A systematic Review and Meta-analysis of Antimicrobial Prescriptions in East Africa

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ACRONYMS AND ABBREVIATIONS

OTC	Over the counter
EML	Essential medicine list
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
ICTRP	International Clinical Trials Registry Platform
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
WHO	World Health Organisation
LMIC	Low- and middle-income countries
HIC	High income countries
LIC	Low-income countries
TB	Tuberculosis
AMR	Antimicrobial Resistance

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PROSPERO REGISTRATION

This study is in the process of registration with the International Prospective Register of Systematic Reviews (PROSPERO), ID number- 261237. Dr. Acam Joan, Paul Kuodi, Dr. Girmay and Prof Eyasu Makonnen: A systematic review and meta-analysis of Antimicrobial Prescriptions in East Africa.

ABSTRACT

Background: Antimicrobial resistance is one of the major global health problems that has been worsened due to poor antibiotic stewardship by health workers and improper use of antimicrobial by the patients among other factors. Quality data representative of the extent of poor antimicrobial stewardship in low- and middle-income countries is scanty, but high incidences of antimicrobial resistance are increasingly reported in many settings across the globe. The objective of the present study was, therefore, to evaluate prescriptions for antimicrobials in East Africa.

Methods: A comprehensive literature search strategy that includes text words and medical subject headings was developed and applied to predefined electronic databases. Two researchers independently screened the titles and abstracts of the outputs of the literature search. Full texts were then independently reviewed by the two researchers. Extracted data from included studies were pooled using meta-analysis.

Results: Majority of the included studies (30.8%) were retrieved from Ethiopia, followed by Sudan, Kenya and Tanzania each contributing 19.2%. The overall proportion of encounter with antimicrobials reported was 57% (95%CI 42%; 73%). Ethiopia had an overall patient encounter with antimicrobials of 63% [95%CI: 50%, 76%] followed by Sudan with an overall encounter with antimicrobials of 62% [95%CI: 34%, 85%]. Studies included from Kenya reported the overall encounter with antimicrobials of 54% [95%CI: 15%, 90%], whereas studies from Tanzania reported an overall patient encounter with antimicrobials of 40% [95%CI: 21%, 60%].

Conclusion: Prescription patterns demonstrated in this review significantly deviate from WHO recommendations suggesting inappropriate antimicrobial use in the East African countries. Considering the global threat posed by antimicrobial resistance, perhaps countries with few research being carried out on antimicrobial use patterns and resistance should focus more resources on this important research agenda as a matter of public health priority.

1. INTRODUCTION

1.1 Background

Antimicrobial resistance is currently a recognised global health problem stemming from poor antibiotic stewardship by health workers and improper use of antimicrobial by the patients among other factors [1]. Quality data representative of the extent of poor antimicrobial stewardship in low- and middle-income countries is scanty, but high incidences of antimicrobial resistance are increasingly reported in many settings across the globe [2]. Reports indicate that misuse of antimicrobials including over prescription and prescription without proper identification of offending pathogens in humans and animals are some of the main drivers of the currently witnessed antibiotic resistance [3].

Studies to estimate the global consumption of antibiotics revealed a more than 65% dramatic increase in antibiotic consumption between 2000 and 2015 fuelled by excessive antibiotic prescription in low- and middle-income countries [4]. One study reported the increasing trends of antimicrobial resistance due to the COVID-19 pandemic caused by antibiotic treatment with no justification [5]. It is estimated that 10 million deaths will occur in Africa and Asia by 2050 if improper antimicrobial use is not tackled as a matter of emergency [5]. Several factors have been attributed to the rise in antimicrobial use especially in Africa and other low- and middle-income countries: high burden of infectious diseases, poor antibiotic stewardship due to inadequate training of health professionals, lack of essential diagnostic equipment, widespread over the counter (OTC) sale of antibiotics, and weak antibiotic regulatory environment [6, 7].

Literature reporting on antibiotic use and prescription patterns is available in a lot of small studies with scanty synthesized evidence for Africa and other low- and middle-income countries [8, 9]. Yet devising interventions to combat the current global upsurge of antimicrobial resistance requires guidance from quality evidence which is limited in its availability. This study is aimed to synthesize available data on this topic to avail policy relevant evidence on antibiotic prescriptions in East Africa in order to guide decisions on antimicrobial resistance interventions.

1.2 Rationale for the review

Establishment of antibiotics stewardship interventions as currently recommended by WHO [10] requires guidance from evidence-based quality data. Unfortunately, such data are scanty in many low-and middle-income countries. The rationale for this review was, therefore, to map using systematic review and meta-analysis methods, the prescription patterns and to estimate appropriate use levels of antimicrobial in East African countries by synthesising available evidence from these countries.

1.3 Statement of the problem

Antibiotic resistance is a global public health problem affecting both LMICs and HICs. For sub-Saharan African countries, the antibiotic resistance problem is of a larger magnitude compared to that for HICs [29, 30]. Quality data to guide interventions to improve interventions to combat antibiotic resistance problem is lacking for East African countries. Anecdotal evidence and scattered literature that needs synthesis to produce quality evidence exists. This systematic review and meta-analysis have collated evidence to guide future interventions and also identified areas gaps for research agenda**.**

2. LITERATURE REVIEW

The name "Antimicrobials" was derived from the Greek words anti (against), mikros (little), and bios (life) to mean agents that kill microorganisms (microbicidal) or cause growth inhibition (microbiostatic) (11). Microorganism are broadly classified as bacteria, viruses, fungi and protozoa. As antimicrobials act against microorganisms, they can be antibacterials, antivirals, antifungals, and antiprotozoal (12). Antimicrobials can be obtained from plants, semisynthetic, or synthetic sources. The term antibiotics is confused with antimicrobials. Antibiotics are substances that are produced by microorganisms that inhibit or kill other microorganisms (11). They have become the most successful form of chemotherapy in the treatment of infections globally since their discovery in the 1950s and 1960s (13). However, they have been misused leading to resistance emergence against them. This problem is more pronounced in the developing world where there is minimal supervision and restricted use of these agents (12).

According to the World Health Organization, Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi, and protozoa change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness, and death (12). As a result of drug resistance, infections become increasingly and impossible to treat. A report by WHO in 2011 estimated that 630,000 out of 12 million cases of Tuberculosis (TB) were due to multi-drug resistant TB (MDR-TB) (14). Resistance against other antimicrobials such as anti-salmonella enterica, anti-staphylococcus aureus, and even antiretrovirals has been reported (14).

Antimicrobial resistance is a growing public health problem that needs urgent attention. According to the WHO, it needs a one health approach which is an intersection of the health of humans, animals, and the environment, and this advises rational use of antimicrobials (12).

Rational use of antimicrobials includes not using these agents in conditions where the diagnosis is negative and carrying out sensitivity test prior to prescribing using them (15). This requires rational prescribing, dispensing and consuming including avoiding self-medication of antimicrobials.

