JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Microbiology and antibiotic resistance of diabetes-related foot infections in Brazil: a systematic review

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Abstract

Introduction: Diabetic foot infections are the main cause of lower limb amputations. Knowing the microbiology of these infections is important because the most effective empirical antibiotic therapy varies by region due to differences in the prevalence of causative pathogens. This study aimed to identify the microbiological profile and antimicrobial resistance patterns of diabetes-related foot infections in Brazil.
Methodology: The study followed a systematic literature review methodology. Manuscripts in the electronic databases PubMed, SciELO and VHL were searched through November 2022. Eligible studies were retrieved using the MeSH terms "diabetic foot" AND "Brazil". Two independent evaluators selected the articles. Of the 466 titles identified, 10 observational studies met the eligibility criteria.
Results: All 10 studies had observational design and covered 7 Federative Units of Brazil. The sample size varied between 17 and 320 cases, and hospital inpatients predominated (9 studies). Two studies performed anaerobic cultures. Among the 1,506 isolates, more than half were Gram-negative (836/55.5%) followed by Gram-positive (624/41.4%) and anaerobic bacteria (46/3.1%). The 3 most common species were *Staphylococcus aureus* (251), *Enterococcus faecalis* (112), and *Pseudomonas aeruginosa* (97). Forty percent (40%) of *Staphylococcus aureus isolates* were methicillin-resistant (MRSA). A fifth (20%) of the *Pseudomonas* spp isolates were resistant to carbapenems. The prevalence of extended-spectrum beta-lactamase-producing (ESBL-producing) was 43%, 33%, and 26% for *K. pneumoniae*, *Proteus* spp, and *E. coli* respectively.
Conclusions: In Brazil, the microbiology of foot infections in persons with diabetes showed Gram-negative predominance. *Staphylococcus aureus* was the most frequently isolated species with a high prevalence of MRSA.

Key words: microbiology; antibiotics; diabetic foot.

J Infect Dev Ctries 2026; 20(3):381-392. doi:10.3855/jidc.20077

(Received 04 March 2024 – Accepted 23 July 2025)

Introduction

Diabetes mellitus (DM) is a major public health problem globally, affecting 10.5% of the adult population aged 20 to 79 years old, amounting to more than 536 million individuals worldwide [1]. Over the years, the prevalence of DM has been growing in different countries [1]. China, India, and Pakistan occupy the top 3 positions among the countries with the highest number of adults with diabetes, and Brazil ranks 6th, with 15.7 million adults with diabetes [1]. The estimated prevalence of DM in Brazil is 9.2%, with a marked difference among the different regions: 6.3% in the North Region, 7.2% in the South, 7.6% in the Central-West, 12.2% in the Northeast, and 12.8% in the Southeast Region [2].

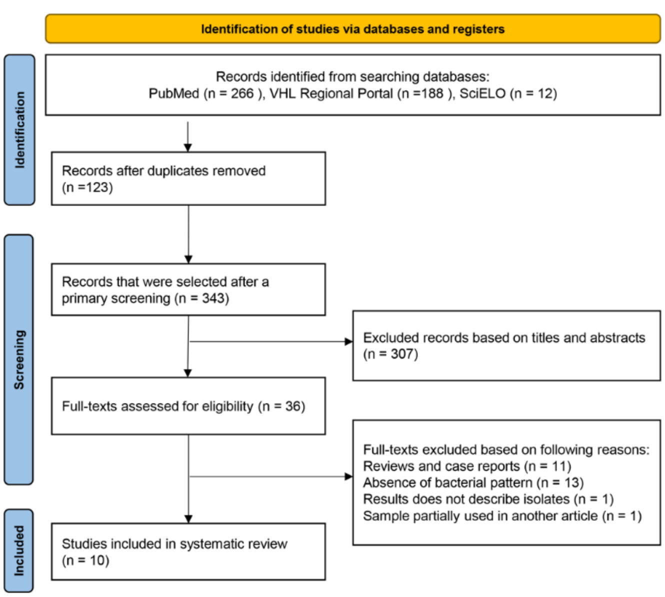
Foot injuries play a prominent role among the chronic complications of DM. DM and its complications are responsible for approximately 80% lower limb amputations worldwide [3]. Neuropathy, infection, and peripheral vascular disease are factors related to extremity wounds in persons with DM [4], and estimates indicate that half of the patients with neuropathic ulcers will develop an infection, with an amputation rate of up to 20% [3]. It was reported that deep lower limb wounds in persons with diabetes, when accompanied by infection and ischemia, present a high risk of limb loss [4–6]. In Latin America, as in other regions of the world, the number of complications from foot wounds related to DM has been increasing in recent years [3]. In Brazil, hospitalizations secondary to diabetic foot wounds have a high cost, prolonged hospitalization time, and elevated morbidity [7].

The greater severity of foot infections in persons with diabetes increases the risk of amputation, and nowadays, there are several classifications for these wounds [4,5,8]. The treatment of wound lesions that have clinical evidence of infection usually starts with empirical antimicrobial therapy, based on studies on the most prevalent microorganisms in diabetic foot infections [9]. Inappropriate use of antibiotics has a significant impact on treatment costs and contributes to the selection of resistant microorganisms, leading to increasing rates of bacterial resistance to antimicrobials in several countries around the world [10–12]. In cases of severe infections, specimen collection — preferably from deep tissue — is recommended to perform culture and antibiogram testing for targeted treatment of the causative pathogen [4].

Results from studies in different countries, mainly in the Northern Hemisphere, indicate the predominance of Gram-positive microorganisms, such as *Staphylococcus aureus*, as the main cause of foot infections in persons with diabetes [9,13]. However, other studies from China, India, Malaysia and Brazil, suggest the predominance of Gram-negative bacilli as responsible for these infections [14–17]. The local microbiology can help select the most appropriate antimicrobials for empirical therapy in foot infections [14]. Given the notably high prevalence and social impact of the disease, understanding the causative pathogens and antimicrobial sensitivity of foot lesions in persons with DM in Brazil is essential to help bring about options for the treatment of wound infection. The study of the microbiology of infections also helps in selecting the appropriate antibiotic therapy and combating the increasing global rate of antimicrobial resistance.

