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Epidemiology of clinical antimicrobial-resistant *Enterobacterales* in Togo over three decades: a systematic review and meta-analysis, with recommendations and alternative solutions

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Abstract

Background According to the World Health Organization (WHO), surveillance programs have become essential at national, regional, and global levels to adjust empirical treatments and target interventions to prevent and control the emergence of antimicrobial resistance (AMR). Therefore, this study aimed to conduct the first systematic review and meta-analysis of clinical *Enterobacterales* resistance to 11 representative antimicrobials from the WHO AWaRe (Access, Watch, Reserve) list, and to provide recommendations to tackle AMR more efficiently in Togo.

Methods The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (The PRISMA 2020) were used to conduct this study and the protocol was registered with PROSPERO (CRD42024606897). Keywords were used to conduct a systematic literature review of electronic databases. Data analysis was conducted using Stata software version 17.0.

Results Twenty research articles reporting 9,327 clinical *Enterobacterales* isolates obtained from 1991 to 2020 were included in this review and were mainly *Escherichia coli* (6,639; 71.2%), and *Klebsiella* spp. (2,542; 27.3%), mainly isolated from urine (14 studies; 70%), and pus/wounds (12; 60%). The pooled *Enterobacterales* resistance rates ranged from 1% (95% CI: 0, 2) imipenem, 3% (95% CI: 1, 5) amikacin, 4% (95% CI: 2, 7) fosfomycin, 50% (95% CI: 40, 60) chloramphenicol, 55% (95% CI: 45, 64) gentamicin, 68% (95% CI: 59, 76) ciprofloxacin, 73% (95% CI: 66, 80) amoxicillin/clavulanic acid (AMC), 79% (95% CI: 71, 86) third-generation cephalosporins (3GC), to 90% (95% CI: 86, 93) sulfamethoxazole/trimethoprim (SXT). The most significant upward trend over 30 years was reported for SXT ($R^2 = 73.24\%$, $p < 0.001$), ciprofloxacin ($R^2 = 61.44\%$, $p < 0.001$), and 3GC ($R^2 = 18.49\%$, $p < 0.001$). *Klebsiella* spp. strains

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were significantly more resistant to chloramphenicol ($p = 0.03$) than *E. coli* isolates, whereas *E. coli* isolates were significantly more resistant to amikacin ($p = 0.04$) than *Klebsiella* spp. isolates.

Conclusion This study revealed high first-line AMR rates with drastic upward trends in clinical *Enterobacterales* isolated in Togo over the past 30 years. Thus, the adjustment of empirical antimicrobial treatments in Togo becomes crucial. Moreover, the implementation of prevention policies, whole-genome sequencing approaches, and the promotion of antibiotic stewardship must be enhanced. Finally, alternative therapeutic approaches, such as phytotherapy and phage therapy, were discussed.

Clinical Trial Not applicable.

Keywords Africa, Critical priority bacteria, *Escherichia coli*, *Klebsiella pneumoniae*, MDR bacteria

Introduction

Antimicrobial resistance (AMR) has emerged as a major global health crisis, placing a significant economic burden on healthcare systems [1, 2]. Currently, AMR is the second leading cause of death in low-income countries, claiming more lives than AIDS/HIV or malaria [3, 4]. In Africa, particularly in the Western region, the AMR-attributable death rate per 100,000 people is the highest among African regions [27.3 (95% CI: 20.9, 35.3)] [3]. A critical concern is AMR in *Enterobacterales*, which is particularly alarming due to the spread of multidrug-resistant (MDR) strains, including those resistant to last-resort antimicrobials, which are challenging to treat.

Togo is a western African country (Fig. 1) with a total land area of 54,390 km^2, a population of 9,586,743 (approximately 0.12% of the total world population), and a population density of 175 per Km^2. Approximately 43.6% of the population is urban and the median age of the population is 18.9 years [5]. Togo is bordered by Benin, Burkina Faso, Ghana, and the Atlantic Ocean. In Togo, the health care system includes both public and private settings. Nevertheless, public hospitals are the most attended by the population and include three university teaching hospitals, and more than 200 other public facilities (regional hospitals, prefectural hospitals, district hospitals, medical-social centers, and peripheral care units) [6]. The life expectancy at birth was 63.9 years in 2021 and gross national income per capita in Togo was 921.69 USD in 2023 [7].

The healthcare system in Togo is fragile. Many factors contribute to the subpar healthcare system in Togo, including insufficient staff, outdated medical instruments and practices, and ineffective financial and insurance resources. The number of hospital beds per 10,000 people was 5.8 in 2019, while the density of physicians per 10,000 people was only 0.8 in 2022 [8]. Only 4.4% of the population is covered by mandatory health insurance (MHI), and nearly all the people covered by the MHI are public-sector workers. For the remaining 95.6% of the Togolese population, access to healthcare is highly contingent on out-of-pocket payments [9]. Therefore, quick access to high-quality medical treatment is a challenge in Togo. Nevertheless, efforts are being made to improve the inadequate healthcare system in Togo. In addition to the government's efforts, several international organizations, such as the Global Fund, the Bill & Melinda Gates Foundation, the World Health Organization (WHO), and the United Nations International Children's Emergency Fund (UNICEF), have contributed to financing research, building medical facilities, and subsidizing the screening and treatment of various diseases [10]. In Togo, the burden of AMR is compounded by limited resources, inadequate surveillance systems, and poor access to quality healthcare and antibiotics. Efforts have been made by public health authorities to reduce the burden of AMR in Togo; however, there is still a long way to go. Two representative studies have reported *Enterobacterales* as the most isolated clinical bacterial family in Togo, with prevalences of 57.6% and 61.9% [11, 12]. Indeed, in low-income countries, the scarcity of impactful national AMR committees and representative research on AMR tends to underestimate the real extent of the AMR burden.

To contribute to the surveillance of AMR and assess the epidemiology of antimicrobial-resistant clinical *Enterobacterales*, including those classified as critical priority by the WHO pathogens [i.e., third-generation cephalosporins (3GC)-resistant and/or carbapenem-resistant isolates] [13] in Togo, we conducted the first comprehensive systematic review and meta-analysis of *Enterobacterales* resistance to 11 medically relevant antimicrobials from the WHO AWaRe (Access, Watch, Reserve) list. We analyzed trends in the epidemiology of AMR in *Enterobacterales* in Togo over the last 30 years, assessing the most prevalent resistance mechanisms. Additionally, we identified temporal patterns of AMR by determining the pooled resistance rates and trends for each antimicrobial over the years. Based on this analysis, we provided recommendations and alternative solutions to track and tackle AMR more efficiently in the country, along with actionable steps to mitigate its impact.

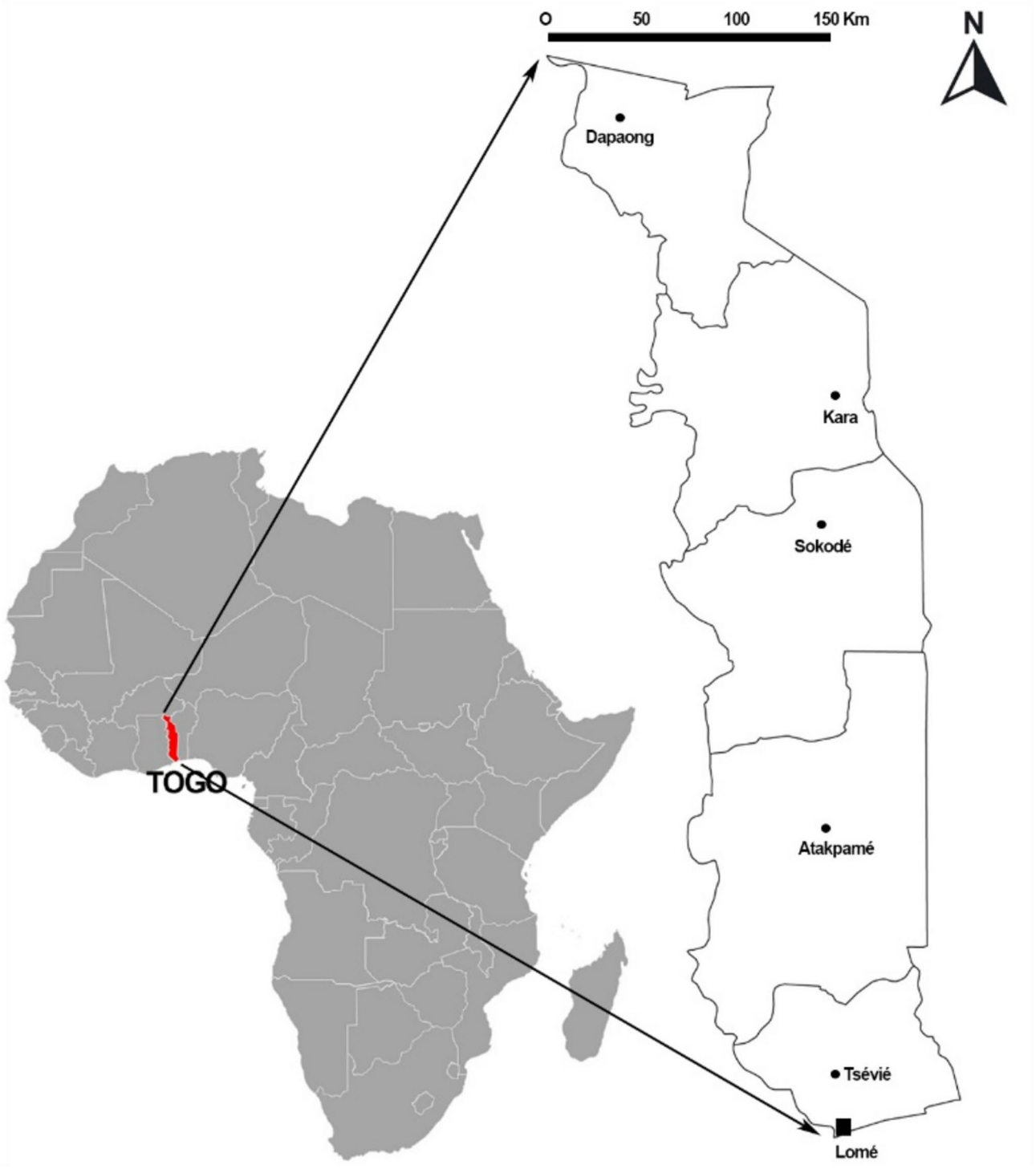

Fig. 1 Map of Togo

Methods

Selection of antimicrobials whose resistance was assessed

The 11 antimicrobials selected for this study included five antimicrobials in the access group [amoxicillin/clavulanic acid (AMC), amikacin, gentamicin, sulfamethoxazole/trimethoprim (SXT), and chloramphenicol], four in the watch group (cefotaxime, ceftriaxone, ceftazidime, and ciprofloxacin), and two in the reserve group (fosfomycin, and imipenem), according to the WHO classification [14].

Guidelines and protocol registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (The PRISMA 2020) [15] were used as guidelines to conduct this systematic reviews and meta-analysis. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with registration identification number of (CRD42024606897).

Search strategy and selection of studies

The search strategy and selection of studies were as follows:

- Systematic literature review on electronic databases using key words "antimicrobial resistance", "antibiotic resistance," "antibiotic susceptibility," and "Togo".
- The electronic databases were: Google Scholar, African Journals Online, PubMed, ResearchGate, Embase, and Scopus.
- Articles published in English or French languages were included to ensure the availability of relevant and comprehensive data.
- The database search was conducted from October 30, 2024, to November 10, 2024.

Eligibility criteria

Original peer-reviewed research articles reporting antimicrobial susceptibility testing (AST) results for *Enterobacterales* strains isolated from humans in Togo were included. The selected studies included the AST results for at least one of the 11 selected antimicrobials. Non-peer-reviewed articles reporting AST results of *Enterobacterales* strains isolated in Togo were excluded to ensure the inclusion of only reliable data. Any research articles reporting AST results for *Enterobacterales* strains isolated from countries other than Togo were also excluded. Research articles reporting AST results for bacteria isolated from non-human samples (i.e., animals, the environment, and food) were excluded, as one of the objectives of our study was to contribute to the adjustment of empirical antimicrobial treatments for Togolese patients. Review and commentary articles were also excluded.

Quality assessment

Two authors assessed the quality of eligible articles using the Joanna Briggs Institute (JBI) prevalence critical appraisal tool [16]. The JBI prevalence appraisal tool includes 10 questions for each article to be answered Yes (Y) or No (N). A positive answer (Y) was worth 10% and the total number of points that could be obtained for an article was 100%. Studies with a score of ≥ 50% were considered to be of good quality and, were therefore, included in the analyses (Additional file 1). The full text of each article, including the abstract and title, was used for the quality assessment.

Data extraction

For each article included in this study, three authors collected the following essential data: year of publication, reference number, sample collection period, type of study, sample, total number of bacteria, number of bacteria resistant to each of the 11 selected antimicrobials, species or genera of isolated bacteria, and the method used for AST. The three authors compared their extraction outputs, corrected, completed, and validated the data.

