Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The Global Prevalence of Methicillin-Resistant Staphylococcus Aureus in Patients with Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis

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Objective: Diabetic foot ulcer (DFU) frequently leads to infections, with infected DFUs being a common cause of amputation. Infection by methicillin-resistant Staphylococcus aureus (MRSA) notably increases the necessity for amputation and surgical debridement in affected individuals. Consequently, determining the prevalence and trends of MRSA in patients with DFU is of critical importance. This study aimed to assess the global prevalence and to identify trends in the occurrence of MRSA in tissue or wound swab samples from DFU patients.

Methods: We conducted a comprehensive literature search across PubMed, Embase, Scopus, and Ovid, spanning from the inception of these databases to July 2023, imposing no language restrictions. The inclusion criteria required that the studies report on 30 or more patients with DFU. Additionally, we categorized our analysis based on geographic region, publication date, and the economic status of the patient's domicile. Our primary endpoint was to ascertain the prevalence of MRSA in DFUs. This systematic review has been registered at (https://www.crd.york.ac.uk/prospero/), with the identifier CRD 42023444360.

Results: Our analysis encompassed 40 studies involving 12,924 patients across 20 countries. We found that the overall prevalence of MRSA in DFU was 17% (95% Confidence Interval [CI] 0.14–0.20). Regional prevalence varied significantly: in South America, it was 61% (95% CI 0.46–0.76), in North America 20% (95% CI 0.12–0.27), in Europe 19% (95% CI 0.14–0.25), in Africa 13% (95% CI 0.06–0.20), and in other subgroups 11% (95% CI 0.08–0.15). The prevalence of MRSA in DFUs also differed according to the economic status of the countries: 19% (95% CI 0.15–0.23) in high-income countries, 24% (95% CI 0.1–0.37) in upper-middle-income countries, 11% (95% CI 0.07–0.15) in lower-middle-income countries, and 20% (95% CI 0.13–0.27) in low-income countries. Notably, there has been a decline in MRSA prevalence, from 25% before 2010 to 9% thereafter.

Conclusion: This meta-analysis reveals a decreasing yet still significant global prevalence of MRSA in DFUs. This trend has important implications for antimicrobial resistance and underscores the need for developing targeted programs focusing on infection prevention and exploring alternative therapeutic strategies.

Keywords: diabetic foot ulcers, global prevalence, epidemiological trends, systematic review, meta-analysis

Introduction

Diabetes mellitus represents a critical global health concern, with its incidence rising annually. It is projected that by 2035, approximately 592 million individuals will be affected.[1] DFUs constitute a frequent complication of diabetes, affecting about 15% of individuals with this condition during their lifetime.[2,3] Diabetic foot infection (DFI) is clinically characterized by signs of inflammation in any tissue below the malleoli in individuals with diabetes mellitus. It ranks among the most severe complications of diabetes, significantly contributing to diminished quality of life for patients and substantial economic losses.[4] Patients with DFU exhibit a dismal prognosis, as evidenced by a comprehensive prospective study. One year following diagnosis, a mere 46% of patients achieved ulcer healing, with a subsequent 10% experiencing recurrence. Additionally, a noteworthy 15% of patients succumbed to the condition, underscoring its life-threatening nature. Furthermore, a substantial

Received: 31 October 2023
Accepted: 16 January 2024
Published: 3 February 2024

17% of patients necessitated lower limb amputation.[5] Presently, the therapeutic approach for DFU encompasses a multifaceted strategy, which comprises the following key principles: Treatment of foot infections, Restoration of tissue perfusion, Pressure offloading and ulcer protection, Local ulcer care, and Person-centered care. These core principles constitute the fundamental pillars of DFU management, reflecting a holistic and patient-centric approach to address the complex challenges associated with this condition.[6] Following the aforementioned therapeutic principles, the majority of patients with DFU experience successful wound healing. However, a subset of patients may encounter severe complications, some of which pose life-threatening risks. Furthermore, the financial burden associated with DFUs is substantial, with annual costs estimated at nearly £1 billion in the United Kingdom, amounting to approximately 1% of the National Health Service (NHS) budget.[7] In contrast, the proportion of healthcare resources dedicated to DFUs is considerably higher in developing countries, underscoring the urgent need for targeted interventions and resource allocation to address this pressing issue.[8]

Staphylococcus aureus, a bacterium, is the predominant microorganism found in diabetic foot infections. These infections can be further classified into two main categories: MRSA and methicillin-sensitive Staphylococcus aureus (MSSA).[9] A study conducted in the United Kingdom revealed that DFUs testing positive for MRSA exhibit a prolonged time to ulcer healing compared to DFUs testing positive for MSSA.[10] In addition, there has been an increase in the requirement for amputation and surgical wound debridement among patients infected with MRSA.[6] The occurrence of MRSA infection in wounds imposes a substantial economic and clinical burden, characterized by elevated hospitalization expenses and an augmented likelihood of patient mortality.[11,12] Factors such as diabetes mellitus, previous exposure to antimicrobial agents, recent hospitalization within the preceding 12 months, the presence of skin or soft tissue infections upon admission, and HIV infection have all been identified as significant contributors to an increased susceptibility to MRSA infection.[13]