The present study aimed to find, through a systematic literature review, the microbiological profile and antimicrobial resistance in diabetes-related foot infections (diabetic foot infections) in Brazil.

Figure 1. PRISMA Flow diagram [18] of eligible studies.



Methodology

The study followed a systematic literature review methodology based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) criteria [18]. The review was carried out at the Federal University of Bahia, Salvador, Bahia, Brazil.

Search strategy

The Medical Subject Headings (MeSH) keywords that could retrieve the largest number of articles on the microbiology of foot infections in persons with diabetes were identified. The selected the terms were: “diabetic foot” AND “Brazil”. The electronic databases searched for articles were PubMed Central® (PMC), Virtual Health Library Regional Portal (VHL), and Scientific Electronic Library Online (SciELO). The search on the aforementioned databases was carried out until 28 November 2022. No filters were applied for dates, language, or publication type.

Eligibility criteria

The search for articles in the databases resulted in 466 titles that were selected according to the flowchart in Figure 1. Original articles that met the following criteria were considered eligible: (1) microbiology of diabetic foot infections was studied, (2) the cultures performed from foot lesions in persons with diabetes were analyzed, (3) patients were treated in the Brazilian territory, and (4) results reported microbiological profile and isolated bacterial species. The articles that did not describe cultures of lower limb infections in persons with diabetes, articles that did not describe the microbiological profile of diabetic wounds, review articles, and case reports were not considered eligible.

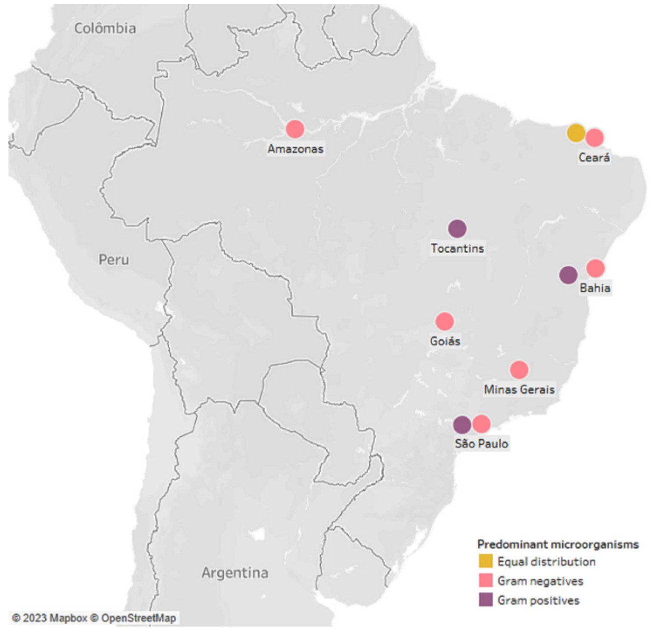
Article selection

All articles that matched the search criteria were reviewed for their titles, considering the research objective and the established selection criteria. Eligible abstracts were read considering the same criteria. The selected abstracts led to the complete reading of 12 articles, which were fully evaluated, according to the eligibility criteria, with the inclusion of a total of 10 articles in this systematic review (Figure 1). Two independent evaluators (VPS and CFS) selected the 10 articles to be included. There were no points of disagreement between the authors. The authors also prepared a spreadsheet in Microsoft Excel® for extracting and analyzing data from the studies included in the review.

Analysis of selected articles

The 10 selected articles were analyzed according to the data extraction spreadsheet prepared by the authors, containing detailed information about the manuscript. Information on first author, year, geographic region, state and city, study design and journal of publication were extracted. As for the included studies sample, data on the materials for culture, wound classification, Gram-positive or Gram-negative predominance, number and species of microorganisms isolated, and antimicrobial bacterial resistance were extracted and analyzed. The year that the studies had finished (2001-2019) was used in order to analyze the temporal trends in prevalence of the main isolates and methicillin resistant *Staphylococcus aureus* (MRSA). The spreadsheet containing the data of the included articles was descriptively analyzed in the Epi-info TM software version 7.2.2.6. A meta-analysis was not performed considering the methodological differences in the selected observational studies. The studies were classified according to the level of evidence from the Oxford Centre for Evidence-Based Medicine [19]. The methodological quality analysis was performed using the Newcastle-Ottawa quality assessment scale and the Downs and Black checklist [20,21]. The Newcastle-Ottawa scale is based on three criteria: selection, comparability, and exposure (observational case-control studies) or outcome (cohort studies). The article could receive a maximum of 9 points. The checklist proposed by Downs and Black had 27 questions that included items such as external validity, internal validity, biases and study power, with a higher number of points depending on the methodological quality of the research [21]. This review did not use questions 4, 8, 14, 15, 17, 19, 21, 22, 23, 24 because all included studies were observational. Questions 1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 16, 18, 20, 25 and 26 of the checklist were considered to have the maximum possible score was 17.

Figure 2. Gram-staining characterization of predominant bacteria isolates in the included studies from the federative units of Brazil.



Results

Characteristics of the studies included in the systematic review

The 10 studies conducted in Brazil were geographically distributed in 4 of the 5 regions of the country, namely Northeast, Southeast, North and Central West, and concentrated in 7 states of the 27 Federation Units: Ceará (2), Bahia (2), São Paulo 2), Minas Gerais (1), Tocantins (1), Amazonas (1) and Goiás (01) (Figure 2). Almost all the studies (09) were conducted in capital cities and only one was carried out in Vitória da Conquista, the third largest city in Bahia.

Table 1. Characteristics of the 10 observational studies.

