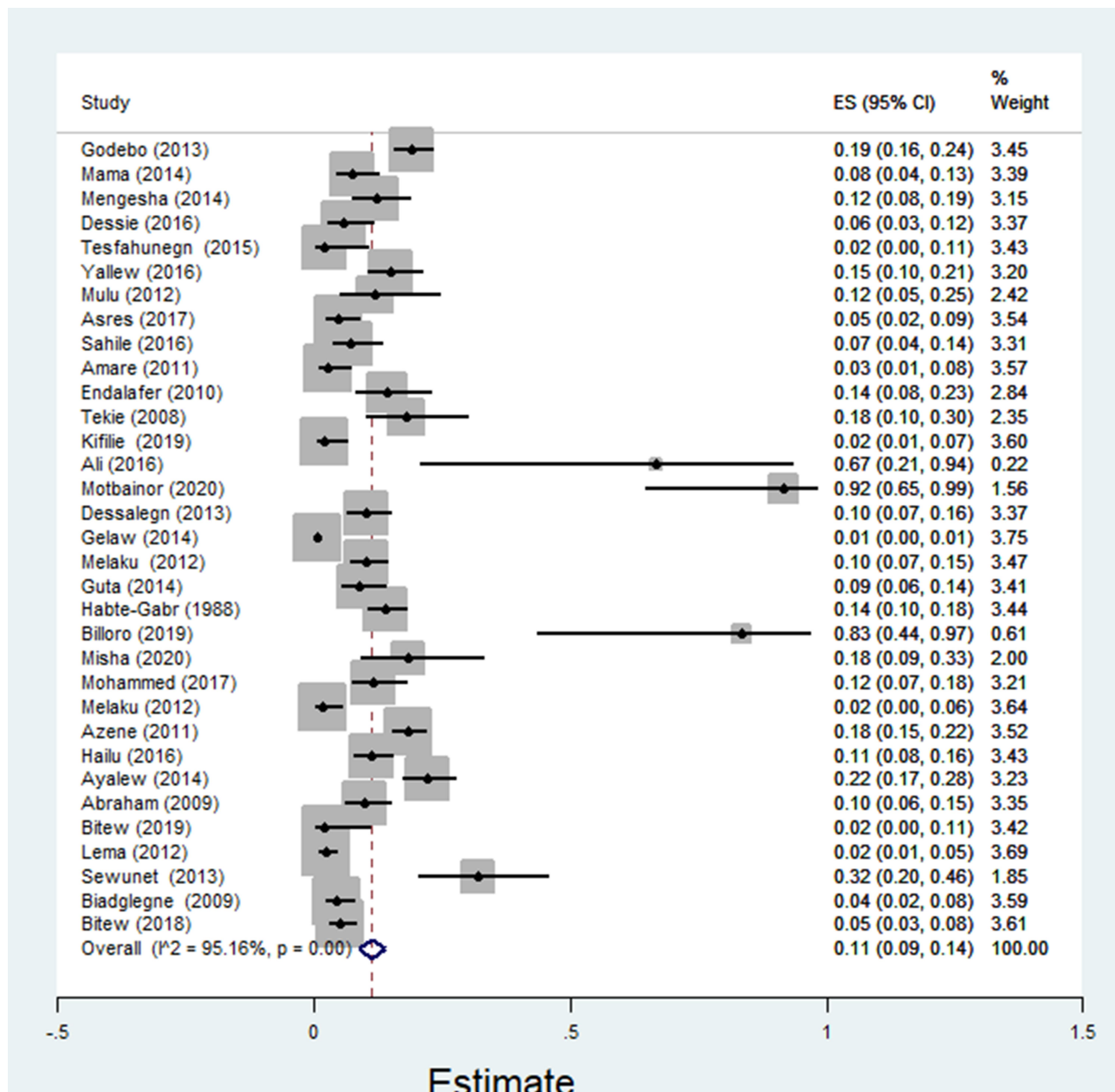


Figure 5 Forest plot showing pooled estimate of *Klebsiella pneumoniae* among patients with wound infection.

antimicrobial resistance, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, Citrobacter species, Enterobacter species and Acinetobacter species, Gram-negative bacteria and Ethiopia. In the advanced searching databases, the searching strategy was built based on the above-mentioned terms using the “Medical Subject Headings (MeSH)” and “All fields” by linking “AND” and “OR” Boolean operator terms as appropriate.

Study Selection and Data Extraction

Data were extracted using a standard extraction format adapted from the Joanna Briggs Institute (JBI) data extraction format.⁴⁷ Two authors (LK and TM) independently reviewed the articles for data quality and methodological validity. Disagreements were resolved by consulting TAM. A pre-designed data collection format was used to extract data from each included study. The extracted information

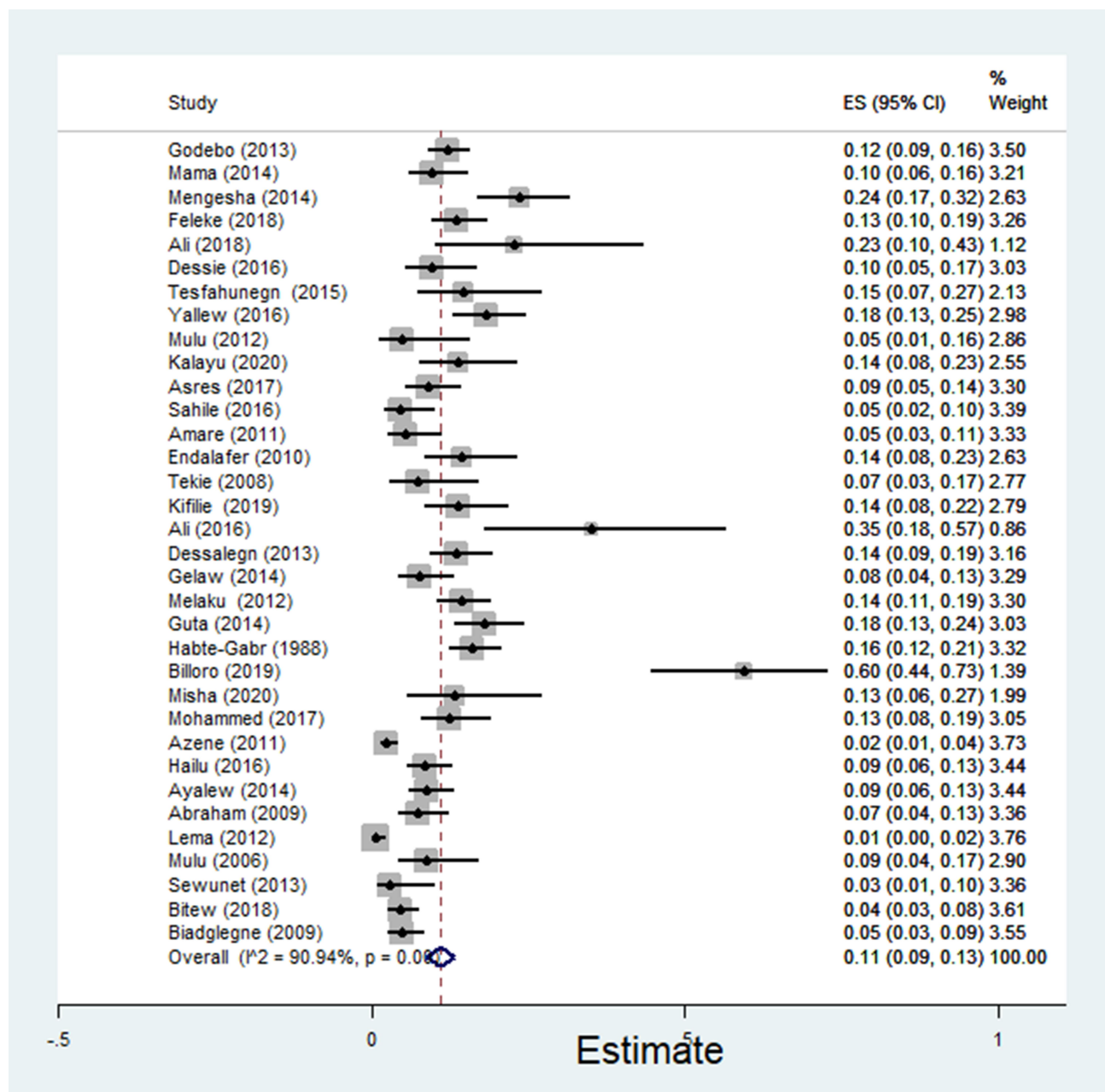


Figure 6 Forest plot showing pooled estimate of *P. aeruginosa* among patients with wound infection.

includes the name of the first author, year of publication, study period, study design, study region, age of patients (years), gender, total sample size, the number of Gram-negative bacteria species and antibiotic resistance patterns for *E. coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, Enterobacter species, Citrobacter species and Acinetobacter species. References and data for each study were carefully cross-checked to avoid duplication of data and maintain the integrity of the meta-analysis. All retrieved studies were exported to Mendeley desktop

reference manager to organize search outcomes and for removal of duplicate articles.

