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Prevalence of TEM-Type Extended Spectrum Beta Lactamases in the Iranian Population: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Extended-spectrum β-lactamases (ESBLs) are enzymes produced by Gram-negative bacteria, which confer resistance to many β-lactam antibiotics. Among these, TEM-type ESBLs, which are typically encoded by genes on plasmids, are highly prevalent and facilitate the spread among various bacterial species, leading to resistance against penicillins and cephalosporins. Ongoing surveillance of the prevalence and characteristics of TEM-ESBLs is crucial for informing antibiotic stewardship and implementing effective infection control measures to curb their dissemination. **Methods:** This meta-analysis aimed to evaluate the overall prevalence of TEM-type ESBLs in the Iranian population derived from studies conducted from 2007 to 2020. Relevant articles were systematically searched in PubMed, Science Direct, Google Scholar, Biological Abstracts, Web of Science, and SID databases, encompassing research from all Iranian provinces. After applying inclusion criteria and screening titles and abstracts, a refined selection of articles was chosen for full-text review and data extraction. The data extracted were analyzed using statistical software, with subgroup analyses performed to investigate sources of heterogeneity. **Results:** Analysis of the 202 studies revealed an overall prevalence of 27% for TEM-type ESBLs in Iran. Subgroup analysis indicated significant regional variations, with prevalence differing markedly among provinces. The highest prevalence was observed in Qom province at 51%. By sample type, the prevalence was notably higher in urine and stool isolates, reaching 76%. Among bacterial species, *Escherichia coli* and *Klebsiella* spp. exhibited the highest prevalence of TEM-type ESBLs, with a combined rate of 43%. The peak prevalence was noted in studies from 2019, at 32%. **Conclusion:** The high prevalence of antimicrobial resistance, particularly among Gram-negative bacteria, represents a critical challenge to public health and calls for specific interventions to manage and reduce ESBL spread. This study highlights the significant presence of TEM-type ESBLs in Iran, demonstrating the urgent need for enhanced surveillance and targeted interventions to address the variations in prevalence across different regions and sample types. The findings emphasize the importance of implementing robust antibiotic stewardship programs and stringent infection control measures to mitigate the dissemination of TEM-type ESBLs and preserve the effectiveness of β-lactam antibiotics.

INTRODUCTION

Antimicrobial resistance (AMR), particularly resistance to β-lactam antibiotics in bacteria, is a global public health threat, leading to increased morbidity and mortality worldwide. This resistance contributes to increased morbidity and mortality, imposes substantial economic burdens, and raises the specter of numerous untreatable infections [1, 2]. Gram-negative bacteria

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carrying antibiotic resistance genes, including those encoding ESBLs, are found in diverse environments and can readily disseminate these genes through various mechanisms, such as horizontal gene transfer. Extended-spectrum beta-lactamases (ESBLs) are a group of enzymes produced by Gram-negative bacteria that confer resistance to a wide range of β-lactam antibiotics. These include penicillins, cephalosporins (first through fourth generations), and monobactams. ESBLs confer resistance by hydrolyzing the β-lactam ring, thus inactivating these antibiotics [3, 4, 5].

Gram-negative bacteria produce a variety of ESBLs, which are classified into four molecular classes (A to D) based on their amino acid sequence homology using the Ambler classification system [6]. The Class A subgroup is the most diverse, encompassing several enzyme families, such as TEM (named after the patient Temoneira), CTX-M (Cefotaximase-Munich), SHV (Sulfhydryl variable), and OXA (oxacillin-hydrolyzing). These enzymes can be transferred horizontally between bacteria, primarily via plasmid-mediated conjugation**,** or less commonly, through other mechanisms such as transduction or transformation. TEM-type ESBLs, which are frequently plasmid-mediated, are particularly prevalent within the Iranian population [7].

The first TEM-type ESBL was identified in an *E. coli* isolate from a blood culture of a patient in Greece in 1963. The enzyme was subsequently named TEM after the patient from whom it was first isolated [8]. Since its initial discovery, more than 220 TEM variants have been identified and characterized, each distinguished by specific mutations in their active sites and variations in amino acid sequences. These variants are classified with a sequential numerical system, such as TEM-1, TEM-2, and so on [9-11]. Among the numerous TEM variants, TEM-1 and TEM-2 are among the most frequently reported types in Iran, reflecting their predominant clinical impact in this geographic area [12, 13].

TEM-type ESBLs confer resistance to a range of β-lactam antibiotics in Gram-negative bacteria, including penicillins and cephalosporins (such as first- and second-generation cephalosporins) [14]. Subsequent TEM variants have emerged from the original TEM-1 and TEM-2 variants through mutations in their active site amino acids. These mutations confer new resistance phenotypes by enabling hydrolysis of a wider range of β-lactams. For example, while bacteria producing TEM-1 exhibit resistance to penicillins and similar first-generation cephalosporins, subsequent mutants such as TEM-10 and TEM-52 confer resistance to later-generation cephalosporins and even β-lactamase inhibitors [11, 15-16].