Statistical analyses

Data analyses were conducted using Stata software, version 17.0 (Stata Corp., College Station, Texas, USA). A random-effects model analysis was used to estimate the pooled resistance rates. Commands such as '*metaprop*' was used to produce forest plots of resistance rates, '*metafunnel*', and '*metabias*' (Egger test) to produce funnel plot and assess the presence of publication bias, and '*meta regress*' and '*estat bubble plot*' to perform meta-regression analyses and produce the bubble plots assessing trends of antibiotic resistance rates over the years. All the pooled prevalences were presented with a 95% confidence interval (CI), and corresponding p-values. Statistical significance was set at $p < 0.05$. In addition, we assessed the potential differences between the resistance rates of *Escherichia coli* and *Klebsiella* spp. isolates. For each antimicrobial, the pooled resistance of *E. coli* isolates was compared to that of *Klebsiella* spp. isolates using the command '*metaprop*', and a forest plot was generated with I^2 and p-values for the overall and subgroups.

Results

Selection of studies

The literature search of electronic databases generated 165 articles. Subsequently, 45, 12, 85, 1, and 2 studies were excluded for duplication, being review and commentary articles, samples collected from countries other than Togo, not being peer-reviewed, and reporting only samples from non-human sources (Fig. 2). The remaining 20 research articles [11, 12, 17–34], were included in this systematic review and meta-analysis, and the data extracted from these 20 articles are listed in the Additional file 2.

Characteristics of included studies

The article quality assessment using the JBI prevalence critical appraisal tool provided an overall risk of publication bias assessment score of 92.5% (Additional file 1). Thirteen of the 20 studies stated the study type and included cross-sectional studies (6; 46.1%), retrospective

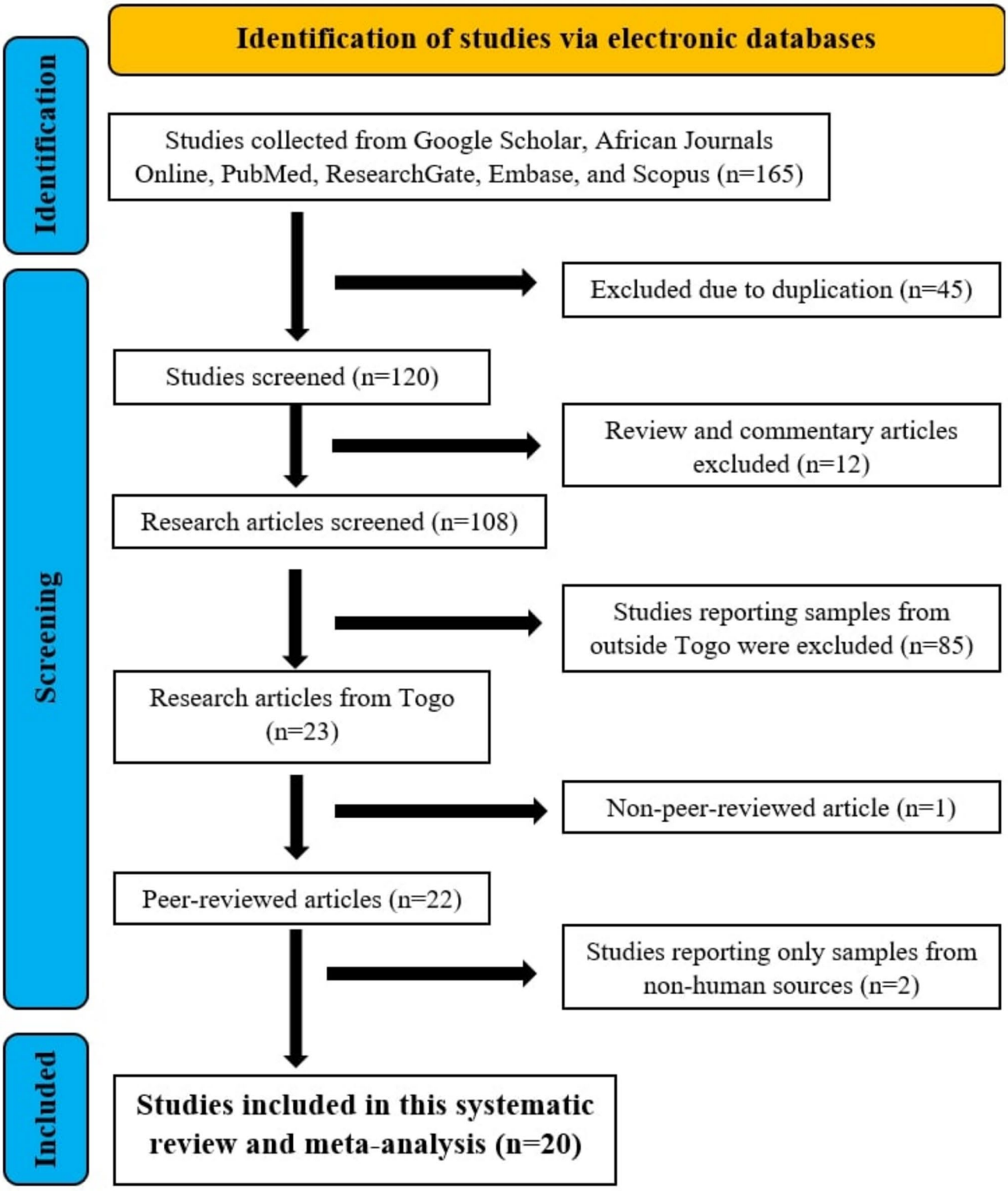

Fig. 2 Diagram search flow

studies (3; 23.1%), prospective studies (3; 23.1%), and a descriptive study (1; 7.7%). A total of 9,327 bacterial strains belonging to the *Enterobacterales* order were reported in the 20 studies. The years of publication were (2003, 2014, 2015, 2017, 2020, 2021, 2023; $n = 1$ article), (2016, 2022, 2024; $n = 2$), (2018; $n = 3$), and (2019; $n = 4$). These strains were isolated over 30 years (1991–2020) and included *E. coli* (6,639; 71.2%), *Klebsiella* spp. (2,542;

27.3%), *Enterobacter* spp. (95; 1.02%), *Proteus* spp. (11; 0.12%), *Citrobacter* spp. (7; 0.08%), *Salmonella* spp. (2; 0.02%) and *Yersinia* spp. (1; 0.01%). One study reported 30 bacterial strains (*E. coli*, *Salmonella* spp., *P. mirabilis*) without stating the number of strains per species or genus. All the 20 studies reported the samples from which the *Enterobacterales* strains were isolated and included urine (14 studies; 70%), pus/wound (12; 60%), genital tract swabs and semen (7; 35%), stool (7; 35%), blood (4; 20%), respiratory tract/throat swabs (2; 10%), sputum (2; 10%), articular and joint fluid (2; 10%), ascitic fluid (1; 5%), and lumbar puncture (1; 5%). All the 20 studies reported the method used for AST and included the Kirby-Bauer disc diffusion method (20 studies; 100%), and gradient diffusion strip (E-test) (1 study; 5%).

The studies included in this review reported only phenotypic resistance results, without mentioning enzyme production markers such as extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, carbapenemases production, or related AMR genes.

Resistance of *Enterobacterales* to access group antibiotics

AMC

Pooled resistance rate Seventeen of the 20 studies reported the AMC resistance rates. The total number of strains was 8,919 with 5,927 AMC-resistant *Enterobacterales*. The pooled resistance rate was 73% (95% CI: 66, 80), $p < 0.001$. A large discrepancy in the AMC resistance rate was observed among the included studies, ranging from 24% (95% CI: 14, 36) to 100% (95% CI: 93, 100). A significantly high level of heterogeneity was observed among studies ($I^2 = 95.76\%$, $p < 0.001$) (Fig. 3; Table 1).

Of the 6,144 *E. coli* isolates tested, 4,061 AMC-resistant were reported, with a pooled prevalence of AMC-resistant *E. coli* of 68% (95% CI: 59, 77), $p < 0.001$ (Additional file 3 and Table 1). Of the 2,268 *Klebsiella* spp. isolates

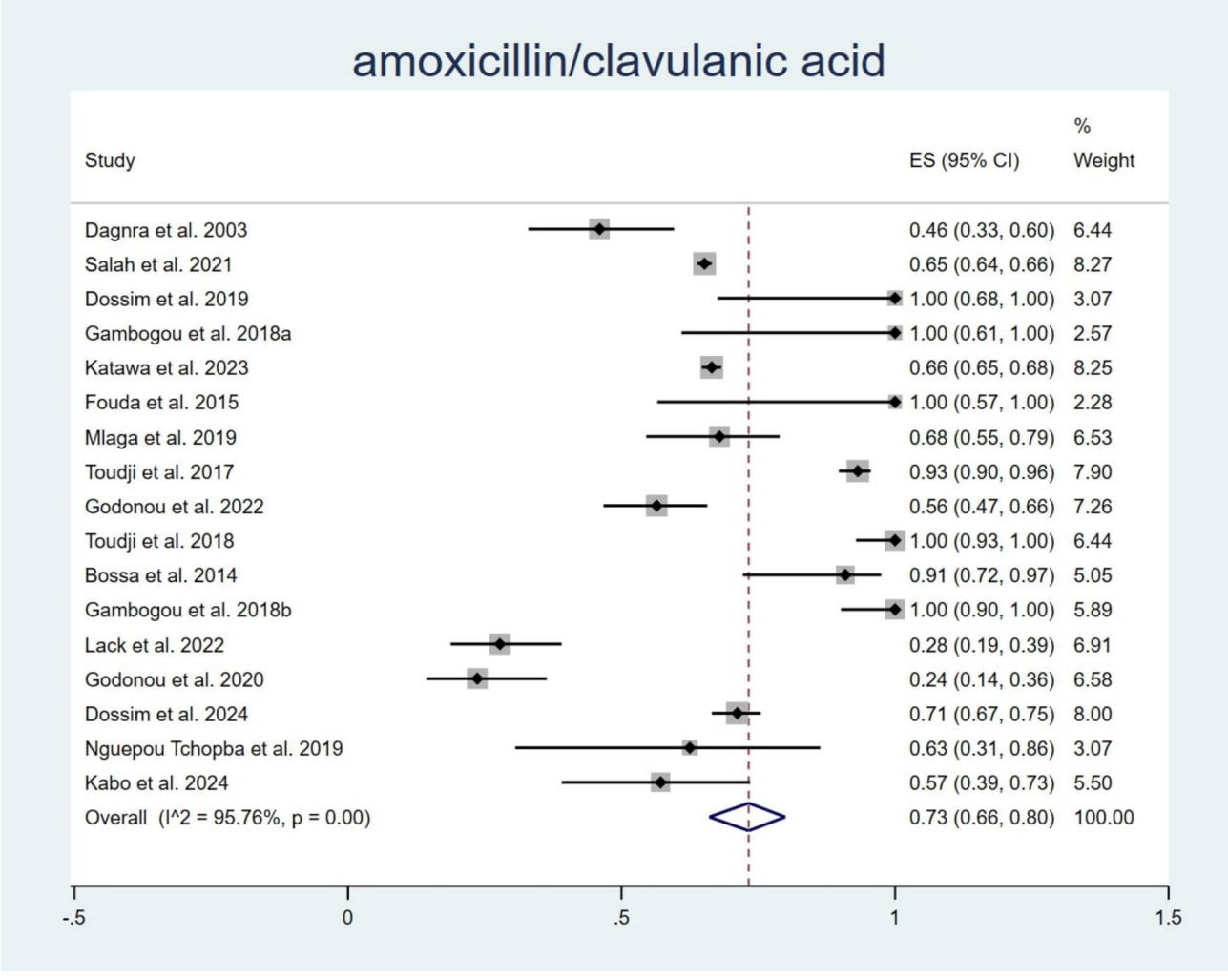

Fig. 3 Forest plot showing the pooled AMC resistance rate from random-effect model analysis

Table 1 Summary of pooled resistance rates

Antimicrobial	All the *Enterobacterales*		Comparison *E. coli* vs. *Klebsiella* spp.		
	Overall pooled resistance rate	Heterogeneity between studies (*p*-value)	Pooled resistance rate *E. coli*	Pooled resistance rate *Klebsiella* spp.	Heterogeneity between pooled resistance rates (*p*-value)
SXT	90% (95% CI: 86, 93)	**< 0.001**	94% (95% CI: 90, 97)	93% (95% CI: 85, 99)	0.87
3GC	79% (95% CI: 71, 86)	**< 0.001**	79% (95% CI: 68, 88)	83% (95% CI: 73, 92)	0.50
AMC	73% (95% CI: 66, 80)	**< 0.001**	68% (95% CI: 59, 77)	76% (95% CI: 59, 89)	0.41
Ciprofloxacin	68% (95% CI: 59, 76)	**< 0.001**	74% (95% CI: 64, 84)	68% (95% CI: 51, 82)	0.52
Gentamicin	55% (95% CI: 45, 64)	**< 0.001**	49% (95% CI: 38, 61)	67% (95% CI: 52, 81)	0.06
Chloramphenicol	50% (95% CI: 40, 60)	**< 0.001**	40% (95% CI: 27, 53)	59% (95% CI: 48, 70)	**0.03**
Fosfomycin	4% (95% CI: 2, 7)	**< 0.001**	0% (95% CI: 0, 2)	3% (95% CI: 0, 10)	0.07
Amikacin	3% (95% CI: 1, 5)	**< 0.001**	0% (95% CI: 0, 2)	0% (95% CI: 0, 0)	**0.04**
Imipenem	1% (95% CI: 0, 2)	**< 0.001**	0% (95% CI: 0, 0)	0% (95% CI: 0, 1)	0.30

tested, 1,502 AMC-resistant were reported, with a pooled prevalence of AMC-resistant *Klebsiella* spp. of 76% (95% CI: 59, 89), $p < 0.001$ (Additional file 3 and Table 1). There was no significant difference between the pooled AMC resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.41$) (Additional file 3 and Table1).