Risk of Bias and Quality Assessment

The quality assessment for the included studies was based on the JBI study quality appraisal criteria established for cross-sectional and cohort studies. The JBI's appraisal criteria consist of nine questions. The first three questions measure the appropriateness of the sampling frame. These questions address the target

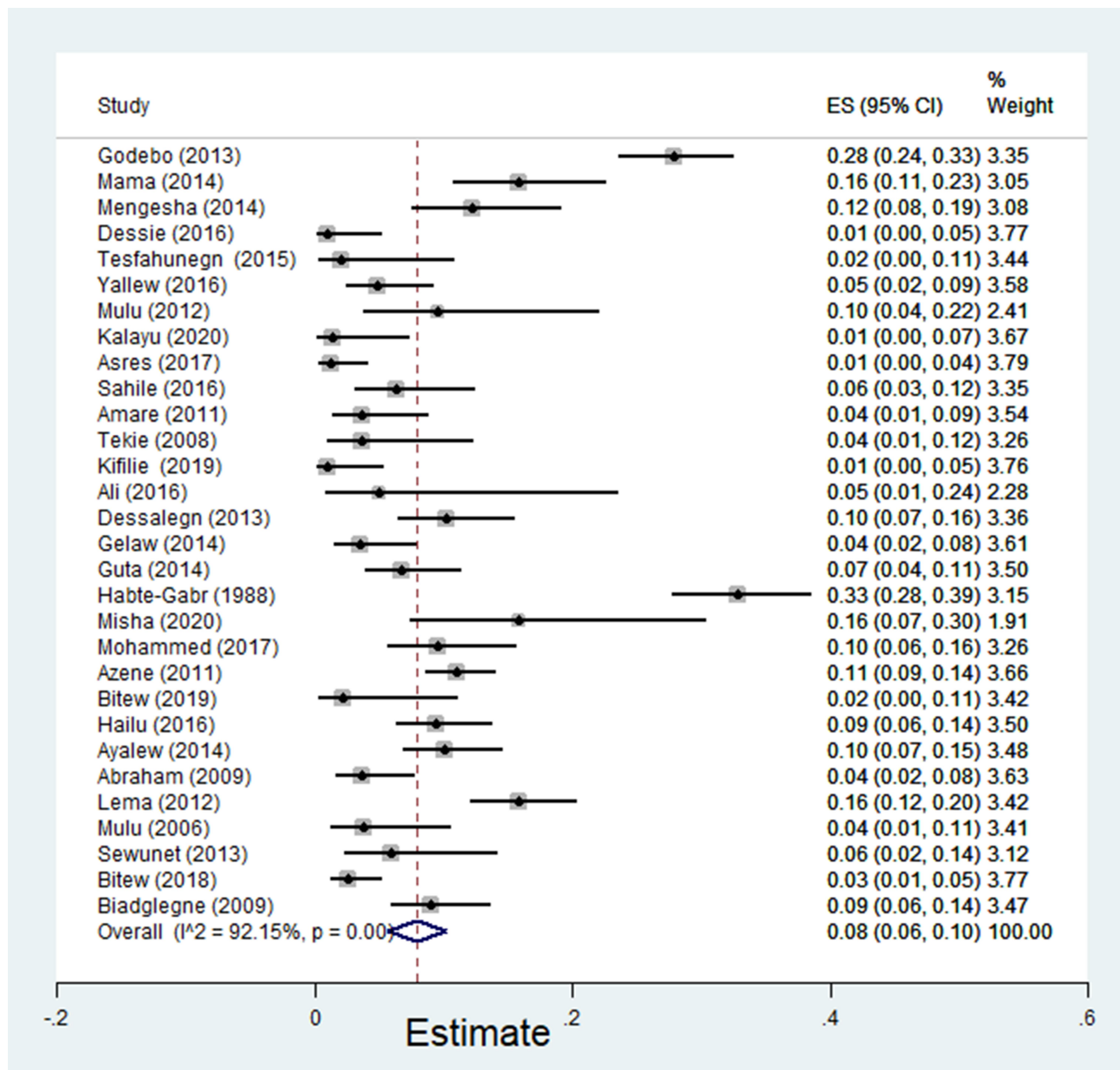


Figure 7 Forest plot showing pooled estimate of *Proteus mirabilis* among patients with wound infection.

population, describing appropriateness of sampling method and adequacy of sample size. The next three questions assess the study subjects and setting. The last three questions measure the appropriateness of the statistical analysis and adequacy of the response rate. Since all the studies that fulfill the eligibility criteria of this systematic review and meta-analysis had scored 50% and above, none of them had poor quality status and all of them were considered.

Eligibility Criteria

The studies were selected based on predefined inclusion criteria. The published and unpublished studies reporting the epidemiology of Gram-negative bacteria and their ABR profile from 1988 to March 2020 in patients with wound infection, according to the criteria of the Clinical Laboratory Standards Institute (CLSI),⁴⁸ were included. All the included studies were published in English and conducted in Ethiopia. Studies conducted on non-clinical

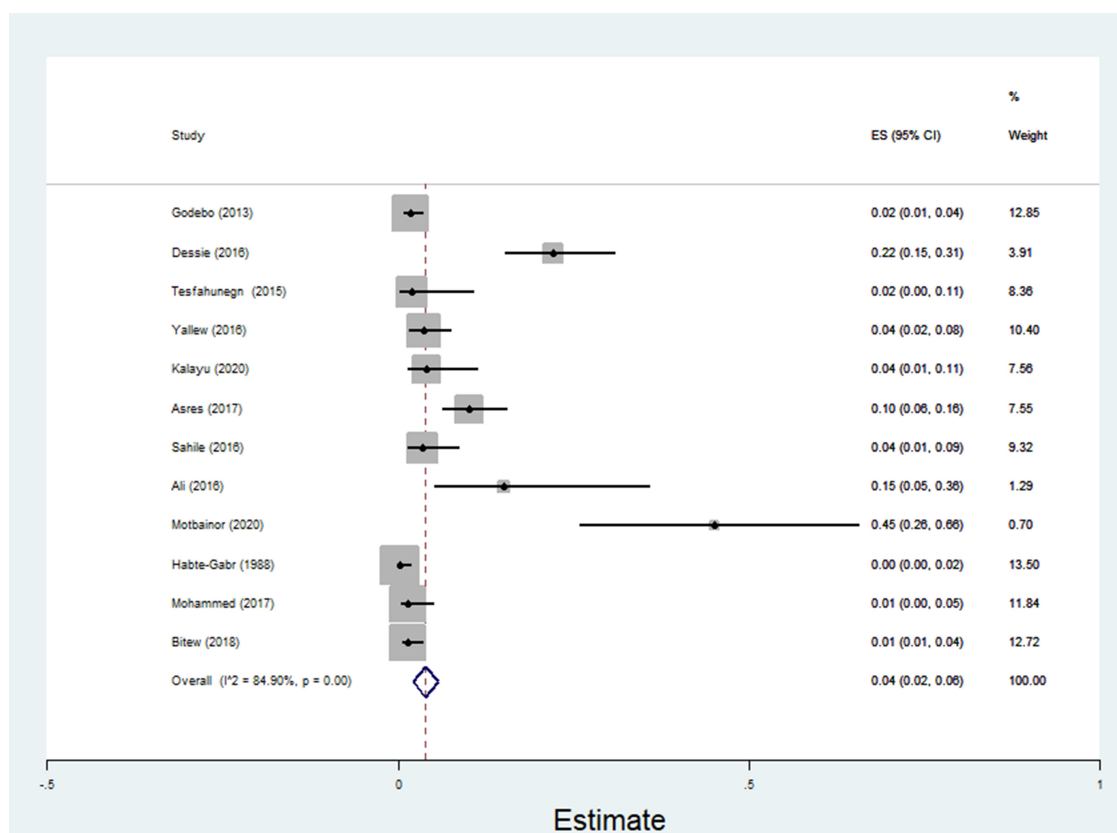


Figure 8 Forest plot showing pooled estimate of *Citrobacter* species among patients with wound infection.

specimens such as foods, food handlers' belongings, health workers' belongings, health workers' carriage or animals and of non-infectious carriage were excluded. Studies without full-text, qualitative studies, reviews, commentaries, case series, case reports, conference proceedings and abstracts were also excluded.

Data Processing and Analysis

Data were extracted in Microsoft Excel format and analyzed using STATA 14.0 statistical software. The prevalence data for ABR were pooled using “metaprop” command. Random effect model was applied to estimate the pooled prevalence and antibiotic resistance pattern of Gram-negative bacteria species in patients with wound infection. A potential source of heterogeneity was investigated by subgroup and meta-regression analysis. The existence of heterogeneity among studies was examined by I^2 heterogeneity test. The I^2 values of 0, 25, 50 and 75% were considered as no, low, moderate and high heterogeneities, respectively.^{49–51} Thus, the DerSimonian–Laird random effects model was employed.⁵² The geographic distribution (regional states),

and year of publication were considered for subgroup analysis to minimize the random variations between the point estimates of the primary study. The Begg's funnel plot and Egger's regression test were used to evaluate the possibility of publication bias. Forest plot format was used to present the pooled prevalence with 95% confidence interval (CI). Two-sided p values < 0.05 were considered as statistically significant.