Global trends in antimicrobial use

The discovery of antibiotics and other antimicrobials was one of the most significant achievements of the 20th century. Since then, these agents have been in use in treating various infectious diseases across the globe (16). The use of antimicrobials stretches back to more than 2000 years ago (17). Bassett *et al* and Nelson *et al* have reported traces of tetracycline in the human skeleton of ancient Sudanese Nubia (18). This has been explained by the fact that tetracycline can concentrate in the bones, and this was basically from taking foods that contained tetracycline.

There has been a general increase in the use of antimicrobials over the past two decades, however, due to availability of limited data, trend was not seen in the periods before 2000, and after 2015. According to a recent review, the global use of antimicrobials is reported to have increased up to 65% between 2000 and 2015 at a rate of 39% over the 15 year review period, attributed mainly to increased use of these agents in low and middle-income countries (19). The increase of antibiotic use in LMICs has been explained by the increased the Gross domestic product (GDP) with increasing global population even though challenges of inequities in access still exist (19).

Similarly, another related study by Boeckel *et al* reported an increase of 35% antimicrobial consumption between 2000 and 2010, and the consumption increased mostly with the reserved antimicrobials like such as carbapenems (45%) and polymixins (13%) (20). This study also predicts the consumption to increase by 200% by 2030. Hogberg *et al* has reported an increase in the consumption of antibacterial agents in Europe with higher use of amoxiclav, and penicillins (20). This increase has been attributed to the changing epidemiology of disease and the increased rate at which drug-resistant infections are becoming endemic.

However, in light of the ongoing COVID-19 pandemic, there is a remarkable increase in antimicrobial use most of which happens without prescription (5). Gouin *et. al* reported increased use of remedies suspected to offer some treatment to the COVID-19 including hydroxychloroquine (+563%) and Azithromycin (+150%) (21). Rose *et al* also reported increased prescription of antibiotics among patients in hospitals due to the increased COVID-19 burden (22). Even though the COVID-19 diagnosis was unavailable, approximately half of the hospitalized patients received ceftriaxone, commonly in combination with azithromycin to help in the relief of flu and cold symptoms (22).

Patterns of antimicrobial use in high-income countries

There has been a marked increase in the inappropriate consumption of antimicrobial agents such as self-medication practices in High-Income countries (HICs), and this is the key driving force to drug resistance (23). A related study conducted in Spain indicated that there was a steady increase in the sales of antimicrobials from 2002 to 2005 (24). There was also a reported increase in the use of antibacterial agents including amoxicillin, amoxicillin/clavulanic acid, clarithromycin, and cefuroxime (24). Similarly, a study done across Europe reported that antibacterial agents including penicillin's are commonly used (15).

A related study in Europe revealed increased rates of drug resistance due to self-medication and over-the-counter consumption of antibiotics and pharmacies and leftover drugs were the most common sources of these self-medication drugs (25). This study is similar to those conducted in the United States which reported that antimicrobial drugs are usually obtained without a prescription and the commonest sources were pharmacies, borrowing from family members, and leftover drugs (26). Up to 72% of the respondents took leftover drugs without a prescription from a physician (26).

Many factors have been reported to be driving the increasing epidemic of self-medication. According to a study done among Iranian women, 76% had a history of self-medication, and 98.9%stored drugs at home. The most important reasons for self-medication are; it is perceived as harmless (41%), having a history of a disease (35.5%), and availability of medications at home (34%) (27). Similarly, a related study by Lukovic *et al* (2014) reported that possession of medications at home was a key driving factor to self-medication. It has also been concluded that the practice of self medication is not limited to any specific groups of people, but even happens among health professionals (28).

Patterns of antimicrobial use in low-income countries

Quantifying antimicrobial use in low and middle-income countries (LMICs) is problematic given scarce data which call for studies to be conducted (29). However, consumption of broad-spectrum antibiotics has reportedly increased in LMICs which happened inside and outside the formal health care delivery system (29).

Studies have reported antimicrobial misuse(using antibiotics for viral infections ,using antiobiotics as growth promoters in animals and in aquaculture) as an increasingly common problem in low and middle-income countries which leads to antimicrobial resistance (30). Many LMICs (Kenya, Mali, Malawi, Nigeria, South Africa, Sudan, Tanzania) have weak implementation of regulations regarding the appropriate use of antimicrobials. In light of this, a recent study reported that Vietnam and Bangladesh have the largest proportions of unlicensed antibiotic distribution points (30).

Many studies have reported non-prescription use of antimicrobials as a commonest practice and form of antimicrobial misuse. A recent review by Ocan *et al* reported that self-medication usually occurs for antimalarial and antibacterial agents (31). This results in shorter durations of treatment, under dosage, and wrong indications which all result in resistance of target microorganisms (31). In the Middle East, studies have reported use of antibacterial agents like ampicillin in the treatment of viral infections like flu (32).

Furthermore, studies have reported irrational dispensing of these antimicrobials. The majority of the studies have reported that all drug distribution points including public health facilities such as pharmacies, drug stores, and friends or relatives are the sources of drugs for self-medication (23,31).

Patterns of antimicrobial use in low-income countries and high-income countries

Analysis of data from 2000 to 2015 indicates that the global per capita consumption of antimicrobials increased by 90.9%, the increament being more in low-income countries (LIC) than high-income countries (HIC) (33). This was associated with the increase in the gross domestic product of LICs greatly contributing to the consumption. Furthermore, there was a decrease in the access-to-watch index, being more in LICs (46.7%) than HICs (16.7%).

The difference in the consumption has been explained by the organization of healthcare systems, availability of diagnostic testing and appropriate antimicrobials, infection prevention and control practices, along with prescribing practices (such as over-the-counter availability of antibiotics) which differ greatly between high-income countries and low-income countries (34).

However, among both high- and low-income countries, the sources of unprescribed medications are reportedly the same. Many studies including those by Do *et al* and Richman *et al* have reported community pharmacies, drug shops, borrowing from friends and relatives, as well as leftover drugs are the commonest sources of unprescribed medications (26,30).

Patterns of antimicrobial use in East Africa

In sub-Saharan Africa, demand for antimicrobial agents for both prophylaxis and treatment has increased due to the increasing epidemiology of endemicity of respiratory tract infections, diarrheal diseases, HIV/AIDs, Tuberculosis and malaria (35). The increased demand has also been associated with the weak health system ranging from limited diagnostic capacity and resources, unregulated access to antimicrobials, constrained access to health facilities, and lack of training on rational antimicrobial use (35). Similarly, another survey reported the emergence of antimicrobial resistance to be driven by many factors including the indiscriminate use of antimicrobials and variable drug efficacy which present a major threat to the control of infectious diseases (36).

There are few data available to quantify antimicrobial use in East Africa. There has been a reported rise in the resistance to antimicrobial use of different categories across the region. Studies conducted in East Africa have reported antimicrobial resistance to commonly used antibiotics that include ampicillin, gentamicin, and ceftriaxone (37).