Presently, the incidence of diabetes mellitus continues to escalate annually, while the worldwide prevalence of antimicrobial drug resistance exhibits a corresponding upward trajectory. Consequently, it becomes imperative to comprehend the prevalence and epidemiological patterns of drug-resistant pathogens, such as MRSA, within the context of DFU. Despite numerous antecedent investigations documenting MRSA prevalence in DFU, a comprehensive global assessment of MRSA prevalence and its epidemiological trends within this specific clinical context remains conspicuously absent. To address this critical knowledge gap, we conducted a systematic review and meta-analysis aimed at elucidating the global prevalence of MRSA in DFU and its temporal prevalence trends.

Methods

Registration

The research endeavor adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for its execution and subsequent reporting. Additionally, it was duly registered with PROSPERO under the registration identifier CRD42023444360.[14]

Search Strategy and Selection Criteria

Two authors conducted independent searches across four databases (PubMed, Embase, Scopus, Ovid) from their inception to July 2023, without imposing any language restrictions. In the aforementioned databases, the following search terms were employed: [("diabetic foot" OR "Diabetic Feet" OR "Diabetic foot infection" OR "diabetic foot ulcer") AND ("Methicillin-Resistant Staphylococcus aureus" OR "MRSA") AND ("Prevalence" OR "incidence" OR "epidemiology" OR "occurrence" OR "rate")] (See Appendix 1).

The articles incorporated in our analysis were observational and focused on documenting the prevalence of MRSA in patients with DFUs in the absence of specific interventions. The studies included in our analysis required minimum recruitment of 30 participants and the utilization of established diagnostic techniques for assessing exudates from ulcer surfaces. In the case of clinical trials, we exclusively extracted baseline data. Articles that could not be accessed in full text and those that exhibited redundancy with the datasets already included, as well as systematic reviews, editorials, case reports, and case series, were excluded from our study.

Data Extraction and Quality Assessment

Data extraction was performed by a single author utilizing a standardized template within an Excel spreadsheet. This extraction was subsequently cross-verified by another author, with any ambiguities or discrepancies resolved through collaborative discussion. The extracted information encompassed details such as the publication year, primary author, publication country, geographical setting, study design, sample size, study duration, source of the study sample, and the reported prevalence.

Our analysis was stratified based on the regions defined by the World Health Organization (WHO), which include Africa, the Eastern Mediterranean, Europe, Southeast Asia, the Americas, and the Western Pacific, as well as the income categories designated by the World Bank. We employed the Joanna Briggs Institute (JBI) Prevalence Essential Assessment Tool to evaluate the quality of the studies included in our analysis.[15] The checklist was divided into three categories of risk of bias, depending on the number of met criteria: high (0–3 items), moderate (4–7 items), and low (8–10 items). The process of data extraction and quality assessment was executed meticulously, with any discrepancies resolved through consensus.

Statistical Analyses

We conducted a meta-analysis of the compiled data employing STATA 16.0 software. To assess inter-study heterogeneity, Cochran's Q test and the I2 index were utilized.[16] When $P > 0.10$ and $I2 \leq 50\%$, it indicated a lack of statistical heterogeneity among study results, and a fixed-effects model was employed for analysis. Conversely, if $P \leq 0.1$ and $I2 > 50\%$, a random-effects model was utilized for the meta-analysis.[17] Additionally, subgroup analyses were performed based on publication year, patient origin, World Health Organization (WHO)-defined region, income level, and diagnostic method type. Prevalence rates were calculated for each subgroup, followed by comparisons of prevalence rates among subgroups using the χ^2 test. It is noteworthy that publication bias was not assessed in this study, as it was deemed unrelated to prevalence.[18]

Results

Study Characteristics

A total of 860 records were retrieved from the four databases. Following the removal of 314 duplicates, the initial screening encompassed 546 documents. Subsequently, after a meticulous evaluation of titles and abstracts, a comprehensive review was conducted on 164 documents, culminating in the inclusion of 40 original articles for analysis (Figure 1).[9,10,19–56] These selected studies involved a collective cohort of 12,924 patients with Diabetic Foot Ulcers (DFU) spanning the years 1999 through 2021 (refer to Table 1). Among the 40 studies, 26 (65%) were conducted on inpatients, six focused on outpatients (15%), and eight did not differentiate between outpatient and inpatient populations (20%). All studies uniformly utilized samples of exudates from ulcer surfaces for bacterial culture. Geographically, the distribution of these studies was as follows: 13 (32.5%) from Europe, 12 (30%) from Asia, 10 (25%) from North America, 4 (10%) from Africa, and 1 (2.5%) from South America, collectively representing 20 different countries in the study design.