First author/year	Study design	City/state	Sample size	Specimen collection	Wound classification system
Aragão *et al*, 2010 [29]	Cross-sectional	Fortaleza/Ceará	17	Surgical debridement	Wagner (2, 3 4 and 5)
Cardoso *et al*, 2017 [25]	Case-control	Belo Horizonte/Minas Gerais	189	Deep tissue	Wagner (3, 4 and 5)
Carvalho *et al*, 2004 [22]	Cross-sectional	Fortaleza/Ceará	141	Swabs	Wagner (1 and 2)
Fernandes *et al*, 2007 [23]	Cross-sectional	Goiânia/Goiás	79[a]	Swabs	Not available
Nascimento *et al*, 2021 [24]	Cross-sectional	Vitória da Conquista/Bahia	34[b]	Swabs	Wagner (1 to 5), University of Texas and PEDIS
Palomo *et al*, 2022 [28]	Cross-sectional	São Paulo/São Paulo	320	Deep tissue	IWGDF (Class III) and WIfI
Perim *et al*, 2015 [27]	Cross-sectional	Palmas/Tocantins	41	Swabs	Superficial or deep ulcers
Pontes *et al*, 2020 [26]	Cross-sectional	Manaus/Amazonas	105	Deep tissue	Wagner (2, 3,4 and 5) and PEDIS
Santos *et al*, 2006 [6]	Cross-sectional	São Paulo/São Paulo	99	Deep tissue	Wagner (3, 4 and 5)
Santos *et al*, 2021 [17]	Cross-sectional	Salvador/Bahia	111[c]	Deep tissue	Wagner (3, 4 and 5), Rutherford, IDSA[d] and WIfI[e]

[a] 50 patients had diabetes-related foot infections. [b]The study analyzed *Staphylococcus aureus*. [c] 80 patients had diabetes mellitus (72%). [d] Infectious Diseases Society of America. [e] Wound, ischemia, and foot infection.

Table 2. Microbiology of diabetes-related foot infections: proportion of Gram-positive, Gram-negative and anaerobic isolates.

First author/ Brazilian state	Microorganisms identified (total)	Gram positives	Gram negatives	Anaerobic	*Enterobacteriaceae* family	Non-fermenters Gram negatives
	N	N (%) [a]	N (%) [a]	N (%) [a]	N (%) [b]	N (%) [b]
Aragão [29] (Ceará)	16	08 (50%)	08 (50%)	NA[c]	05 (62.5%)	03 (37.5%)
Cardoso [25] (Minas Gerais)	275	70 (25.5%)	205 (74.5%)	NA	139 (67.8%)	66 (32.2%)
Carvalho [22] (Ceará)	298	85 (28.5%)	177 (59.4%)	36 (12.1%)	156 (88.1%)	21 (11.9%)
Fernandes [23] (GoiásO)	66	22 (33.3%)	44 (66.7%)	NA	33 (75%)	11 (25%)
Nascimento [24] (Bahia)[d]	17	17 (100%)[b]	NA[d]	NA[d]	NA[d]	NA[d]
Palomo [28] (São Paulo)	276	188 (68.1%)	88 (31.9%)	NA	55 (62.5%)	33 (37.5%)
Perim [27] (Tocantins)	89	61 (68.5%)	28 (31.5%)	NA	24 (85.7%)	4 (14.3%)
Pontes [26] (Amazonas)	95	40 (42.1%)	55 (57.9%)	NA	49 (89.1%)	6 (10.9%)
Santos [6] (São Paulo)	189	81 (42.9%)	98 (51.8%)	10 (5.3%)	76 (77.6%)	22(22.4%)
Santos [17] (Bahia)	185	52 (28.1%)	133 (71.9%)	NA	104 (78.2%)	29 (21.8%)
Total	1.506	624 (41.4%)	836 (55.5%)	46 (3.1%)	641 (76.7%)	195 (23.3%)

[a] Percentage of the total number of microorganisms isolated in the study; [b] Percentage of the total number of Gram-negative microorganisms isolated in the study; [c] Not available; [d] The study analyzed *Staphylococcus aureus* isolates.

All the studies had observational study design. Nine studies were cross-sectional and 1 was a case-control study (Table 1). The samples ranged from 17 to 320 cases, with 8 to 320 wound cultures. The sample size calculation was not described. Five studies collected deep tissue samples for analysis, 4 collected swab samples after wound debridement, and one study reported collecting material from surgical debridement. Only two studies reported anaerobic cultures and isolates (Table 2) [6,22]. Nine studies included hospitalized patients (inpatients), and one included outpatients. Five studies reported previous use of antibiotics. Considering the selection of participants, 8 studies included diabetic foot ulcers/infection, and 2 included lower extremity wounds. Fernandes *et al.* included patients with diabetic foot (50 patients) and venous ulcers (29 cases) in their study. While microbiological species were described separately, antimicrobial susceptibility was reported together [23]. Dos Santos *et al.* studied 111 cases of which 80 (72%) had diabetic lower extremity wounds [17]. The scope of the study by Nascimento *et al.* was limited to describe positive cultures for *Staphylococcus aureus* in a half (17) of the individuals of the sample (34) not including other Gram-positive or Gram-negative isolates [24]. Eight studies had different ways of describing antibiotic resistance and had their own antibiotic selection. Two studies did not describe the antibiotic sensitivity or resistance of isolated microorganisms [6,25] and one analyzed resistant bacteria of the venous ulcers and diabetic foot together [23].

Microbiology of diabetic foot infections in Brazil

A quantitative microbiological profile synthesis pooled all studies (10) considering that among 1107 cases only 31 were non-diabetic wounds with statistically comparable microbiological characteristics. Regarding the microbiology of diabetic foot infections in Brazil, there was a predominance of Gram-negative microorganisms (836/55.5%), followed by Gram-positive (624/41.4%) and anaerobes (46/3.1%) in 1506 bacterial isolates (Figure 3). Six studies showed a predominance of Gram-negative bacteria [6,17,22,23,25,26] (Table 2). Two studies found a predominance of Gram-positive isolates [27,28] and one study described only *S. aureus* isolates [24] (Figure 4). One study found equal Gram-positive and negative distribution [29].

Figure 3. Predominant microorganisms based on Gram-staining characterization in the major regions of Brazil.