Recent surveillance data indicates that resistance has increased from 11·8% to 90·5% by *Klebsiella* species, 0·7% to 30·3% by *E. coli*, and from 30·4% to 71·9% by other Enterobacteriaceae between 2003 and 2016 (38). Similarly, other studies conducted among East African countries have reported resistance by Salmonella (38%), Shigella (38%), Vibrio (11%), and E. coli (13%) from 1974 to 2013 (36). These showed resistance has emerged to Amphotericin, Chloramphenicol, and Tetracycline. Though many factors have been reported to contribute to antimicrobial resistance, no study had quantified their contributory roles in the East African region.

Magnitude of inappropriate antimicrobial use in low-income countries

The use of antimicrobials in Low and Middle-Income countries has increased over the past decades, almost catching up with High-income countries, however, the usage is often unnecessary due to lack of supportive regulation and widespread informal use (39). This usage has been witnessed through the high rates of self-medication that happens across a range of distribution points(23,31).

Results of a recent survey across eight LMICs in Africa indicated that antibiotics were prescribed to 80.5% of children with respiratory tract infections between 2006 and 2016 yet large proportions were not necessary (21). Another similar survey reports that global antibiotic use in humans increased by 35% between 2000 and 2010, and this was more pronounced in LMICs with this use happening both inside and outside the formal health care system (20). This, therefore, implies that inappropriate use of antimicrobials happens at all distribution points, both licensed and unlicensed.

Many studies among LMICs have reported high rates of self-medication. Ocan *et al* and Torres *et al* have reported 39% and 8 to 93% prevalence of self-medication, respectively, and this occurs across pharmacies and all drug distribution points including borrowing from friends (23,24). This self-medication has been reported to the severity of illness, economic status, past successful use of antibiotics, as well as, accessibility and affordability of health care (24). Results of a most recent study by Torres *et al* reported a prevalence of 38.8% as the majority of the respondents obtained the drugs from pharmacies (40).

2. OBJECTIVES

2.1 General Objective:

To characterise the antimicrobial prescription patterns in East African countries

2.2 Specific objective:

- To estimate the proportion of patients encounters with antimicrobial prescriptions in East African countries

3. METHODS

3.1 Methodological framework

We followed recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two researchers independently screened the titles and abstracts of the result of the literature search. Full texts were then independently reviewed by the two researchers. Eligible studies were formally assessed for quality and risk of bias using a scoring tool. Predefined variables were extracted from each paper and the extracted data from included studies were pooled using meta-analysis. Where data were available, sub-group analyses were performed to obtain pooled within group estimates. The findings are summarized using forest plots and tables. Key findings are reported in a narrative text.

3.2 The literature search strategy

We used both text words and medical subject heading (MeSH) terms (all fields) in the literature search. We used the following key terms; “antimicrobial” or “antibiotic” or “anti-infective agent”. No time and language restrictions were applied during database searching. Eight electronic databases were searched (PubMed, EBSCOhost, Web of Science, Cochrane Library, Scopus, International Clinical Trials Registry Platform (ICTRP), Mednar) for relevant literature

The search strategy developed for use in the PubMed database

Search strategies that incorporate the population, and study design and setting were developed in a way that keeps the balance between sensitive and precise searches. For MEDLINE (PubMed), search term was created in the “PubMed Advanced search” and MeSH (Medical Subject Headings) and text words (synonyms and related terms) were used to come up with the search terms as written below:

(("primary health care"[mesh] OR primary care[tw] OR primary health*[tw] OR community health*[tw] OR community care[tw] OR community worker*[tw] OR clinic[tw] OR clinics[tw] OR “general practitioners” [mesh] OR general practi*[tw] OR family medicine[tw] OR family practi*[tw] OR “physicians, family” [mesh] OR family physician*[tw] OR family doctor*[tw] OR "physicians, primary care"[mesh])) AND (("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR "anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR antibiotic*[tw] OR antimicrobial*[tw] OR antibacterial*[tw] OR anti-bacterial*[tw] OR anti-infective*[tw])) AND ("therapeutic use"[sh] OR "drug prescriptions"[mesh] OR "drug utilization"[mesh] OR “inappropriate prescribing” [mesh] OR “drug utilization review” [mesh] OR "practice patterns, physicians'"[mesh] OR use[tiab] OR user*[tiab] OR used[tiab] OR overuse*[tiab] OR underuse*[tiab] OR misuse*[tiab] OR utiliz*[tiab] OR overutili*[tiab] OR underutili*[tiab] OR prescri*[tw] OR overprescri*[tiab] OR underprescri*[tiab])

3.3 Types of studies included in the review

In this review we included studies conducted in East African counties (Ethiopia, Kenya, Tanzania, Sudan, Uganda, Eritrea) and reported the proportion of patients receiving any antibiotic prescription irrespective of facility setting or level. The following study types were included in the review: cross-sectional studies, cohort studies, and RCTs (randomized controlled trials).

3.4 Eligibility of studies

- Reviews of all kinds, economic evaluation studies, qualitative studies, mathematical modelling and non-primary research publications such as: commentaries, editorials and conference proceedings were not eligible for this review.
- Studies reporting antibiotic use in animals i.e., those focused on veterinary use of antibiotics, and those focused on special cohorts of patients such as surgical prophylaxis where use of antibiotics is justified, were not eligible for inclusion in this review.

3.5 Data collection and analysis

Selection of studies

All outputs of electronic database search were imported into Rayyan Software for screening and selection (41). Two of the researchers independently screened 100% titles and abstracts for inclusion of potentially eligible studies obtained from the database searches. The first reviewer (JA), collected full-text articles/publications of potentially eligible studies and then JA and the second reviewer (PKO) independently screened 100% of full-text articles for inclusion. Where disagreement occurred between the two reviewers, the last reviewer (EM) was consulted. Each step of the study selection process was documented and where a study was excluded, the reason(s) for exclusion was recorded and entered into the PRISMA flow diagram

Data extraction and management

Data were independently extracted in text, tables and figures of the included studies by the first and second researchers and recorded on a standardized, pre-designed extraction form. In the case of unclear data, corresponding authors were contacted for clarifications. Data management was the duty of the first reviewer (JA) in consultation with the second reviewer (PKO). Completed data extraction forms were maintained on both a password secured laptop and USB memory stick and exported to STATA for analysis.

The following data points were extracted from the included studies:

Study characteristics: year(s) of data collection, study design, source of data, population or participants and objectives of the study.

Study setting: country, income level, health facility level.

Outcome measures: number of individuals receiving at least one antimicrobial prescription to the number of persons attending a given health facility within a specified time period.

Risk of bias assessment

The methodological quality of studies including risk of bias was assessed using a checklist to assess for internal and external validity. A modified check list originally developed by Hoy and colleagues (42) was used to score; sampling strategies used, outcome assessment, outcome measurement and statistical reporting and higher overall scores represented higher methodological quality. Each article was independently scored by the first and second reviewers (JA and PKO) in consultation with the research advisors (EM and GM).