Meta-Analysis Results

We conducted a comprehensive meta-analysis utilizing data extracted from 40 studies that met the stipulated inclusion criteria. The analysis estimated the global prevalence of MRSA among patients with DFU to be 17.0% (95% CI 0.14–0.27) (Figure 2). Interestingly, the risk of MRSA contraction from DFUs has exhibited a declining trend over the past two decades. Before 2010, the prevalence was 25% (95% CI 0.13–0.37), whereas it reduced to 9% (95% CI 0.05–0.13) after the year 2021 (Figure 3). The prevalence of MRSA in DFUs exhibited geographical variations, with South America recording the highest prevalence at 61% (95% CI 0.46–0.76), followed by North America (20%, 95% CI 0.12–0.27), Europe (19%, 95% CI 0.14–0.25), Africa (13%, 95% CI 0.06–0.20), and the lowest prevalence observed in the subgroup (11%, 95% CI 0.08–0.15) (Figure 4). Furthermore, we categorized our analysis according to the latest World Bank classification (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups), which segregated countries into low-income, middle-income, and high-income groups. This revealed that the prevalence of MRSA in diabetic foot ulcers

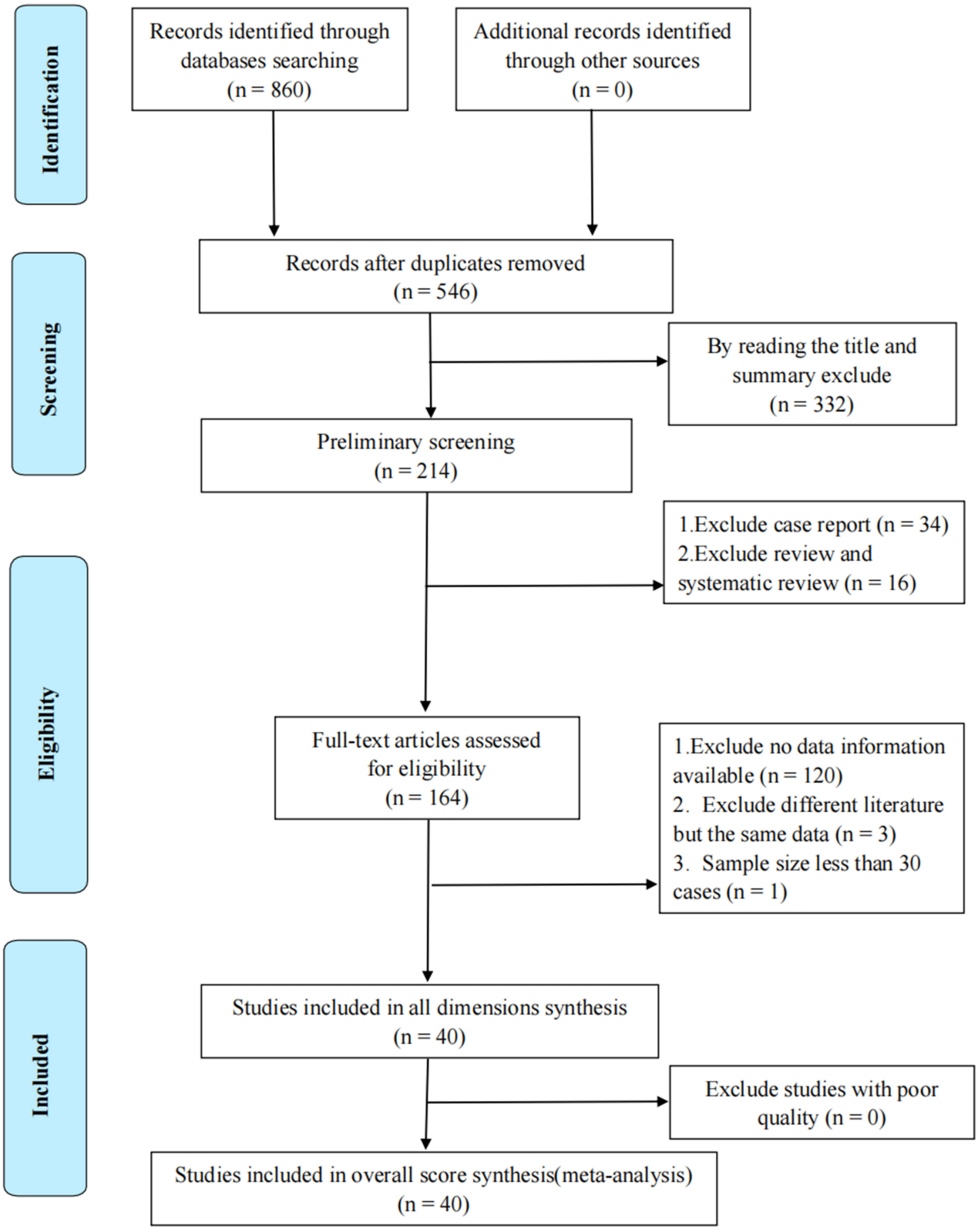

Figure 1 Study selection.

was 19% (95% CI 0.15–0.23) in high-income countries, 13% (95% CI 0.09–0.17) in middle-income countries, and 20% (95% CI 0.13–0.27) in low-income countries (Figure 5). Importantly, it is worth noting that all 40 studies included in our analysis were assessed as low-risk based on the JBI assessment tool.