Outcome Measurement

The three major outcomes reported in this systematic review and meta-analysis were the pooled prevalence estimates, the rate of antibiotic resistance isolates and the rate of multidrug resistance of Gram-negative bacteria isolates in patients with infected wounds in Ethiopia. The pooled prevalence estimates of common Gram-negative bacteria species were the number of each Gram-negative bacteria isolates divided by the number of all the detected isolates. The pooled estimates of resistance to each tested antibiotic was calculated by dividing the number of resistance isolates of each species by the total number of all the detected isolates of the species. Multidrug resistance was defined as

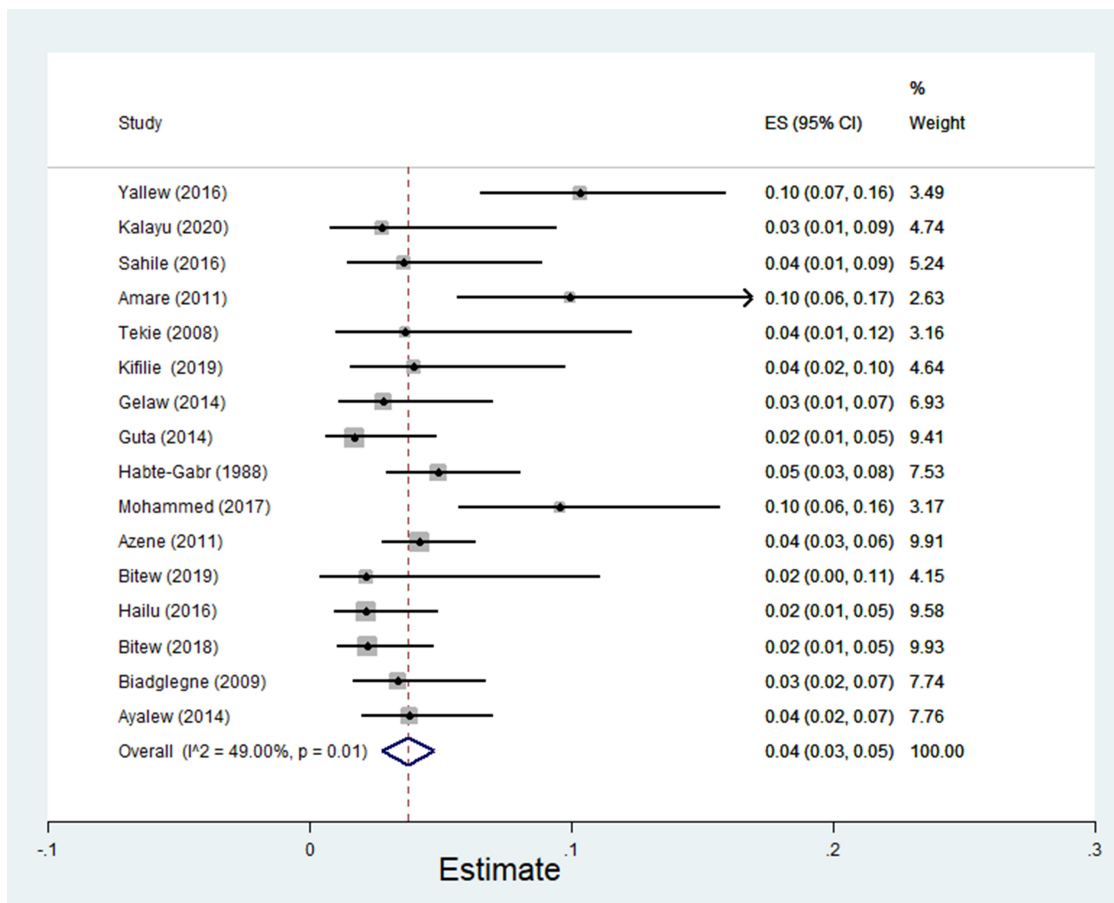


Figure 9 Forest plot showing pooled estimate of Enterobacter species among patients with wound infection.

resistance to at least two antibiotics by the isolated Gram-negative bacteria for the various antibiotics.

Results

Characteristics of the Included Studies

Of 987 identified studies, 497 were duplicates and were excluded upon reviewing the titles and abstracts. Further, 392 studies were excluded because they were irrelevant. Then, 98 full articles were assessed for eligibility. Of these, 62 articles were excluded, as irrelevant ($N = 56$) and review articles ($N = 6$). Finally, 36 studies meeting the inclusion were included in this review (Figure 1).

All studies were conducted from April 1983 to September 2018 and published online from 1988 to 2020. Of the 36 included studies, 32 were cross sectional and 4 were cohort studies. All but 6 studies were unpublished, which were obtained from Addis Ababa and Jimma University repositories. Over two-thirds of the studies were conducted in Amhara region ($n = 15$) followed by Addis Ababa city ($n = 11$), Oromia region ($n = 5$), SNNPR

($n = 3$), and Tigray region ($n = 2$). The age of the study participants in the included studies ranged from 1 month to 100 years and the sample size ranged from 50 to 1627. Table 1 summarizes the study characteristics and the number of Gram-negative (*E. coli*, *P. aeruginosa*, *K. pneumonia*, *P. mirabilis*, Enterobacter species, Citrobacter species, and Acinetobacter species) isolates recovered from wound samples.

Pooled Estimates of Gram-Negative Bacteria Isolates from Wound Samples

A total of 5,376 bacterial isolates, the majority ($n = 3150$, 58.6%) being Gram-negative isolates, were recovered from 15,647 wound samples. In the random-effects model, the pooled estimate of Gram-negative bacteria was 59% [95% CI: 52–65%, $I^2 = 96.41\%$, $\chi^2 = 973.93$, $p < 0.001$, Figure 2] with substantial heterogeneity. The estimates of common Gram-negative bacteria isolated from wound samples are described in Table 2.

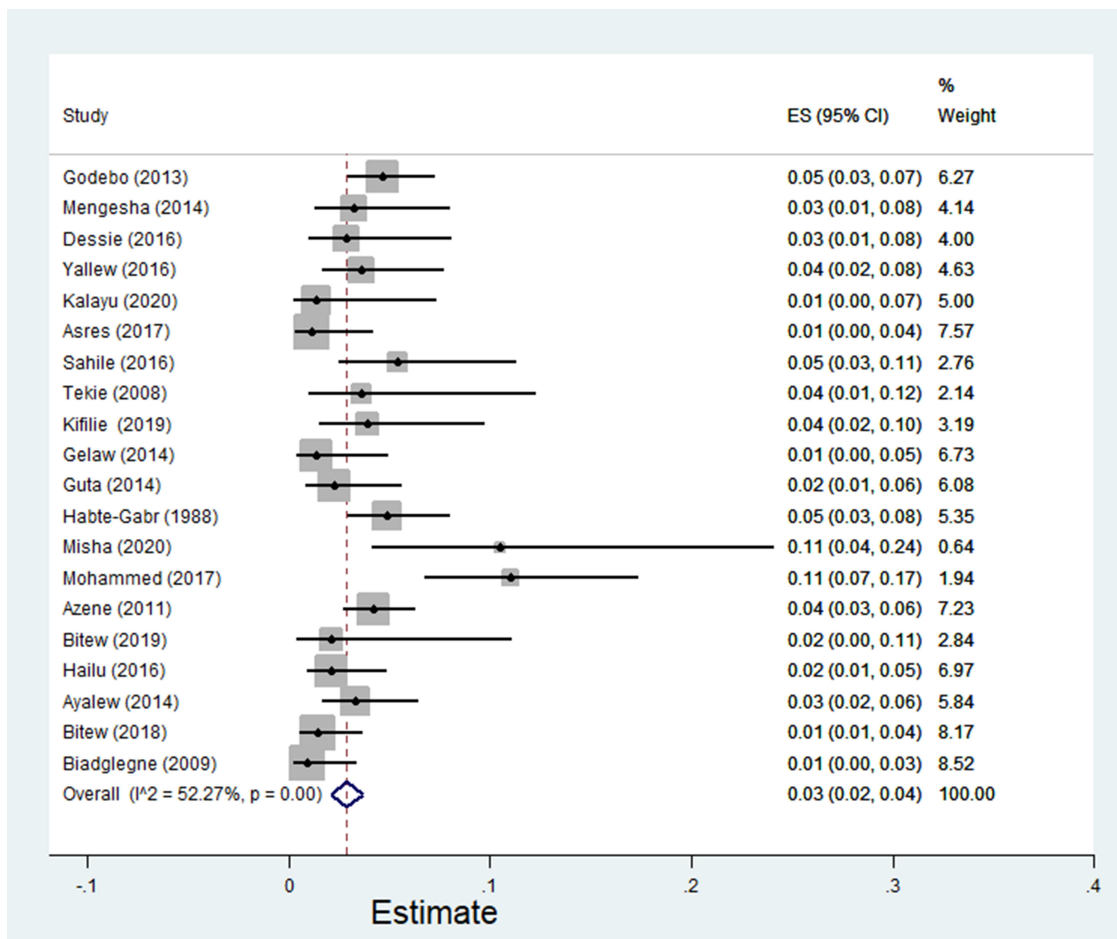


Figure 10 Forest plot showing pooled estimate of *Acinetobacter* species among patients with wound infection.

The symmetry of the funnel plot visual inspection of standard error with prevalence of Gram-negative bacteria indicated the absence of publication bias. This finding was statistically confirmed by Egger's regression test ($p = 0.12$) and Begg's test, ($p = 0.87$) [Figure 3].

