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Inappropriate ceftriaxone utilization and predictor factors in Ethiopia: a systematic review and meta-analysis

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Ceftriaxone stands as a cornerstone in global antibiotic therapy owing to its potent antibacterial activity, broad spectrum coverage, and low toxicity. Nevertheless, its efficacy is impeded by widespread inappropriate prescribing and utilization practices, significantly contributing to bacterial resistance. The aim of this study is to determine the overall national pooled prevalence of inappropriate ceftriaxone utilization and its predictor factors in Ethiopia. A systematic search was conducted across multiple databases including, PubMed, Science Direct, Hinari, Global Index Medicus, Scopus, Embase, and a search engine, Google Scholar, to identify relevant literatures that meet the research question, from March 20 to 30, 2024. This meta-analysis, which was conducted in Ethiopia by incorporating 17 full-text articles, unveiled a national pooled inappropriate ceftriaxone utilization of 55.24% (95% CI, 42.17%, 68.30%) with a substantial heterogeneity index (I2 = 99.24%, p value < 0.001). The review has also identified predictive factors for the inappropriate use of ceftriaxone: empiric therapy (AOR 21.43, 95% CI; 9.26–49.59); multiple medication co-prescription (AOR: 4.12, 95% CI; 1.62–8.05). Emergency ward (AOR: 4.22, 95% CI; 1.8-12.24), surgery ward (AOR: 2.6, 95% CI; 1.44–7.82) compared to medical ward, prophylactic use (AOR: 500, 95% CI; 41.7–1000), longer hospital stay-8-14 Days; (AOR: 0.167, 95% CI; 0.09–0.29), > 14 days; (AOR: 0.18, 95% CI; 0.1–0.32). The study reveals a high national pooled prevalence of inappropriate ceftriaxone utilization, standing at 55.24%, highlighting a significant hazard in the use of this antibiotic. This could be attributed to instances of overuse, misuse or prescription practices that deviates from established guidelines. This eminent challenge can lead to the development of antibiotic resistance, increased healthcare costs, adverse drug reactions, and treatment failures, necessitating multifaceted approach such as improved antibiotic stewardship, better adherence to guidelines, and enhanced clinician education on appropriate antibiotic use.

Keywords Inappropriate utilization, Ceftriaxone, Meta-analysis, Ethiopia

Irrational use of medication presents a significant global challenge, particularly in developing nations. Assessing the pattern of drug utilization plays a pivotal role in pinpointing gaps in medicine utilization and enables the implementation of targeted strategies for promoting rational drug use[1]. Rational use of medicines is the process by which patients receive medications tailored to their clinical needs, in doses that meet their requirements, for a sufficient duration of time, and at the lowest cost[2]. This approach minimizes the incidence of adverse drug events while maximizing the benefits that can be gained from the optimal use of medications. Furthermore, the rational use of drugs can also lead to efficient allocation of scarce healthcare resources[3].

Rational drug use (RDU), is the process of appropriate prescribing, dispensing, and patient use of drugs for diagnosis, prevention, and treatment of diseases[4]. Conversely, irrational use of medicines arises when one or more of the above-mentioned conditions are not met[5]. The indiscriminate use of medications can lead to treatment failures and adverse drug events. Particularly concerning is the misuse of antibiotics, which exacerbates drug

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resistance, limiting available therapeutic options and rendering alternative treatments unaffordable for many. Consequently, patient confidence in the healthcare system wanes[3].

Antibiotics are among the most commonly prescribed medication classes and essential parts of modern medicine, serving as key tools both for the prevention and treatment of infectious diseases. However, the current trend of their misuse can lead to significant morbidity, pronounced healthcare costs, and predominantly the emergence of antimicrobial resistance[6,7].

Ceftriaxone, a third-generation cephalosporin, serves as a pivotal element in global antibiotic therapy. It's extensively prescribed and empirically used for its high antibacterial potency, wide spectrum of activity, and low potential for toxicity. However, despite its pivotal role, there exists a concerning prevalence of inappropriate prescription and usage of ceftriaxone in both developing and developed nations, contributing to bacterial resistance[8–10].

According to the WHO report, inappropriate prescribing and dispensing of medicines accounts for over 50% of all medicines globally, and approximately 50% of patients fail to adhere to their prescribed medication regimen[11]. Out of many antibiotics, ceftriaxone is a very commonly used and at the same time commonly misused antibiotic[12]. Hence, the first logical step to assess the misuse of antimicrobial agents is to evaluate the suitability of its usage. However, relying solely on data gathered from individual hospitals offers limited insights for effective policy-making[13]. As a result, we conducted a Systematic Review and Meta-Analysis to comprehensively examine the appropriateness of ceftriaxone utilization. Therefore, the current systematic review and meta-analysis aimed to determine the overall national pooled prevalence of inappropriate ceftriaxone utilization and its predictor factors in Ethiopia.

Methods

Protocol and registration

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol[14] (Supplementary File S1). There was no registered protocol for this systematic review and Meta-Analysis.

Search strategy

A systematic search was conducted across multiple databases including, PubMed, Science Direct, Hinari, Global Index Medicus, Scopus, Embase, and a search engine, Google Scholar, to identify relevant literatures that meet the research question at hand. In addition, the reference lists of all eligible articles were searched manually to retrieve additional relevant articles. The search was carried out from March 20 to April 10, 2024, using specific key terms such as "(((Ceftriaxone [MeSH Terms]) OR (Ceftriaxone use)) AND ((Drug utilization [MeSH Terms]) OR (Drug use))) AND (Ethiopia [MeSH Terms]). Various search strategies were incorporated including truncation (*), Boolean operators ('OR' and 'AND'), and phrase searching ("…"). Additionally, we employed synonyms to expand the scope of the search, and search terms from each database were saved, and exported as detailed in (Supplementary File S1).