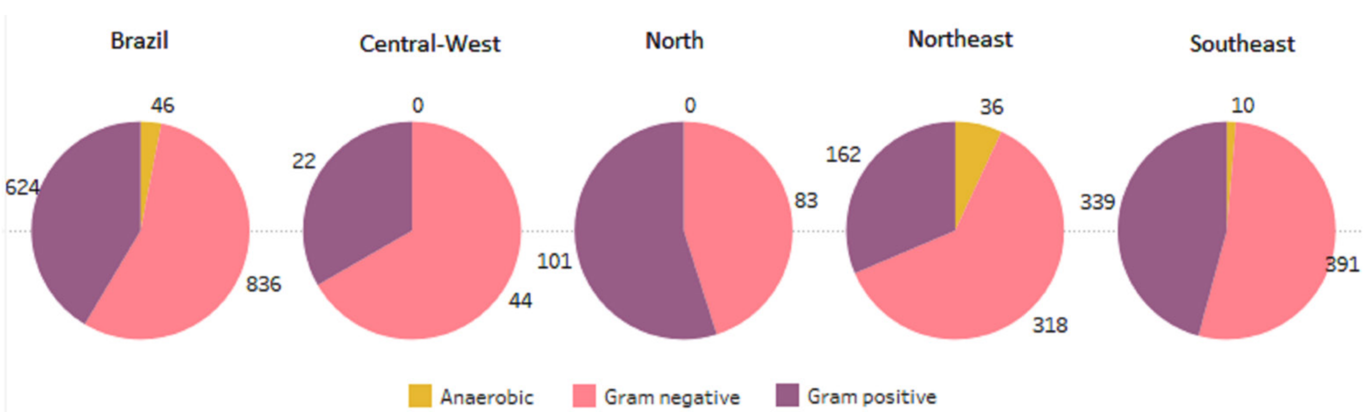


Table 3. Microbiology of diabetes-related foot infections in Brazil (1,506 isolates).

Microorganisms identified	N (%); 1,506 (100%)
Gram-positives	**624 (41.4%)**
Enterococcus spp	192 (12.7%)
Enterococcus spp	70
E. faecalis	112
E. avium	3
E. faecium	7
Staphylococcus spp	384 (25.4%)
Staphylococcus spp	70
S.aureus	251
S. epidermidis	45
S saprophyticus	18
Streptococcus spp	47 (3.1%)
Streptococcus spp	16
S. agalactiae	15
S.viridans	3
S. pneumoinae	2
S. pyogenes	11
Corynebacterium	1 (0.6%)
Gram-negatives	**836 (55.5%)**
Proteus spp	173 (11.5%)
Proteus spp	58
P. mirabilis	87
P. peneri	11
P.vulgaris	17
Pseudomonas spp	138 (9.1%)
Pseudomonas spp	41
P. aeruginosa	97
Escherichia spp	111 (7.4%)
Escherichia spp	27
E. coli	84
Klebsiella spp	100 (6.6%)
Klebsiella spp	8
K. pneumoniae	78
K. oxytoca	14
Morganellaspp	94 (6.2%)
Morganellaspp	35
M. morgani	59
Citrobacter spp	33 (2.1%)
Citrobacter spp	11
C. freundi	11
C. koseri	02
C. youngae	01
C. amalonaticus	01
C. diversus	07
Providencia spp	19 (1.2%)
P. stuartii	07
P. rettigeri	11
P. alcalifaciens	01
Enterobacter spp	82 (5.4%)
Enterobacter spp	43
E. aerogenes	15
E.gergoviae	05
E. cloacae	15
E. sakazakii	03
E.agglomerans	01
Acinetobacter spp	46 (3%)
Acinetobacter spp	34
A. baumanii	11
A. iwofii	1
Serratia spp	16 (1%)
Serratia spp	5
S. marcescens	8
S. liquefaciens	2
S. odorifera	1
Stenotrophomonas spp	9 (0.5%)
Stenotrophomonas spp	2
S. maltophilia	7
Burkholderiacepacia	1 (0.06%)
Achromobacterxylosoxidans	1 (0.06%)
Enterobacteriales(Order)	13 (0.8%)

Table 3 *(continued)*. Microbiology of diabetes-related foot infections in Brazil (1,506 isolates).

Microorganisms identified	N (%); 1,506 (100%)
Anaerobic	**46 (3.1%)**
Bacteroides spp	18 (1.2%)
Bacteroides spp	8
B. fragilis	10
Peptostreptococcusspp	10 (0.6%)
Other anaerobic isolates	18 (1.2%)

Figure 4. Number of bacterial isolates based on Gram-staining in the ten included studies.

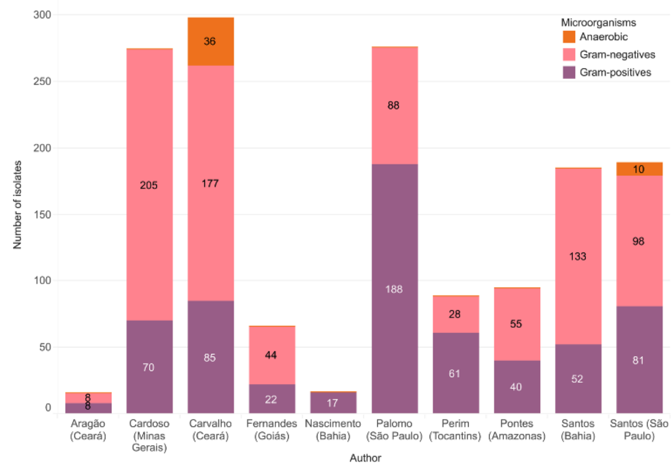
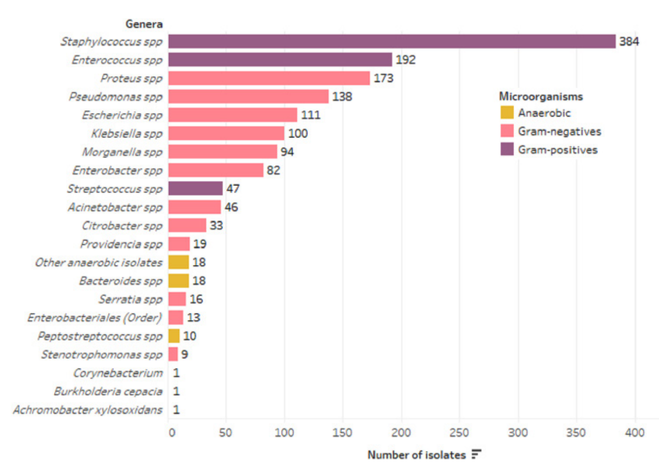


Figure 5. Number of isolates from different bacterial genera identified in the included studies.