The pooled estimate of *E. coli* isolates recovered from 5205 wound samples was 17% [95% CI: 14–20%, Figure 4]. Similarly, the pooled estimate of *K. pneumonia* was 11% [95% CI: 9–13%, Figure 5], *P. aeruginosa*, 11% [95% CI: 8–13%, Figure 6], *P. mirabilis*, 8% [95% CI: 6–10%, Figure 7], *Citrobacter* species, 3% [95% CI: 2–4%, Figure 8], *Enterobacter* species, 4% [95% CI: 3–5%, Figure 9] and *Acinetobacter* species, 4% [95% CI: 2–6%, Figure 10].

Antibiotic Resistance Patterns of Gram-Negative Bacteria Isolates

This finding indicated the Gram-negative bacteria *E. coli* exhibited the highest resistance to ampicillin, 82% [95%

CI: 76–88%]. Isolates of *E. coli* were also resistant to amoxicillin, 79% [95% CI: 55–85%], tetracycline, 70% [95% CI: 61–78%], doxycycline, 39% [95% CI: 0–78%], amoxicillin-clavulanic acid, 66% [95% CI: 52–81%], cotrimoxazole, 59% [95% CI: 48–69%], ceftazidime, 56% [95% CI: 25–86%], cefotaxime, 56% [95% CI: 21–90%], ceftriaxone, 42% [95% CI: 30–53%], chloramphenicol, 46% [95% CI: 12–72%], amikacin 42% [95% CI: 12–72%] and gentamicin, 42% [95% CI: 24–61%]. Relatively lower rates of resistance were observed to norfloxacin, 22% [95% CI: 10–35%] and ciprofloxacin, 35% [95% CI: 17–53%] among *E. coli* isolates.

Similarly, the highest pooled estimates of resistance among *K. pneumonia* isolates were observed to ampicillin, 89% [95% CI: 85–93%], amoxicillin, 86% [95% CI: 80–93%], amoxicillin-clavulanic acid, 76% [95% CI: 64–88%], cefepime, 76% [95% CI: 56–92%], cefotaxime, 46% [95% CI: 19–72%], and ciprofloxacin, 45% [95% CI: 28–61%]. However, the lowest resistance profile of *K.*

Table 3 The Pooled Estimates of Antimicrobial Resistance Among Gram-Negative Bacteria Isolates of Wound Samples

Antimicrobials	Pooled Estimates of Resistant Isolates														
	<i>E. coli</i>					<i>K. pneumoniae</i>					<i>P. aeruginosa</i>				
	No. of Studies	Sample Size	Case	ES [95% CI]	I ² (%)	No. of Studies	Sample Size	Case	Estimate [95% CI]	I ² (%)	No. of Studies	Sample Size	Case	ES [95% CI]	I ² (%)
Amoxicillin	14	335	204	70 [55–85]	92.59	11	184	153	86[80–93]	48.43	ND	ND	ND	ND	ND
Augmentin*	12	281	182	66[52–81]	89.53	11	178	126	76[64–88]	78.27	ND	ND	ND	ND	ND
Ampicillin	20	415	334	82 [76–88]	78.01	18	266	227	89[85–93]	00.00	ND	ND	ND	ND	ND
Ceftriaxone	20	546	216	42 [30–53]	90.94	19	322	181	60[48–73]	86.44	ND	ND	ND	ND	ND
Cefotaxime	4	97	57	56[21–90]	94.61	6	111	44	46[19–72]	91.50	ND	ND	ND	ND	ND
Ceftazidime	5	128	59	56[25–86]	94.02	6	66	35	55[31–79]	82.10	7	77	43	45[11–79]	93.28
Cefepime	ND	ND	ND	ND	ND	2	22	16	76[56–92]	-NS	ND	ND	ND	ND	ND
Piperacillin/Tazobactam	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	4	61	38	54[5–100]	98.01
Ciprofloxacin	19	503	174	35 [17–53]	97.06	17	270	113	45[28–61]	91.81	17	318	148	45[24–67]	96.77
Norfloxacin	8	143	34	22[10–35]	81.97	8	152	42	26[15–38]	63.92	ND	ND	ND	ND	ND
Gentamicin	20	504	244	42[24–61]	97.56	22	349	164	50[36–64]	91.19	23	443	192	38[17–59]	97.98
Amikacin	5	124	46	42[12–72]	95.06	3	55	13	28[7–48]	66.08	3	39	29	61[4–100]	94.12
Tetracycline	17	372	266	70[61–78]	72.40	14	213	133	64[50–77]	83.79	ND	ND	ND	ND	ND
Doxycycline	4	157	36	39[0–78]	97.56	4	74	54	72[52–92]	71.76	ND	ND	ND	ND	ND
Colrimoxazole	21	524	318	59[48–69]	88.82	17	274	171	61[48–75]	88.52	ND	ND	ND	ND	ND
Chloramphenicol	19	495	246	46[32–60]	92.73	18	270	167	63[51–75]	81.01	16	369	254	67[54–81]	90.04
Meropenem	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2	21	7	31[12–50]	-
Citrobacter Species															
	No. of studies	Sample size	Case	ES [95% CI]	I ² (%)	No. of studies	Sample size	Case	Estimate [95% CI]	I ² (%)	No. of studies	Sample size	Case	ES [95% CI]	I ² (%)
Amoxicillin	7	161	98	73[54–92]	88.90	5	48	25	63[27–99]	88.92	7	48	25	60[41–80]	48.14
Augmentin*	8	122	69	59[37–82]	86.84	3	13	8	65[40–89]	00.00	4	16	9	58[34–81]	00.00
Ampicillin	16	322	249	81[74–89]	69.02	8	57	48	87[79–96]	58.74	9	60	51	90[83–97]	00.00
Ceftriaxone	15	316	111	49[33–66]	93.29	7	66	25	42[24–59]	–	8	76	27	34[21–47]	32.01
Cefotaxime	5	146	24	30[11–49]	86.50	2	15	4	26[4–48]	–	4	32	10	30[15–46]	00.00
Ciprofloxacin	13	326	95	40[18–61]	96.85	7	55	30	52[30–75]	67.87	5	60	23	38[9–67]	84.63
Norfloxacin	7	224	27	16[7–26]	75.52	2	7	5	72[39–100]	–	3	28	6	23[0–45]	40.77
Gentamicin	18	389	158	38[18–57]	96.40	11	85	51	55[31–78]	86.19	7	74	41	53[31–75]	73.84
Amikacin	2	26	10	38[20–57]	–	2	16	11	70[48–92]	–	ND	ND	ND	ND	ND
Tetracycline	11	213	167	76[66–86]	66.93	8	75	50	66[50–83]	61.94	8	64	42	67[53–80]	23.83
Doxycycline	4	189	98	49[7–91]	97.78	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Colrimoxazole	14	354	209	54[40–67]	84.74	10	82	51	58[39–77]	74.54	8	76	53	61[37–84]	86.29
Chloramphenicol	13	329	217	59[46–72]	82.09	7	70	46	66[47–85]	72.51	6	70	51	72[54–90]	69.26

Acinetobacter species						
Antimicrobials	No of studies	Sample size	case	Estimate [95% CI]	I ² (%)	
Amoxicillin-clavulanic acid	5	122	47	85[76-94]	00.00	
Ampicillin	7	52	43	85[74-97]	22.58	
Ceftriaxone	7	65	51	81[69-93]	32.54	
Cefotaxime	5	59	48	85[74-96]	30.15	
Ciprofloxacin	9	72	44	57[39-75]	63.68	
Norfloxacin	2	11	3	16[1-45]	-	
Gentamicin	8	69	44	68[56-79]	12.01	
Tetracycline	6	59	38	70[50-90]	65.87	
Cotrimoxazole	6	44	34	89[68-93]	16.32	
Chloramphenicol	5	52	37	72[60-84]	00.00	
Cefazidime	6	59	50	88[80-96]	00.00	
Cefepime	2	6	3	50[12-88]	-	
Piperacillin-Tazobactam	2	12	10	86[67-100]	-	

pneumonia was observed to norfloxacin, 26% [95% CI: 15–38%] and amikacin, 28% [95% CI: 7–48%]. The highest rate of resistance among *P. aeruginosa* isolates was associated with chloramphenicol, 67% [95% CI: 54–81%], amikacin, 61% [95% CI: 4–100%], and piperacillin, 54% [95% CI: 5–100%], but meropenem, 31% [95% CI: 12–50%] tended to have the highest barrier to resistance [Table 3 and Figure 11].