Publication bias The funnel plot showed an absence of publication bias with 53% of the studies skewed to the right side of the triangular zone (Fig. 4A). The Egger's test also supported the absence of publication bias ($p = 0.619$), with a bias coefficient of 0.31.

Trend of AMC resistance rate over the years Meta-regression analysis of AMC resistance rates in *Enterobacterales* strains isolated in Togo over 30 years (1991–2020) revealed a significant upward trend ($R^2 = 8.99\%$, $p = 0.022$) (Fig. 5A).

Amikacin

Pooled resistance rate Seventeen of the 20 studies reported amikacin resistance rates. The total number of strains tested was 9,130, including 189 amikacin-resistant strains. The pooled resistance rate was 3% (95% CI: 1, 5), $p < 0.001$. A large discrepancy in the amikacin resistance rate was observed among the included studies, ranging from 0% (95% CI: 0, 4) to 36% (95% CI: 20, 57). A significantly high level of heterogeneity was observed among the studies ($I^2 = 86.73\%$, $p < 0.001$) (Fig. 6; Table 1).

Of the 6,299 *E. coli* isolates tested, 148 amikacin-resistant strains were reported, with a pooled prevalence of amikacin-resistant *E. coli* of 0% (95% CI: 0, 2), $p < 0.001$ (Additional file 3 and Table1). Of the 2,367 *Klebsiella* spp. strains tested, 23 amikacin-resistant were reported, with a pooled prevalence of amikacin-resistant *Klebsiella* spp. of 0% (95% CI: 0, 0), $p < 0.001$ (Additional file 3 and Table 1). The pooled amikacin resistance rate of *E. coli* was significantly higher than that of *Klebsiella* spp. ($p = 0.04$) (Additional file 3 and Table1).

Publication bias The funnel plot showed the presence of publication bias (Fig. 4B). The Egger's test also supported the presence of publication bias ($p = 0.017$), with a bias coefficient of 0.47.

Trend of amikacin resistance rate over the years Meta-regression analysis of amikacin resistance rates in *Enterobacterales* strains isolated in Togo over 12 years (2009–2020) did not reveal any significant variation ($R^2 < 0.001\%$, $p = 0.639$) (Fig. 5B).

Gentamicin

Pooled resistance rate Eighteen of the 20 studies reported gentamicin resistance rates. The total number of strains was 8,857, including 3,642 gentamicin-resistant strains. The pooled resistance rate was 55% (95% CI: 45, 64), $p < 0.001$. A large discrepancy in gentamicin resistance rate was observed among the included studies, ranging from 0% (95% CI: 0, 39) to 90% (95% CI: 79, 96). A significantly high level of heterogeneity was observed among the studies ($I^2 = 97.64\%$, $p < 0.001$) (Fig. 7; Table 1).

Of the 6,026 *E. coli* strains tested, 2,251 gentamicin-resistant strains were reported, with a pooled prevalence of gentamicin-resistant *E. coli* of 49% (95% CI: 38, 61), $p < 0.001$ (Additional file 3 and Table 1). Of the 2,320 *Klebsiella* spp. isolates tested, 1,118 gentamicin-resistant were reported, with a pooled prevalence of gentamicin-resistant *Klebsiella* spp. of 67% (95% CI: 52, 81), $p < 0.001$ (Additional file 3 and Table 1). There was no significant difference between the pooled resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.06$) (Additional file 3 and Table1).

Publication bias The funnel plot showed the presence of publication bias, with 61% of the studies skewed to the

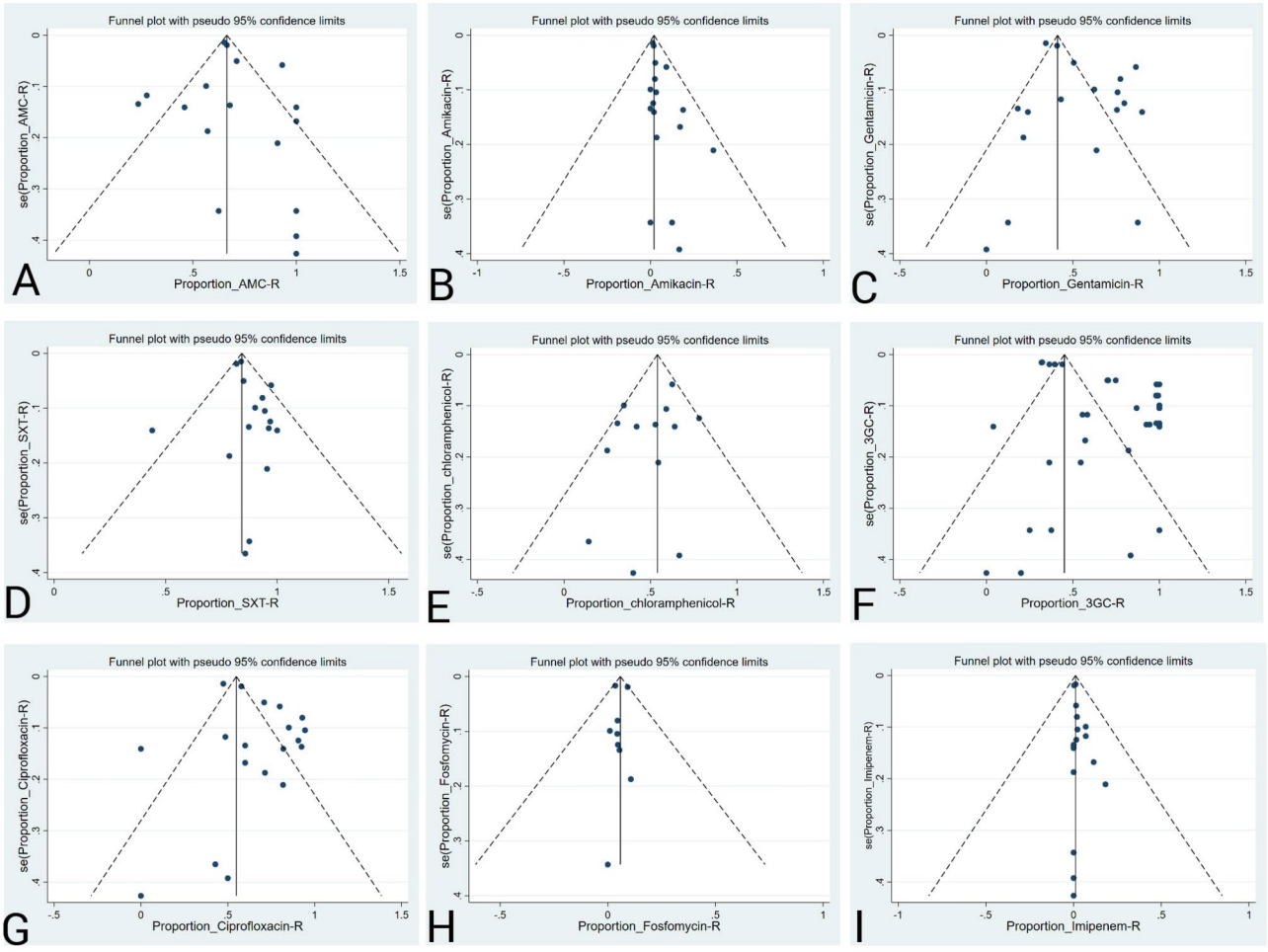

Fig. 4 Funnel plots on antimicrobial resistance rate in Togo. **A**: AMC; **B**: amikacin; **C**: gentamicin; **D**: SXT; **E**: chloramphenicol; **F**: 3GC; **G**: ciprofloxacin; **H**: fosfomycin; **I**: imipenem

right side of the triangular zone (Fig. 4C). The Egger's test also supported the presence of publication bias ($p = 0.036$), with a bias coefficient of 1.92.

Trend of gentamicin resistance rates over the years Meta-regression analysis of gentamicin resistance rates in *Enterobacterales* strains isolated in Togo over 30 years (1991–2020) revealed a significant increase ($R^2 = 12.67\%$, $p = 0.006$) (Fig. 5C).

SXT

Pooled resistance rate Sixteen of the 20 studies reported the SXT resistance rates. The total number of strains was 8,493 including 7,146 SXT-resistant *Enterobacterales* isolates. The pooled *Enterobacterales* resistance rate was 90% (95% CI: 86, 93), $p < 0.001$. A large discrepancy in SXT resistance rate was observed among the included studies, ranging from 44% (95% CI: 31, 58) to 100% (95% CI: 93, 100). A significantly high level of heterogeneity was observed among the studies ($I^2 = 91.98\%$, $p < 0.001$) (Fig. 8; Table 1).

Of the 5,798 *E. coli* strains tested, 5,003 resistant to SXT were reported, with a pooled prevalence of SXT-resistant *E. coli* of 94% (95% CI: 90, 97), $p < 0.001$ (Additional file 3 and Table1). Of the 2,203 *Klebsiella* spp. strains tested, 1,732 SXT-resistant were reported, with a pooled prevalence of SXT-resistant *Klebsiella* spp. of 93% (95% CI: 85, 99), $p < 0.001$ (Additional file 3 and Table1). There was no significant difference between the pooled resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.87$) (Additional file 3 and Table 1).

Publication bias The funnel plot showed the presence of publication bias, with 75% of the studies skewed to the right side of the triangular zone (Fig. 4D). However, the Egger's test revealed an absence of publication bias ($p = 0.22$), with a bias coefficient of 0.49.

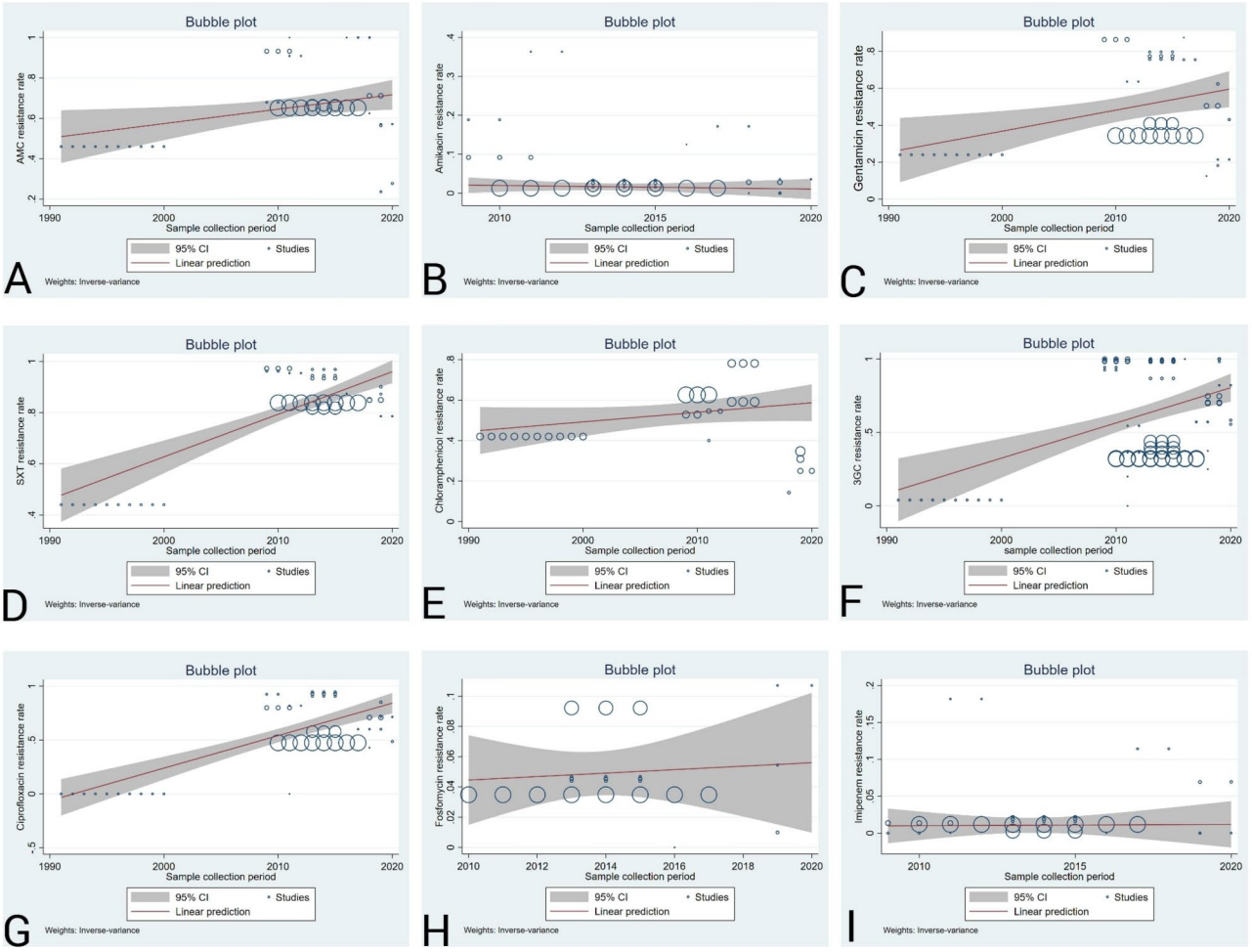

Fig. 5 Meta-regressions of antimicrobial resistance rates in *Enterobacterales* strains isolated in Togo from 1991 to 2020. **A**: AMC; **B**: amikacin; **C**: gentamicin; **D**: SXT; **E**: chloramphenicol; **F**: 3GC; **G**: ciprofloxacin; **H**: fosfomycin; **I**: imipenem

Trend of SXT resistance rates over the years Meta-regression analysis of SXT resistance rates in *Enterobacterales* strains isolated in Togo over 30 years (1991–2020) revealed a significant increase ($R^2 = 73.24\%$, $p < 0.001$) (Fig. 5D).