Table 1 Basic Information

Author	Year of Publication	Case	Sample Size	Source	Country	Income Group
Tentolouris et al[10]	1999	30	75	Hospitalized patients	UK	High income
Ahmed T[19]	2000	9	30	Hospitalized patients	Kingdom of Saudi Arabia	High income
Dang et al[20]	2003	19	63	Hospitalized patients	UK	High income
Shankar et al[21]	2005	8	77	Hospitalized patients	South India	Middle income
Lipsky et al[22]	2005	135	586	Hospitalized patients	USA	High income
Tentolouris et al[23]	2006	36	59	Outpatients	Greece	High income
Martínez-Gómez et al[24]	2007	10	84	Hospitalized patients	Spain	High income
Lagacé-Wiens et al[25]	2009	91	5103	Hospitalized patients	Canadian	High income
Mendes et al[26]	2012	12	49	All	Portugal	High income
Lipsky et al[27]	2011	349	868	Hospitalized patients	USA	High income
Feng et al[28]	2013	57	429	Hospitalized patients	China	Middle income
Djahmi et al[29]	2013	73	128	Hospitalized patients	France	High income
Sugandhi et al[30]	2014	4	50	Outpatients	India	Middle income
Senneville et al[31]	2013	8	157	Outpatients	France	High income
Małecki et al[32]	2014	2	102	Hospitalized patients	Poland	High income
Lavery et al[33]	2014	17	57	Hospitalized patients	USA	High income
Ahmed et al[34]	2014	9	52	Hospitalized patients	Egypt	Middle income
Cezimbra et al[35]	2015	25	41	Hospitalized patients	Brasil	Middle income
Parsa et al[36]	2015	30	500	Hospitalized patients	Iran	Middle income
Commons et al[37]	2015	77	177	Hospitalized patients	New Zealand.	High income
Reveles et al[38]	2016	48	318	Hospitalized patients	USA	High income
Pobiega et al[39]	2016	7	68	Outpatients	Poland	High income
Wu et al[40]	2017	21	260	Hospitalized patients	China	Middle income
Dunyach-Remy et al[41]	2017	17	276	Hospitalized patients	France	High income
van Asten et al[42]	2017	21	143	Hospitalized patients	USA	High income
Obeid et al[43]	2018	6	128	Hospitalized patients	Lebanon	Middle income
Neves et al[44]	2019	19	87	Hospitalized patients	Portugal	High income
Kananizadeh et al[45]	2019	30	145	Hospitalized patients	Iran	Middle income
Ullah et al[46]	2020	23	114	Hospitalized patients	Peshawar-Pakistan	Middle income
Lin et al[47]	2020	6	112	Hospitalized patients	Taiwan	High income
Kim et al[48]	2020	30	158	Outpatients	USA	High income
Jouhar et al[49]	2020	9	179	Hospitalized patients	Lebanon	Middle income
Anafo et al[50]	2021	6	100	Outpatients	Ghana	Middle income
Woldeteklie et al[51]	2022	26	130	No report	Ethiopia	Low income
Stańkowska et al[52]	2022	31	863	No report	Poland	High income
Pany et al[53]	2022	85	402	Hospitalized patients	India	Middle income
Hockney et al[54]	2022	5	305	Hospitalized patients	USA	High income
Brondo et al[55]	2022	25	200	Hospitalized patients	USA	High income
Arfaoui et al[56]	2022	6	64	Hospitalized patients	Tunisia	Middle income
Moore et al[9]	2023	4	185	Outpatients	UK	High income

Discussion

This marks the inaugural systematic review and meta-analysis to delineate the global prevalence of MRSA in DFU. Within the scope of this investigation, we have furnished a comprehensive meta-analysis, encompassing diverse geographical regions, to ascertain the prevalence of MRSA in DFU. Our findings indicate a worldwide MRSA prevalence of 17%, a figure in alignment with previous reports (18%), thus reinforcing the high incidence of MRSA in this context.[9] However, our study further contributes by offering a detailed breakdown of MRSA prevalence across various geographical locations, encompassing a spectrum of economic strata, while also affording insight into the temporal trends of MRSA prevalence.