Treatment of missing data

Authors of articles with missing data were contacted to provide the missing data points. In cases where the missing data were impossible to obtain, full descriptions are provided about the nature of the missing data and the implications on the results of this systematic review was described.

Assessment of Heterogeneity

Forest plots were used to assess the presence of statistical heterogeneity and we assessed heterogeneity quantitatively by calculating Chi^2 (threshold $P > 0.1$) and I^2 statistics (threshold $I^2 > 40\%$). The values of I^2 were categorized for heterogeneity as follows: "not important" (0 to 40%), "moderate" (41 to 60%), "substantial" (61 to 80%), and "considerable" (81 to 100%). Where "not important" or "moderate" heterogeneity exists between studies ($I^2 \leq 40\%$), the outcomes were pooled in a meta-analysis and reported using forest plots. Where "substantial" or "considerable" heterogeneity exist between studies ($I^2 > 40\%$), the outcomes were pooled and reported in narrative form using forest plots.

Data synthesis

Data from the included studies were combined using random effects model to account for variability between studies. This is because substantial between-studies heterogeneity was anticipated considering the different study designs included in the systematic review. STATA software (College Station, Texas 77845 USA) was used to perform the meta-analysis. Subgroup analysis was done to assess antimicrobial use patterns in different East African states.

Sensitivity analysis

Sensitivity analyses was performed to assess if methodological differences in outcome measurement influenced the results of the review.

3.6 Ethical consideration

The systematic review and meta-analysis used data extracted from publicly available research articles and does not involve human or animal research participants. The study therefore poses no risks and is exempt from ethical review.

4. RESULTS

4.1 Process of selection of included studies

The literature search resulted in 4284 records from the searched 8 databases and the process followed to arrive at the final studies included in the review are summarized in Figure 1. From PubMed database, 224 records were retrieved. Results from other databases searched include: 1018 records from EBSCOhost, , 458 records from Web of Science, 1118 records from Cochrane Library, 1452 records from Scopus, 11 records and from from International Clinical Trials Registry Platform (ICTRP), 3 records from Mednar were retrieved.

After removal of 1224 duplicates, 3060 records were screened by reading the title and abstract of each record, 3010 studies were excluded for failure to meet the inclusion criteria. The excluded studies included; 204 Review articles, 905 studies from non-target regions, 1161 non-primary research studies and 70 records excluded for other reasons.

Fifty studies were eligible for a full text screening. After full text screening, 26 studies met the inclusion criteria and were thus selected as the final studies for inclusion, full text review, data extraction and systematic review**. Figure 1** shows the process followed to arrive at the final studies included in the review.

4.2 Characteristics of included studies

Characteristics of the studies included in the review are summarized in **Table 1**. Eight studies (30.8%) that met the final inclusion criteria were conducted in Ethiopia (43-50). Fifteen studies were from Sudan (51-55), Kenya (56-60) and Tanzania (61-65), each country contributing 5

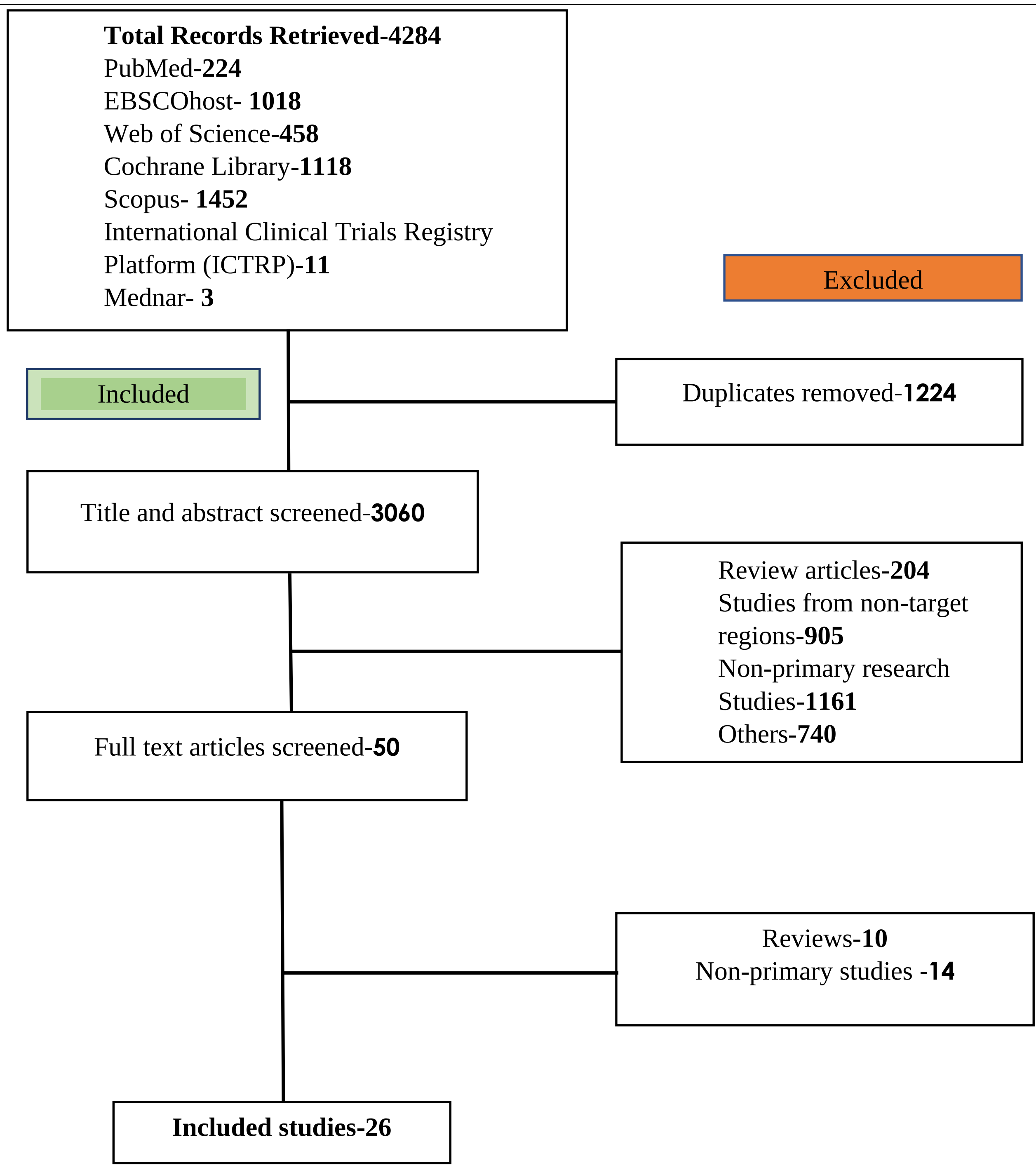

Figure 1. Flow diagram showing selection of eligible articles

studies (19.2%). Two studies (7.7%) were conducted in Eritrea (66-67), whereas 1 (3.9%) study was retrieved from Uganda (68). The included studies reported antimicrobial use among various population segments including, adult in-patients, adults attending outpatient department and children admitted in paediatric wards. In terms of study settings, included studies reported results from tertiary level (45-55) and primary level (43-44, 48-67) care settings.