Data selection

All searched articles were uploaded to EndNote software to remove any duplicates. Following this, studies were selected based on the eligibility criteria by two independent investigators. The two researchers, screened the titles, abstracts, and the full text of all retrieved references to identify potentially eligible studies based on the inclusion criteria. Seventeen eligible studies were identified from a total of 988 search results. Then data extraction from the 17 studies was independently done by the two investigators and any differences between the reviewers were resolved through discussion.

Data extraction and analysis

A pre-prepared EXCEL data extraction sheet was employed to gather data from the eligible studies that consisted name of the primary author, year of publication, region of the country, study setting, study design, sampling technique, sample size, and proportion of inappropriate ceftriaxone utilization. In addition, the extraction sheet encompasses factors associated with inappropriate ceftriaxone usage and presents adjusted odds ratio along with their corresponding 95% confidence interval (CI) derived from the selected studies.

After this, data was exported to STATA version 17 statistical software for meta-analysis. Pooled prevalence was investigated using a random-effects model with the Dersimonian-Laird method[15]. Finally, the results were presented through textual descriptions, tables, and various graphical plots. A forest plot was used to estimate pooled prevalence along with a 95% CI to provide a visual summary of the data. To evaluate heterogeneity among included studies, the I-squared (I2) index, with was employed[16,17]. Furthermore, to explore sources of heterogeneity among the studies, Meta-regression was employed. Subsequently, subgroup analyses were performed by region of the country and study setting, to explore the impact of geography and institutional hierarchy on inappropriate ceftriaxone utilization. Additionally, sampling technique was evaluated to understand ceftriaxone utilization across different sampling methods. Funnel plots was employed to visually examine publication bias, supplemented by Begg's and Egger's regression tests for more objective assessment. These tests were chosen due to their heightened sensitivity in detecting publication bias compared to other methods[17,18].

Risk of bias (quality) assessment

Methodological Quality of each included study was assessed by two independent Authors, (CT & DGD). The studies underwent critical appraisal for quality using the Newcastle Ottawa appraisal tool for nonrandomized studies in meta-analyses, which rates study quality out of 10 points[19]. The two authors independently scored the articles and any disagreement in scoring was solved through discussion and involving a third author. Ultimately,

the study quality scores were derived by summing assigned values. Studies with a minimum score of 6 were selected for inclusion in the final analysis[20].

Eligibility criteria

Inclusion criteria
This review included all types of studies, both observational and interventional, that focused on ceftriaxone prescribing pattern or rational drug use in Ethiopia and published in English-language. This review puts no restriction to the study period, articles accessed within the search period, from March 20 to April 10, 2024, were included.

Exclusion criteria
Articles lacking abstracts or full texts, anonymous reports, and editorials. Studies that did not explicitly explain the outcome variable or lacking clear reporting of outcome variable were excluded.

Outcome measurement
The primary outcome of this study was assessing inappropriate ceftriaxone utilization among patients prescribed with this medication. It was determined as the proportion of patients who were using this medication inappropriately, calculated against the total number of patients who had received the drug. Inappropriateness was defined by a set of criteria aligned with the Ethiopian treatment guidelines, encompassing four key parameters: indication for use, dosage, frequency of administration, and duration of therapy. Appropriateness was declared when the use was in line with this guideline[21]. The secondary outcome was to determine predictors of inappropriate ceftriaxone utilization.

Result
Search results
As detailed in the flowchart below, (Fig. 1), from a manual and database searches, a total of 988 articles were identified. After an initial and exhaustive screening process for duplicates, one-hundred-forty-nine were identified and eliminated leaving 839 refined collections. Of these, 818 records were deemed irrelevant to the focus of this review based on titles and abstracts, and thus were excluded from further considerations. Subsequently, the remaining 21 full articles were prepared for retrieval to be thoroughly assessed for eligibility based on the inclusion criteria. Four studies were excluded from our analysis for various reasons, one study failed to define and report the outcome variable at all[22], another lacked full-text availability and could not be retrieved for further analysis[23]. The remaining two studies did not contain the outcome of interest[24,25]. Ultimately, 17 full articles[8,26–41] met the inclusion criteria and were included in the meta-analysis.