Among *P. mirabilis* isolates, higher rates of resistance were reported to ampicillin, 81% [95% CI: 74–89%], tetracycline, 76% [95% CI: 66–86%], amoxicillin, 73% [95% CI: 54–92%], amoxicillin-clavulanic acid, 59% [95% CI: 37–82%], and chloramphenicol, 59% [95% CI: 46–72%]. However, the isolates appeared relatively sensitive to norfloxacin, 16% [95% CI: 7–26%], cefotaxime, 30% [95% CI: 11–49%], amikacin, 38% [95% CI: 20–57%], and gentamicin, 38% [95% CI: 18–57%]. Although Enterobacter species were fairly sensitive to cefotaxime, 26% [95% CI: 4–48%] and ceftriaxone, 42% [95% CI: 24–59%], a significant proportion of isolates were resistant to ampicillin, 87% [95% CI: 79–96%], norfloxacin, 72% [95% CI: 39–100%], and amikacin, 70% [95% CI: 48–92%]. Besides, the lowest pooled rate of resistance to norfloxacin, 23% [95% CI: 0–45%], cefotaxime, 30% [95% CI: 15–46%], and ceftriaxone, 34% [95% CI: 21–47%] was observed among Citrobacter species. Resistance rates of Acinetobacter species were also reported by 12 studies consisting of 1786 samples. High levels of resistance were observed to cotrimoxazole 89% [95% CI: 68–93%], ceftazidime, 88% [95% CI: 80–96%], piperacillin, 86% [95% CI: 67–100%], cefotaxime, 85% [95% CI: 74–96%], and ampicillin, 85% [95% CI: 74–97%], while norfloxacin, 16% [95% CI: 1–45%] tended to have a more effective barrier to resistance in Acinetobacter species [Table 3 and Figure 12].

Patterns of Multidrug Resistance Among Gram-Negative Bacteria Isolates

The data of multidrug resistance profiles of Gram-negative bacteria for the various antibiotics tested in the included studies was analyzed. Accordingly, the pooled estimate of MDR in *E. coli* was 76% [95% CI: 66–86%], (Figure 13). The pooled estimates of MDR in *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, Citrobacter species, Enterobacter species, and Acinetobacter species were 84% [95% CI: 78–91%], (Figure 14), 66% [95% CI: 43–

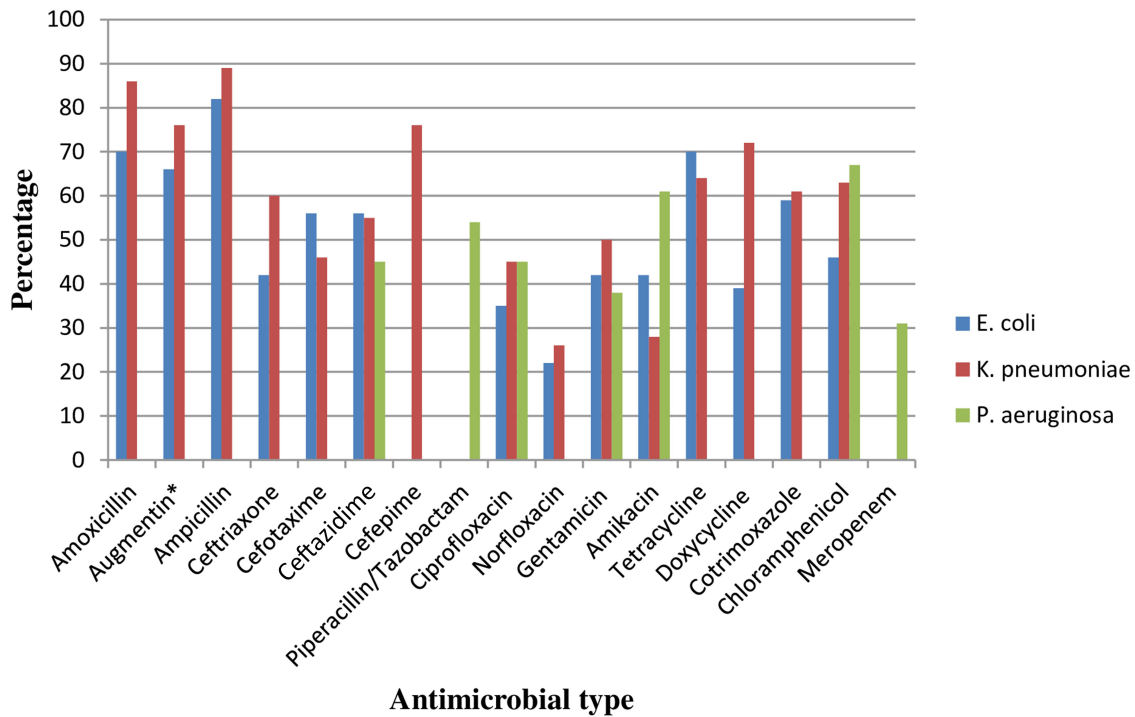


Figure 11 Percentage of *E. coli*, *K pneumoniae*, and *P. aeruginosa* resistant to different antibiotics commonly in use in Ethiopian settings.

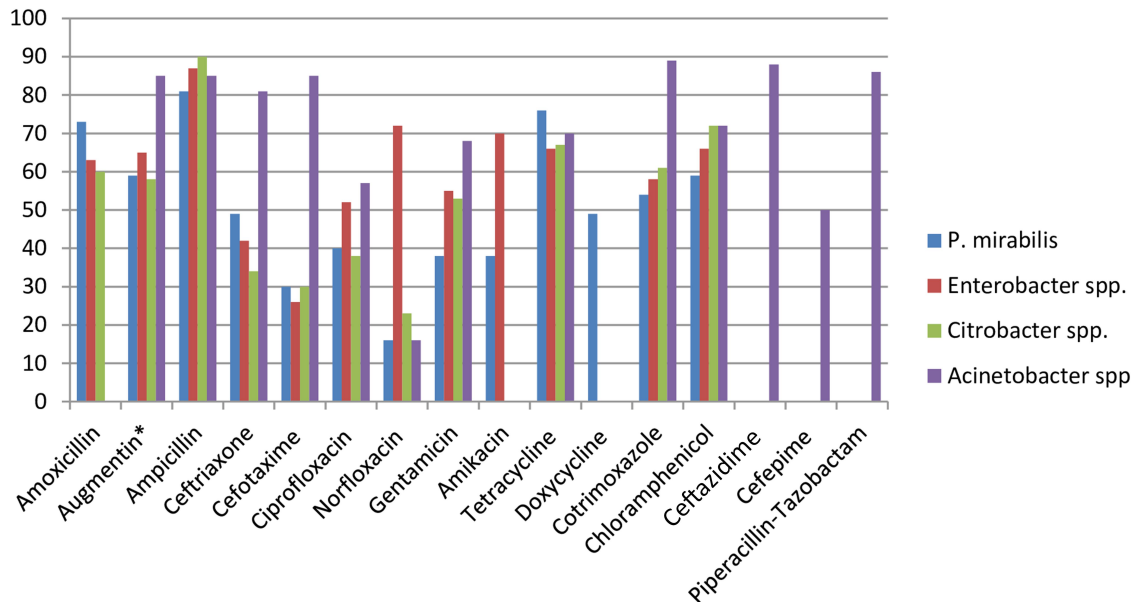


Figure 12 Percentage of *P. mirabilis*, *Enterobacter* species, *Citrobacter* species, and *Acinetobacter* species resistant to different antibiotics commonly in use in Ethiopian settings.

88%], (Figure 15), 83%[95% CI: 75–91%], (Figure 16), 87% [95% CI: 78–96%], (Figure 17), 68%[95% CI:50–87%], (Figure 18) and 71%[95% CI: 46–96%], (Figure 19), respectively.

Therefore, it is prudent to observe that more than two-thirds of the Gram-negative bacteria isolates recovered from wound samples were resistant to at least two antibiotics i.e. had multidrug resistance.

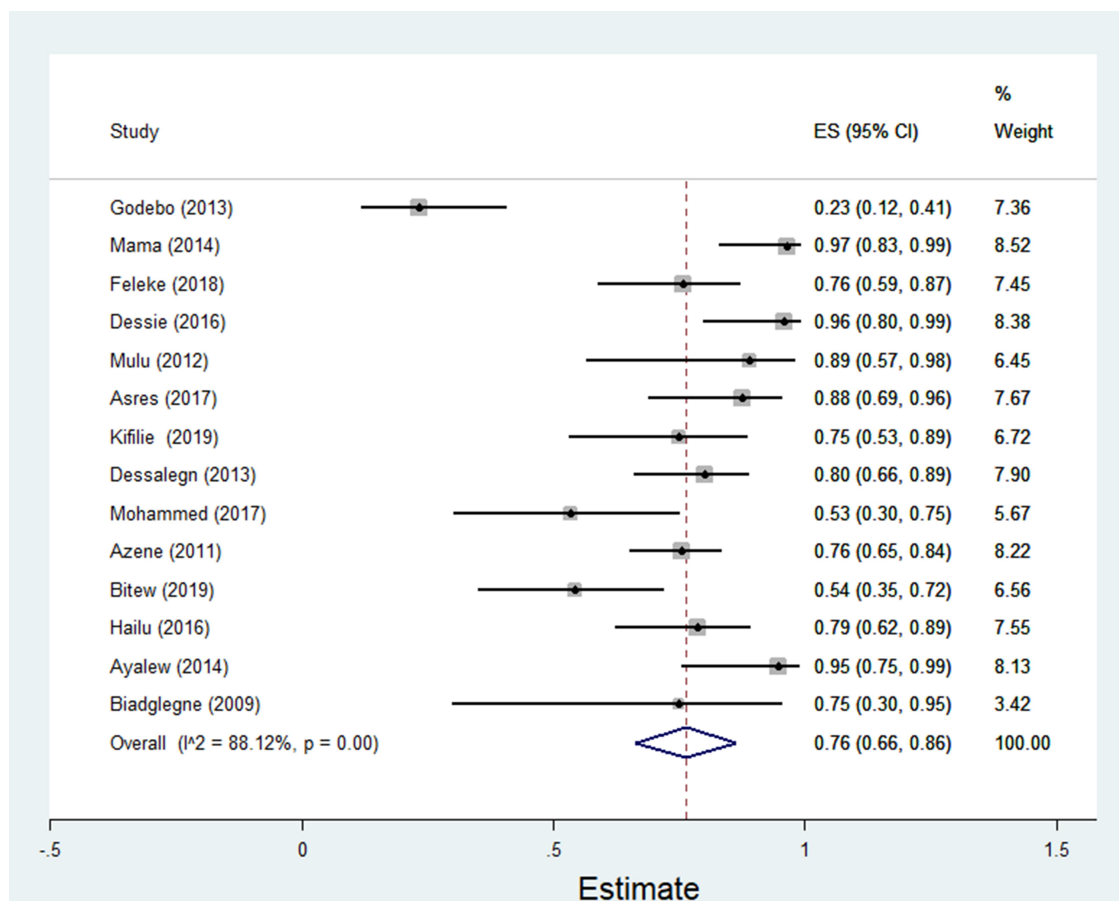


Figure 13 Percentage of multidrug resistance in *E. coli* to different antimicrobials commonly in use in Ethiopia.