Chloramphenicol

Pooled resistance rate Thirteen of the 20 studies reported chloramphenicol resistance rates. The total number of strains was 823, including 445 chloramphenicol-resistant *Enterobacterales* strains. The pooled resistance rate was 50% (95% CI: 40, 60), $p < 0.001$. A large discrepancy in chloramphenicol resistance rate was observed among the included studies, ranging from 14% (95% CI: 3, 51) to 78% (95% CI: 67, 86). A significantly high level of heterogeneity was observed among the studies ($I^2 = 83.63\%$, $p < 0.001$) (Fig. 9; Table 1).

Of the 463 *E. coli* strains tested, 212 were resistant to chloramphenicol, with a pooled prevalence of chloramphenicol-resistant *E. coli* of 40% (95% CI: 27, 53), $p < 0.001$ (Additional file 3 and Table 1). Of the 263 *Klebsiella* spp. strains tested, 161 chloramphenicol-resistant were reported, with a pooled prevalence of chloramphenicol-resistant *Klebsiella* spp. of 59% (95% CI: 48, 70), $p = 0.03$ (Additional file 3 and Table1). The pooled chloramphenicol resistance rate of *Klebsiella* spp. was significantly higher than that of *E. coli* ($p = 0.03$) (Additional file 3 and Table 1).

Publication bias The funnel plot showed the absence of publication bias, with 53% of the studies skewed to the left side of the triangular zone (Fig. 4E). The Egger's test also supported the absence of publication bias ($p = 0.221$), with a bias coefficient of -0.90.

Trend of chloramphenicol resistance rate over the years Meta-regression analysis of chloramphenicol resistance rates in *Enterobacterales* strains isolated in Togo

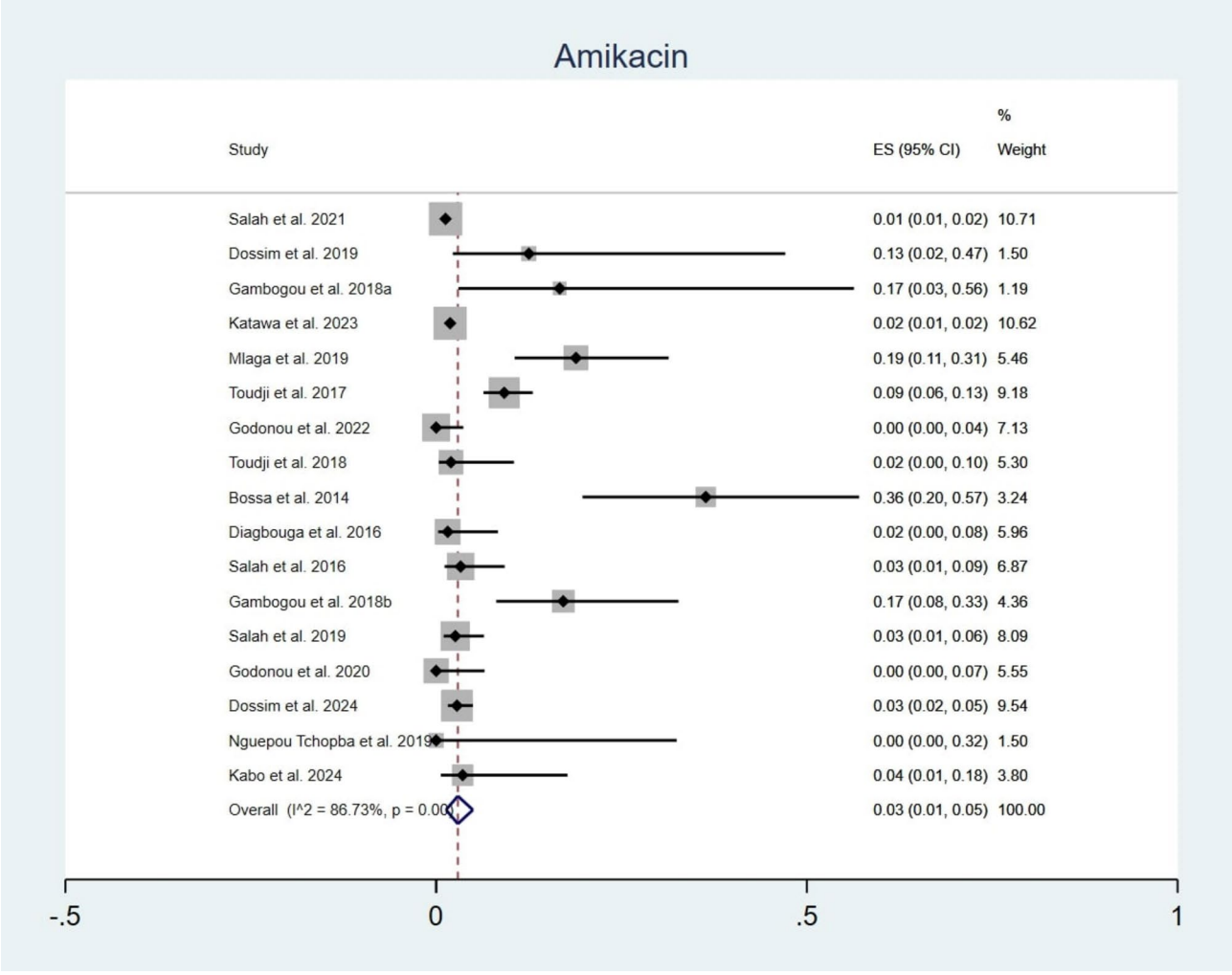

Fig. 6 Forest plot showing the pooled amikacin resistance rate from random-effect model analysis

over 30 years (1991–2020) did not reveal any significant variation ($R^2 = 23.25\%$, $p = 0.13$) (Fig. 5E).

Resistance of *Enterobacterales* to watch group antimicrobials

3GC

Pooled resistance rates Fourteen, 13, and 18 of the 20 studies reported resistance rates to cefotaxime, ceftriaxone and ceftazidime, respectively. The total number of *Enterobacterales* strains tested was 3,878 including 2,054 cefotaxime-resistant strains; 8,296 including 3,469 ceftriaxone-resistant strains, and 8,194 including 3,655 ceftazidime-resistant strains. The pooled resistance rate for the 3GC-resistant *Enterobacterales* was 79% (95% CI: 71, 86), $p < 0.001$. A large discrepancy in the 3GC resistance rate was observed among the included studies, ranging from 0% (95% CI: 0, 43) to 100% (95% CI: 99, 100). A significantly high level of heterogeneity was observed among the studies ($I^2 = 99.24\%$, $p < 0.001$) whereas heterogeneity was not observed between the three groups ($p = 0.934$) (Fig. 10; Table 1). The pooled resistance rates were 76% (95% CI: 51, 94), $p < 0.001$ for cefotaxime, 79% (95% CI: 65, 90), $p < 0.001$ for ceftazidime, and 80% (95% CI: 64, 93), $p < 0.001$ for ceftriaxone (Fig. 10).

Of the 13,807 *E. coli* strains tested, 5,568 were identified as resistant to 3GC with a pooled prevalence of 3GC-resistant *E. coli* of 79% (95% CI: 68, 88), $p < 0.001$ (Additional file 3 and Table1). Of the 5,127 *Klebsiella* spp. strains tested, 2,560 3GC-resistant strains were reported, with a pooled prevalence of 3GC-resistant *Klebsiella* spp. of 83% (95% CI: 73, 92), $p < 0.001$ (Additional file 3 and Table1). There was no significant difference between the pooled 3GC resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.50$) (Additional file 3 and Table 1).

Publication bias The funnel plot showed the presence of publication bias, with 66% of the studies skewed to the right side of the triangular zone (Fig. 4F). The Egger's test

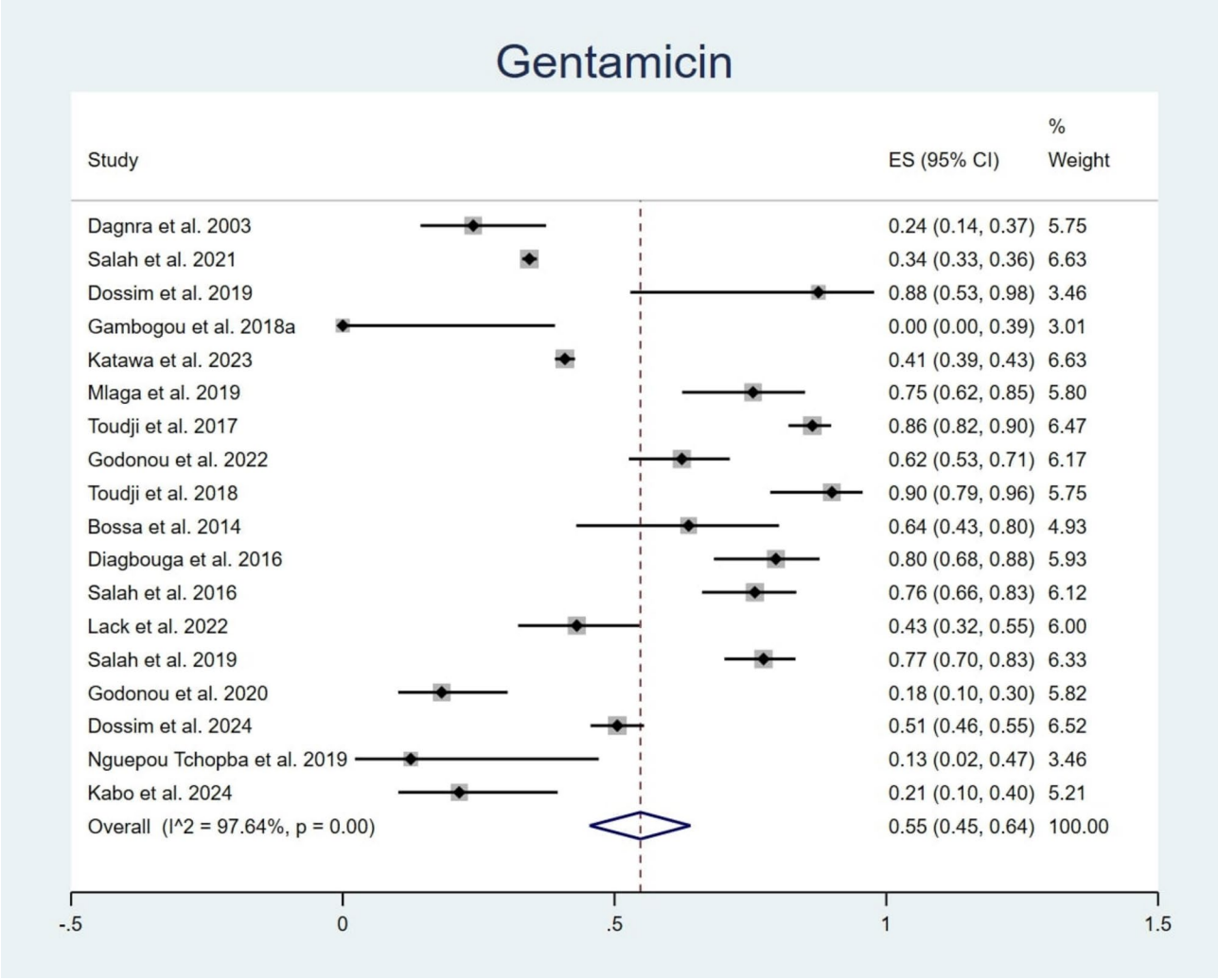

Fig. 7 Forest plot showing the pooled gentamicin resistance rate from random-effect model analysis

also supported the presence of publication bias ($p < 0.001$), with a bias coefficient of 3.71.

Trend of 3GC resistance rates over the years Meta-regression of the 3GC resistance rates in *Enterobacterales* strains isolated in Togo over 30 years (1991–2020) revealed a significant upward trend ($R^2 = 18.49\%$, $p < 0.001$) (Fig. 5F).