Table 1. Characteristics of included studies

Author & year	Country	Drug encounter	No prescription	Mean number of prescriptions	Number of antimicrobial encounters	Injection prescription	Generic name prescription	Essential drug list prescription
Ahmed et al 2010	Sudan		600	2	488	21	296	343
Amaha et al 2018	Eritrea		100	1.29	79	82	97	100
Amaha et al 2018	Eritrea		1056		349	47		
Awad et al 2006	Sudan		1800	14.3	1332			
Awad et al 2006	Sudan		200	1.9	130	21	87	
Bilal et al 2016	Ethiopia	1426	636		525	71		
Cheraghali et al 2009	Sudan		100	2.3	66	27		
Desalegn, 2013	Ethiopia	2451	1290	1.9	749	491	1273	1246
Dessie et al 2020	Ethiopia	1580	770	1.935	578	50		
Elmannan et al 2015	Sudan		1175		284		138	
Gwimile et.al, 2012	Tanzania		384		326			
Kabede et al,2017	Ethiopia		474	2	407	407		373
Kiguba et al,2016	Uganda	1985	762		603	491		
Maina et al, 2020	Kenya		3590	2	1675			
Massele et al 2001	Tanzania		1200	2.3	420	228	906	
Massele et al,1993	Tanzania		779	2.3	310	265	616	678
Mekuria et al, 2019	Kenya		85484		2187			
Mubi et al 2013	Tanzania		195		41			
Muyu et al 2013	Kenya	1506	391	3.85	266	37	341	375
Njozi et al 2013	Tanzania		11648	2.4	2265			
Okoth et al	Kenya		269	1.8	182			
Sisay et al.,2017	Ethiopia	3503	1500	2.34	868	163		
Summoro et al.,2015	Ethiopia		100	2.085	67	38	96	
Talaam et al.,2017	Kenya		394	1.6	364	332		
Ylma & Liben, 2020	Ethiopia		751	1.96	225	162	679	648
Yimenu et al.,2019	Ethiopia		968	1.6	418	38	929	923

Operational definitions

- **Injection prescription:** Prescribing medicines given by way of syringe and a needle
- **Generic name:** A medication created to be the same as an existing approved brand name drug in dosage, safety, strength, quality and performance characteristics
- **Essential drug list prescription:** Drugs that satisfy the priority healthcare needs of the population and have evidence on efficacy, safety and comparative cost-effectiveness**.**
- **Number of antimicrobial encounters:** number of times a patient is prescribed an antimicrobial agent at any encounter at the health facility

4.3 Patterns of antimicrobial prescriptions in East Africa

The patterns of antimicrobial prescriptions assessed in this systematic review followed the recommended WHO metrics for assessing prescriptions of drugs which include; the proportion of patient encounters with antimicrobials prescriptions, proportion of patient encounters with injectable antimicrobials prescriptions, proportion of patient encounters with antimicrobial prescriptions from the essential medicines list and proportion of encounters with antimicrobial prescriptions in generic names.

4.3.1 Proportions of patient encounters with antimicrobials prescriptions in East African countries

The overall proportion of encounter with antimicrobial reported in the included studies was 57% [95%CI: 42%-73%]. Uganda had an overall patient encounter with antimicrobials of 79% [95%CI: 76%-82%] followed by Ethiopia with an overall encounter with antimicrobials of 63% [95%CI: 50%-76%] .Included studies from Sudan reported an overall encounter with antimicrobials of 62% [95%CI: 34%-85%] whereas included included studies from Kenya reported the overall encounter with antimicrobials of 54% [95%CI: 15%- 90%]. Included studies from Tanzania and Eritrea reported patient encounters with antimicrobials of 40%

[95%CI: 21%-60%]. and 37% [95%CI: 34%-40%] respectively. **Figure 2** shows the proportion of patient encounters with antimicrobial prescriptions in East African countries.