Table 4 depicts patterns of MDR Gram-negative bacteria isolates recovered from wound samples.

Discussions

Antibiotic resistance is a natural process which occurs when bacteria evolve to resist the medicines that are being used to combat them. It is one of the greatest tragedies of the 21st century, which has undermined progress in health care, food production, and life expectancy.⁸⁹

This review summarized the epidemiology of Gram-negative bacteria and their antibiotic-resistance pattern in patients with wound infection in Ethiopia. Accordingly, the rate of wound infection by Gram-negative bacteria was 59%. This finding is relatively lower than a study in Tanzania where Gram-negative bacteria accounted for 85.2% of the cases.¹⁵ It was noted that the pooled estimates of *E. coli* (17%), *K. pneumonia* (11%), *P. aeruginosa* (11%), *P. mirabilis* (8%), *Acinetobacter* species (4%), *Citrobacter* species (4%), and *Enterobacter* species

(3%) is in agreement with a study conducted in Tanzania where the prevalence of *P. mirabilis* (16%) and *P. aeruginosa* (13%) was higher in wound infections than in those with no wound infection (9% and 6%, respectively).¹⁵ Moreover, a previous review in Ethiopia also reported that the pooled estimates of *E. coli*, *K. pneumonia*, *P. aeruginosa*, and *P. mirabilis* were 13%, 9%, 9%, and 8%, respectively.⁴⁴

Therefore, *E. coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, *Citrobacter* species, *Enterobacter* species, and *Acinetobacter* species were the most prevalent Gram-negative pathogens with an alarming rate of resistance to commonly used antibiotics. The rates of antibiotic resistance among important Gram-negative pathogens are increasing.^{90,91} This study showed the prevalence of drug resistance among *E. coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, *Enterobacter* species, and *Acinetobacter* species has exceeded 50% for penicillin. More than 40% of the strains were also resistant to third-generation cephalosporin and aminoglycosides. These pathogens are

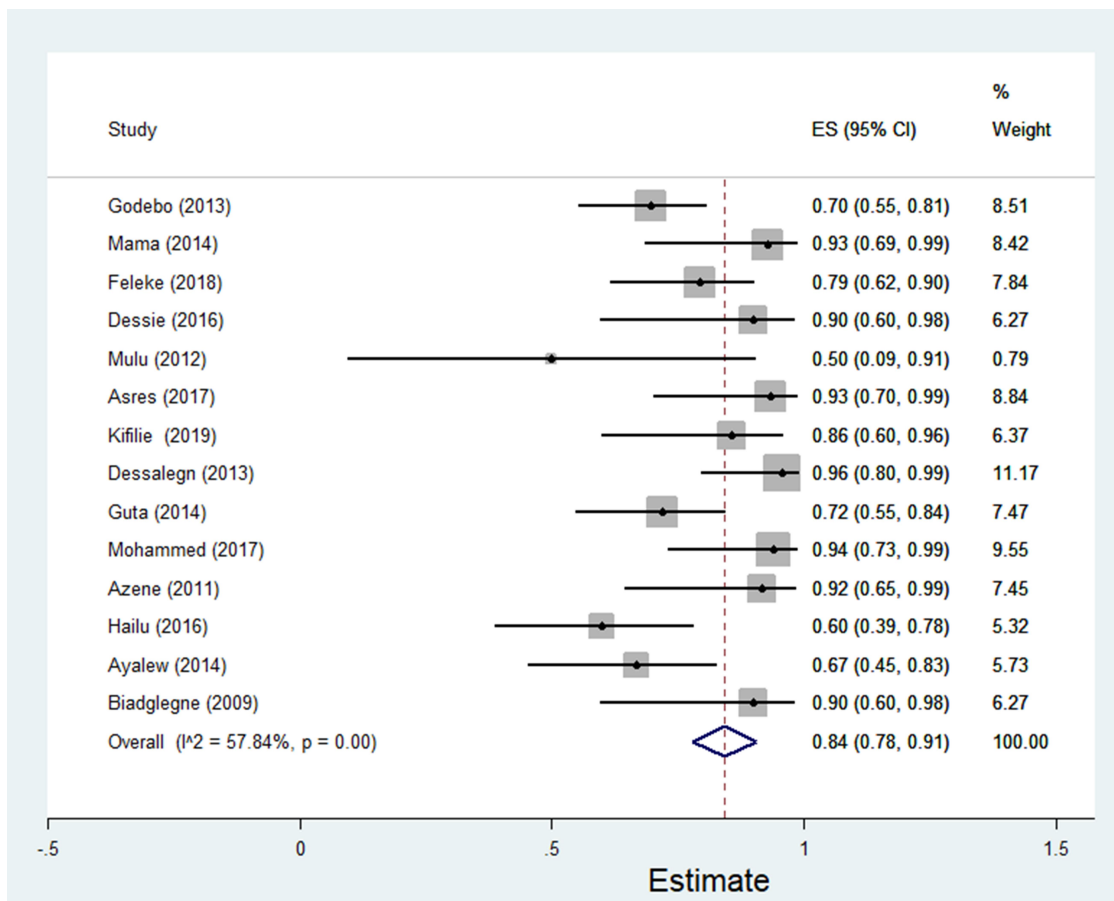


Figure 14 Percentage of multidrug resistance in *K. pneumoniae* to different antimicrobials commonly in use in Ethiopia.

commonly implicated in both community and nosocomial infections.⁹² Lucas et al.⁹³ reported 50–100% resistance to ampicillin and cotrimoxazole, 20–47% to gentamicin, and 46–69% to ceftriaxone among strains of *K. pneumoniae* and *E. coli*. In other studies, nosocomial Gram-negative pathogens such as *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are becoming increasingly resistant to commonly used antimicrobial agents such as third-generation cephalosporin and penicillin.^{92,94} These antibiotics, the vital lifelines that are the backbone of health-care systems in low- and middle-income countries, are becoming obsolete due to the emerging threat of antibiotic resistance. The adverse outcomes of this disaster are huge and concerning. It is estimated to cost more than 700,000 lives annually worldwide and the number is expected to grow to 10 million by the year 2050.⁹⁵ If no action is taken, the lost global production between now and 2050 would be an enormous 100 trillion USD.⁹⁵ In low- and low-middle-income countries, it will be more tragic as the already crippled health

systems will be further compromised due to limited antibiotics choices and unaffordable treatment costs.⁹⁶

A large pool of evidence shows that the reckless use of antibiotics plays a pivotal role in the advent of multidrug resistant bacteria.^{97–99} According to this review, *Citrobacter* species (87%), *K. pneumoniae* (84%), *P. mirabilis* (83%), *E. coli* (76%), *Acinetobacter* species (71%), *Enterobacter* species (68%), and *P. aeruginosa* (66%) were the most recognized multidrug resistant bacteria in Ethiopian settings. Lim et al. found *K. pneumoniae*, *Acinetobacter* species, *E. coli*, *P. aeruginosa* as the most common multidrug resistant bacteria posing a significant threat to the health-care system.¹⁰⁰ Similarly, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are identified as the common multidrug resistant Gram-negative bacilli inflicting an intolerable harm to global health. They are associated with substantial morbidity and mortality, and increased health-care costs.¹⁰¹ Furthermore, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *Acinetobacter* species are resistant to almost all currently available antibiotics.¹⁰²