Ciprofloxacin

Pooled resistance rate Nineteen of the 20 studies reported ciprofloxacin resistance rates. The total number of *Enterobacterales* strains was 9,214 including 5,059 ciprofloxacin-resistant strains. The pooled resistance rate was 68% (95% CI: 59, 76), $p < 0.001$. A large discrepancy in ciprofloxacin resistance rate was observed among the included studies, ranging from 0% (95% CI: 0, 7) to 95% (95% CI: 88, 98). A significantly high level of heterogeneity was observed among the studies ($I^2 = 97.63\%$, $p < 0.001$) (Fig. 11; Table 1).

Of the 6,308 *E. coli* isolates tested, 3,336 ciprofloxacin-resistant strains were reported, with a pooled prevalence of ciprofloxacin-resistant *E. coli* of 74% (95% CI: 64, 84), $p < 0.001$ (Additional file 3 and Table1). Of the 2,405 *Klebsiella* spp. isolates tested, 1,398 ciprofloxacin-resistant were reported, with a pooled prevalence of ciprofloxacin-resistant *Klebsiella* spp. of 68% (95% CI: 51, 82), $p < 0.001$ (Additional file 3 and Table1). There was no significant difference between the pooled ciprofloxacin resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.52$) (Additional file 3 and Table 1).

Publication bias The funnel plot showed the presence of publication bias, with 68% of the studies skewed to the right side of the triangular zone (Fig. 4G). The Egger's test

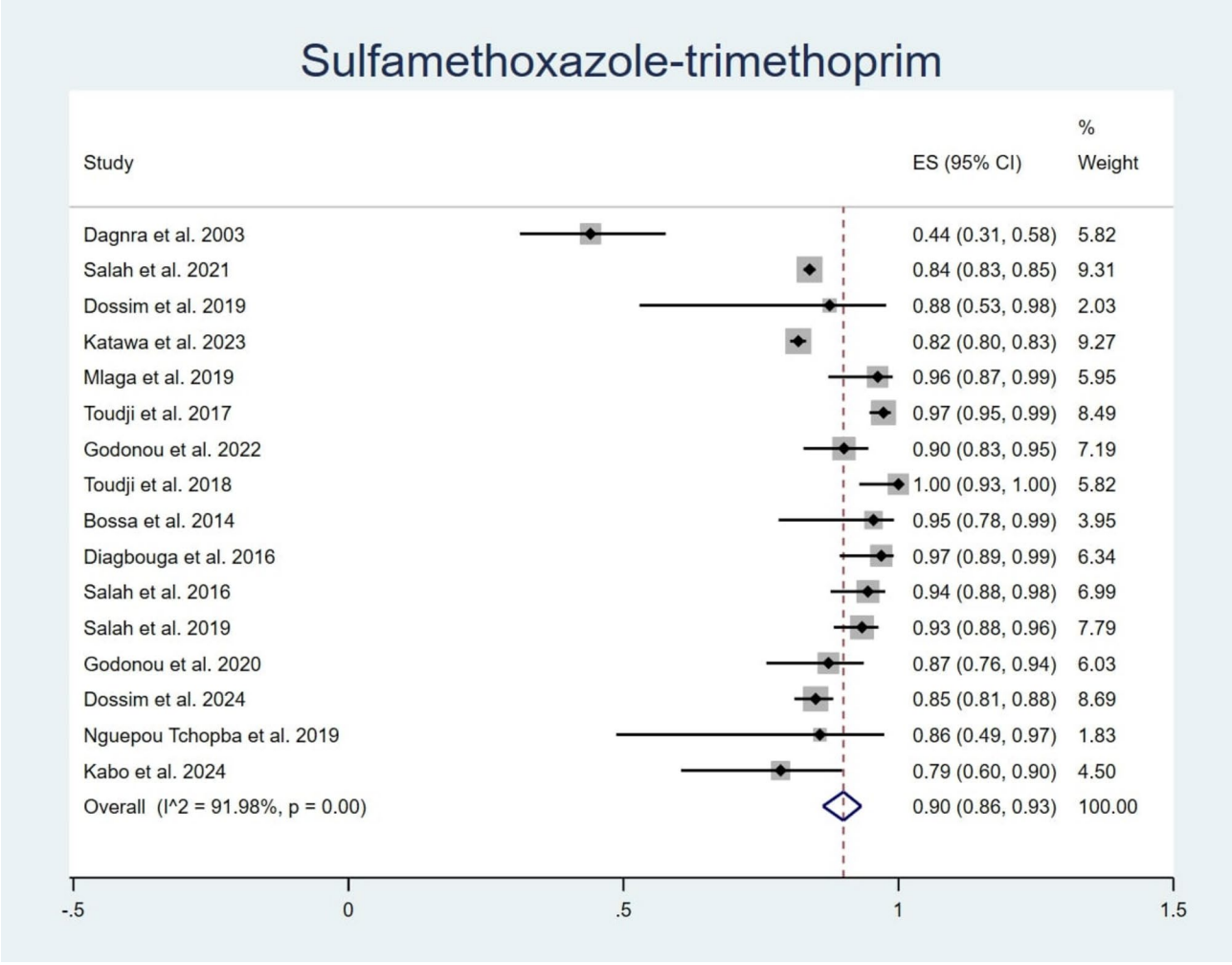

Fig. 8 Forest plot showing the pooled SXT resistance rate from random-effect model analysis

also supported the presence of publication bias ($p = 0.04$), with a bias coefficient of 1.67.

Trend of ciprofloxacin resistance rate over the years Meta-regression analysis of ciprofloxacin resistance rates in *Enterobacterales* strains isolated in Togo over 30 years (1991–2020) revealed a significant upward trend ($R^2 = 61.44\%$, $p < 0.001$) (Fig. 5G).

Resistance of *Enterobacterales* to reserve group antibiotics

Fosfomycin

Pooled resistance rate Nine of the 20 studies reported the fosfomycin resistance rates. The total number of strains was 6,767, including 395 fosfomycin-resistant *Enterobacterales* isolates. The pooled resistance rate was 4% (95% CI: 2, 7), $p < 0.001$. A slight discrepancy in the fosfomycin resistance rate was observed among the included studies, ranging from 0% (95% CI: 0, 32) to 11% (95% CI: 4, 27). A significantly high level of heterogeneity was observed among studies ($I^2 = 91.8\%$, $p < 0.001$) (Fig. 12; Table 1).

Of the 4,909 *E. coli* isolates tested, 192 fosfomycin-resistant strains were reported, with a pooled prevalence of fosfomycin-resistant *E. coli* of 0% (95% CI: 0, 2), $p < 0.001$ (Additional file 3 and Table1). Of the 1,845 *Klebsiella* spp. isolates tested, 202 fosfomycin-resistant were reported, with a pooled prevalence of fosfomycin-resistant *Klebsiella* spp. of 3% (95% CI: 0, 10), $p < 0.001$ (Additional file 3 and Table1). There was no significant difference between the pooled resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.07$) (Additional file 3 and Table1).

Publication bias The funnel plot showed an absence of publication bias (Fig. 4H). The Egger's test also supported the absence of publication bias ($p = 0.822$), with a bias coefficient of -0.09.

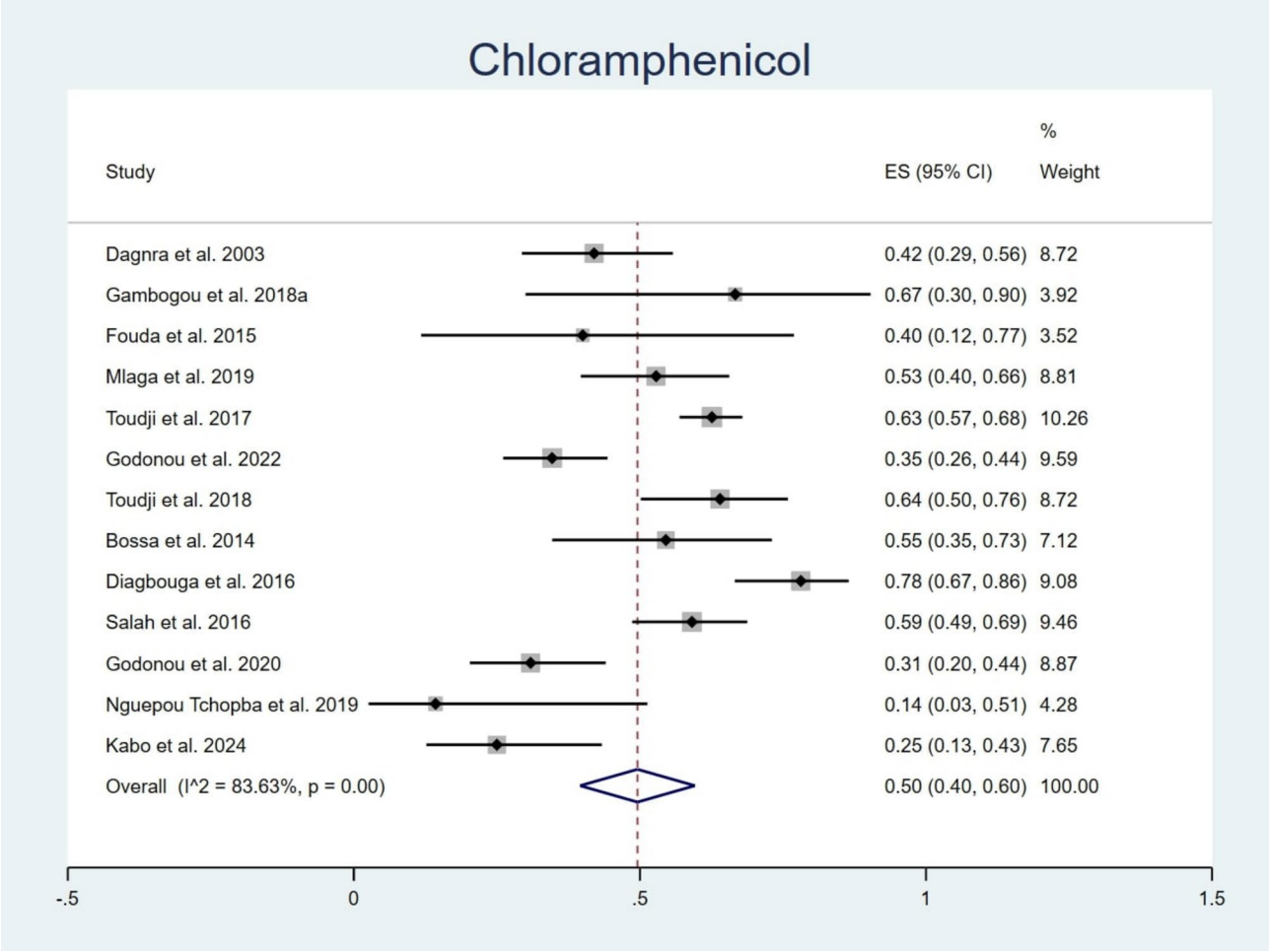

Fig. 9 Forest plot showing the pooled chloramphenicol resistance rate from random-effect model analysis

Trend of fosfomycin resistance rates over the years Meta-regression analysis of fosfomycin resistance rates in *Enterobacterales* strains isolated in Togo over 11 years (2010–2020) did not reveal any significant variation ($R^2 < 0.001\%$, $p = 0.747$) (Fig. 5H).

Imipenem

Pooled resistance rate Seventeen of the 20 studies reported the imipenem resistance rates. The total number of *Enterobacterales* strains was 7,238 including 78 imipenem-resistant strains. The pooled *Enterobacterales* imipenem resistance rate was 1% (95% CI: 0, 2), $p < 0.001$. A slight discrepancy in imipenem resistance rates was observed among the included studies, ranging from 0% (95% CI: 0, 1) to 18% (95% CI: 7, 39). A significant level of heterogeneity was observed among the studies ($I^2 = 78.24\%$, $p < 0.001$) (Fig. 13; Table 1).

Of the 5,149 *E. coli* strains tested, 44 imipenem-resistant strains were reported, with a pooled prevalence of imipenem-resistant *E. coli* of 0% (95% CI: 0, 0), $p < 0.001$ (Additional file 3 and Table1). Of the 2,004 *Klebsiella* spp. strains tested, 31 imipenem-resistant were reported, with a pooled prevalence of imipenem-resistant *Klebsiella* spp. of 0% (95% CI: 0, 1), $p < 0.001$ (Additional file 3 and Table 1). There was no difference between the pooled imipenem resistance rates of *E. coli* and *Klebsiella* spp. ($p = 0.30$) (Additional file 3 and Table 1).

Publication bias The funnel plot showed the absence of publication bias (Fig. 4I), and the Egger's test also supported the absence of publication bias ($p = 0.055$), with a bias coefficient of 0.20.

Trend of imipenem resistance rates over the years Meta-regression analysis of imipenem resistance rates in *Enterobacterales* strains isolated in Togo over 12 years (2009–2020) did not reveal any significant variation ($R^2 = 61.86\%$, $p = 0.935$) (Fig. 5I).