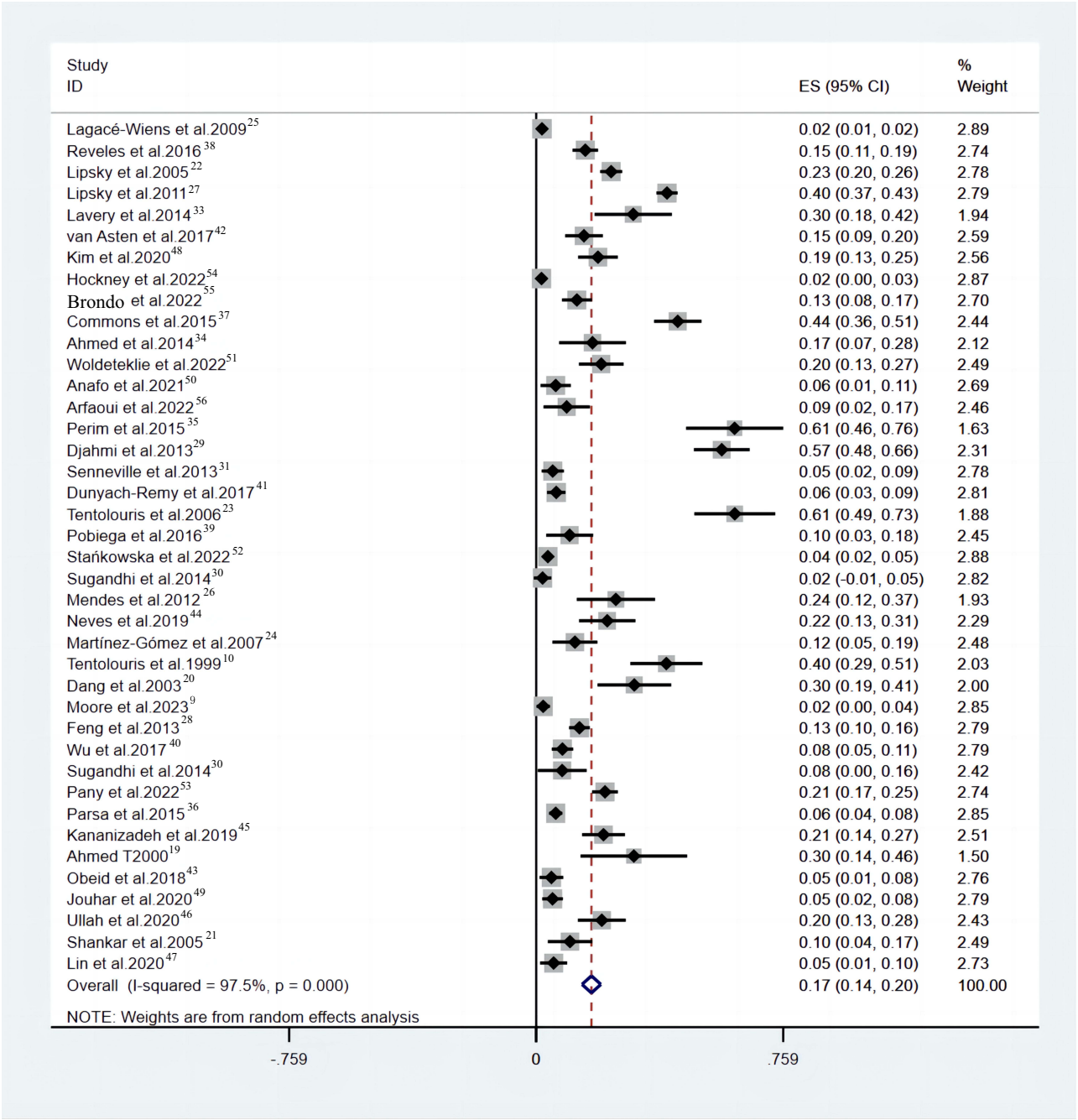

Figure 2 Global prevalence of MRSA in patients with diabetic foot ulcers.

Furthermore, we identified a paucity of relevant evidence in numerous regions across the globe, with only approximately 20 countries furnishing robust data. This observation underscores the pronounced regional disparities in MRSA prevalence, potentially associated with the respective countries' economic status and healthcare infrastructure. Notably, our analysis revealed a relatively diminished MRSA prevalence in low-income regions, a trend likely attributed to factors such as delayed access to healthcare services for individuals with Diabetic Foot Ulcers (DFU) or limited availability of antibiotic treatment. These discrepancies are reflected in the limited data contributions from countries characterized by lower economic income. Moreover, our findings indicate a discernible decrease in the prevalence of MRSA in Diabetic Foot Infections (DFI) over time, aligning with the observations made by Moore et al.[8] The plausible rationale behind this declining trend could be the implementation of standardized antibiotic protocols.