The most isolated species was *Staphylococcus aureus*, followed by *Enterococcus faecalis* and *Pseudomonas aeruginosa* (Table 3). *P. aeruginosa*, *P. mirabilis*, *E. coli* and *K. pneumoniae* were the most common Gram-negative pathogens. Only two studies described anaerobes [6,22] with a predominance of *Bacteroides spp.* (Figure 5). The Figure 6 summarizes the overview of causative pathogens in diabetes-related foot infections in Brazil. Generally, the temporal trends of the number of the 6 main isolates suggest that their prevalence is increasing over time. Figure 7 presents the temporal trends in the prevalence of the main isolates in the Brazilian studies.

Antimicrobial resistance of diabetic foot infections in Brazil

Antimicrobial resistance data were unavailable for two studies [6,25]; and one [23] was excluded from this analysis because it presented the resistance pattern by adding cases of venous and diabetic wounds in graph format. The remaining 7 studies adopted various methods to describe antibiotic resistance and sensitivity and this difference was a challenge for pooled analysis. Numbers, percentages, mechanisms, tables, and graphs were employed to describe the sensitivity or resistance for numerous classes and antibiotics. Therefore, only 7 studies were considered for general antimicrobial resistance analysis. Considering these 7 studies, 40% of *Staphylococcus aureus* tested (71/178) were

Figure 6. Causative pathogens in diabetes-related foot infections in Brazil.

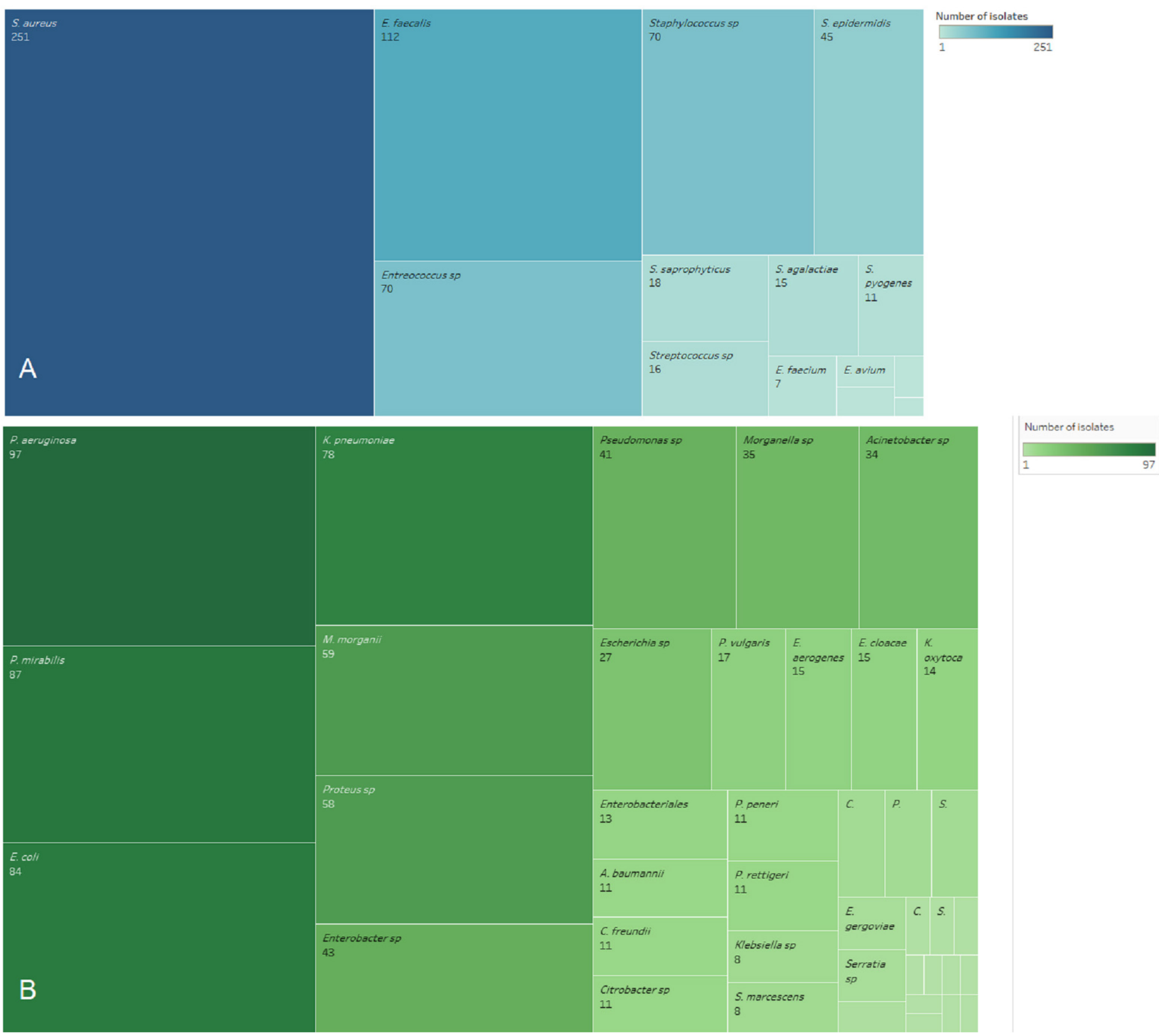
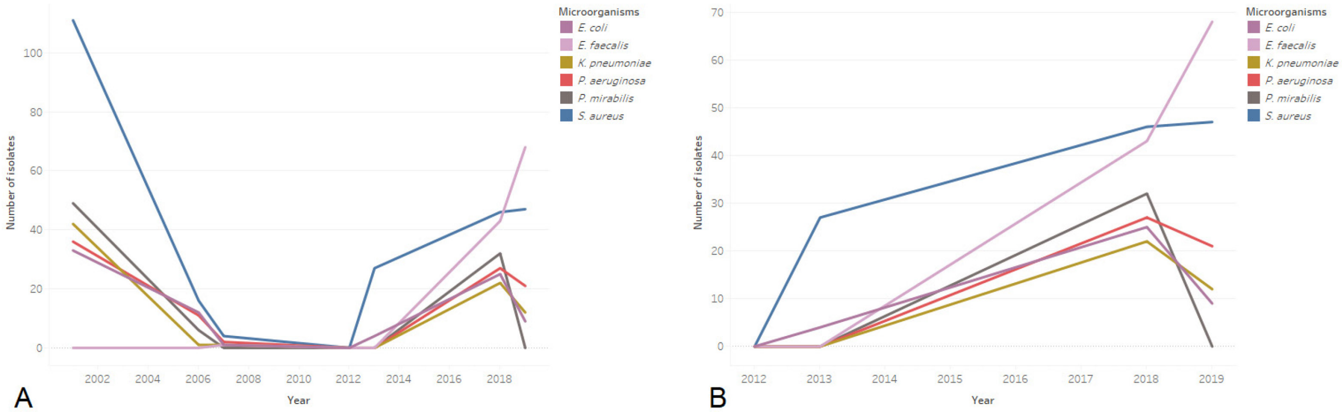