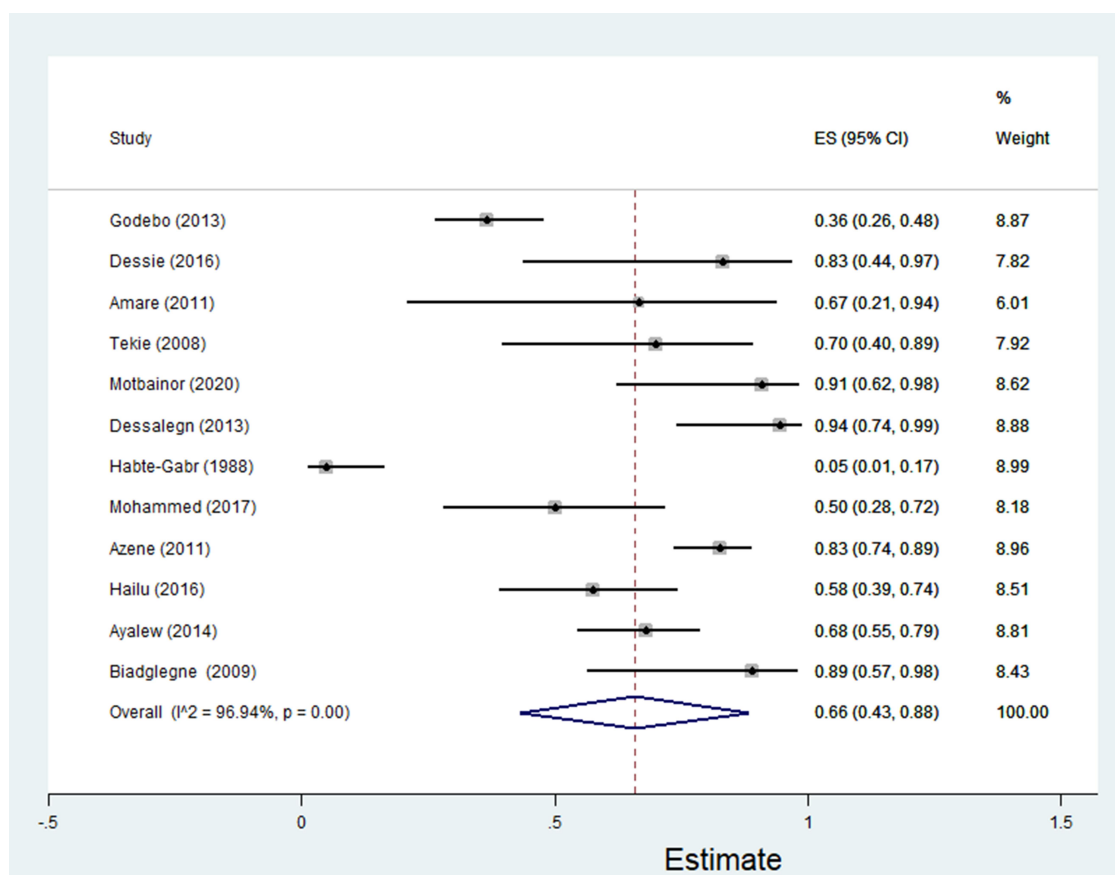


Figure 15 Percentage of multidrug resistance in *P. aeruginosa* to different antimicrobials commonly in use in Ethiopia.

The essence of epidemiological surveillance of bacterial infection and bacterial resistance to existing antibiotics is to create awareness and strengthen the implementation of infection prevention and control (IPC) strategies.¹⁰³ Given the frequent polymicrobial nature of wound infection, a compiled data set of bacteriological investigations is required to demonstrate the burden of resistant pathogens in sub-Saharan Africa, a region which lacks data on the true extent of the problem.⁹² This is also indispensable for resource-limited settings such as Ethiopia, where the health-care facilities have a rudimentary antimicrobial stewardship and poor IPC activities.¹⁰³ Available antimicrobial resistance data will sensitize clinicians and policy-makers. These data have a grave importance for revising the existing national treatment protocols to guide optimal antimicrobial therapy. These data also contribute to combat antimicrobial drug resistance and re-direct the habit of antimicrobial prescription in health-care facilities. Over time, all bacteria will acquire mechanisms of resistance to current and future antibiotics. This is a harsh fact that will continue to become a deadly reality to the planet.

Therefore, this is a critical time which needs the initiation of programs to curtail antibiotic resistance and the development of newer antibiotic agents.

Strength and Limitations of the Study

Although this review addresses an important evidence gap through identifying and synthesizing data about the prevalence of Gram-negative bacteria species, patterns of antibiotic resistance and multidrug resistance among patients with wound infection in Ethiopia, the authors acknowledge that this review has some limitations. The major limitations were the issue of heterogeneity and representativeness. The study period, hospital settings, population characteristics, methods of bacterial identification, and antibiotic susceptibility tests were also varied across the studies questioning the appropriateness of combining the study findings to create a single pooled estimate. While the conclusion of high antibiotic resistance among Gram-negative bacteria in patients with wound infection was drawn from the study findings, the original studies included in the analyses were only from four

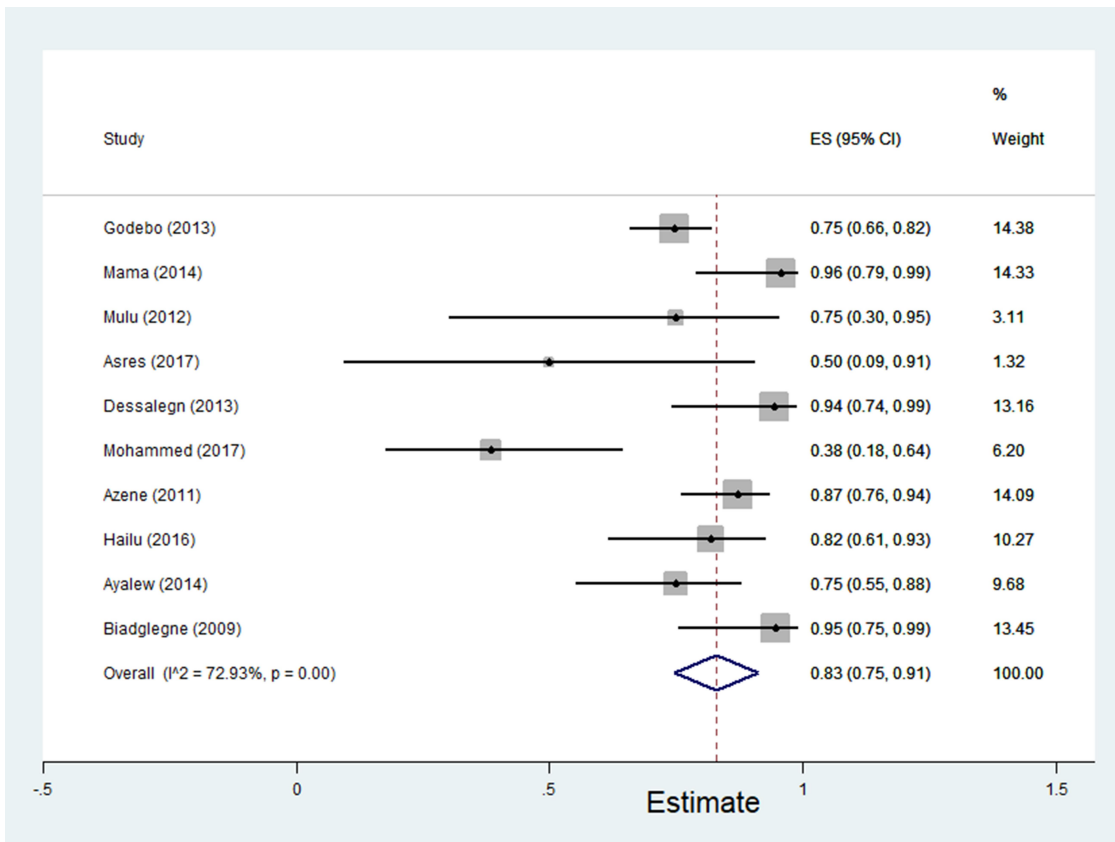


Figure 16 Percentage of multidrug resistance in *P. mirabilis* to different antimicrobials commonly in use in Ethiopia.

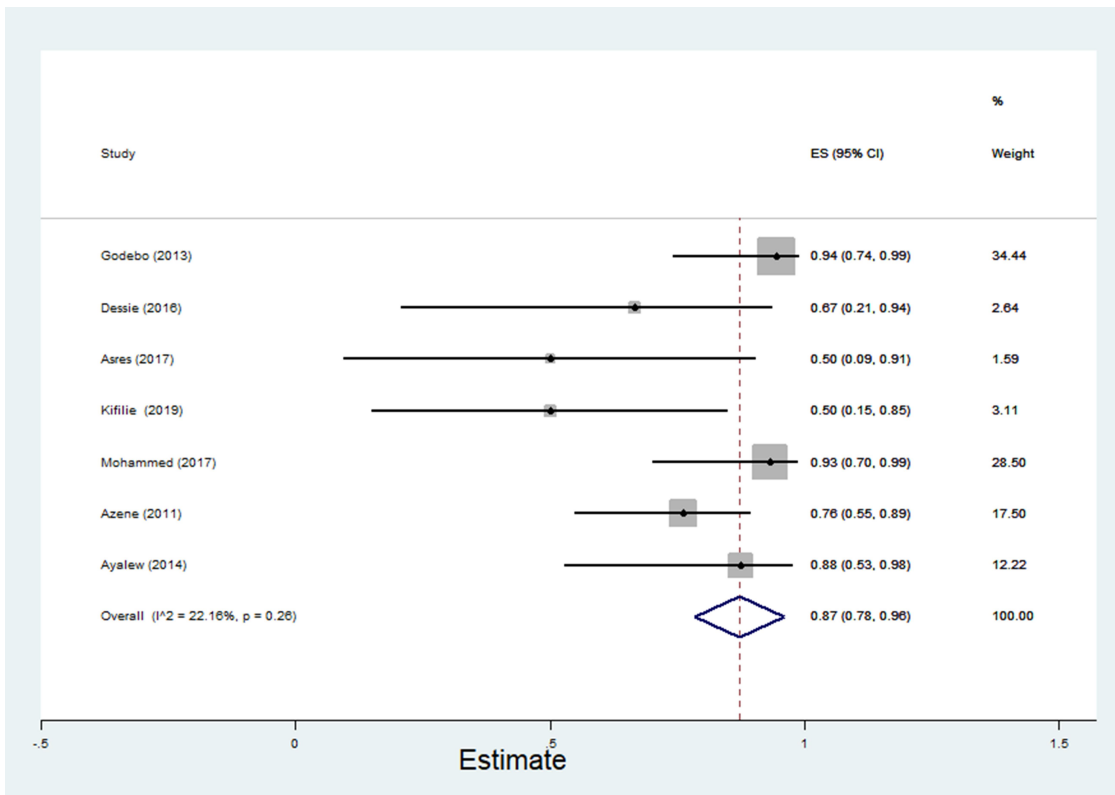


Figure 17 Percentage of multidrug resistance in *Enterobacter* species to different antimicrobials commonly in use in Ethiopia.