Characteristics of the studies included
In this meta-analysis, we incorporated 17 studies that evaluated ceftriaxone drug use pattern and published in the year between 2012 and 2023. The key findings are illustrated in Table 1. The sample sizes of these studies varied from 127 to 800, with a cumulative sample size of 6130. The populations studied primarily consisted of the general population encompassing a diverse age range, from newborns (1 day) to older adults (over 65 years). When classified geographically, two of the studies were conducted in Tigray Regional state, six in Addis Ababa, four in Amhara, one in South Western part of Ethiopia and the remaining four in Oromia. All the included studies employed a cross-sectional study design. In terms of sampling technique, nine studies utilized systematic random sampling, four of them simple random sampling and the remaining four were conducted on the entire patient population (Census). In terms of type of therapy, the proportion of empiric therapy varied significantly among studies, with rates as high as 98.4% (e.g., in the Federal Police Referral Hospital study) and as low as 59.7% in Ras-Desta Memorial General Hospital. This suggests a reliance on clinical expertise and experience in initiating treatment before confirming a diagnosis.
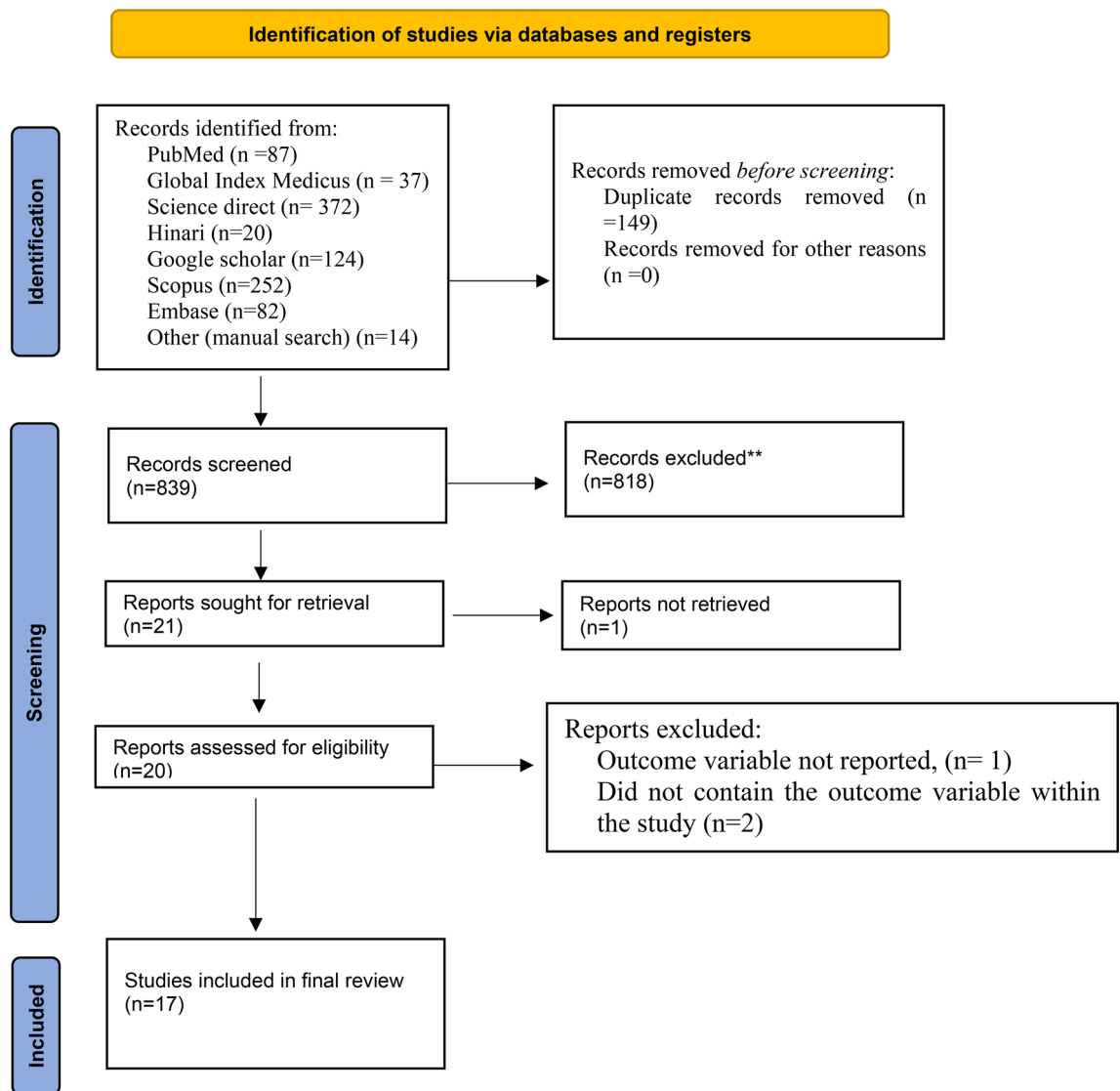
Risk of bias assessment
The comprehensive assessment conducted in this systematic review and meta-analysis revealed that all studies, evaluated using the rigorous Newcastle-Ottawa Scale quality appraisal criteria, demonstrated negligible risk. Consequently, all studies were deemed suitable for inclusion in our review and subsequent analysis.

The pooled prevalence of inappropriate ceftriaxone utilization
Using the random effect model, the national pooled prevalence of inappropriate ceftriaxone utilization turned out to be 55.24% (95% CI, 42.17%, 68.30%) with the heterogeneity index ($I2 = 99.24\%$, p value < 0.001), displaying marked heterogeneity among the studies. The prevalence of inappropriate ceftriaxone utilization for the individual studies ranged from 8%[30] to 87.9%[8]. Weights assigned to individual studies in a forest plot reflect their respective contributions to the overall pooled outcome[42]. The current study revealed a very close distribution of weight across the studies, ranging from 5.72% to 5.92% (Fig. 2).

Sensitivity analysis
In meta-analysis, sensitivity test reveal how much the overall findings are influenced by each individual studies included in the meta-analysis. It evaluates the robustness of the observed outcomes to the assumptions made in performing the analysis. This helps identify whether any single study has a disproportionate effect on the pooled estimate[43,44]. Consequently, the results from a random-effects model in the present study indicated that no single study influenced the overall pooled level of inappropriate ceftriaxone utilization. (Fig. 3).

Fig. 1. The PRISMA 2020 statement: an updated guideline for reporting systematic review.

Subgroup analysis of inappropriate ceftriaxone utilization

In response to the observed heterogeneity among the studies, we conducted meta-regression to investigate potential predictors of variability and gain a comprehensive understanding of the overall effect. Subsequently, regression analysis was performed by region of the country, study setting and sampling technique. However, none of these factors showed a statistical significant association. Nevertheless, we proceeded with a subgroup analysis encompassing all three of the above factors. Region and study setting were specifically included in our analysis to determine the pooled prevalence of inappropriate ceftriaxone utilization across geographical areas and different institutions, respectively. Meanwhile, the incorporation of sampling technique was to assess its distribution across various sampling methods (Table 2).

The pooled prevalence of inappropriate ceftriaxone utilization exhibited minimal variability among the five states included, the highest being 60.20(95% CI 41.77–78.64) in Addis Ababa and the lowest, 51.06(95% CI 12.37–89.75) in Amhara regional state. On the other hand, a significant variability was observed in terms of study setting ranging between 43.86 (95% CI 30.73–56.99), in General Hospitals and 87.9% (95% CI 84.29–91.55) in Specialized Hospital. Meanwhile, a more consistent distribution was noticed on the different sampling techniques employed, falling within 54.31(95% CI 19.10, 89.52) and 55.76 (95% CI 43.78, 67.74) for simple random sampling and Systematic random sampling respectively.