Figure 7. Temporal trends in the prevalence of the main isolates (A) Including all 10 studies (research that was completed in the period 2001–2019) (B) Including more recent six studies (research that was completed in the period 2012–2019).



methicillin-resistant (MRSA*)* (Table 4). Resistance to vancomycin was described for *Enterococcus faecalis* and *Staphylococcus aureus* [26–28]. There was an apparent increase in the proportion of *S. aureus* infections due to MRSA (Figure 8). With respect to Gram-negative isolates the large number of species and antibiotics, added to different methodologies, became especially difficult to make a synthesis.

Three to five studies detailed antimicrobial resistance in the four more frequent Gram-negatives (*P. aeruginosa*, *Proteus spp.*, *K. pneumoniae* and *E. coli*). One study described *Enterobacteriaceae* resistance and other extended-spectrum beta-lactamases (ESBL) and carbapenem-resistant Gram-negatives. In this review analysis, the prevalence of ESBL isolates was 43% for *K. pneumoniae*, 33% for *Proteus spp.*, and 26% for *E. coli*. Twenty percent (20%) of *Pseudomonas spp.* isolates (11/54) in 5 studies were carbapenem-resistant (Table 4).

Table 4. Antimicrobial resistance (AMR) patterns for the most frequent isolates [a].

Antimicrobial resistance	Tested N/Resistant N (%)
Gram positives	
Staphylococcus aureus	178[b]
Methicillin-resistant *S. aureus* (MRSA)	71 (40%)
Staphylococcus aureus	73 [c]
Vancomicin-resistant *S. aureus* (VRSA)	08 (11%)
Enterococcus faecalis	44 [d]
Vancomicin-resistant *E. faecalis* (VRE)	01 (2%)
Gram negatives[c]	
P. aeruginosa or *Pseudomonas sp.*	54 [c]
Carbapenem-resistance-*Pseudomonas*	11 (20%)
P. mirabilis or *Proteus sp*	45 [d]
Extended-spectrum beta-lactamase producing (ESBL)-*Proteus*	15 (33%)
E. coli	58 [e]
Extended-spectrum beta-lactamase producing (ESBL)-*E. coli*	15 (26%)
K. pneumoniae	67 [e]
Extended-spectrum beta-lactamase producing (ESBL)-*K. pneumoniae*	29 (43%)

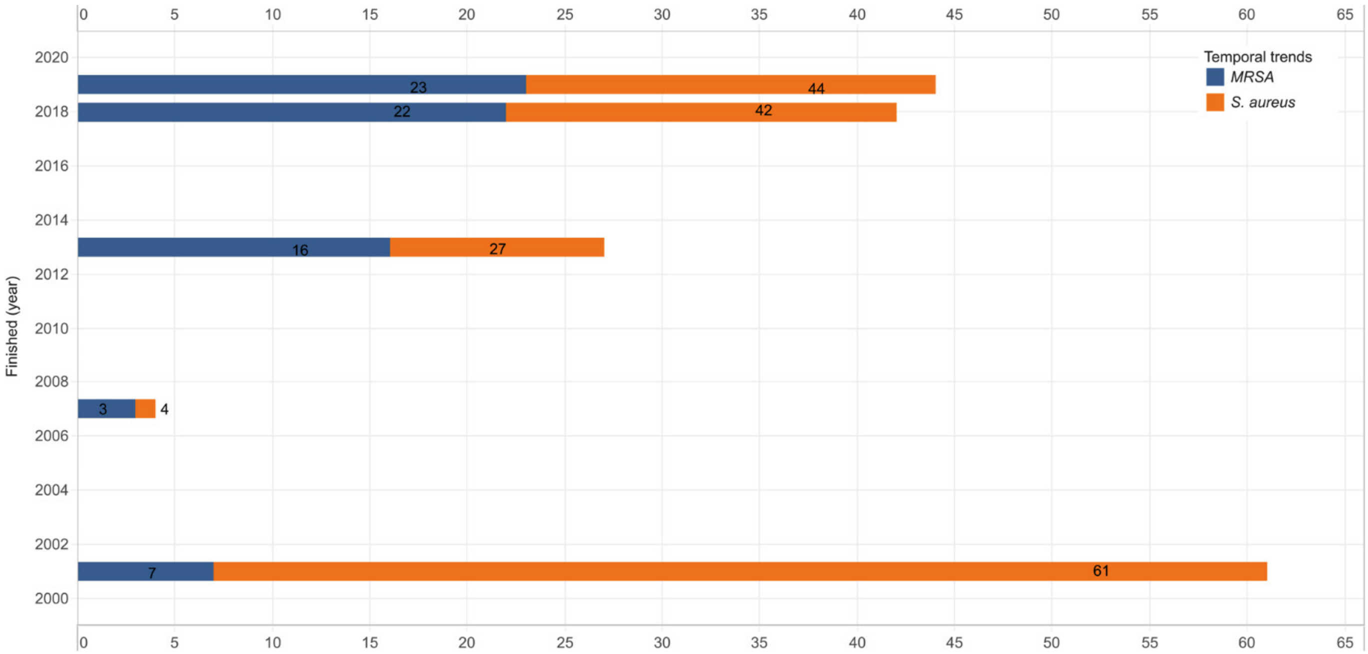
[a] Cardoso (2017) [25], Fernandes (2007) [23] and Santos (2006) [6] were not included in the analysis. [b] Considering 7 studies (MRSA prevalence ranged from 11 to 75%). [c] Considering 5 studies. [d] Considering 3 studies. [e] Considering 4 studies.