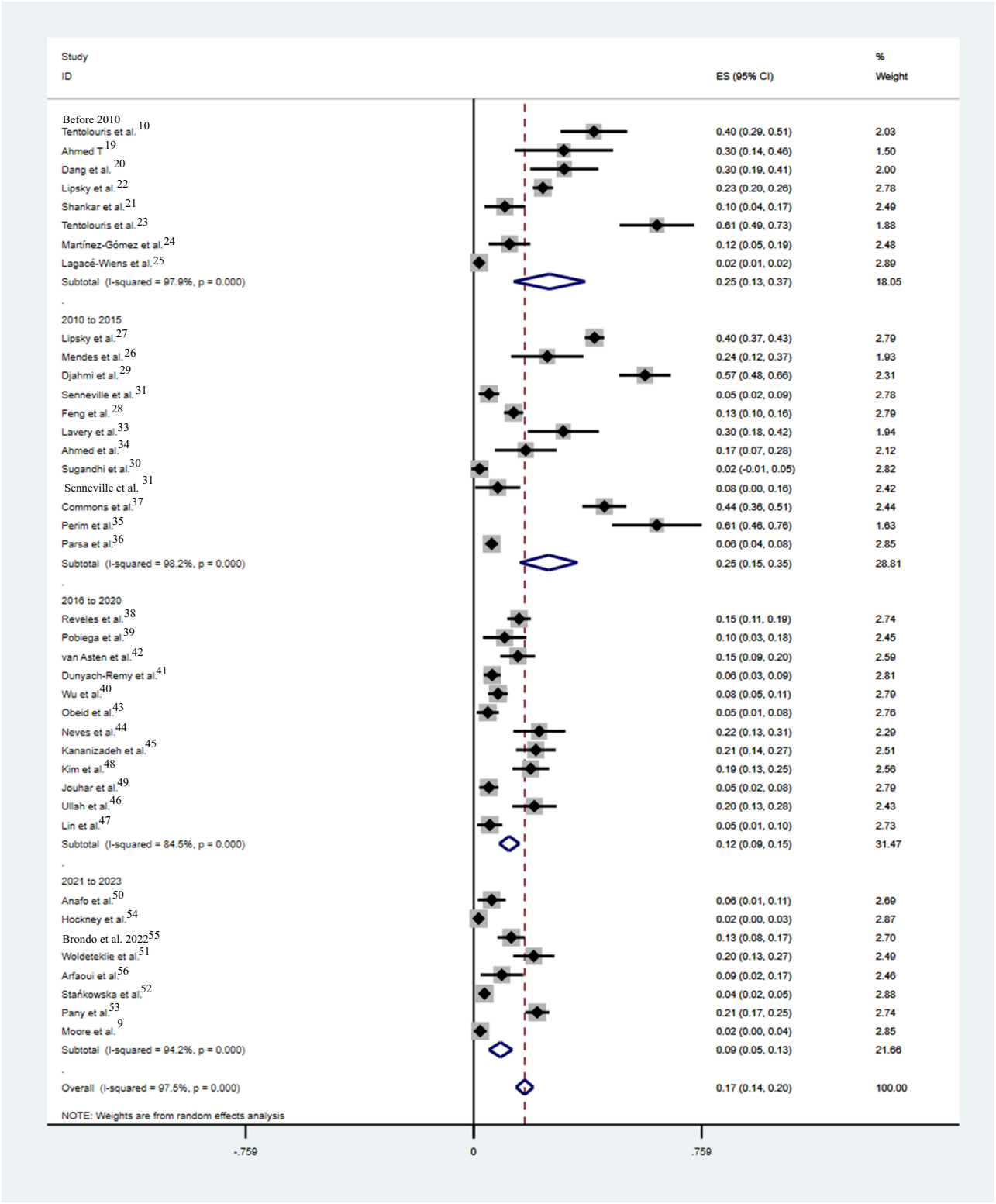

Figure 3 Global prevalence of MRSA in diabetic foot ulcers, by time of study publication.

Long-term DFU and prolonged antibiotic use are associated with MRSA infections.[10] Chronic ulcers represent the most significant risk factor for MRSA infection. Additionally, chronic kidney disease presents another risk factor for MRSA isolation.[6] One study has indicated an association between MRSA isolated from DFU and nasal MRSA