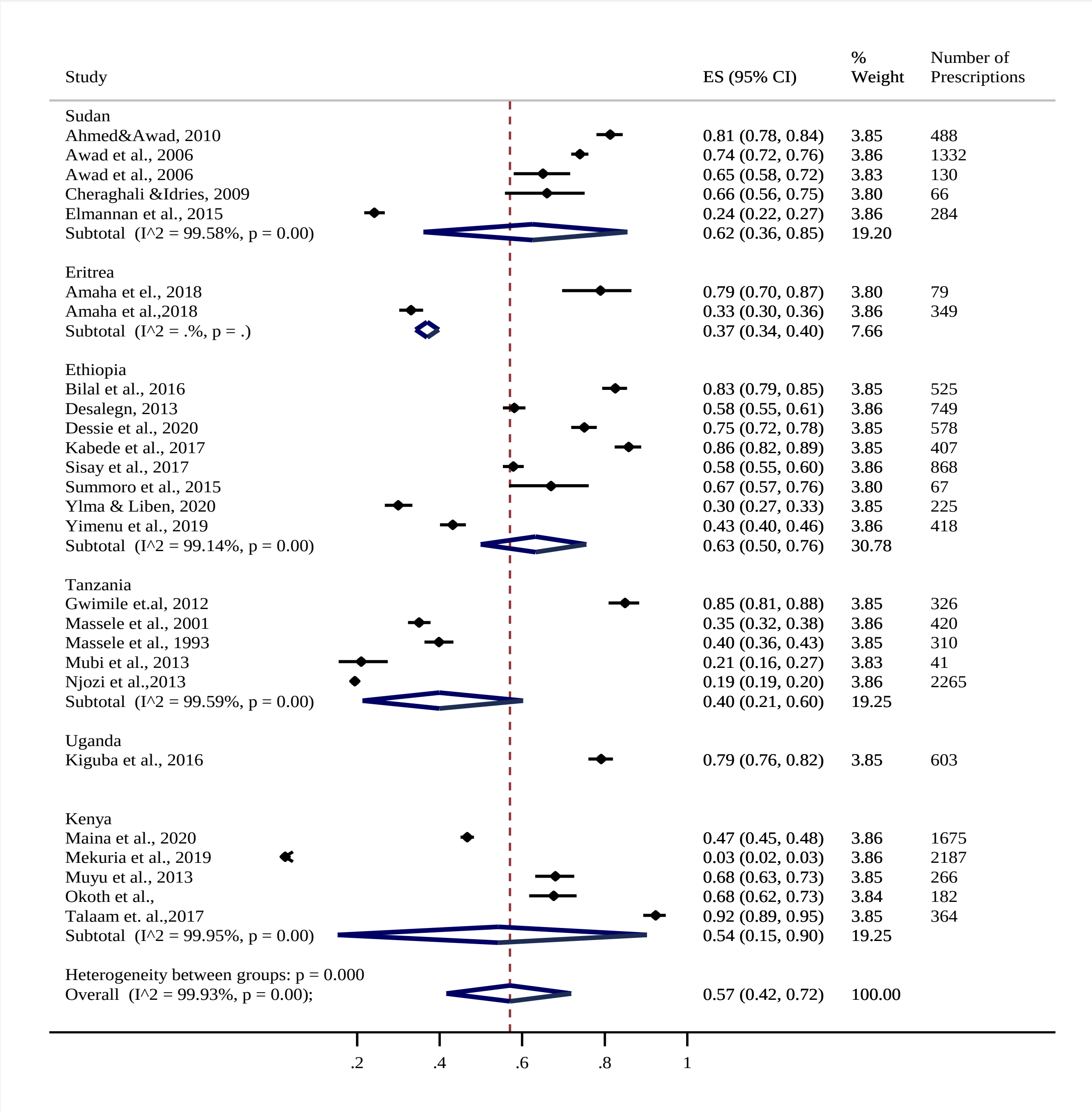

Figure 2 Forest plot showing proportions of patient encounter with antimicrobials in east African states

4.3.2 Proportion of patient encounters with injectable antimicrobials prescriptions in East African states

Eighteen studies reported patient encounters with injectable antimicrobials. Overall, patient encounter with injectable antimicrobials was 28% [95%:16%- 41%] for all the East Africa countries. Heterogeneity among the estimates reported in the papers include in the meta-analysis was 99.6%, p-value 0.000. The forest plot in **Figure 3**, shows a summary of studies reporting proportions of patient encounters with injectable antimicrobial agents.

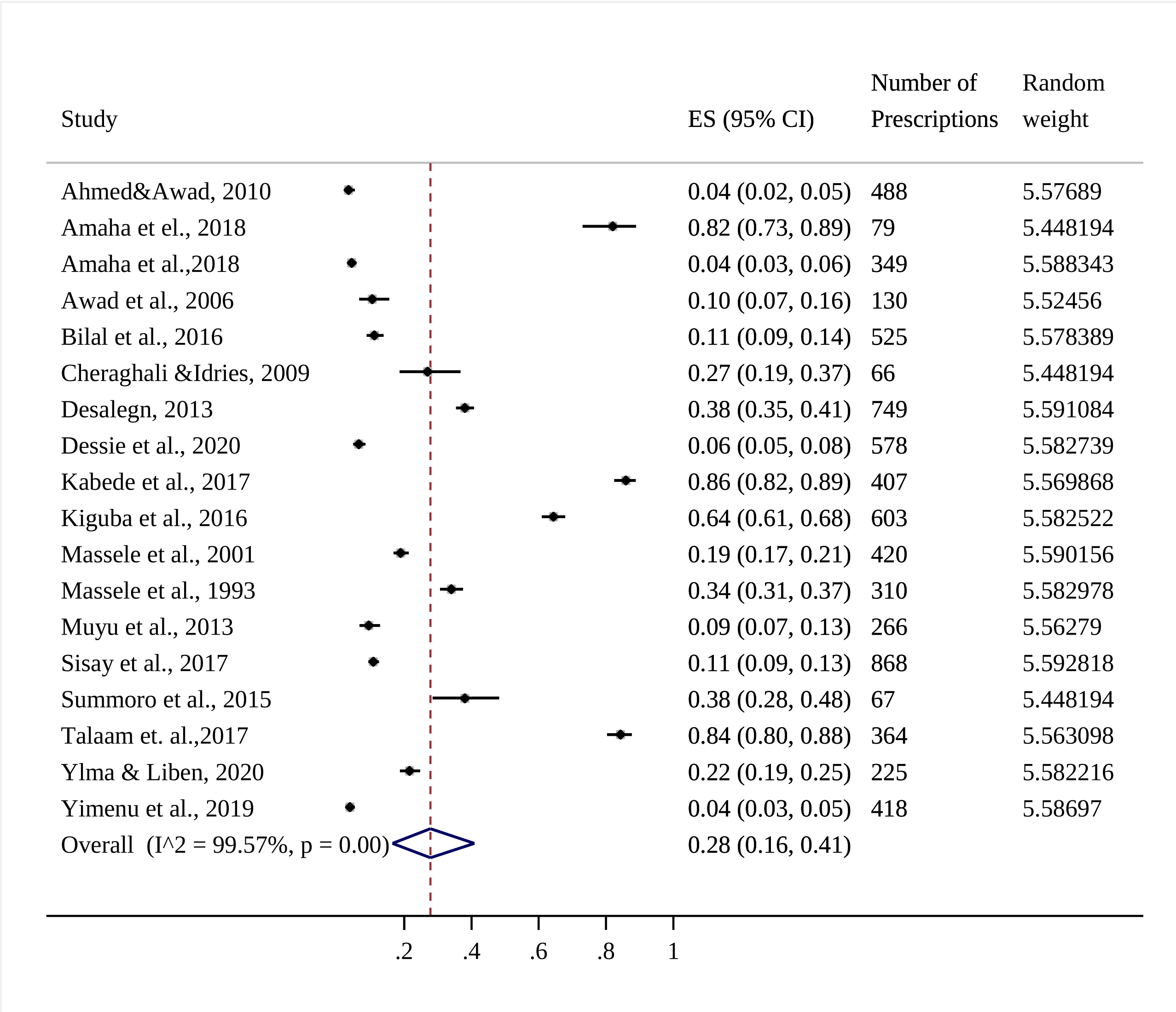

Figure 3. Proportion of encounters with injectable antimicrobials in East Africa

4.3.3 Proportion of patient encounters with antimicrobial prescriptions from the essential medicines list

Eight out of the 26 studies that met the review's inclusion criteria reported patient encounter with antimicrobial prescriptions from the essential medicines list. Overall, the proportion of prescriptions from the essential medicines list were 90% [95% CI: 81%- 96%]. **Figure 4** summarises the results from studies reporting antimicrobial prescriptions from essential medicines list.