Table 5. Methodological quality score distribution according to Oxford Centre for Evidence-Based Medicine: Levels of Evidence, Newcastle-Ottawa Scale, and Downs and Black Quality Assessment Checklist.

First author/year	Oxford Level of Evidence [a]	New-Castle-Otawa scale [b]	Downs & Black Checklist[c]
Aragão *et al*, 2010 [29]	4	Selection (*) Comparability (0) Outcome (***)	10
Cardoso *et al*, 2017 [25]	3B	Selection (*) Comparability (*) Exposure (***)	13
Carvalho *et al*, 2004 [22]	4	Selection (*) Comparability (0) Outcome (***)	10
Fernandes *et al*, 2007 [23]	4	Selection (*) Comparability (0) Outcome (***)	09
Nascimento *et al*, 2021 [24]	4	Selection (*) Comparability (0) Outcome (***)	10
Palomo *et al*, 2022 [28]	4	Selection (*) Comparability (0) Outcome (***)	10
Perim *et al*, 2015 [27]	4	Selection (*) Comparability (0) Outcome (***)	10
Pontes *et al*, 2020[26]	4	Selection (*) Comparability (0) Outcome (***)	10
Santos *et al*, 2006 [6]	3B	Selection (**) Comparability (*) Outcome (***)	12
Santos *et al*, 2021 [17]	4	Selection (**) Comparability (*) Outcome (***)	12

[a] Oxford Centre for Evidence-Based Medicine: Levels of Evidence. [b] Newcastle-Ottawa Scale: selection (maximum of 4 stars), comparability (maximum of 2 stars), and outcome for cohort studies or exposure for case-control studies (maximum of 3 stars); [c] Downs and Black Quality Assessment Checklist: The review did not apply questions 4, 8, 14, 15, 17, 19, 21, 22, 23, 24 because the included studies were observational. Considering the questions 1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 16, 18, 20, 25, and 26, the maximum possible score was 17.

Figure 8. (A) Temporal prevalence of the Staphylococcus aureus and methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in 7 studies (research that had been completed in the period 2001–2019) (B) MRSA prevalence in the Federative units of Brazil.



Methodological analysis of the studies included in the systematic review

Considering the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence, 8 descriptive cross-sectional studies were classified as level 4 and two retrospective comparative studies as 3B (Table 5) [19]. The methodological quality of the studies involved the application of the Newcastle-Ottawa and the Downs and Black scales [20,21]. No study presented a flowchart of case inclusion and exclusion. The studies received 4 to 6 points on the Newcastle-Ottawa scale due to the sample characteristics. In the Downs and Black checklist, the study with the highest score received 13 points, with a maximum possible score of 17 points (Table 5). The methodological evaluation represented a challenge for this review, since all the included studies had observational design and many studies used retrospective methods, leading to difficulty in adapting the scales for the methodological quality assessment which includes characteristics like selection, comparability, exposure, outcomes, confounding variables and external validity. The studies included in this systematic review (SR) had case-series or case-control design; and, according to OCEBM were a level 4 evidence which relies on observational data, and small and non-controlled samples. Since this evidence is supported by observational descriptive studies, with methodological deficiencies and limitations, it constitutes low quality evidence [30].

Discussion

This systematic literature review concluded that the causative pathogens of foot infections in persons with diabetes (diabetic foot) in Brazil were predominantly Gram-negative microorganisms, notably from the *Enterobacteriaceae* family. *Staphylococcus aureus* was the most frequently isolated species, with a high prevalence of MRSA (40%). Among Gram-negative organisms, *Pseudomonas aeruginosa* was the most prevalent, exhibiting a 20% rate of carbapenem resistance. Approximately one-third of the predominant *Enterobacteriaceae* isolates — *K. pneumoniae*, *Proteus spp*., and *E. coli* — were ESBL producers, with prevalence ranging from 26% to 43%.

The microbiology of foot infections in persons with diabetes has several controversies in the literature. Since the choice of the empirical antibiotic therapy considers the most prevalent flora in each local or geographic region, understanding this subject is very relevant [31,32]. Various studies have demonstrated the predominance of Gram-negative bacteria in diabetic foot infections [33–36]. A multi-center study in Turkey showed that 60.02% of the 387 microorganisms cultivated were Gram-negative, with *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus spp.* being the three most frequently identified organisms [33]. Another multicenter study also found a predominance of Gram-negative bacteria (56.1%) in moderate infections [35]. A study carried out in a tertiary hospital in India revealed that among the 289 bacteria (178 tissue wound samples in persons with diabetes), 58.5% (165) were Gram-negatives, with 102 (61.8%) belonging to the *Enterobacteriaceae* family [34]. In China, a retrospective multicenter study (included 456 patients) found predominance of Gram-negative microorganisms (57.5%/317) among 551 causative pathogens of diabetic foot infections (*Enterobacteriaceae* family represented 41.0% (226) of the isolates) [15].

On the other hand, various studies, including a systematic review, have shown the high prevalence of Gram-positive bacteria, particularly *Staphylococcus aureus*, in persons with diabetic foot infections [9,13,37,38]. A study conducted in the southern region of China that included 581 persons with diabetes and superficial or deep wounds, identified 656 species and found 387 Gram-positive (58.99%) and 235 Gram-negative (35.82%) isolates [38]. Gram-positive microorganisms were also more prevalent (920/80.3%) in a North American multicenter study that detected 1,145 aerobic bacteria (454 samples), with *Staphylococcus spp*. being the most frequent bacterial genus. The authors found only 225 Gram-negative isolates (19.7%) among the pathogens related to foot infections in persons with diabetes [37]. Another systematic review reported a predominance of Gram-positive microorganisms in diabetic foot infections, mainly in high-income countries. The authors found that the three microorganisms most frequently identified among the 55 included studies that analyzed aerobic and anaerobic cultures were *Staphylococcus aureus*, *Enterococcus spp*. and *Pseudomonas spp.* [39]. This systematic review also showed that *Staphylococcus aureus*, *Enterococcus faecalis, P. aeruginosa*, *Proteus mirabilis*, *K. pneumonia*, and *E. coli* are the main causative pathogens in diabetes-related foot infection in Brazil.