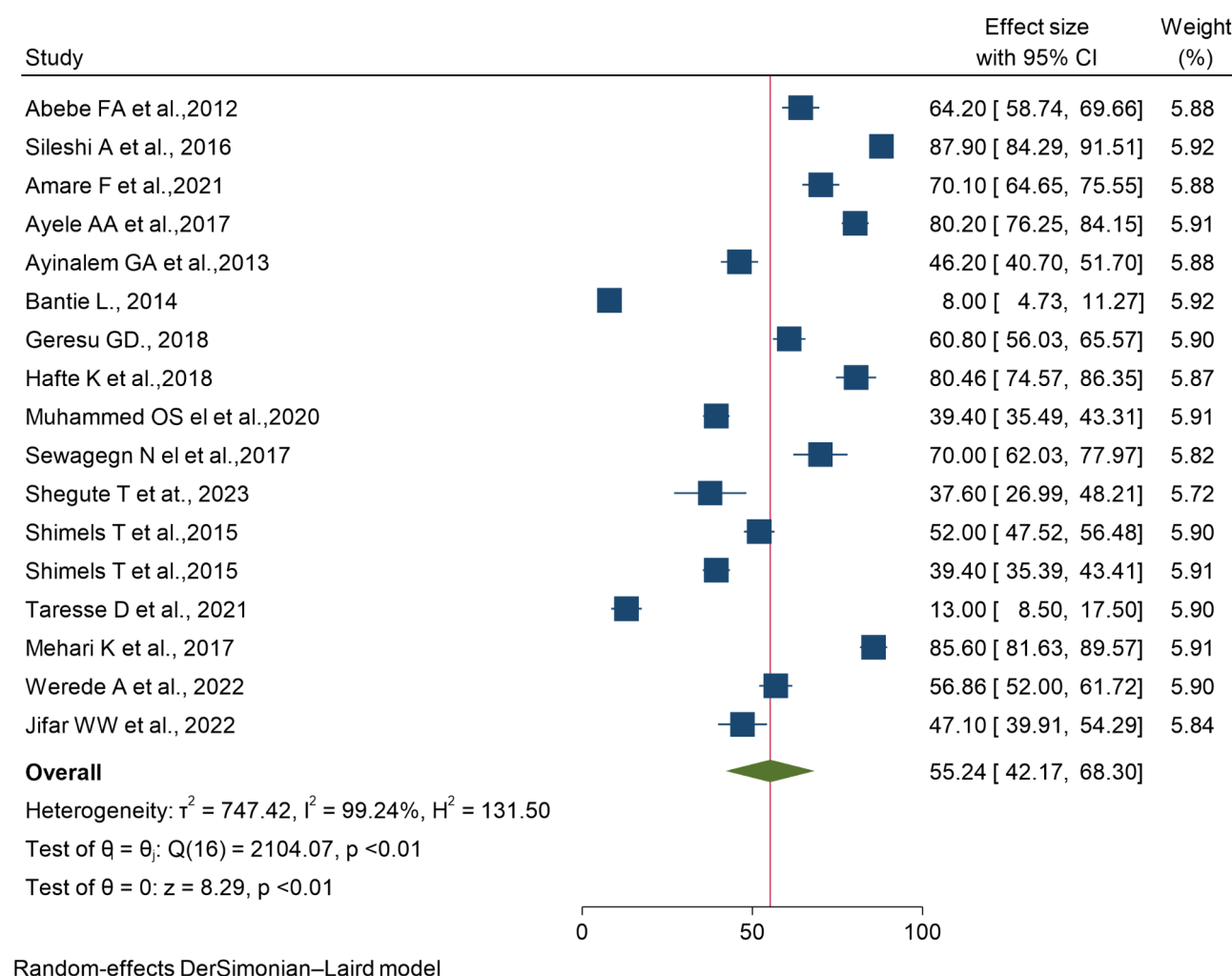### Pooled predictor of inappropriate ceftriaxone utilization

As depicted in Fig. 4, out of the reviewed articles, three distinct studies outlined the impact of empiric therapy on inappropriate ceftriaxone usage. Notably, patients that received empiric treatment exhibited a significantly higher likelihood, 21.43 times more (AOR, 95% CI (9.26, 49.59))—of improper medication intake compared to those prescribed with definitive therapy.