Bacteria harboring ESBL genes often exhibit multidrug resistance due to the simultaneous acquisition of other resistance genes encoding resistance to various antibiotic classes, either on plasmids or resulting from chromosomal mutations. TEM genes are frequently located on plasmids that can also harbor genes conferring resistance to other antibiotic classes, including aminoglycosides, fluoroquinolones, and sulfonamides. The acquisition of these plasmids can lead to multidrug resistance (MDR) in Gram-negative bacteria, posing a significant public health threat. Although MDR bacteria are predominantly associated with nosocomial infections, their rising prevalence in community-acquired infections is a growing concern. This trend is associated with increased morbidity, mortality, healthcare costs, and antibiotic consumption [1].

Since the initial identification of TEM-type ESBLs in *E. coli*, the genes encoding these enzymes have been detected in a wide range of bacterial species, including other Enterobacteriaceae, various other Gram-negative bacteria, and even some Gram-positive species. Therefore, these genes represent a widely disseminated source of antibiotic resistance in both pathogenic and commensal bacterial populations, facilitating the spread of resistance across diverse ecological niches [17]. The genes encoding TEM-type ESBLs are frequently transferred among bacteria within the human microbiota. The increasing prevalence of antibiotic-resistant strains over the past decades, along with the associated treatment failures in bacterial infections, has heightened public awareness regarding the implications of antibiotic misuse. Broad-spectrum antibiotic use exerts selective pressure on the bacterial microbiota, promoting the emergence of multidrug-resistant (MDR) bacteria and perpetuating a cycle of treatment failures and the evolution of novel resistance mechanisms [15].

The emergence and global dissemination of ESBL-producing bacteria poses a significant public health challenge. Of these, TEM-type ESBLs have attracted significant attention due to their extensive distribution and the resultant challenge to antibiotic therapy. In Iran, where antimicrobial resistance is notably high, a comprehensive investigation into the prevalence of TEM-type ESBLs within its population is imperative**.**

This systematic review and meta-analysis aims to determine the prevalence of TEM-type ESBLs in the Iranian population by analyzing the existing literature. This study synthesizes data from multiple sources to elucidate the current prevalence and distribution of TEM-type ESBLs in Iran, to inform public health interventions and antimicrobial stewardship programs in the region.

METHODS

Search strategy and selection criteria. A comprehensive literature search was conducted to identify articles reporting the prevalence of TEM-type ESBLs in various bacterial species within the Iranian population published between 2007 and 2020. The following online databases were searched: PubMed, Science Direct, Google Scholar, Biological Abstract, ISI Web of Knowledge, and SID. Keywords were combined with Boolean operators (AND, OR) to refine the search: "TEM," "β-lactamase," "beta-lactamase," and "Iran." The search was focused on articles published in English to ensure consistency in analysis and interpretation. Iterative searches were conducted to ensure comprehensive retrieval of relevant manuscripts. Exclusion criteria included: letters to the editor, review studies, meta-analyses, case reports or case series, and studies not reporting outcomes in terms of odds ratio (OR) or relative

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risk (RR). The reference lists of all included articles were also manually searched to find additional eligible articles.

Data extraction and management. After initial screening of titles and abstracts by two independent reviewers, the full texts of potentially eligible articles were retrieved. Full-text screening was then performed by two independent reviewers. Data extraction was performed independently by two reviewers using a standardized checklist to record the following information: first author, study location (city and province), year of the study, sample size, bacterial species studied, sample type, prevalence of TEM β-lactamase, and prevalence of ESBLs.

Quality assessment. The Newcastle-Ottawa Quality Assessment Scale (NOS), adapted for cross-sectional studies, uses a "star" rating system based on criteria for selection, comparability, and assessment of the outcome. Scores range from 0 stars (lowest quality) to 9 stars (highest quality). Studies were classified into three quality categories: low (0-4 stars), moderate (5-7 stars), or high (8-9 stars).

Inclusion criteria. 1) Research articles with available full texts; 2) Articles were included if the full text or abstract was available in English, with an exception for Persian abstracts to encompass local research; 3) Published peer-reviewed conference abstracts were considered for inclusion to capture emerging research.

Exclusion criteria. 1) Review articles, meta-analyses, and systematic reviews, as they aggregate data rather than provide original prevalence data; 2) Studies not reporting specific data on the prevalence of TEM-type ESBLs (*e.g.*, studies focusing solely on genetic mechanisms or treatment of TEM-producing bacteria); 3) Studies lacking accessible full text or adequate abstract data despite author contact attempts.