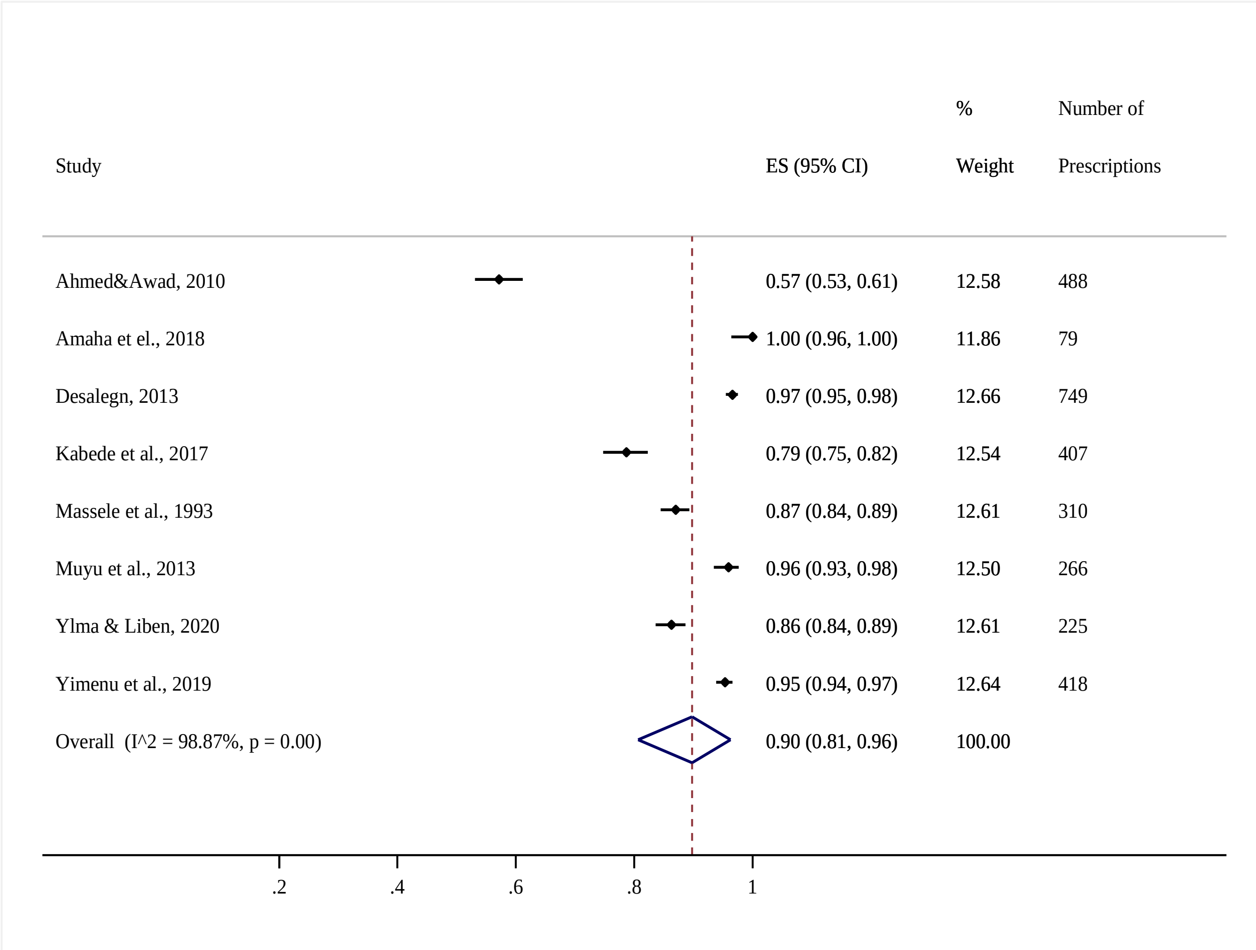

Figure 4. Proportion of encounters with antimicrobial prescriptions from essential medicines list

4.3.4 Proportion of encounters with antimicrobial prescriptions in generic names

Eleven studies reported patient encounters with antimicrobial prescriptions in generic names. Overall, prescriptions in generic names were 79% [95% CI: 58%-94%]. **Figure 5** provides a summary of proportions of patient encounters with antimicrobial prescriptions in East African countries.

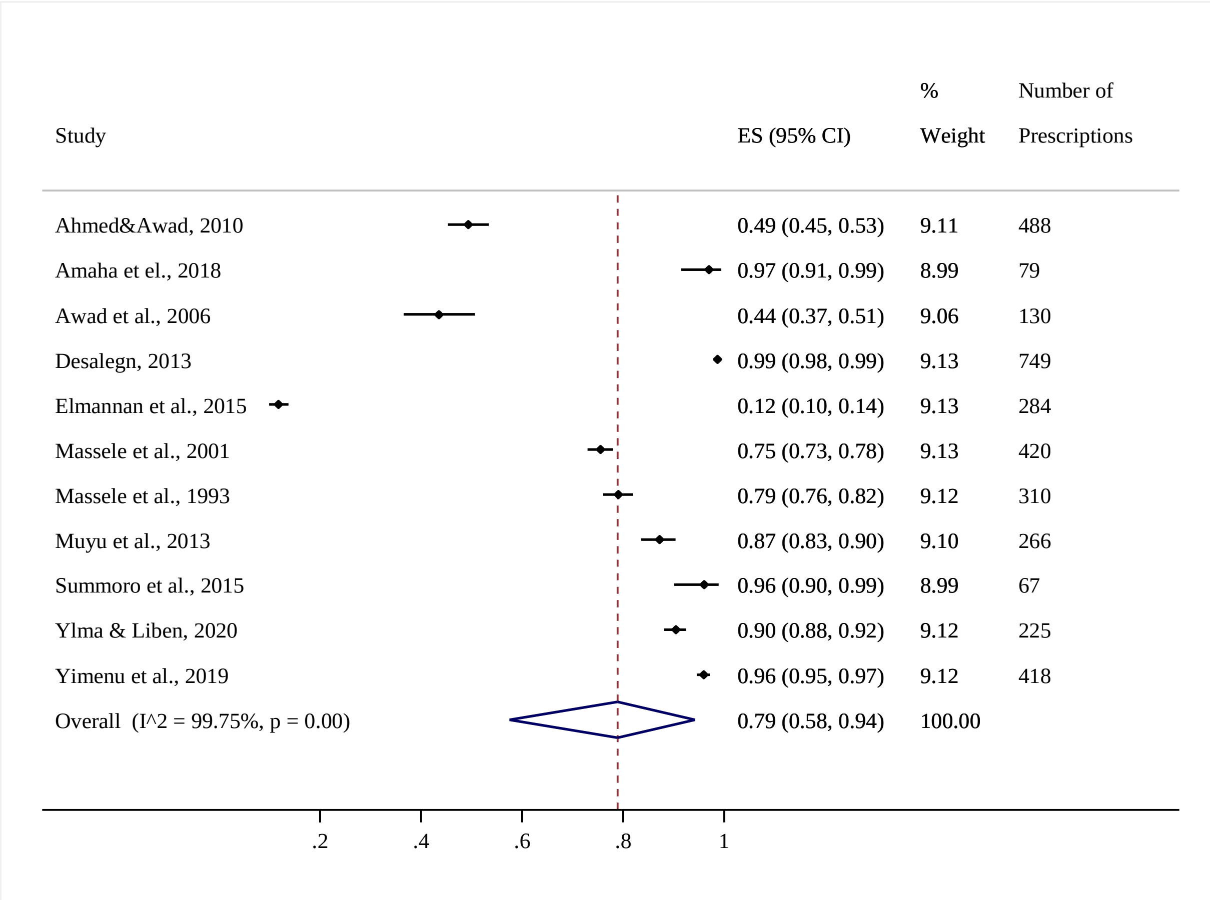

Figure 5. Proportion of encounters with antimicrobial prescriptions in generic names

4.3.5 Appropriateness of Antimicrobial prescriptions in East African countries

To assess appropriateness of antimicrobial prescriptions in East African countries, systematic review findings were compared with WHO recommended values, **Table 2**.