Author (s), Year	Region in the country	Study setting	Study design	Sampling technique	Sample size	Population characteristics	Proportion of Empiric vs. Definitive Therapy	Objective
Abebe FA et al.,2012	Tigray	Referral Hospital	Cross-sectional	Systematic RS	296	General population, aged 1 day-83 years, with average age of 34.3	Not specified	To evaluate the use and appropriateness of ceftriaxone in different wards of Ayder Referral Hospital, North Ethiopia
Sileshi A et al., 2016	Addis Ababa	Specialized Hospital	Cross-sectional	SRS	314	General population, aged ≥ 18, 18–65, 285(90.8%) ≥ 65, 29(9.2%)	Empiric-274(87.3%) Specific- 5(1.6%) Prophylactic-35(11.1%)	To evaluate the appropriateness of ceftriaxone utilization and to assess reasons for its inappropriate use in medical and emergency wards of Tikur Anbessa Specialized Hospital.
Amare F et al.,2021	Oromia	Multi-center	Cross-sectional	SRS	271	General population, aged 1 day to ≥ 60 years, Age groups, 20–29 years were dominant, 98(36.2%)	Not specified	To evaluate the appropriateness of ceftriaxone utilization and to assess major areas of inappropriate use in government hospitals in Harar town.
Ayele AA et al.,2017	Amhara	Referral Hospital	Cross-sectional	Census	390	General population, aged ≥ 18 18–65, 367 (94.1%) ≥ 65, 23(5.9%)	Empiric- 310 (79.5%) Specific- 16 (4.1%) Prophylactic- 64 (16.4%)	To evaluate the use and appropriateness of ceftriaxone in internal medicine and emergency wards of Gondar University referral hospital (GURH), Northwest Ethiopia.
Ayinalem GA et al.,2013	Amhara	Referral Hospital	Cross-sectional	SRS	316	General population, aged ≥ 18 (18–83) Average age- 34.3	Not specified	To evaluate the rational use of ceftriaxone in Medical ward of Dessie referral Hospital, Dessie-Ethiopia.
Bantie L., 2014	Amhara	Referral Hospital	Cross-sectional	Census	264	General population, aged ≤ 5 years to > 65 with average age-48years	Not Specified	Aimed at assessing the drug use pattern of Ceftriaxone injection in the in-patient wards of FHRH.
Geresu GD., 2018	South Western	General Hospital	Cross-sectional	Systematic RS	403	General population, aged ≥ 15 years Most encountered age groups 25–34 (35.73%)	Not Specified	To evaluate the utilization of ceftriaxone in medical ward of Mizan Aman general hospita
Hafte K et al.,2018	Oromia	Referral Hospital	Cross-sectional	Census	174	General population, aged < 15 to > 65 years 90% were in the age group of 15–65 years	Not Specified	To evaluate the use of ceftriaxone by using performance improvement method that focuses on evaluation and improvement of drug use processes.
Muhammed OS el et al.,2020	Addis Ababa	General Hospital	cross-sectional	Systematic RS	601	General population, aged 3 months to > 65 years Most encountered (14–65 years, 496 (82.5%)	Empiric- 359 (59.7%) Specific- 3 (0.005%) Prophylactic-239(39.8%)	To evaluate ceftriaxone utilization in different wards of Ras-Desta Memorial General Hospital (RDMGH) in Ethiopia.
Sewagegn N el et al.,2017	Amhara	Referral Hospital	Cross-sectional	Systematic RS	127	General population, aged < 15 to > 65 years Most encountered (15–65 years, 92%)	Not Specified	To evaluate the use of Ceftriaxone in Felege Hiwot Referral Hospital
Shegute T et at., 2023	Tigray	General Hospital	Cross-sectional	Systematic RS	800	General population: age distribution 204(25.5%) infants and children and 596 (74.5%)	Empiric- 637(79.6%) Specific- 61 (7.65%) Prophylactic-102 (12.75)	To evaluate the appropriateness of ceftriaxone use at Kahsay Abera and Mearg hospitals in the Western zone of Tigray, Ethiopia
Shimels T et al.,2015	Addis Ababa	General Hospital	Cross-sectional	Census	477	General population aged 14–65 (87.5& and >65 (12.5%) years	Not specified	To evaluate the appropriateness of ceftriaxone utilization in the medicine wards of general hospitals in Addis Ababa.
Shimels T et al.,2015	Addis Ababa	Referral Hospital	Cross-sectional	Systematic RS	571	General population, aged < 14, 61(10.7%) 14–65, 471(82.5%) > 65, 39(6.8%)	Empiric- 562(98.4%) Specific- 9 (1.6%)	To assess the utilization of ceftriaxone in different wards of the Federal Police Referral Hospital (FPRH), Addis Ababa, Ethiopia.
Taresse D et al., 2021	Oromia	General Hospital	Cross-sectional	SRS	215	General population, agen 15 to > 50 15–25 being the most frequent, 66(30.5%)	Empiric- 173(80.5%) Specific- 41 (19.1%) Prophylactic-1 (0.4%)	To assess appropriateness of ceftriaxone prescription at Haramaya Hospital, East Hararghe and Eastern Ethiopia
Mehari K et al., 2017	Addis Ababa	Referral Hospital	Cross-sectional	Systematic RS	300	General population, aged ≥ 18 years, 18–65(96%)	Empiric- 188(62.7%) Specific- 10 (3.3%) Prophylactic-102 (34%)	To evaluate the rational use of ceftriaxone at Armed Force Referral and Teaching Hospital Addis Ababa, Ethiopia
Continued								