Data synthesis and meta-analysis. Duplicate studies were removed before data extraction. Two reviewers independently screened the titles and abstracts of the collected articles based on the inclusion and exclusion criteria. Full-text screening was then performed for potentially eligible studies, and any disagreements were resolved through discussion and consensus or by consulting a third reviewer. Data were extracted into a standardized spreadsheet using a predefined data extraction form. The prevalence of TEM-type ESBLs was pooled using a random-effects model with the metaprop command in Stata, which calculates the pooled prevalence with its 95% confidence interval (CI). Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. A random-effects model (DerSimonian-Laird method) was used for the primary analysis, as it accounts for variability between studies. Subgroup analyses were performed to explore potential sources of heterogeneity. Publication bias was assessed visually with funnel plots and statistically with Egger's test. Sensitivity analysis included sequentially omitting each study to recalculate pooled prevalence to assess the robustness of results. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

The initial search across PubMed, Scopus, and Web of Science yielded 6,088 articles. After deduplication, 4,108 articles underwent title and abstract screening, resulting in 827 for full-text review. Of these, 625 were excluded for reasons including: meta-analyses and review articles (as they are secondary sources), irrelevance to the study topic, duplicate reports, lack of valid experimental methodology (*e.g.*, inadequate controls or sample size); inaccessibility of full texts despite attempts to retrieve them, and non-original research articles. Following a thorough evaluation of study quality and relevance, 202 articles were included in the meta-analysis. The article selection process is illustrated in the PRISMA flow diagram (Figure 1).

The pooled prevalence of TEM-type ESBLs was estimated at 27% (95% CI: 24%-30%). Substantial heterogeneity was evident, with a Q statistic of 5197.11 *(*$P < 0.0001$*)* and an I^2 of 96.1%. Due to this heterogeneity, a random-effects model was adopted, acknowledging variability in true effect sizes between studies. Subgroup analyses examined the impact of factors such as province; sample characteristics; bacterial species; familial classification of organisms; and study year on the heterogeneity of TEM-type ESBL prevalence.

Figure 2 presents the results of the subgroup analysis by province. Qom showed the highest prevalence at 51% (95% CI: 46%-57%), with Khorasan Shomali at the lowest, 4% (95% CI: 1%-9%). Figure 2's forest plot illustrates the pooled prevalence and 95% CIs for each province.

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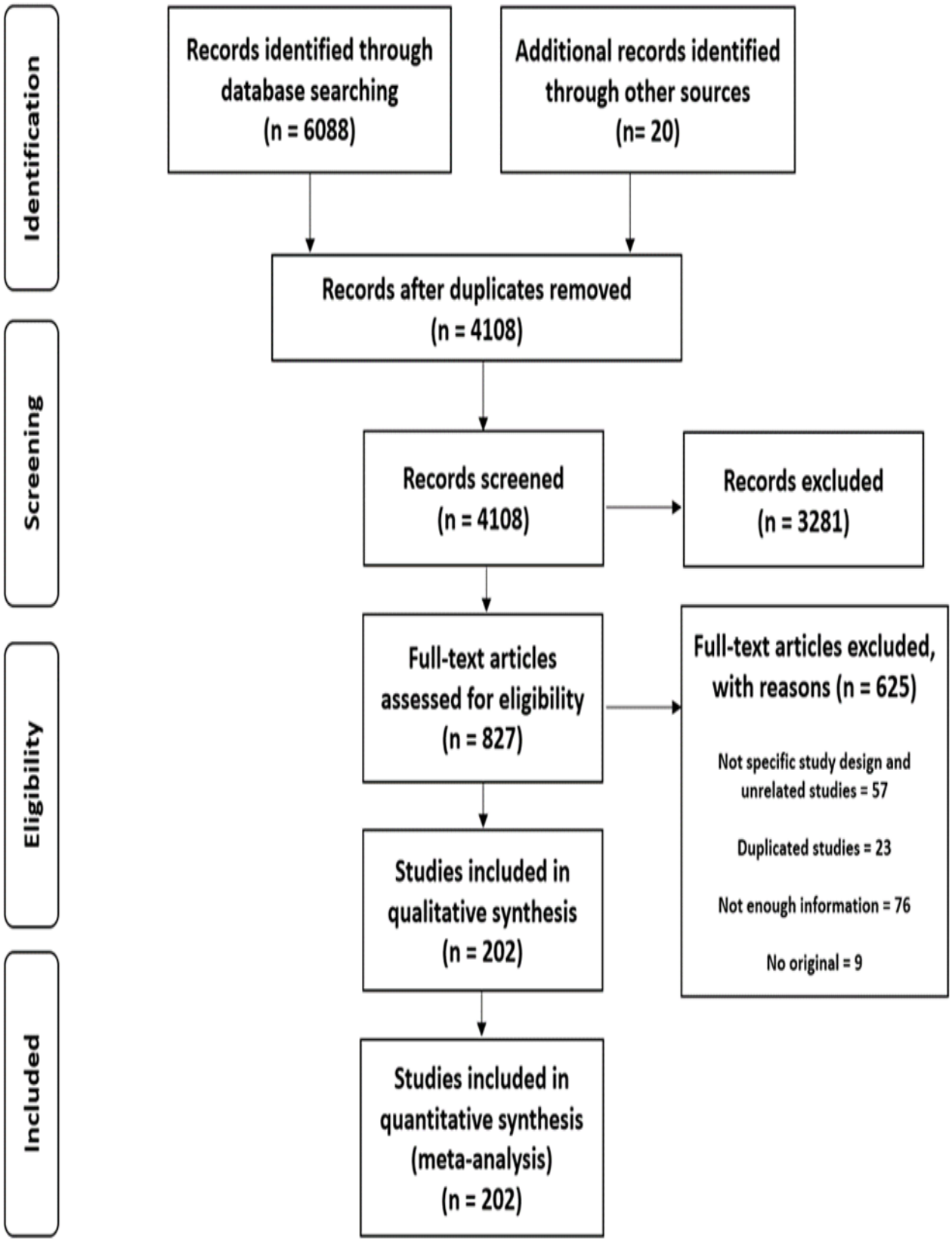

Fig 1. PRISMA flowchart that illustrates the study selection process from identification, screening, exclusion, to inclusion.