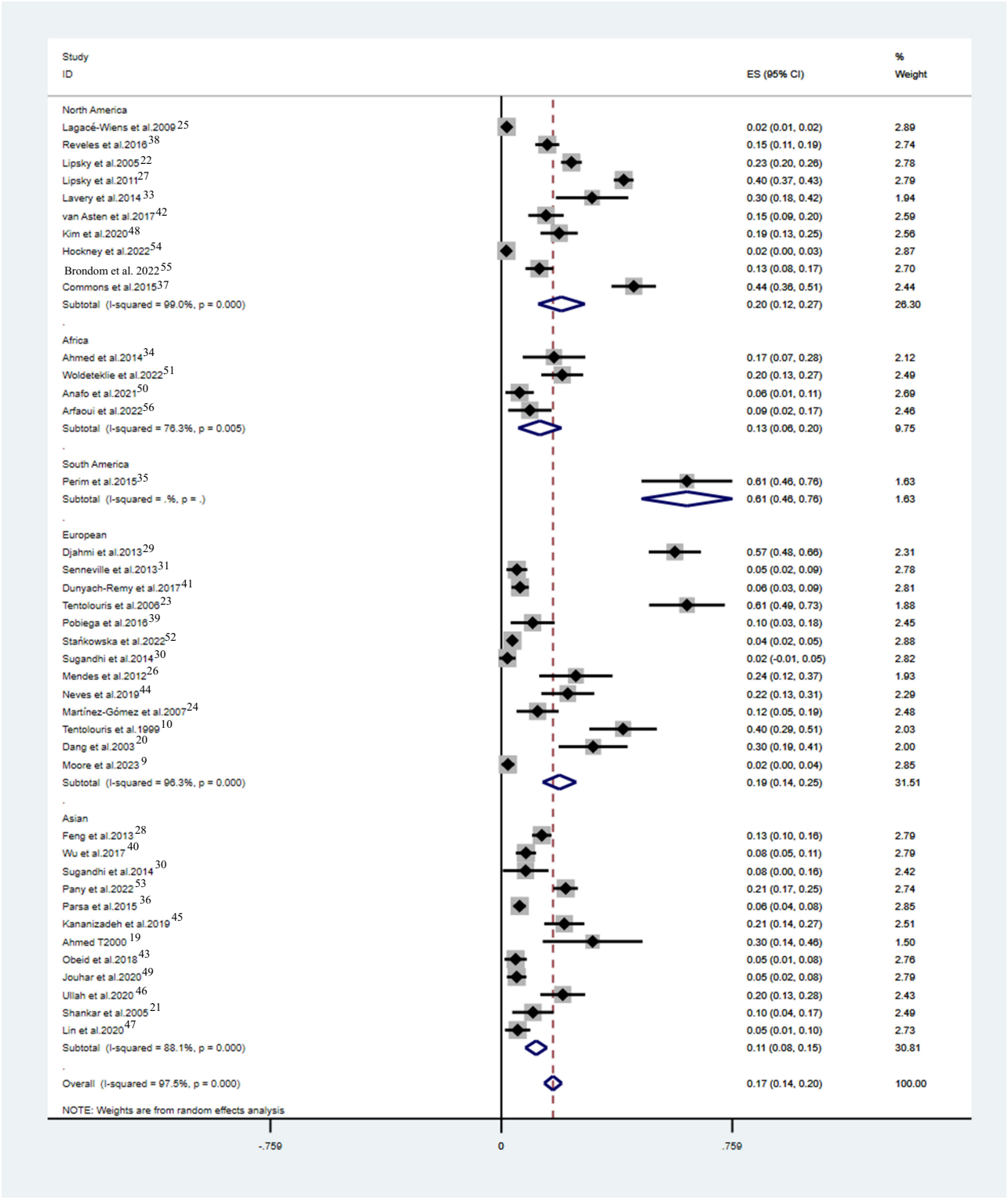

Figure 4 Global prevalence of diabetic foot ulcer MRSA, by geographic location.

carriage.[57] Long-term or inappropriate antibiotic use and previous hospitalizations are contributing factors to MRSA infections. It is crucial to note that MRSA infections not only prolong wound healing times but also elevate the risk of amputation in cases of DFI.[10,58] Moreover, MRSA escalates the likelihood of osteomyelitis development in DFUs.[52] Consequently, understanding the prevalence and temporal trends of MRSA in DFU is paramount for clinical practice.