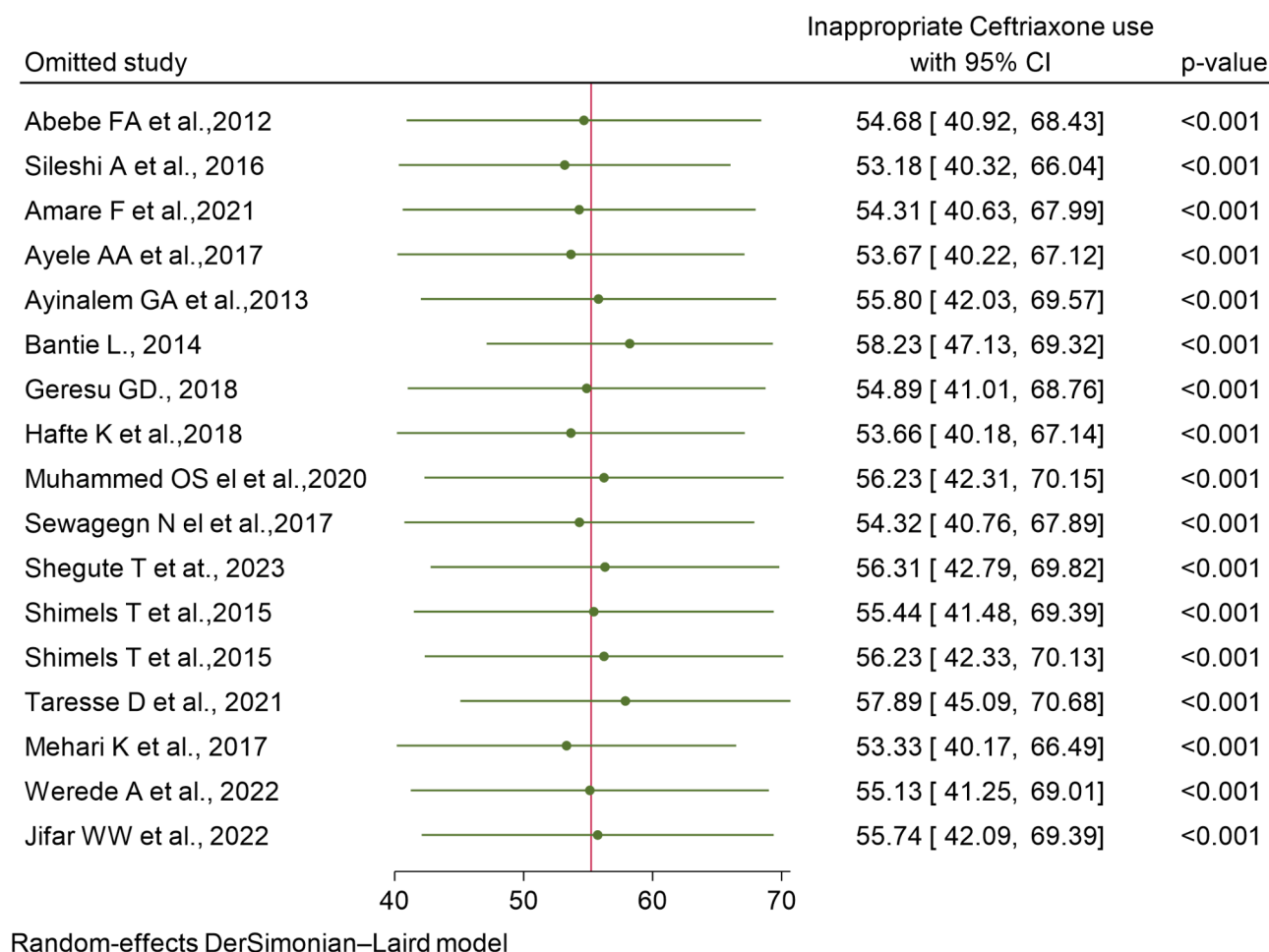| Author (s), Year	Region in the country	Study setting	Study design	Sampling technique	Sample size	Population characteristics	Proportion of Empiric vs. Definitive Therapy	Objective
Werede A et al., 2022	Addis Ababa	General	Cross-sectional	Systematic RS	399	General population with mean age and standard deviation of 45.53 ± 18.67	Not Specified	To evaluate use of ceftriaxone in medical wards of Ras Desta Damtew Memorial Hospital
Jifar WW et al., 2022	Oromia	General	Cross-sectional	Systematic RS	212	General population aged, ≥ 18 years, Most frequent age group 18–65 (80.5%)	Empiric-95% Prophylactic-5%	To evaluate the utilization pattern of ceftriaxone at Medical Ward in Bedele General Hospital, Bedele, South West Oromia, Ethiopia

Table 1. Descriptive summary of the 17 included studies in the meta-analysis of Ceftriaxone drug utilization pattern, Ethiopia. SRS, Simple random sampling; RS, Random sampling.

Fig. 2. Forest plot displaying a pooled value of inappropriate ceftriaxone utilization in Ethiopia, 2024 ($n = 17$).

Factors associated inappropriate utilization of ceftriaxone

Among the studies examined, a study conducted by Ayele et al. uncovered a significant association between multiple medication co-prescription and an increased likelihood of inappropriate ceftriaxone utilization, with AOR 4.12 (95% CI 1.62, 8.05). A higher likelihood of non-compliance with guidelines was also noticed among patients admitted to Emergency and surgery departments with AOR 4.22 (95% CI 1.8, 12.24) and AOR 2.6 (95% CI 1.44, 7.82) respectively, compared to those in medical ward, in a study conducted by Muhammed et al.,. This result was further supported in a research carried out by Shimels et al., where, patients admitted to Gynecology and Obstetrics, Medical and Pediatrics departments showed a decreased propensity for inappropriate ceftriaxone utilization by 69%, 67.6% and 80.8% respectively (Table 3). Meanwhile, prophylactic use demonstrated a 500-
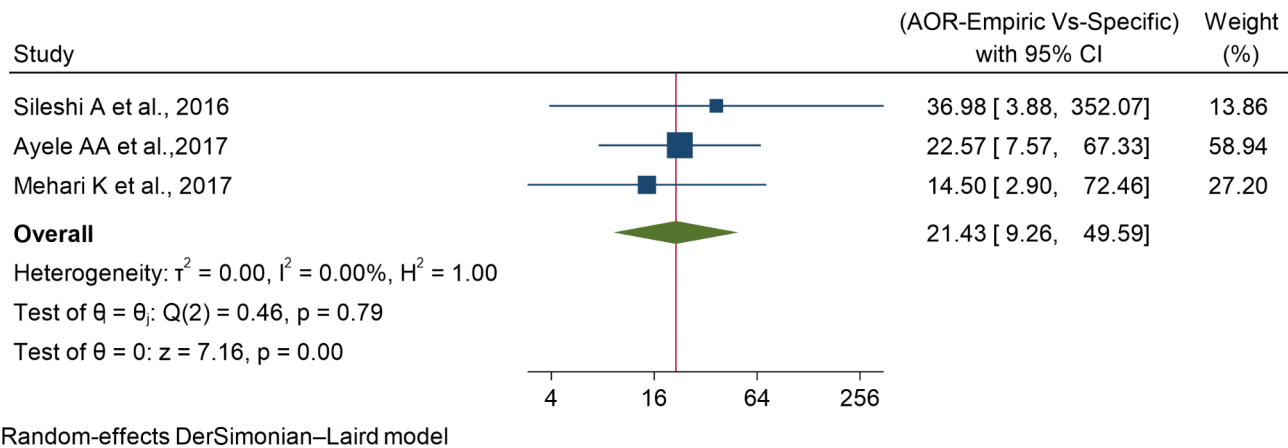
Fig. 3. Sensitivity analysis of inappropriate ceftriaxone utilization in Ethiopia, 2024 ($n = 17$).