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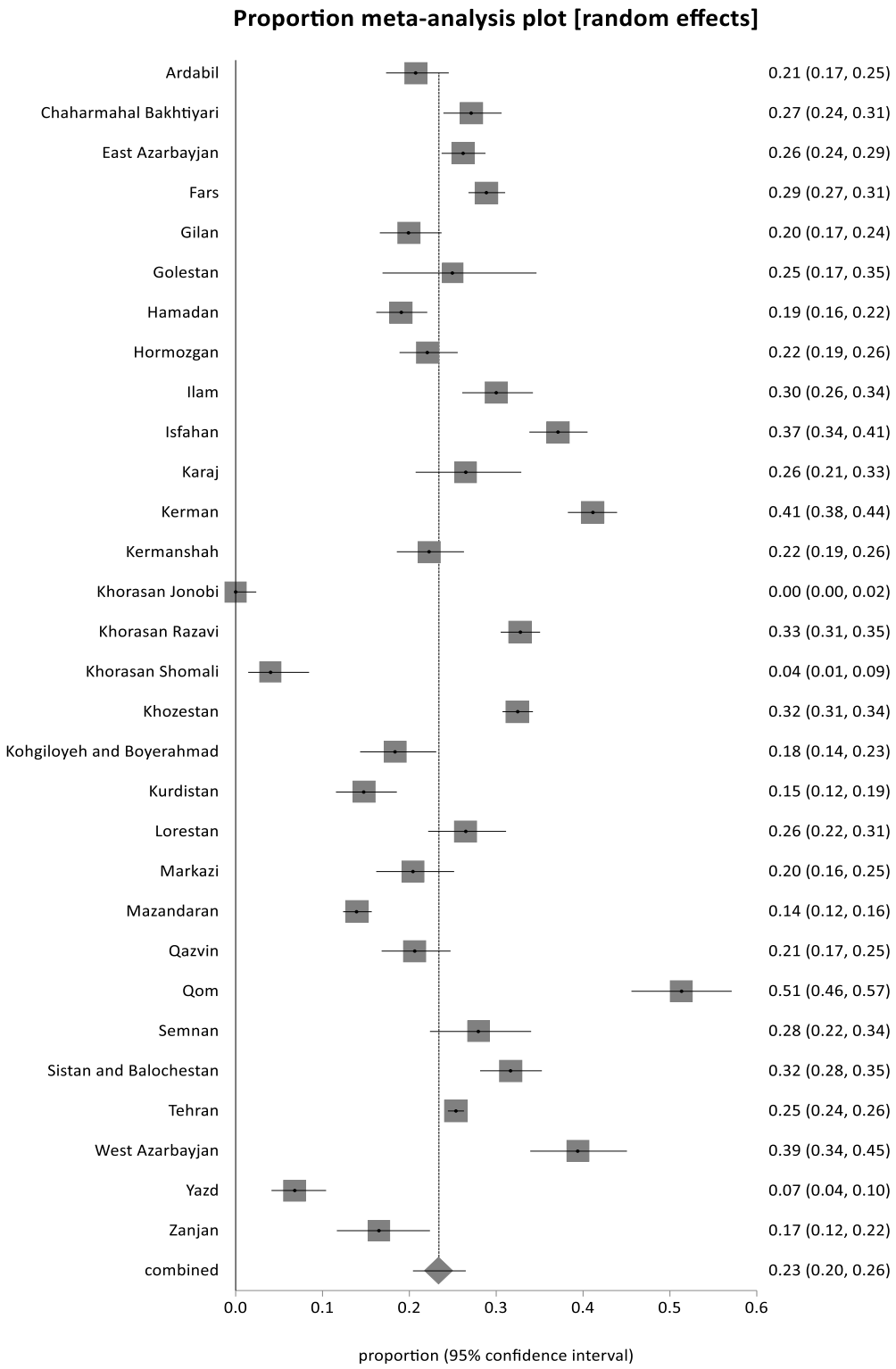

Fig. 2. Distribution of TEM-type ESBL prevalence across Iranian provinces.

Subgroup analysis by sample type, as depicted in Figure 3, revealed urine and stool samples exhibited the highest pooled prevalence at 76% (95% CI: 72%-81%). Sewage samples followed with 62%, and hospital environmental samples at 57%.