Table 2. Comparison of systematic review findings on patterns of antimicrobial use and WHO recommended ideal values

Patterns of drug use (including antimicrobials)	Systematic review finding estimate 95% CI	WHO recommendation [39]
% Encounters with antimicrobials	57% [42%-72%]	20% or less
% Encounter with injection prescriptions	28% [16%-41%]	10% or less
% Generic name prescribing	79% [58%-94%]	100%
%Drugs prescribed from EML	90% [81%-96%]	100%

5. DISCUSSION

According to available literature, we found the patterns of antimicrobial prescriptions across East Africa countries heterogenous. Majority of the studies (30.8%) included in this review originated from Ethiopia, followed by Sudan, Kenya and Tanzania each contributing 19.2% of the included studies. In addition, Ethiopia, Sudan, Kenya and Uganda had patient encounters with antimicrobial prescriptions greater than 50%. The least number of included studies was retrieved from Uganda (3.9%). Based upon the review, it is clear that East African countries are not at the same level reading the research-based evidence of antimicrobial resistance patterns. The results from this review demonstrates how much research is being carried in each country represented in the review regarding antimicrobial use patterns Considering the global threat posed by antimicrobial resistance, perhaps countries with few researches being carried out on use patterns and antimicrobial resistance should focus more resources on this research agenda as a matter of public health priority. The research approach to pursue could include; antimicrobial use audits and implementation of interventions in order to combat this global emergency that has far reaching health implications on the economy and health of the people in these countries.

We found a higher magnitude of patient encounter with antimicrobial agents in East Africa. Overall, patient encounter with antimicrobial agents in East Africa was 57%. This percentage of antimicrobial encounter is higher than the WHO recommended value of 20% or less (69). Furthermore, none of the countries represented in the systematic review reported lower antimicrobial prescription encounters less than the WHO recommended value of 20% or less. Several countries from East Africa were included with the hope to make meaningful comparison. The overall patient encounter with injectable antimicrobials prescriptions was found to be 28%. This is also a deviation from the ideal WHO recommended value of 10% or less for injectable prescriptions (69). Prescription of antimicrobials by generic names and prescriptions of antimicrobials from the essential medicines list were found to be lower than the recommended values 100%. The WHO provides essential drug lists from which countries generate their essential drug lists. However, countries in LMIC including East African countries have limited antimicrobial medication available on their essential list and this will be prescribed for any condition. Furthermore, increase of inappropriate antimicrobial use in low-income countries is reportedly due to weak policies in place and a poor health system with a few skilled workforces and fewer diagnostics as compared to high-income countries coupled with few of antimicrobial agents being available of essential drug lists of most countries as seen by the deviations shown with in this study.

Strengths and limitations of the review

A comprehensive literature search strategy was used to retrieve studies for inclusion in the review. High level of heterogeneity which was undertaken by using random effects model in which the effects underlying different studies assumed to be drawn from a normal distribution made a meta-analysis not credible, therefore results were synthesised narratively, and the forest plots were used for illustrative purposes only and to augment the narrative synthesis.

6. Conclusion and recommendations

Prescription patterns observed in this review shows significant deviation in the region from what WHO recommends. This suggests existence of inappropriate antimicrobial use in the region leading to antimicrobial resistance. Because of the high-level of heterogeneity among included studies in this systematic review, the reliability of pooled estimate as a measure of poor antimicrobial stewardship in East African countries was considered less reliable. The findings of this study highlight the areas for action to improve antimicrobial prescription practices.

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APPENDIX

Appendix 1: showing risk of bias assessment results

Author_details	Was the st	Was the sa	Was some	Was the li	Were data	Was an ac	Was the st	Was the sa	Were the	Summary	Summary of risk of Bia
Ahmed&Awad, 2010	1	1	0	1	1	1	1	1	1	8	Low Risk
Amaha et el., 2018	1	1	1	1	1	1	1	1	1	9	Low Risk
Amaha et al.,2018	1	1	1	1	1	1	1	1	1	9	Low Risk
Awad et al., 2006	1	1	1	1	1	1	1	1	1	9	Low Risk
Awad et al., 2006	1	1	1	1	1	1	1	1	1	9	Low Risk
Bilal et al., 2016	1	1	1	1	1	1	1	1	1	9	Low Risk
Cheraghali &Idries, 2009	1	1	1	1	1	1	1	1	1	9	Low Risk
Desalegn, 2013	1	0	0	1	1	1	1	1	1	7	Low Risk
Dessie et al., 2020	1	1	1	1	1	1	1	1	1	9	Low Risk
Elmannan et al., 2015	1	1	1	1	1	1	1	1	1	9	Low Risk
Gwimile et.al, 2012	1	1	1	1	1	1	1	1	1	9	Low Risk
Kabede et al., 2017	1	1	1	1	1	1	1	1	1	9	Low Risk
Kiguba et al., 2016	1	0	1	1	1	1	1	1	1	8	Low Risk
Maina et al., 2020	1	0	1	1	1	1	1	1	1	8	Low Risk
Massele et al., 2001	0	0	1	1	1	1	1	1	1	7	Low Risk
Massele et al., 1993	0	0	0	1	1	1	1	1	1	6	Moderate Risk
Mekuria et al., 2019	1	1	1	1	1	1	1	1	1	9	Low Risk
Mubi et al., 2013	1	1	1	1	1	1	1	1	1	9	Low Risk
Muyu et al., 2013	1	1	1	1	1	1	1	1	1	9	Low Risk
Njozi et al.,2013	0	1	1	0	1	1	1	1	1	8	Low Risk
Okoth et al., 2018	1	1	1	1	1	1	1	1	1	9	Low Risk
Sisay et al., 2017	1	1	1	1	1	1	1	1	1	9	Low Risk
Summoro et al., 2015	1	1	1	1	1	1	1	1	1	9	Low Risk
Talaam et. al.,2017	1	1	1	1	1	1	1	1	1	9	Low Risk
Ylma & Liben, 2020	1	1	1	1	1	1	1	1	1	9	Low Risk
Yimenu et al., 2019	1	1	1	1	1	1	1	1	1	9	Low Risk

Appendix 2: Search strategy for use in EBSCOhost, Web of Science, Cochrane Library, Scopus, International Clinical Trials Registry Platform (ICTRP) and Mednar databases		
Query	**Fields**	**Search term**
#1	All	((((antimicrobial) OR (antiviral)) OR (antimalarial)) OR (antifungal)) OR (antibiotic))))
#2	All	((prescription) OR (patterns))
#3	All	((East Africa))
#4	#1 AND #2 AND #3	