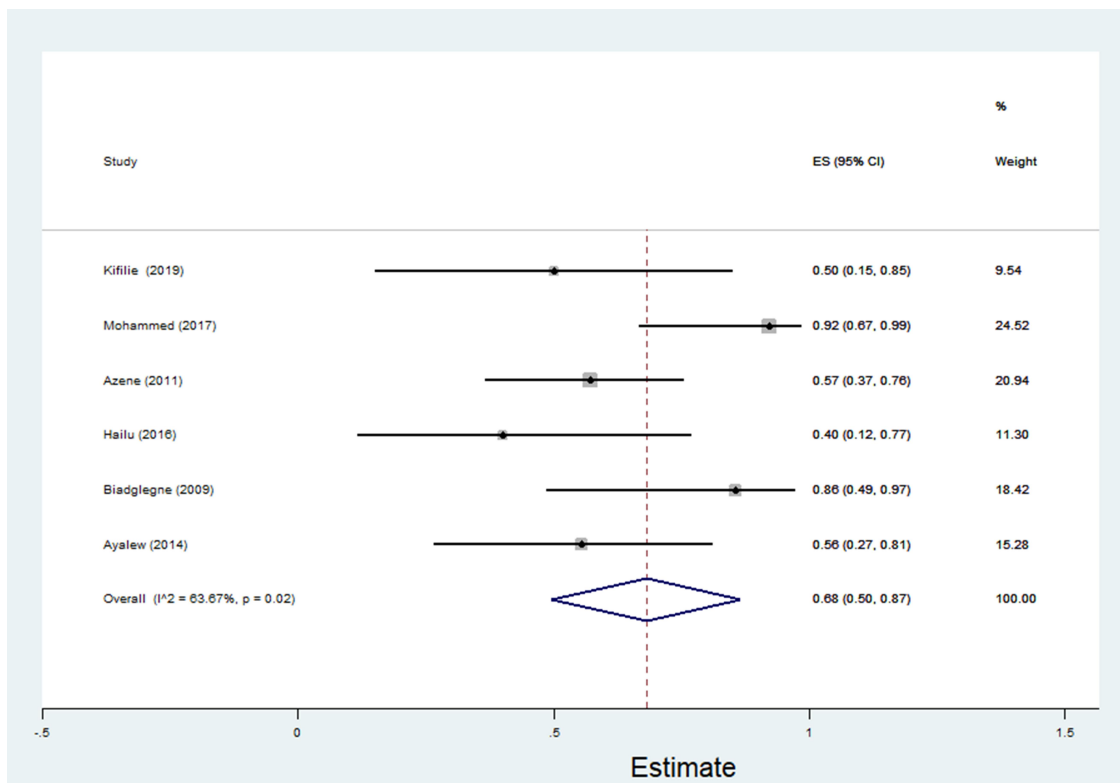


Figure 18 Percentage of multidrug resistance in *Citrobacter* species to different antimicrobials commonly in use in Ethiopia.

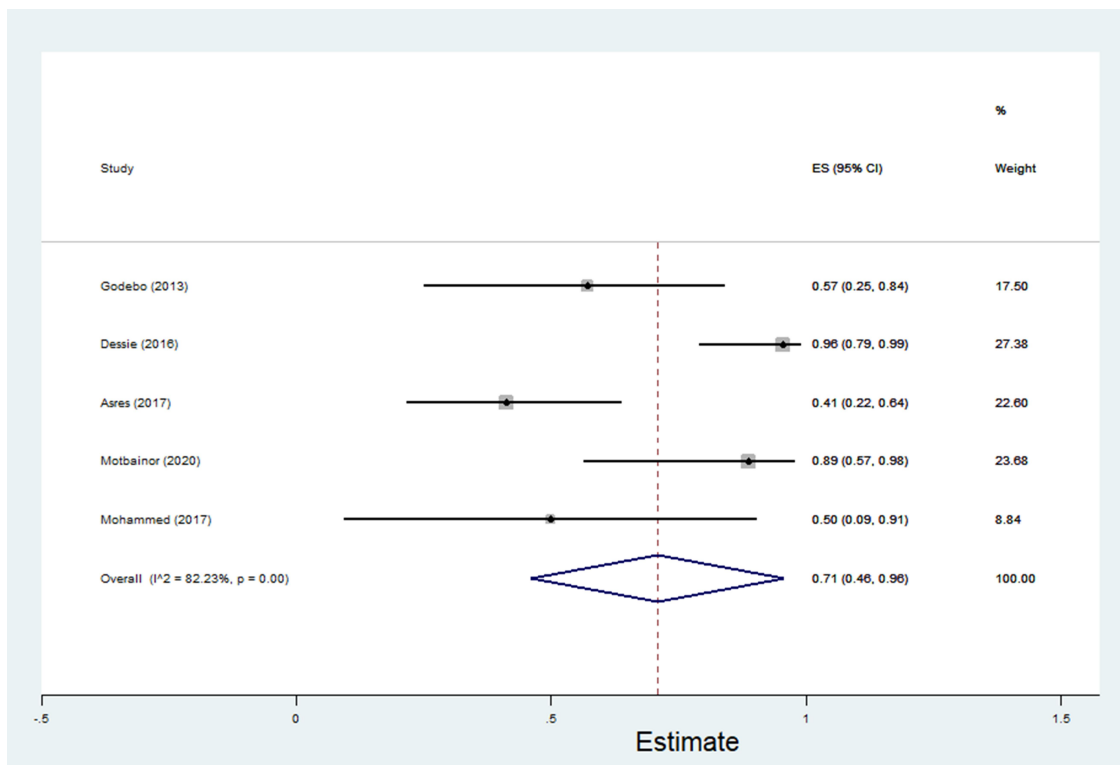


Figure 19 Percentage of multidrug resistance in *Acinetobacter* species to different antimicrobials commonly in use in Ethiopia.

Table 4 Pooled Estimates of Multidrug Resistance Among Gram-Negative Bacteria Isolates of Wound Samples

Bacteria	Pooled Estimates of Multidrug Resistant Isolates				
	No. of Studies	Sample Size	Case	Estimate [95% CI]	I ² (%)
<i>E. coli</i>	14	391	293	76[66–86]	88.12
<i>K. pneumoniae</i>	14	266	212	84[78–91]	57.84
<i>P. aeruginosa</i>	12	358	213	66[43–88]	96.94
<i>P. mirabilis</i>	10	287	230	83[75–91]	72.93
Citrobacter species	7	71	59	87[78–96]	22.16
Enterobacter species	6	59	39	68[50–87]	63.67
Acinetobacter species	5	58	42	71[46–96]	82.23

Abbreviation: CI, confidence interval.

regions and one city out of the nine regions and two cities of the country. Hence, the representativeness of the results to the remaining regions and city of the country might be questioned. Moreover, the reader should note that the protocol of this review was not published online ahead of the actual meta-analysis.

However, this review provides useful information about the current status of antibiotic resistance among Gram-negative bacteria in wound infection. Despite the considerable variations in the location of the study, sample size and duration across studies which contribute to the differences between groups, the current review has paramount importance in providing a full picture of the problem at national level to help policymakers to design cost-effective control and treatment strategies. Besides, the findings could help the concerned bodies to pay attention to further research in the areas where there is paucity of data or even no published study.

Conclusion

Resistance among Gram-negative organisms is widespread to commonly used antibiotics in Ethiopian patients with infected wounds. These data warrant the need for regular epidemiological surveillance of antibiotic resistance and implementation of an efficient infection control and stewardship program. Future research efforts should also focus on the transmission dynamics and enhanced generation and aggregation of the solitary data. The need for research and development to enrich the pipeline for novel antimicrobial compounds is a matter of survival. This will invigorate the hope of mankind on the planet and an excellent tool to counteract the threat posed by antibacterial resistance.

Abbreviations

ABR, antibiotic resistance; GNB, Gram-negative bacteria; CI, confidence interval; MDR, multi-drug resistance; ;

SNNPR, Southern Nation, Nationalities, and People's Region; STATA, South Texas Art Therapy Association.

Data Sharing Statement

All relevant data are within the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Author Contributions

LC, TM, and TAM conducted the database search, screening, and quality assessment. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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