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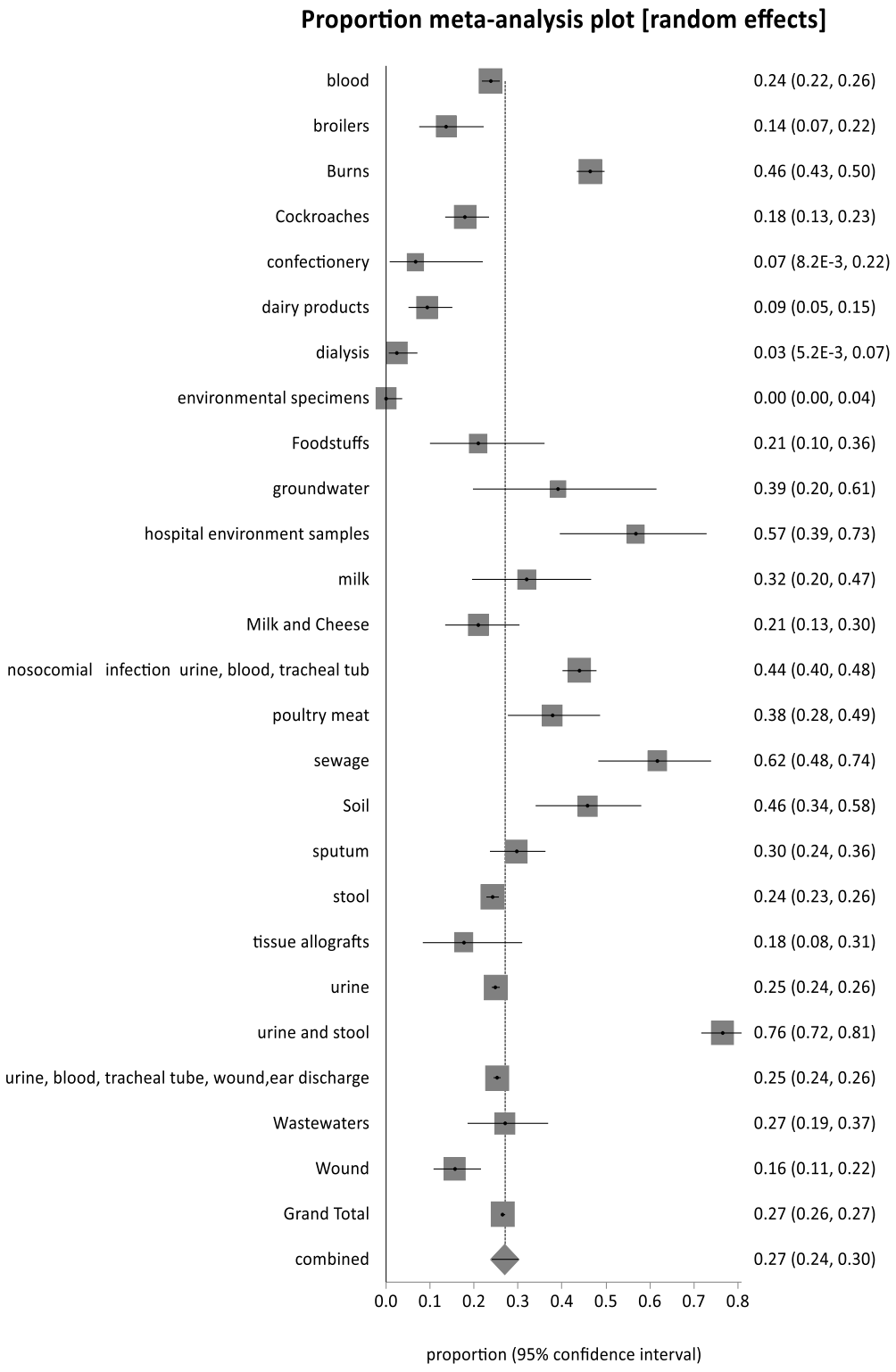

Fig. 3. Distribution of TEM-type ESBL prevalence by sample type.

Subgroup analysis by bacterial species (Figure 4) showed a 25% pooled prevalence (95% CI: 22%-27%) for TEM-type ESBLs. Notably, no TEM-type ESBLs were found in *Serratia* spp. The highest prevalence was 43% (95% CI: 38%-48%) in *E. coli* and *Klebsiella* spp. together.