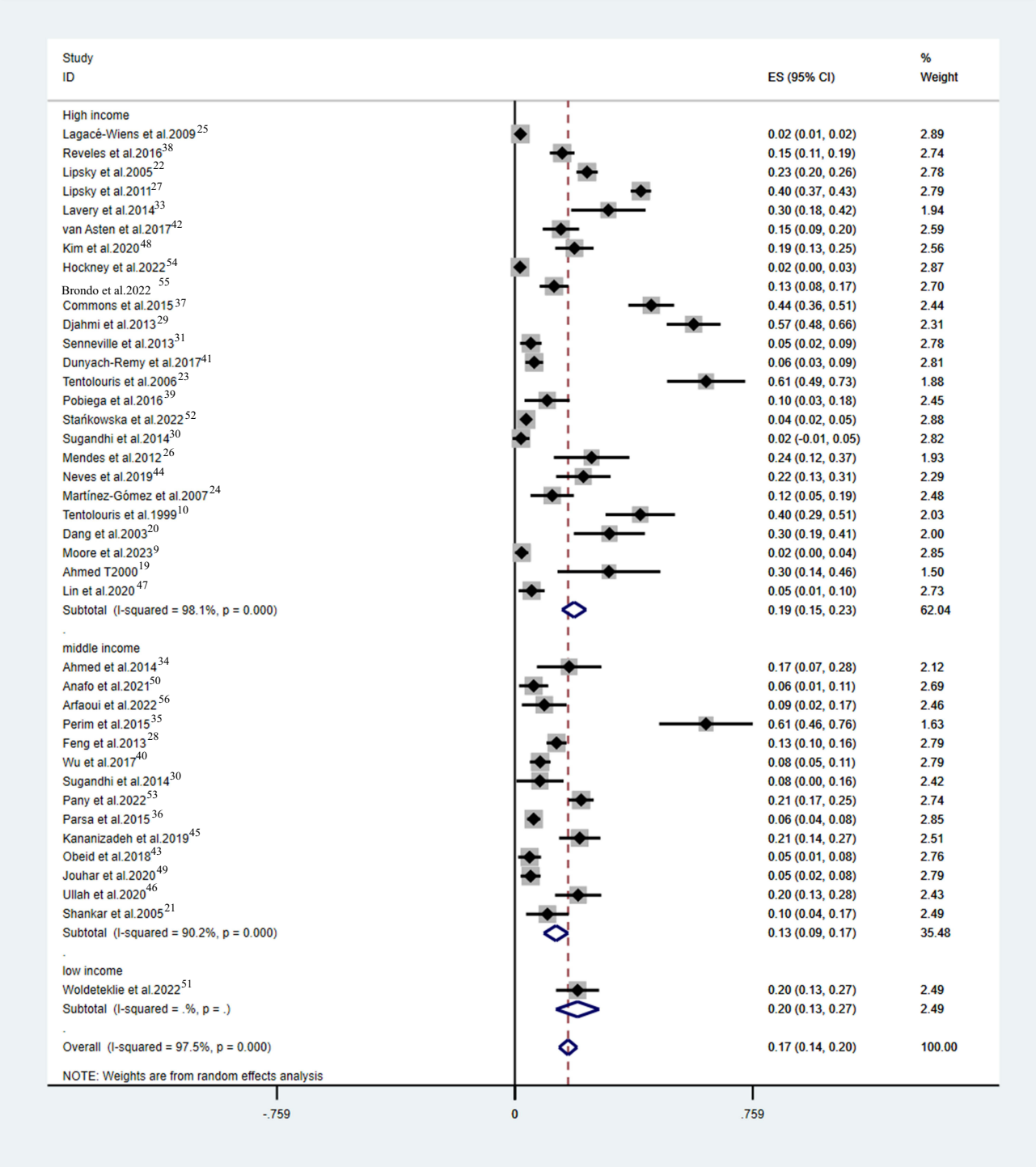

Figure 5 Global prevalence of MRSA in diaxbetic foot ulcers, by income.

Firstly, it serves as a reminder to healthcare providers to exercise restraint in antibiotic utilization. Secondly, it underscores the importance of healthcare practitioners and policymakers focusing on preventive measures, timely detection, and appropriate management of DFIs, thus providing valuable insights for policy decisions.

Several limitations must be acknowledged in this study. It is crucial to recognize that significant heterogeneity existed among the studies, likely attributed to population diversity and variations in hygienic environments. While certain studies

exclusively included patients hospitalized for their initial episode, others might have encompassed recurrent hospitalizations. Such substantial heterogeneity among these studies may potentially limit the interpretability of pooled estimates.

Furthermore, subanalyses conducted by geographical regions, although beneficial for assessing overall trends, may offer relatively lower resolution due to the intricate factors underlying MRSA prevalence. Additionally, the lack of standardized criteria for classifying the degree of ulceration in patients with diabetic foot ulcers, coupled with the varying degrees of ulceration observed across the included studies, introduces an additional layer of complexity.

To address these limitations, further research is warranted, particularly investigations specifically focused on MRSA in patients with diabetic foot ulcers. Such endeavors would bolster the evidence base and facilitate more refined stratification of data in future analyses.

Conclusions

In summary, the findings of this study reveal that while there is a declining trend in MRSA prevalence among patients with DFU, it remains at a relatively elevated level. Our comprehensive assessment has quantified these global trends in MRSA prevalence within the context of DFU, providing essential foundational data for future research and clinical endeavors. These insights can also inform healthcare policymakers in devising programs and interventions aimed at improving hygiene practices and mitigating adverse outcomes. There is a pressing need for concerted efforts within the healthcare sector to educate both clinical personnel and patients afflicted with DFUs about preventive measures, thus reducing the risk of unfavorable prognoses in this patient population. Furthermore, considering the rising levels of antibiotic resistance, it is imperative to prioritize research into alternative therapies, alongside continued efforts in infection prevention.[59]

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author Contributions

All authors made significant contributions to the work reported in the conception, study design, execution, acquisition, analysis, and interpretation of data. All authors took part in drafting, revising or critically reviewing the article and gave final approval of the version to be published. All authors have agreed to the approval of the final manuscript for publication in the current journal and to be accountable for all aspects of this work.

Funding

This study was supported by the Construction project for Shanghai Municipal Health Commission key clinical speciality (shslczdzk03801).

Disclosure

All the authors declare no conflicts of interest.

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