Variables by category	No of studies	Pooled non-adherence (95% CI)	I² (p-value)
Region			
Addis Ababa	6	60.204 (41.77, 78.64)	99.18(<0.001)
Amhara	4	51.06 (12.37, 89.75)	99.64(0.01)
Oromia	4	52.64 (19.66, 85.63)	99.27 (0.002)
South Western	1	60.80 (56.03, 65.57)	-
Tigray	2	51.31 (25.25, 77.36)	94.76(<0.001)
Study setting			
General Hospital	7	43.86 (30.73, 56.99)	97.83(<0.001)
Multi-Center	1	70.10 (64.65, 75.55)	-
Referral Hospital	8	59.23 (36.84, 81.61)	99.48(<0.001)
Specialized Hospital	1	87.90 (84.29, 91.51)	-
Sampling technique			
Census	4	55.13 (17.61, 92.66)	99.68(0.004)
Simple Random Sampling	4	54.31 (19.10, 89.52)	99.56(0.002)
Systematic Random Sampling	9	55.76 (43.78, 67.74)	97.95(<0.001)

Table 2. Subgroup analysis of inappropriate ceftriaxone utilization based on different variables.

fold increased likelihood for inappropriate ceftriaxone utilization compared to specific therapy (95% CI, 41.7, 1000).

In contrast, longer hospital stays of, 8–14 days and > 14 days displayed 83.3% and 78% lesser likelihood, respectively, of inappropriate ceftriaxone use pattern when compared to stays of 0–7 days. Additionally, the

Fig. 4. A forest plot displaying the pooled effect of empiric therapy compared to specific therapy for inappropriate ceftriaxone usage, 2024, Ethiopia.

Author (s), Year	Region of the country	Study design	Sampling technique	Sample size	Factors (AOR, 95%CI)
Ayele et al., 2022[28]	Amhara	Cross-sectional	Census	390	Co-prescribed medications ≥ 1 (4.12, 1.62–8.05)
Muhammed et al.,2020[34]	Addis Ababa	Cross-sectional	SystematicRS	601	Ward- Emergency (4.22, 1.8-12.24), Surgery (2.6, 1.44–7.82), (Reference-Medicine)
Shimels et al. 2015[37]	Addis Ababa	Cross-sectional	Census	477	Days of Hospital stay-8-14D (0.167, 0.09–0.29), > 14 days (0.18, 0.1–0.32)
Shimels et al. 2015[38]	Addis Ababa	Cross-sectional	Systematic RS	571	Ward-Gynecology (0.31, 0.15–0.63), Medical (0.32, 0.15–0.70), pediatrics (0.192, 0.056–0.66) (Reference-Surgical ward). Free service (7.75, 2.85–21.27) (Reference-Charged)
Mehari 2017[33]	Addis Ababa	Cross-sectional	Systematic RS	300	Treatment type Prophylaxis (500, 41.7–1000) (reference –specific)

Table 3. Identified predictors for inappropriate ceftriaxone utilization in Ethiopia, 2024.

provision of free health service was linked to an 87.1% lesser likelihood of compliance to guidelines when compared with charged patients.

Meta-analysis
Publication bias
A funnel plot is a scatter plot frequently utilized in meta-analyses to unveil publication bias through visual detection. As depicted in Fig. 5, the plot displays asymmetry in the distribution of the included studies. However, when evaluated using more objective measures, such as Egger's and Begg's test, the results were statistically insignificant ($p = 0.9676$ and $p = 0.9016$, respectively), suggesting the absence of publication bias.
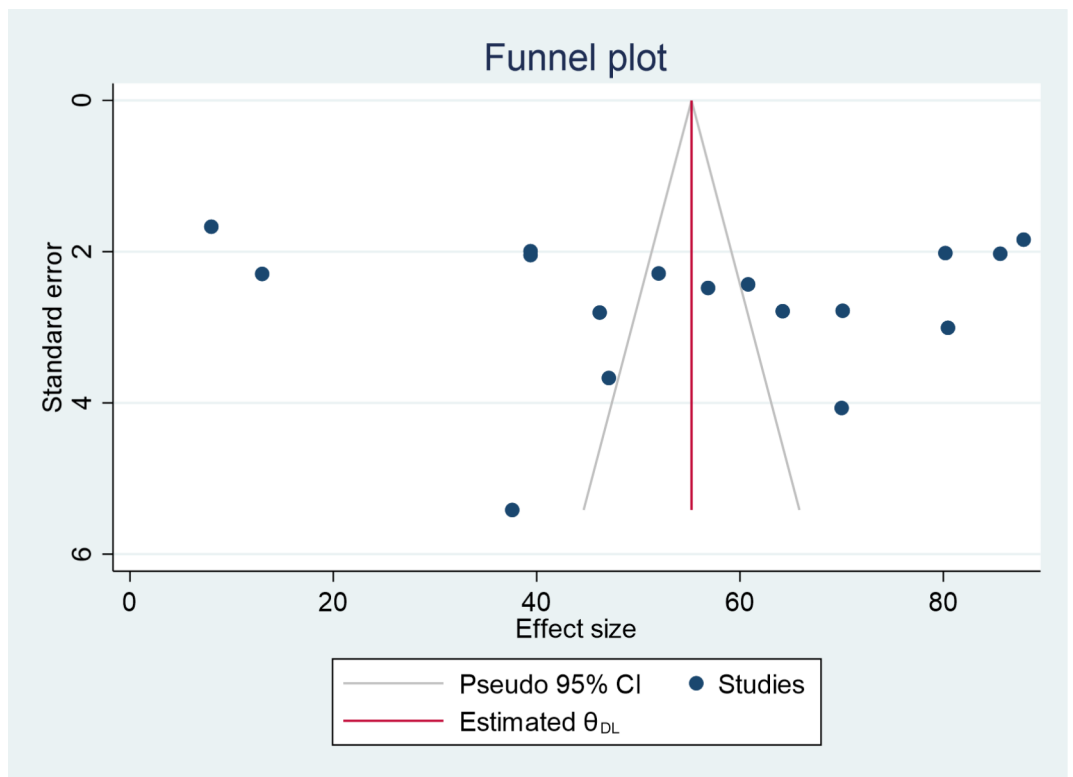
Discussion
This systematic review and meta-analysis aimed to generate the national pooled estimate of inappropriate ceftriaxone utilization pattern in Ethiopia, along with identifying key predictor factors associated with its misuse. Making our primary focus, ceftriaxone, owing to its frequent misuse due to higher rate of utilization[45], this review provides targeted insights into its prescribing practices in the Ethiopian context. This helps promote rational antibiotic use and combat antimicrobial resistance which usually happens due to overuse of antimicrobials and has become a major public health concern to health institutions and the global society as a whole[46].