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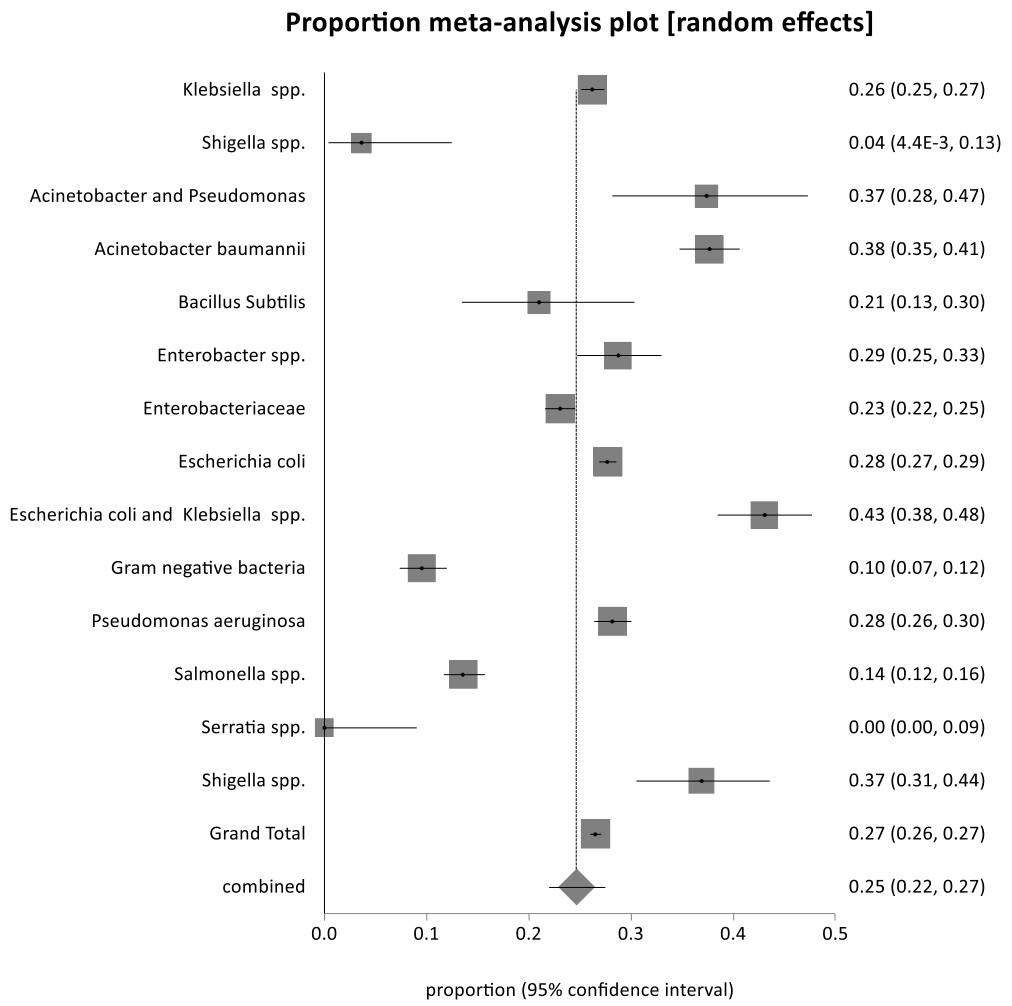

Fig. 4. ESBL prevalence in different bacterial species.

Over the study period, there was a notable increase in both the sample size and diversity of samples examined, with the largest sample size analyzed in 2020. An increasing trend in the prevalence of TEM-type ESBLs was observed across the years under investigation in Iran, with an overall pooled prevalence of 24% over the study period (Table 1).

Table 1. Annual prevalence of TEM-type ESBLs in Iranian samples.

Year	Sample size	Number of TEM-positive samples	Prevalence (95% CI)
2007	221	64	28.96% (23.07%-35.42%)
2008	485	158	32.58% (28.42%-36.95%)
2009	462	46	9.96% (7.38%-13.06%)
2010	329	84	25.53% (20.91%-30.60%)
2011	175	27	15.43% (10.42%-21.65%)
2012	951	215	22.61% (19.98%-25.40%)
2013	517	77	14.89% (11.94%-18.26%)
2014	1344	330	24.55% (22.27%-26.95%)
2015	2373	590	24.86% (23.13%-26.65%)
2016	3741	903	24.14% (22.77%-25.54%)
2017	2284	507	22.20% (20.51%-23.96%)
2018	4732	1291	27.28% (26.02%-28.58%)
2019	3707	1222	32.96% (31.45%-34.50%)
2020	6494	1866	28.73% (27.64%-29.85%)

Assessment of publication bias. Assessment of publication bias was conducted through a funnel plot (Figure 5) and Egger's linear regression test (Table 2). Publication bias can skew meta-analysis results towards

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statistically significant findings. The funnel plot was relatively symmetrical, indicating no clear bias. Egger's test was non-significant, indicating minimal influence of publication bias on our findings.

Table 2. Heterogeneity and publication bias analysis for TEM-type ESBL prevalence studies.

Subgroup analysis	Heterogeneity analysis	Egger's Test for publication bias	Model used
Q	P	I^2 (%)	Intercept
Province	973.5	0.000	97
Sample	975.42	0.000	97.4
Bacterial species	486.7	0.000	97.1
Bacterial family	208.93	0.000	97.1
Year of publication	292.64	0.000	95.6

Note: Q: Cochran's Q statistic (tests for heterogeneity). *P*-value: p-value for the Q statistic (values < 0.05 indicate significant heterogeneity). I^2: Percentage of variation across studies due to heterogeneity rather than chance.