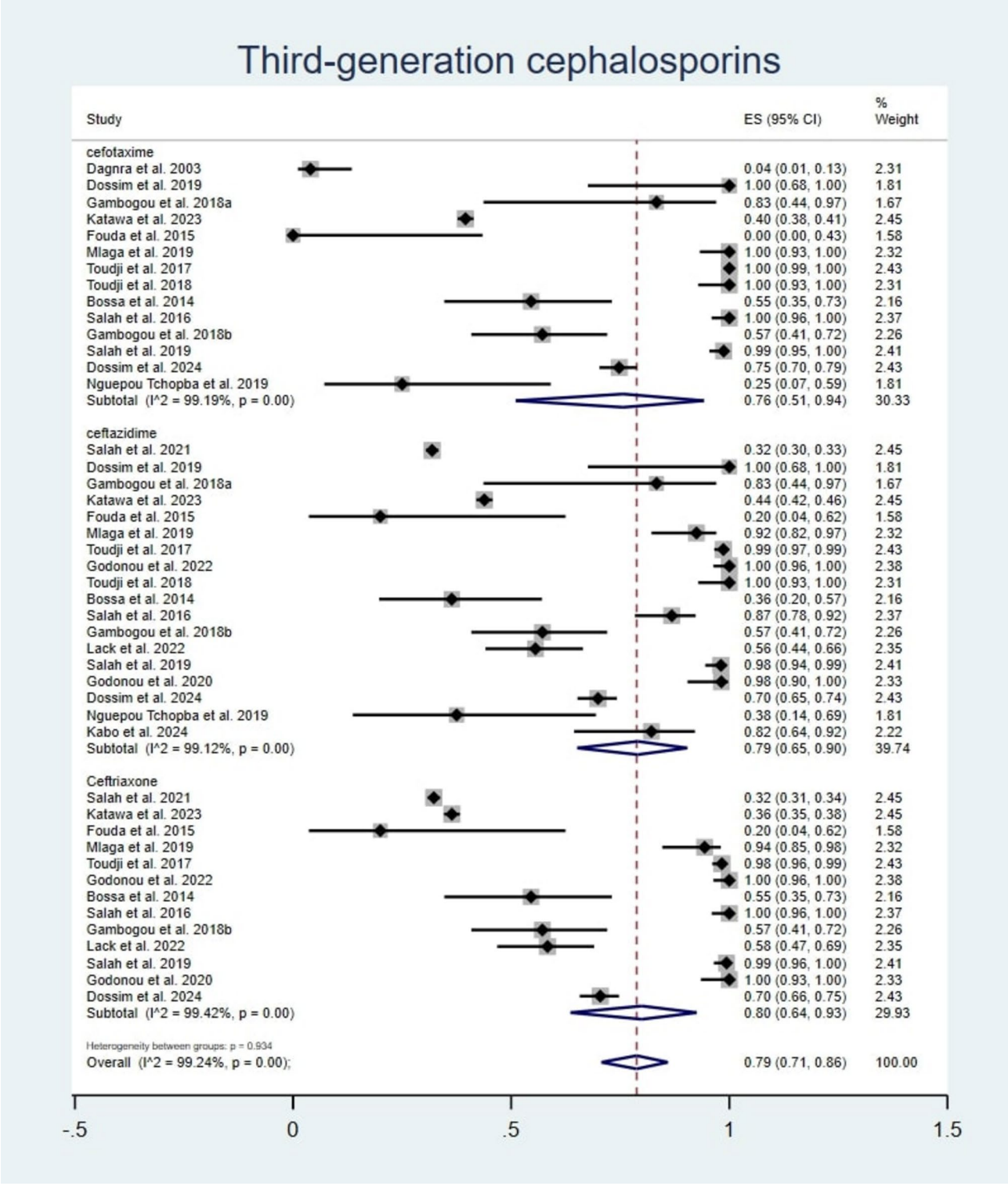

Fig. 10 Forest plot showing the pooled 3GC resistance rates from random-effect model analysis

Discussion

In this study, we performed the first systematic review and meta-analysis of antimicrobial-resistant *Enterobacterales* in Togo, and determined the pooled resistance rates and trends in resistance to 11 antimicrobials over the last three decades.

Global reports have observed a significant increase in the number of research articles on AMR published

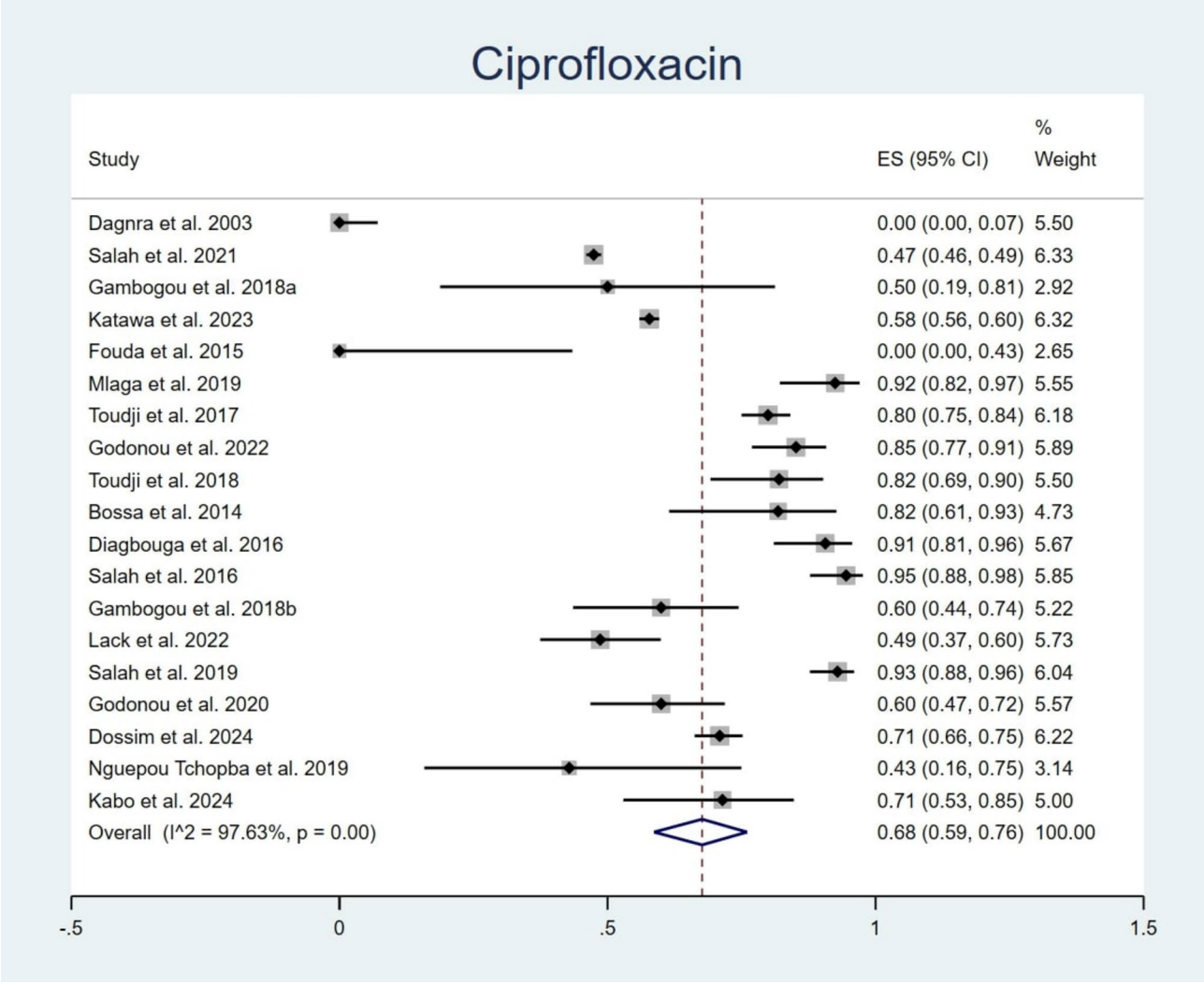

Fig. 11 Forest plot showing the pooled ciprofloxacin resistance rate from random-effect model analysis

annually, as evidenced by the rise of 450% between 1999 and 2018 [35, 36]. In this regard, the number of research articles published on AMR has increased over the years in Togo, suggesting that research teams from Togo have made efforts to investigate and determine the resistance profiles of *Enterabacterales* in this country. Despite these efforts, Togolese public health authorities and funders should direct more funds towards the fight against AMR. Indeed, there are still many gaps in the genotypic data of such pathogens, which could contribute to a better understanding of this scenario. A critical barrier is the lack of funding to address this issue, an essential challenge faced by low-income countries, such as Togo.

Resistance of *Enterobacterales* to antimicrobials

AMC

The combination of amoxicillin and clavulanic acid is widely used in the treatment of respiratory tract infections, otitis media, sinusitis, skin infections, and urinary tract infections [37, 38]. For many decades, AMC has been a key drug used in both hospitals and communities because clavulanic acid inhibits the activity of β-lactamases, allowing amoxicillin to exert its bactericidal activity against bacteria. However, our results suggest that the clinical effectiveness of AMC has been compromised in Togo, with a high pooled resistance rate of 73% (95% CI: 66, 80), $p < 0.001$, combined with a significant upward trend ($R^2 = 8.99\%$, $p = 0.022$) for *Enterobacterales* isolated between 1991 and 2020.

The pooled prevalence rates of AMC-resistant *E. coli* and *Klebsiella* spp. were 68% (95% CI: 59, 77), $p < 0.001$ and 76% (95% CI: 59, 89), $p < 0.001$, respectively. Our findings were quite similar to those reported in Ethiopia (52% and 77%) *E. coli*, (57% and 80%) *Klebsiella* spp. [39, 40], and in 23 countries of sub-Saharan African regions (51.8% and 71.6%) *E. coli*, (75.5% and 82.2%) *Klebsiella* spp. [41].

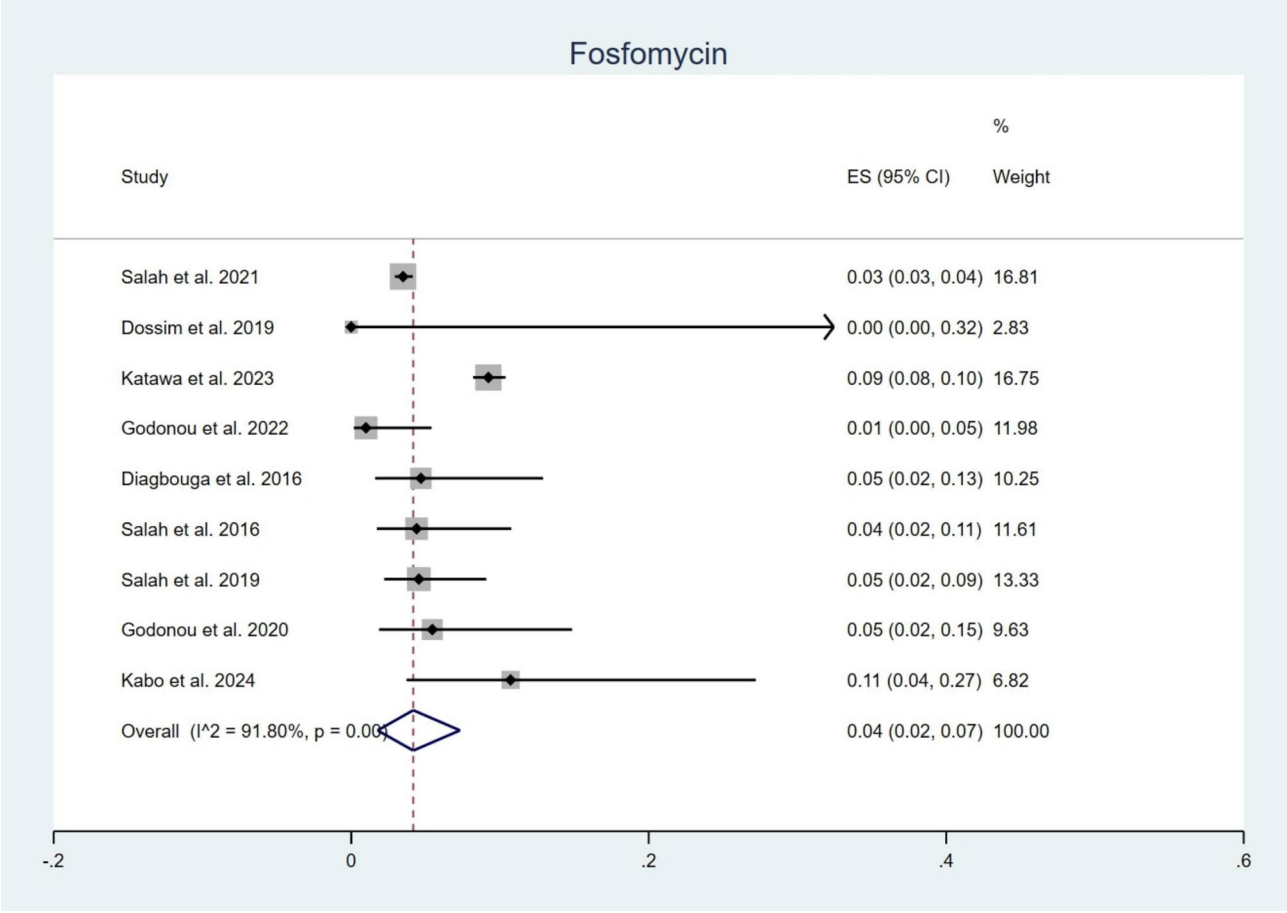

Fig. 12 Forest plot showing the pooled fosfomycin resistance rate from random-effect model analysis

3GC

The pooled prevalence of the critical-priority pathogen 3GC-resistant *Enterobacterales* in Togo was 79% (95% CI: 71, 86), $p < 0.001$, with a significant upward trend for strains isolated from 1991 to 2020 ($R^2 = 18.49\%$, $p < 0.001$). This is a notable concern, because 3GCs are often used as first-line probabilistic antibiotics in Togo. Our results suggest that 3GCs would no longer constitute reliable empirical treatments for *Enterobacterales*-associated infections in Togo. Further representative epidemiological research in Togo may strengthen our findings.