The literature suggests that Gram-negative infections are predominant in upper-middle and lower-middle income countries, while in high-income countries Gram-positive pathogens are more common, implying that these differences may be linked to poor sanitation or climatic conditions. A meta-analysis included 11 articles and also found that the most common species in sub-Saharan Africa were *S. aureus* (34.34%), *E. coli* (21.16%), *P. aeruginosa* (20.98%), and *K. pneumoniae* (11.72%); indicating a Gram-negative predominance [40]. A systematic review conducted in Uganda also reported a predominance of Gram-negative organisms. The review included two observational studies and identified *Klebsiella spp*. (26), *Pseudomonas spp*. (23), *Escherichia coli* (23), and *Staphylococcus spp.* (23) as the most frequently isolated bacteria [41]. However, drawing inferences about a country's income level and microbiological profile is a complex and multifaceted endeavor. In our understanding, the differences in the microbiology of foot infections in persons with diabetes may be mostly related to the characteristics of the wounds, such as the depth and severity of the infection. Although it is difficult, it would be necessary to separate the characteristics of each case, in each geographic region, providing detailed information not only about the country, but also about family income. Our perception is that people in situations of social vulnerability have more wound care challenges and difficulties impacting access to the healthcare system that can lead to deeper wounds, more severe disease and higher Gram-negative prevalence. The 6 studies in this review that included Brazil's universal public health system (SUS) users in their sample showed a Gram-negative predominance. Two studies revealed a predominance of Gram-positive pathogens [27,28] and one described only *S. aureus* [24]. The studies performed in Palmas (TO) [27] and São Paulo [28] that show Gram-positive predominance did not evaluate Wagner system classification. Furthermore, this review selected studies with small samples, methodological limitations, and different wound classification systems making it difficult to be precise about the microbiological profile in Brazil and compare with other countries. The predominance of Gram-positive pathogens (58.99%) found in the study conducted in southern China occurred mainly in more superficial wounds (Wagner 1 to 3: Grade 1: 96.67%, Grade 2: 76.52%, and Grade 3: 62.81%) [38]. However, Gram-negative pathogens were more frequent among grade 4 and 5 wounds (Grade 4: 51.46% and Grade 5: 60%) [38]. The International Working Group on the Diabetic Foot (IWGDF) recommends a severity classification of the foot infections in persons with diabetes and suggests Gram-negative coverage in moderate to severe foot infections [32].

Currently, antimicrobial resistance (AMR) is considered a major global health problem. Performing a pooled analysis of AMR in the selected studies is challenging due to several aspects. These include various types of data collection, number of drugs and isolates tested, and the lack of standardized methodologies for presenting data. There was a high prevalence of MRSA (40%) in this systematic review. Another systematic review of the literature that included 112 studies, 3 of which were carried out in Brazil [23,25,27], reported *Staphylococcus aureus* as the most cultivated species with 18% of MRSA [39].

Several methodological issues probably impact this difference. Among the 10 observational selected studies, only 8 reported AMR, almost all authors included only inpatients, and a half of them had a history of prior antibiotic use. The small number of studies in this review (8) could be another reason for this difference. Several studies have demonstrated a decreased Gram-negative susceptibility to antibiotics and resistance to major classes of antibiotics, emphasizing the presence of ESBL and carbapenem-resistance [14,36,42]. This review identified the frequency and antibiotic resistance pattern of the most common Gram-negative bacteria. Approximately one third of the main *Enterobacteriaceae* isolates were ESBL producers, and 20% of *Pseudomonas spp*. were carbapenem-resistant. A systematic review focusing on Sub-Saharan Africa revealed a higher AMR prevalence of *E. coli* and *K. pneumoniae*, with 78.07% and 86.86% percent of ceftriaxone resistance. A literature review that included 63 articles in China found a Gram-negative predominance (6441 isolates; 52.4%) and more than 50% of the Gram-negatives were resistant to third-generation cephalosporins [43]. Again, methodological aspects, country income, geographical, and clinical issues may interact with other complex factors to impact antimicrobial resistance throughout the world. Diabetic foot infections caused by resistant isolates are very relevant to the health system, morbidity, and quality of life of persons with diabetes. *Escherichia coli*, *S. aureus*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* are four of the five leading pathogens associated with infection-related deaths globally in 2019 [44].

This systematic review has limitations. Brazil is a country with a large territory with 27 federative units, and there are few studies and incomplete geographical data coverage. There is a lack of standardization and paucity of detailed data for antimicrobial resistance. In addition, there were different ways of presenting antimicrobial resistance, such as text, graphs and tables, and different types of antibiotics. While some studies considered species, others used bacterial genus, or both; and there is a relative scarcity of information about the severity of the infection. The evidence was derived from observational studies with methodological deficiencies conducted more than 5 years ago, as a small sample, failure to present a case inclusion flowchart, lack of details on the clinical severity, and representing an evidence that might be questionable. Despite these limitations, this review adopted a systematic methodology, contributing to the microbiological profile of foot infections in persons with diabetes in Brazil, and highlighting potential gaps in the existing knowledge to further studies in different geographic regions.

Conclusions

This systematic review suggests that Gram-negative microorganisms are the predominate pathogens that cause infection of lower extremity wounds in persons with diabetes in Brazil, with the three most prevalent species being *Staphylococcus aureus*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. Antimicrobial resistance is high and more than a third of the *Staphylococcus aureus* were methicillin-resistant (MRSA). This review highlights the need for more comprehensive studies on the microbiology of diabetes-related foot infections in Brazil.

Acknowledgements

We gratefully acknowledge The National Council for Scientific and Technological Development (CNPq) – Institutional Scientific Initiation Scholarship Program - PIBIC for the student scholarship to scientific initiation.
The study was supported by the Undergraduate Research Scholarship Program – PIBIC/UFBA – CNPq (National Council for Scientific and Technological Development).

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Conflict of interest

No conflict of interest is declared.

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