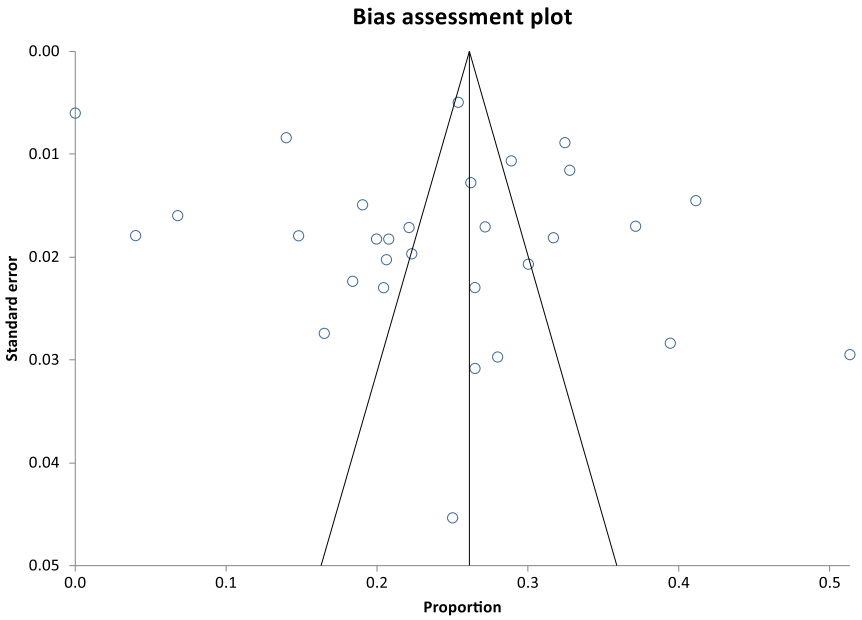

Fig. 5. Funnel plot analysis of publication bias for TEM-type ESBL prevalence studies across Iranian provinces.

DISCUSSION

Antimicrobial resistance, particularly driven by ESBL enzymes that confer resistance against commonly used broad-spectrum β-lactam antibiotics, is a growing global health concern. The widespread use of newer β-lactam antibiotics has led to selective pressure, facilitating the evolution and spread of new or modified β-lactamase enzymes. Since their initial detection, TEM-1 has been found in up to 90% of ampicillin-resistant *E. coli* isolates in some regions, highlighting its enduring prevalence. In contrast to previous meta-analyses of ESBL enzymes, which primarily focused on clinical specimens or specific bacterial strains [4, 10, 13, 18], our study provides a more comprehensive assessment of TEM-type ESBL prevalence by encompassing diverse sample types (clinical, non-clinical, and environmental) and bacterial species in Iran. Furthermore, this study identified key factors influencing prevalence, including geographical location, sample type, bacterial species, and temporal trends.

This meta-analysis revealed a pooled TEM-type ESBL prevalence of 27% (95% CI: 24%-30%) in Iran, representing the overall prevalence across all included studies, which encompassed a wide range of sample types and bacterial species. This broad scope differs from previous studies that focused on specific specimen types or bacterial species. Our findings show a lower prevalence than some earlier reports, which could be due to several factors, including the inclusion of non-clinical and environmental samples, differences in study populations or methodologies, and changes in TEM-type ESBL prevalence over time. For instance, a review study from Asian countries reported a 39.5% prevalence of TEM-type ESBLs in drug-resistant *Klebsiella pneumoniae* [19]. In Turkey, the TEM-type ESBL prevalence was 53.6% in *Acinetobacter baumannii* [20], a species not belonging to the Enterobacteriaceae family. In Erbil, Iraq, among isolates producing ESBLs, TEM-type was found in 81% of *E. coli* and 64.7% of *K. pneumoniae* [21]. In Lahore, Pakistan, a study focusing on metallo-β-lactamase-

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producing Gram-negative bacilli found a 46% prevalence of TEM β-lactamases [22]. Another study in India reported a 48.7% TEM-type ESBL prevalence in *K. pneumoniae* and *E. coli* [23]. These findings from various regions, along with our meta-analysis results, underscore the significant variability in TEM-type ESBL prevalence and highlight the importance of considering methodological differences when comparing prevalence estimates across studies. Furthermore, it suggests that TEM-type ESBL prevalence is influenced by a multitude of factors, including local patterns of antibiotic use, infection control practices, and population characteristics.

Our analysis encompassed 202 studies across all Iranian provinces, offering a comprehensive view of TEM-type ESBL prevalence nationwide. The pooled prevalence varied from 4% in Khorasan Shomali to 51% in Qom, a 12-fold difference. Provinces with a prevalence below 20% included Mazandaran (13%), Kurdistan (14%), and Zanjan (16%). Conversely, the highest prevalences (above 30%) were observed in Kerman (41%), Isfahan (37%), and West Azerbaijan (39%). This geographical variation likely stems from differences in antibiotic use, infection control, sanitation infrastructure, and water cleanliness. Poor sanitation facilitates the dissemination of resistant bacteria via environmental fecal contamination, thereby potentially elevating the transmission risk of TEM-type ESBLs. Overuse and misuse of antibiotics in human and veterinary medicine exert selective pressure favoring resistant bacteria, including those with ESBL genes, through mechanisms like direct selection and enhanced horizontal gene transfer. Moreover, suboptimal infection control in healthcare can exacerbate nosocomial spread of ESBL-producing organisms [19]. Further research into province-specific factors influencing TEM-type ESBL prevalence is necessary to tailor interventions like antimicrobial stewardship programs, enhanced infection control in medical facilities, and improved sanitation to curb environmental spread of resistant strains**.**