In the present study, our analysis revealed a pooled prevalence of inappropriate ceftriaxone utilization at 55.24% (95% CI, 42.17%, 68.30%). This finding indicates that a little over half of the studied patients did not receive appropriate treatment regimen involving ceftriaxone, posing a serious challenge to effective therapy, and warranting immediate attention. This emphasizes the need for targeted interventions to address this pressing issue. Targeted interventions are essential to improve prescribing practices, as inappropriate use of antibiotics has been strongly linked to the emergence and spread of antimicrobial resistance. Antimicrobial resistance, largely stemming from the misuse and over-prescription of antibiotics, presents a formidable global crisis that demands a multifaceted approach. This approach should include promoting judicious antibiotic usage through education and guidelines for healthcare providers, enhancing surveillance of antimicrobial resistance patterns, and enforcing stringent regulations on antibiotic utilization within the healthcare system and other sectors[9,47–49].

Ceftriaxone misuse is a widespread and highly prevalent issue in healthcare facilities globally, though comprehensive meta-analyses on this topic are limited. A study conducted by Durham et al.,. in Alabama and west Georgia found a 53% inappropriate ceftriaxone use, closely aligning with our findings[50]. Similarly,

Fig. 5. Funnel plot showing the asymmetric distribution of 17 articles of Ceftriaxone utilization in Ethiopia.

this concerning trend extends to the East African region with reported rates of 32.1% in Uganda[45], , 62.4% in Eritrea[46], , and as high as 68.9% in terms of frequency in Sudan[51].

The present study has also identified factors that contributed to the inappropriate usage of ceftriaxone, that deviate from established guidelines. Accordingly, treatment modalities, particularly patients that received empiric therapy, exhibited a higher likelihood of improper usage compared to those prescribed specific therapy (Fig. 5). Likewise, findings from a study conducted in Portugal indicated that over a third of patients receiving empiric ceftriaxone prescriptions were deemed inappropriate[52]. This surge in empiric therapy, notably prevalent in developing countries, like Ethiopia is largely attributable to limited access to diagnostic laboratories.

While empiric treatment may seem an attractive and cost effective treatment strategy, its widespread adoption often leads to inappropriate antibiotic usage[53]. Consequently, there is a pressing need for rapid diagnostic tests capable of identifying causative agents at the point of care. Such tests would enable healthcare providers to rapidly and accurately identify infections, facilitating the precise administration of narrow-spectrum antibiotics. This targeted treatment approach ensures optimal patient care and helps mitigate the emergence of antibiotic resistance, preserving the effectiveness of antibiotics for future generations[54–57]. Moreover, it reduces health care costs related to inappropriate antibiotic usage that are estimated in millions of dollars[58].

Specific therapy, defined as the use of ceftriaxone after a definitive diagnosis has been established typically following culture and sensitivity results[59], was notably low across the studies, ranging from only 1.6–19.1%. This indicates that the majority of ceftriaxone treatments were initiated without confirming the diagnosis, relying heavily on clinical judgment rather than objective diagnostic evidence.

This reliance on empiric therapy over specific therapy may highlight significant gaps in diagnostic capabilities or practices related to antibiotic stewardship in the studied hospitals. Such practices can lead to inappropriate ceftriaxone utilization, as treatments may be administered without ensuring that the antibiotic is necessary or effective for the diagnosed condition[52,60,61]. This situation highlights the need for education of healthcare staff, awareness of local antimicrobial resistance patterns, improved diagnostic protocols and adherence to evidence-based treatment guidelines to enhance the appropriateness of ceftriaxone use and minimize the risks associated with its overuse[62,63].

Limitations of the study

Although this Systematic review and Meta-analysis provides a summarized overview of the inappropriate ceftriaxone utilization and its predictor factors in Ethiopia, its scope was restricted due to the exclusion of articles published in languages other than English and those lacking full texts. Consequently, this limitation may have led to an incomplete representation of the available literatures, possibly overlooking valuable insights.

Conclusion

The study reveals a high national pooled prevalence of inappropriate ceftriaxone utilization, standing at 55.24%. This highlights a significant hazard in the use of this antibiotic, suggesting potential instances of overuse, misuse or prescription practices that deviates from established guidelines. This noteworthy challenge can lead to the development of antibiotic resistance, increased healthcare costs, adverse drug reactions, and treatment failures. Addressing these issues requires a multifaceted approach involving improved antibiotic stewardship, better adherence to guidelines, and enhanced clinician education on appropriate antibiotic use.

Moreover, the current investigation suggests several factors, including Empiric therapy, multiple medication co-prescription, and certain hospital departments, particularly emergency and surgery wards, were significantly linked with increased likelihood of inappropriate ceftriaxone utilization. These observations emphasizes the urgent need for improved prescribing practices even within healthcare departments to mitigate the overuse or misuse of this critical antibiotic. In a nut shell, these findings offer valuable insights, to healthcare providers, researchers, and policymakers aiming to address the challenges associated with inappropriate ceftriaxone utilization both on a global scale and particularly within Ethiopia.

Data availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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C.T, D.G.D, B.B.T, D.E, O.A, A.Y, A.T.Y, E.A.S participated in conception, literature review, and data extraction. C.T and M.B.Y. did the analysis and interpretation of data. Z.D.A and K.F participated in manuscript preparation. All authors reviewed and approved the final manuscript.

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