In this review, the pooled prevalences of 3GC-resistant *E. coli* and *Klebsiella* spp. were 79% (95% CI: 68, 88), $p < 0.001$ and 83% (95% CI: 73, 92), $p < 0.001$, respectively. Our findings were significantly higher than those reported in the USA, Europe and European Economic Area, Japan, Ethiopia, WHO Africa zone: (11.1%, 11.3%, 13.8%, 14.9%, 28.9%, 38%, 45%, 52%, 58.3%, 74%) for *E. coli* and (10.7%, 11.4%, 33.9%, 34.3%, 40%, 54%, 61.8%, 63%, 74%, 80%) for *Klebsiella* spp. [39, 40, 42–47].

Imipenem

The pooled prevalence of the critical priority pathogen imipenem-resistant *Enterobacterales* in Togo was 1% (95% CI: 0, 2), $p < 0.001$. Our results suggest that carbapenems can be considered last-resort antimicrobials for the treatment of *Enterobacterales*-associated infections in Togo. However, the use of carbapenems must be strictly controlled. The availability of more representative epidemiological data in Togo, especially on carbapenem-resistant *Acinetobacter* spp. and *Pseudomonas* spp., will help obtain more accurate overall data.

The pooled prevalence of imipenem-resistant *E. coli* and *Klebsiella* spp. were 0% (95% CI: 0, 0), $p < 0.001$ and 0% (95% CI: 0, 1), $p < 0.001$, respectively. Our results obtained for *E. coli* were quite similar to those reported for *E. coli* in the USA, Japan, and Europe and European Economic Area, with pooled resistance rates of (0.0%, 0.2%, and 0.5%) [42–46]. However, the pooled prevalence of imipenem-resistant *Klebsiella* spp. reported in this study was significantly lower than that reported for Europe and European Economic Area, WHO Africa region, and for 23 sub-Saharan African countries (4.9%, 10.0%, 11.7%, 28.4%) [41–43, 47].

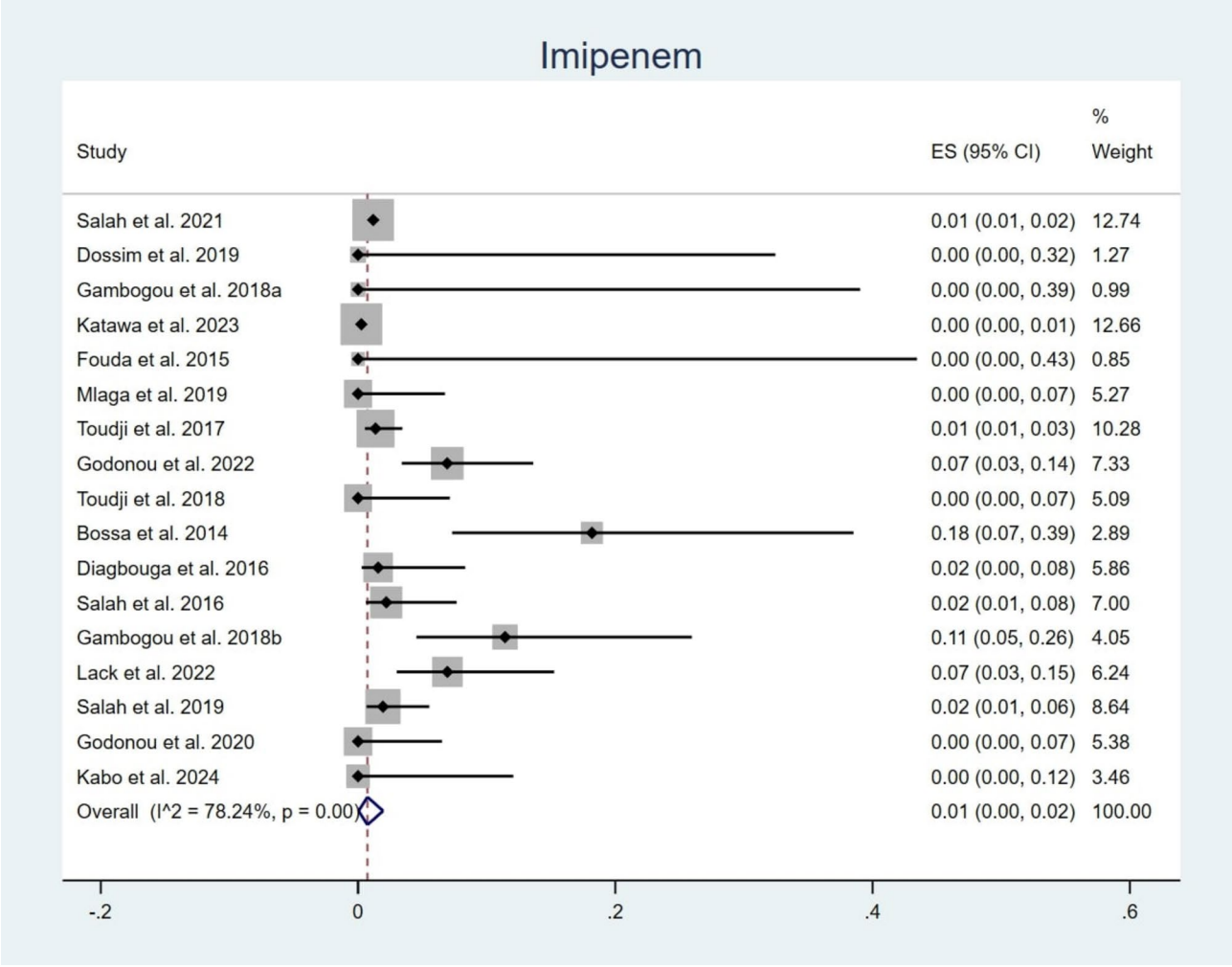

Fig. 13 Forest plot showing the pooled imipenem resistance rate from random-effect model analysis

Aminoglycosides

Aminoglycosides are broad-spectrum antimicrobials effective against a wide range of *Enterobacterales* strains and other Gram-negative bacteria, making them essential for treating serious infections. In addition, these drugs have been used in combination with other antimicrobials to enhance efficacy and prevent AMR. Conversely, aminoglycosides may present toxicity effects, with the potential for nephrotoxicity and ototoxicity, especially in prolonged or high-dose treatments.

In this review, the pooled prevalence of gentamicin-resistant *Enterobacterales* in Togo was 55% (95% CI: 45, 64), $p < 0.001$, with a significant upward trend over 30 years ($R^2 = 12.67\%$, $p = 0.006$). This is a challenge because gentamicin is widely used as a treatment of choice for systemic, ophthalmic, and skin infections [48, 49], and has also the advantage of being effective against bacterial biofilms [50, 51]. Our results indicated that the emergence of resistant strains has compromised the effectiveness of gentamicin monotherapy.

The pooled gentamicin-resistant *E. coli* and *Klebsiella* spp. resistance rates were 49% (95% CI: 38, 61), $p < 0.001$ and 67% (95% CI: 52, 81), $p < 0.001$, respectively. Our findings were significantly higher than those reported for Europe and the European Economic Area (10.9% and 9.6%) *E. coli* and 23.7% *Klebsiella* spp. [42, 43]; and quite similar to the (40.7%, 41.6%, 42.7%) gentamicin-resistant *E. coli* obtained in Burkina Faso from 2010 to 2021 and in 23 Sub-Saharan African countries [41, 52]. However, Ethiopia and the 23 Sub-Saharan African countries showed higher pooled prevalences of gentamicin-resistant *E. coli* (73%) and *Klebsiella* spp. (77.6%, 78%) [39, 41].

In contrast, amikacin retained excellent activity against *Enterobacterales* isolated in Togo from 2009 to 2020 with a pooled resistance rate of 3% (95% CI: 1, 5), $p < 0.001$. Therefore, our results suggest that amikacin remains a valuable alternative antimicrobial for the treatment of MDR *Enterobacterales* in Togo. However, the prescription of amikacin should be strictly controlled and

reserved only for severe infections or guided by AST whenever possible. These measures could help delay the emergence of amikacin-resistant bacterial clones in Togo. A part from Togo, amikacin has been reported to retain good activity against carbapenem-resistant bacteria in West African countries [53].

In this review, the prevalence rates of amikacin-resistant *E. coli* and *Klebsiella* spp. were 0% (95% CI: 0, 2), $p < 0.001$ and 0% (95% CI: 0, 0), $p < 0.001$, respectively. Our findings were significantly lower than those reported in Ethiopia (10% *E. coli*, 10% *Klebsiella* spp.) [40], and in 23 countries of the sub-Saharan African regions (3.1% and 10.4%) *E. coli*; (11.8% and 24.7%) *Klebsiella* spp. [41].

SXT

The association of sulfamethoxazole and trimethoprim, also known as co-trimoxazole, is a cost-affordable drug widely used in the treatment of bronchitis, otitis in pediatrics, treatment and prophylaxis of travelers' diarrhea, urinary tract infections (UTIs), and shigellosis [54]. The very low price of SXT makes it widely used in the community, often without any formal prescriptions. This massive and uncontrolled use of SXT may be one of the reasons for the very high resistance rate of 90% (95% CI: 86, 93), $p < 0.001$, observed in this study. In addition, SXT had the highest upward trend ($R^2 = 73.24\%$) among the 11 antimicrobials assessed in this study. Our findings suggest that SXT is no longer an effective empirical treatment for *Enterobacterales*-associated infections in Togo.

The pooled SXT resistance rates reported in this study for *E. coli* and *Klebsiella* spp. were 94% (95% CI: 90, 97), $p < 0.001$ and 93% (95% CI: 85, 99), $p < 0.001$, respectively. Our findings were higher than those reported in 23 sub-Saharan African countries and Ethiopia: (59%, 68.1%, 80.1%, 83%) for *E. coli*, and (62%, 82%, 85.5%, 89.9%) for *Klebsiella* spp. [39–41]. However, lower *E. coli* and *Klebsiella* spp. resistance rates to SXT (29-36%) and (27-46%), respectively have been reported in Romania [55].

Chloramphenicol

Chloramphenicol, which is generally used in the management and treatment of superficial eye infections, and otitis externa [56], appears to retain acceptable activity [pooled resistance rate of 50% (95% CI: 40, 60), $p < 0.001$] against *Enterobacterales* strains isolated in Togo from 1991 to 2020. In addition a steady trend ($R^2 = 23.25\%$, $p = 0.13$) was reported.

The chloramphenicol pooled-resistance rates reported in this study for *E. coli* and *Klebsiella* spp. were 40% (95% CI: 27, 53), $p < 0.001$ and 59% (95% CI: 48, 70), $p = 0.03$, respectively. Our findings were quite similar to those reported for the African continent, and Ethiopia: (36% and 40.9%) for *E. coli*, (45% and 62.8%) for *Klebsiella* spp. [40, 57].

Ciprofloxacin

Ciprofloxacin is one of the first-line drugs used to treat gastroenteritis, typhoidal fever and gonorrhea. These infections are of particular concern in Togo, as they have a high prevalence and incidence. The massive and inappropriate use of ciprofloxacin may have significantly contributed to the selection and emergence of ciprofloxacin-resistant bacterial clones. The high prevalence of ciprofloxacin-resistant *Enterobacterales*, 68% (95% CI: 59, 76), $p < 0.001$, reported in this study, seems to compromise the use of ciprofloxacin as a reliable probabilistic antimicrobial in Togo. Similarly, Dobbyn et al. [58] also reported that fluoroquinolones should no longer be used as a first-line empirical treatment in Canada, a high-income country.

In this study, the pooled prevalences of ciprofloxacin-resistant *E. coli* and *Klebsiella* spp. were 74% (95% CI: 64, 84), $p < 0.001$ and 68% (95% CI: 51, 82), $p < 0.001$, respectively. Lower pooled prevalences of ciprofloxacin-resistant *E. coli* (21.3%, 21.9%, 23.8%) and *Klebsiella* spp. (15.5%, 33.6%, 33.8%) were reported in Europe and European Economic Area, and Vietnam [42–44]. Moreover, similar pooled prevalences of ciprofloxacin-resistant *E. coli* and *Klebsiella* spp. were reported in Burkina Faso and Ethiopia (70.5%, 77% for *E coli*, and 73% for *Klebsiella* spp.) [39, 52]. Alarmingly, *Enterobacterales* harboring ESBL-producing genes often carry fluoroquinolone and aminoglycoside resistance genes [59–62]. This may explain the concomitantly high pooled prevalence of 3GC-, gentamicin-, and ciprofloxacin-resistant *Enterobacterales* observed in this study.