Urine and stool samples were found to have the highest pooled prevalence of TEM-type ESBLs at 76%, underscoring their critical role in the surveillance of these pathogens. These bacteria can asymptomatically colonize the gastrointestinal tract, acting as hidden reservoirs for resistance genes, which can facilitate their spread within community and healthcare settings. Sewage, frequently contaminated with human waste, also had a high prevalence at 61%, highlighting the need for effective sanitation infrastructure and wastewater treatment to curb antibiotic resistance spread [4]. Furthermore, a significant prevalence in hospital environmental samples (57%) highlights an ongoing challenge, reinforcing the necessity for stringent infection control measures in healthcare to curb the transmission of resistant organisms [13]. These measures include hand hygiene, environmental disinfection, and the use of contact precautions for patients colonized or infected with ESBL-producing organisms [1].

The bacterial species with the highest pooled prevalence of TEM-type ESBLs were *E. coli* and *Klebsiella* spp. (43%), followed by *Acinetobacter* spp. and *Pseudomonas* spp. (37%). These species are known for causing various infections, such as urinary tract infections, pneumonia, and bloodstream infections, due to their commonality as Gram-negative pathogens. Their proficiency in acquiring and disseminating resistance genes, notably TEM-type ESBLs, is especially concerning in *E. coli* and *Klebsiella* spp., due to their role as leading ESBL producers within Enterobacteriaceae. The mobility of TEM genes via plasmids facilitates their spread, enhancing bacterial resistance through conjugation and transformation processes. These plasmids may also harbor genes conferring resistance to other classes of antibiotics, contributing to the development of MDR bacteria. MDR infections lead to increased morbidity and mortality, prolonged hospital stays, and higher healthcare costs, posing a major threat to public health [5].

Our analysis revealed an increasing trend in the pooled prevalence of TEM-type ESBLs in Iran over the study period from 2007 to 2020, with the peak in 2019 at 32% and the lowest point in 2009 at 10%. This upward trend could indicate a real increase in TEM-producing bacteria prevalence, although other factors might also influence this observation. For example, advancements in testing sensitivity could partially explain this rise by better detection rather than an actual increase in prevalence. Additionally, shifts in research emphasis or reporting standards might have influenced the visibility of ESBL cases. Further research, such as longitudinal studies or surveillance programs with standardized methodologies, is necessary to clarify the reasons behind this trend and to determine if it reflects a broader national increase in antibiotic resistance**.**

While systematic reviews and meta-analyses provide a comprehensive overview of the prevalence of TEM-type ESBLs in Iran, it is important to acknowledge several limitations that may affect the interpretation of the findings. One limitation is that the included studies may not fully represent the entire Iranian population. For instance, many studies were conducted in large urban centers, potentially skewing the generalizability of the findings to rural or less densely populated areas. Differences in antibiotic use patterns, sanitation infrastructure, and access to healthcare between urban and rural settings could lead to variations in TEM-type ESBL prevalence. Therefore, when extrapolating these findings to the entire Iranian population, it is crucial to consider these urban-rural disparities or to expand research into underrepresented areas.

The rising tide of antimicrobial resistance, exemplified by the spread of ESBL-producing organisms, presents a formidable challenge to public health, exacerbating

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treatment failures, morbidity, mortality, and healthcare expenditures. This study, through systematic review and meta-analysis, offers crucial insights into the landscape of TEM-type ESBLs across Iran, highlighting an overall pooled prevalence of 27% with notable regional variability. Given the observed rise in TEM prevalence, even if not statistically significant, the high occurrence of TEM-producing bacteria emphasizes the critical need for robust antimicrobial stewardship in Iran. Effective strategies should encompass the development of antibiotic use guidelines in human and veterinary sectors, educational initiatives for healthcare professionals on antimicrobial stewardship, and the enhancement of surveillance systems to track resistance patterns and inform timely interventions.

Overuse and misuse of antibiotics drive antibiotic resistance by exerting selective pressure on bacteria, promoting survival of resistant strains and gene transfer. To curb resistance emergence and spread, it is imperative to develop and enforce comprehensive antibiotic use guidelines across healthcare and agriculture. These should define clear diagnostic criteria, advocate for local resistance-based antibiotic choices, and prescribe optimal treatment durations. Moreover, enhancing surveillance through laboratory-based systems, sentinel sites, and community surveys is vital to track resistance trends and steer public health responses. Such data are pivotal for early detection of resistance trends, informing prescribing policies, and assessing interventions designed to combat antibiotic resistance.

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Daem Roshani, Soheyla Barzegar, Mohsen Arzanlou, and Rashid Ramazanzadeh made significant contributions to various aspects of this article. Prof. Rashid Ramazanzadeh was responsible for project organization and coordination. Prof. Daem Roshani conducted data analysis. Soheyla Barzegar performed data preparation and manuscript writing. Dr. Majid Mansouri served as the principal investigator overseeing the study. All authors have reviewed and approved the final version of the manuscript for publication.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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