Fosfomycin

Fosfomycin is a re-emerging bactericidal agent, recommended for the treatment of complicated UTIs and prostatitis. In addition, its high tissue penetration makes it an excellent choice for the treatment of infections affecting the central nervous system, soft tissues, bones, and lungs. Moreover, studies have confirmed the effectiveness of fosfomycin in the treatment of MDR, extensively drug-resistant (XDR), and pan-drug-resistant (PDR) bacteria [63–65]. The pooled prevalence of fosfomycin-resistant *Enterobacterales* in this study was 4% (95% CI: 2, 7), $p < 0.001$. Our results suggest that fosfomycin would constitute a key alternative antimicrobial for the treatment of severe infections caused by *Enterobacterales* in Togo. However, monotherapy should be avoided because of the rapid development of resistance observed in vitro to fosfomycin [66, 67].

The pooled fosfomycin resistance rates reported for *E. coli* and *Klebsiella* spp. in this study were 0% (95% CI: 0, 2), $p < 0.001$ and 3% (95% CI: 0, 10), $p < 0.001$, respectively. Similar *E. coli* fosfomycin resistance rates (0-5%) have been reported in Romania [55].

This review revealed high pooled AMR rates, with drastic upward trends over the years in Togo. Several factors may have contributed to the high AMR rates observed in the present study. These contributing factors include inadequate infection control practices, poor antibiotic stewardship, and lack of diagnostic infrastructure.

Recommendations to help mitigate AMR in Togo

Strengthening infection prevention and control measures

According to the WHO, infection prevention and control (IPC) programs should be the primary weapon to improve health and reduce the burden of AMR, especially in low-income countries with fragile healthcare systems such as Togo [68, 69]. Every infection prevented is an antibiotic therapy avoided, money saved, and an occurrence of an AMR pathogen prevented. The IPC programs must be implemented in both communities and healthcare facilities. The interventions include the promotion of hand hygiene, safe processing and storage of food products, improvement of hospital hygiene, and provision of clean and well-functioning equipment [70].

In 2023, with the support of the WHO, the Togolese Ministry of Health and Public Hygiene (MSHP) implemented the national IPC program in 31 pilot health districts. This program aimed to improve the quality of care and hospital infrastructure to better fight healthcare-associated infections (HAI). Around a hundred healthcare staff members were trained in IPC and additional cleaning staff were recruited for healthcare settings. The hospitals were equipped with essential equipments, such as sterilizing ovens, personal protective equipments, incinerators, and cleaning solutions. These actions have reduced the prevalence of surgical site infections from 0.99% in 2022 to 0.83% in 2023 [71].

Despite efforts to implement of IPC programs in Togo, there is still a large gap to be filled. Strengthening these IPC measures will surely help significantly lessen the burden of AMR in Togo.

Strengthening surveillance of antimicrobial-resistant Enterobacterales through a One Health approach

Togo faces several challenges in addressing AMR, including limited laboratory capacity, insufficient data on resistant *Enterobacterales*, and a lack of coordinated efforts among health sectors. The existing surveillance systems may not adequately capture the complexity of AMR, hindering the ability to respond effectively to outbreaks and public health threats. It is presumed that similar situations have been occurring in animals and the environment, further complicating the AMR landscape. Following the global agenda on AMR, a comprehensive One Health surveillance initiative should also be encouraged in this country to bridge gaps between the human, animal, and environmental health sectors, as the spread of antimicrobial-resistant *Enterobacterales*, including critical priority strains, transcends no borders and is expanding beyond human hospital walls [72].

Enhancing genomic surveillance

The rising prevalence of antimicrobial-resistant *Enterobacterales* in Togo, coupled with the lack of comprehensive genomic data on these pathogens, underscores the urgent need to enhance genomic surveillance systems. Indeed, there is scant genomic information on *Enterobacterales*, and implementing advanced genomic surveillance, particularly whole-genome sequencing (WGS), can facilitate the early identification of emerging resistance trends and potential outbreaks, thereby enabling timely public health responses in the country. For instance, WGS can be instrumental in tracking resistance patterns, identifying virulence factors, and recognizing specific circulating clones [73]. However, next-generation sequencing platforms are almost non-existent in Togo. The main reason is the lack of funding for this area. Therefore, substantial financial investment in genomic platforms has become imperative in Togo. While awaiting this, performing WGS through partner laboratories or international collaborations with scientific groups could serve as a short-term solution.

Raising awareness and educating on antimicrobial resistance

In most low-income countries, inadequate behavior within communities and healthcare facilities tends to sponsor the emergence of AMR. For example, two systematic reviews conducted on knowledge, attitudes, and practices regarding AMR across multisectoral African populations (hospital practitioners, and people from communities) showed a low level of knowledge about AMR and extensive misuse of antimicrobial medicines [74, 75]. In Togo, efforts have been made, and for several years, antimicrobials can be purchased in drug stores if only the buyers have a formal prescription. Nevertheless, populations continue to buy antimicrobials from unauthorized drug sellers who sell black-marketed antimicrobials.

According to the WHO, the promotion of antimicrobial stewardship constitutes a key strategy to mitigate AMR [68, 76], and the promotion of awareness and education on AMR must be implemented in multiple sectors (humans and agriculture) and multiple levels (adults, teenagers, children, educated and uneducated people). Apart from AMR education courses and training, which can be implemented in schools, universities, and agricultural training programs, recurrent posts on social media can be used to reach every layer of the Togolese population. In addition, healthcare workers must be continually informed about AMR through up-to-date training and conferences and prevent unnecessary antibiotic

prescriptions. All these actions must state the need to prescribe antimicrobials only if needed, the importance of completing the antimicrobial therapy prescribed by the physician, the interdiction of consuming antimicrobials without formal prescription, and the danger of buying antimicrobials from black market sellers.

Expanding access to affordable diagnostic technologies to help guide targeted antibiotic therapy

Cost-affordable point-of-care (PoC) diagnostic tools are essential in low-income countries to control AMR, given their "ASSURED" characteristics (Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable) [77]. Some tests, such as FebriDx®, facilitate the rapid differentiation between bacterial and viral acute respiratory infections (ARIs), helping to prevent unnecessary antibiotic use and thereby reduce the risk of resistance [78].

Chromogenic culture media, including CHROMagar™ mSuperCARBA™, ChromID™ CARBA, ChromID™ CARBA SMART, and Brilliance™ CRE Agar, enable the isolation of critical priority pathogens, such as CRE, which produce KPC, VIM, GIM, NDM, and OXA-48 [79]. Meanwhile, media such as CHROMagar™ ESBL, Brilliance™ ESBL, and ChromID™ ESBL are specifically designed to isolate ESBL-producing *Enterobacterales* [80, 81]. Additionally, NG-Test® CARBA 5, a multiplex lateral flow immunoassay (LFI), allows for the rapid detection and differentiation of key carbapenemases (KPC, OXA-48, VIM, IMP, and NDM) in less than 15 min from bacterial colonies or direct biological samples. NG-Test® Blood Culture Prep offers a quick and direct detection of carbapenemases in positive blood culture samples, whereas NG-Test® CTX-M MULTI can detect the five major CTX-M-type groups (Groups 1, 2, 8, 9, and 25) in *Enterobacterales* within 15 min from bacterial colonies or direct biological samples. The NG-Test® MCR-1, on the other hand, facilitates the rapid detection of colistin resistance in bacterial colonies in under 15 min [82–84].

Beyond PoC tests, automated systems for bacterial identification and resistance phenotype determination, such as VITEK® 2, and BD Phoenix™, are playing an increasingly crucial role in healthcare settings. These systems provide rapid and precise identification of bacterial species, along with comprehensive resistance profiles, including the detection of ESBLs and carbapenemases. This functionality is essential for informing targeted antimicrobial therapy. While the costs of such systems are higher compared to traditional PoC tests, their integration into centralized healthcare facilities can significantly enhance diagnostic capacity and improve patient outcomes [85–87].

Alternative therapies to help mitigate AMR in Togo

Phytotherapy as promising strategy against AMR in Togo

The discovery of new effective antimicrobials is a rare occurrence in the field of medicine, largely due to the extensive research and development needed to identify compounds that can effectively target pathogens without causing significant harm to human cells. Over the past few decades, the rate of new antimicrobial discovery has declined sharply, resulting in a growing reliance on existing antimicrobials that are increasingly facing resistance. This situation poses a significant challenge to public health, as the effectiveness of current treatment options diminishes and the threat of untreatable infections looms larger. Additionally, the financial costs associated with developing new antimicrobials are substantial, often requiring millions of dollars and years of investment to bring a single new drug to market. As a result, there is an urgent need for innovative approaches to antimicrobial development, including alternative therapies [88].

Phytomedicine is a promising solution to tackle AMR [89–92]. Indeed, several medicinal plants have been reported to contain compounds that are active against antimicrobial-resistant bacteria and even against MDR and XDR bacteria. Preparations of medicinal plants, either alone or in combination with conventional drugs, have demonstrated significant antibacterial activity worldwide and in Togo. For example, some medicinal plant preparations active against ciprofloxacin and gentamicin-resistant *Enterobacterales*, or enhancing the activity of gentamicin and ciprofloxacin, have been reported in Nigeria [93, 94], India [95], Chile [96], Iran [97], Türkiye [98], Brazil [99], Poland [100], and Italy [101].

In Togo, ethnobotanical surveys and original research have highlighted the potential of phytomedicines against AMR. For example, the in vitro antibacterial activity of aqueous garlic extract, has been reported for the treatment of women UTIs [20] and a recipe composed of *Carica papaya*, *Cocos nucifera*, and *Persea americana* has demonstrated a good in vitro antibacterial activity against typhoid fever [102]. Almost all these studies on the potential of phytomedicines against AMR in Togo have provided insights without further in vivo and clinical trials. Thus, there must be a shift in herbal medicine and more funding must be allocated before the appearance of the first phytomedicines approved against AMR in Togo.

Phage therapy to mitigate AMR-associated infections

Phage therapy is a promising alternative for tackling MDR and XDR-associated infections. Bacteriophages (BPs) are viruses that infect and lyse the bacterial hosts. BPs inject their DNA, hijack the bacterial machinery to replicate, and cause bacterial lysis [103]. BPs have several advantages, including host specificity and their ability

to replicate within the host and at the site of infection without adverse effects [104]. BPs can breakthrough and disturb biofilms, making them a powerful tool for curing biofilm-associated infections [104]. In single-phage or phage cocktail therapy, BPs can be administered via intraperitoneal, intramuscular, subcutaneous, intravenous, topical, and oral routes [105]. Moreover, the combination of BPs with conventional antibiotics has greater antimicrobial activity than the sum of either BPs or antibiotics alone [103] and prevents or delays the development of antibiotic and phage resistance. Numerous in vitro, in vivo, and clinical trials have reported that BPs have excellent antimicrobial activity worldwide. in India, phage *590 B*, isolated from community sewage, showed excellent activity against MDR, and XDR uropathogenic *E. coli* [106]. In Japan, phage *øKp_21* has shown excellent activity against carbapenemase-producing *K. pneumoniae* isolated from sewage [107]. In Senegal, phages *vAbaIN10*, *vAbBal23*, and *vAbAbd25* isolated from wastewater have shown excellent bacteriolytic activity against XDR carbapenem-resistant *Acinetobacter baumannii*, whether in planktonic environments or in biofilms [108, 109]. In Togo, consistent studies on phage therapy could offer efficient alternative weapons to mitigate AMR-associated infections.

Conclusion

This systematic review and meta-analysis reported high first-line AMR rates with drastic upward trends in clinical *Enterobacterales* isolated in Togo over 30 years. Nevertheless, imipenem, amikacin, and fosfomycin retained their excellent activity. The inclusion of other last-line drugs, such as tigecycline and polymyxins, as well as novel β-lactam–β-lactamase inhibitor combinations (e.g., ceftolozane–tazobactam, ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam), in AST may help identify additional antimicrobials with strong activity against clinical *Enterobacterales* strains in this country. In addition, the results of this study suggest a need for adjustment of empirical antimicrobial guidelines in Togo. In addition, more next-generation sequencing-related research become imperative to strengthen AMR surveillance, and the implementation of prevention policies, the level of healthcare system in Togo and the promotion of antimicrobial stewardship, should be upgraded. Moreover, public health authorities must allocate more funding to the national AMR committee and more studies should focus on AMR. Furthermore, the development of herbal medicine and phage therapy can lead to alternative therapies that may serve as adjuncts to conventional medicine. We hope that all these actions will collectively lead to a significant reduction in the morbidity and mortality rates associated with AMR in Togo. Finally, we urge public health authorities, healthcare professionals, and researchers to implement these recommendations at their respective levels.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
KMD, FPS and SD conceptualized the study. KMD, IACA, KAD, CAGA and YSE collected research articles. KMD, IACA, KAD, CAGA and KDBB extracted data from articles. KMD, EEI, ASA and AEK analyzed data. KMD and FPS drafted the original manuscript. FPS, EEI, YSE, ASA, KDBB, AEK and SD substantively revised the manuscript. All authors have made intellectual contributions to the work and approved the final version of the manuscript for submission.

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