IJID Regions 12 (2024) 100401

Contents lists available at ScienceDirect

IJID Regions

journal homepage: www.elsevier.com/locate/ijregi

Assessing the burden of disease of gram-negative bloodstream infections in a Brazilian hospital: A retrospective cohort study from 2015 to 2019

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ARTICLE INFO

Keywords:
Bloodstream infections
Gram-negative bacteria
Disability-adjusted life-years
Carbapenem-resistant gram-negative bacteria
Brazilian Public Health

ABSTRACT

Objectives: This study aimed to estimate the disease burden of BSIs caused by gram-negative bacteria (GNB-BSIs) in a Brazilian hospital from 2015 to 2019, measured in disability-adjusted life-years (DALYs).

Methods: A retrospective cohort study of adult patients with GNB-BSI was conducted from April 01, 2015 to March 31, 2019. This study was carried out in a 356-bed private hospital with a 68-bed medical intensive care unit located in Salvador, Brazil. Demographic and clinical data were collected through a review of medical records. DALYs were estimated using Monte Carlo Simulations, using life tables for Brazilians estimated for 2020 and the Global Burden of Diseases 2010 (GBD 2010).

Results: A total of 519 GNB-BSI episodes in 498 individuals were identified. The mean age was 59.92 ± 17.97 years, with 61.1% being male. The most common bacterial infections were *Klebsiella pneumoniae* and *Escherichia coli* (66.5%), whereas carbapenem-resistant gram-negative bacteria (CR-GNB) accounted for 32.7% of cases. The highest overall DALYs were observed in 2018 (752, 95% confidence interval [CI]: 520-1021 with Brazilian Life Tables and 782, 95% CI: 540-1062 with GBD 2010). Infections due to CR-GNB had the highest DALYs, particularly, in 2017, reaching 7050 (95% CI: 3200-12,150 with Brazilian Life Tables and 7350, 95% CI: 3350-12,700 with GBD 2010) DALYs per 1000 patient days and an estimated mortality rate of 40% per 1000 patient days.

Conclusions: The persistently high DALYs associated with CR-GNB raise alarming concerns, potentially leading to over 300 deaths per 1000 patient days in the coming years. These findings underscore the urgency of addressing GNB-BSI as a significant public health issue in Brazil. These results are expected to provide helpful information for public health policymakers to prioritize interventions for infections due to antibiotic-resistant bacteria.

Introduction

Bloodstream infections (BSIs) are not just illnesses, they are urgent health crises with alarming rates of morbidity and mortality on a global scale. They impose significant social and financial burdens on health care systems [1–3]. In 2013, the annual worldwide incidence of BSI ranged from 80 to 257 cases per 100,000 person-years [4,5], with the United States alone accounting for over 500,000 cases annually [6].

Although specific data on BSI incidence in Brazil is not readily available, some studies had contributed to understanding the scope of this issue. They reveal a prevalence of BSIs ranging from 4.1% to 10.8%, with variations attributed to the methodology used in each study [7,8]. From an economic standpoint, BSI prolongs the patients' length of stay and leads to higher hospital charges, with an estimated investment of $46,000 per BSI case [9–11].

The high incidence of BSI, coupled with the increasing prevalence of antibiotic resistance to treatment options, poses a significant

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https://doi.org/10.1016/j.ijregi.2024.100401
Received 22 April 2024; Received in revised form 27 June 2024; Accepted 2 July 2024

concerning for human health [12,13]. However, when gram-negative bacteria (GNB) are involved, the risk is even more pronounced owing to their potential for propagation and the emergence of new resistance mechanisms [14,15].

Estimates of the potential long-term impact of BSI and antimicrobial resistance are crucial for evidence-based prioritization of intervention strategies. In this study, we use disability-adjusted life-years (DALYs) as a comprehensive metric, encompassing years lost due to premature mortality (YLLs) and years lived with disability (YLDs), reflecting the total health loss associated with a specific disease [16–18]. These metrics reflects the total health loss associated with a specific disease, providing measurable and comparable indicators for understanding the burden of bacterial infection on society. It is a valuable tool for health care policymakers.

This study aimed to measure the burden of BSIs caused by GNB in a medium- and high-complexity hospital in Salvador, Brazil. This knowledge can inform future health care assistance and stimulate the development new approaches to enhance BSI prevention and treatment measures.

Method

Design and data source

A retrospective cohort study of patients who received health assistance at Hospital São Rafael located in Salvador, Bahia, Brazil from April 2015 to May 2019 was performed. Suspected cases were identified through daily laboratory-based surveillance of positive blood cultures. The study population consisted of patients aged 18 years and older with GNB-BSI, defined as a positive blood culture accompanied by signs and symptoms of infection. Demographic and clinical data were collected by reviewing medical records, including information such as hospitalization unit, previous hospitalization within the last 6 months, history of previous health care assistance, previous infections, comorbidities, presented symptoms, potential sources and risk factors for bacteremia, antibiotics use within the last 6 months, and outcomes. Duplicate cases, i.e. patients who experienced two episodes of BSI within 30 days, were excluded, and only the initial episode was analyzed.

Hospital description

Hospital São Rafael is one of the largest private tertiary hospitals in the north-northeast of Brazil. It has more than 250 beds, with over 70 designated for critical care units. The hospital's mission is based on three pillars: assistance, teaching, and research. It offers more than 20 medical residency programs in clinical and surgical specialties. The main areas of focus include oncology, onco-hematology with a bone marrow and CAR T-cell transplant unit, kidney and liver transplantation, and pediatrics. In addition, the hospital has a strong regional presence in microbiology, featuring a unit that uses advanced diagnostic methodologies such as matrix-assisted laser desorption/ionization–time of flight and molecular identification of antimicrobial resistance mechanisms and viral pathogens.

Definitions

Carbapenem-resistant GNB (CR-GNB) were those bacteria resistant to imipenem and/or meropenem. Community-acquired infections (CAIs) were those BSIs occurring within 48 hours of hospital admission, whereas health care–associated CAIs (HCAIs) were BSIs occurring 48 hours or more after hospital admission. The severity of underlying conditions upon admission was assessed using the Charlson comorbidity index [19]. The severity of BSI episodes was evaluated using the Pitt bacteremia score, with a score of 4 or higher typically indicating critical illness and an increased risk of death [20]. In addition, a distinction was made between patients who had been hospitalized in the intensive care unit (ICU) and those who had not (non-ICU).

Data management and statistical analysis

The data were stored in Epi Info version 3.5.1 (CDC, Atlanta, GA, USA). Descriptive statistics were used to describe and delineate the study population concerning sociodemographic, behavioral, and clinical characteristics. Frequencies were used to describe categorical variables, whereas means with SDs were used for continuous measures. Crude logistic regression models were used to estimate the measure of association between the variables and CR-GNB. Odd ratios (ORs) and their corresponding 95% confidence interval (CI) were calculated using the generalized linear model method. All the analyses were performed using RStudio (2023.03.0+386).

Monte Carlo simulation

Monte Carlo simulations were performed to calculate the DALYs using the DALY Calculator (1.5.0), a free tool within the RStudio program. This tool computes the number of DALYs (years of life lost and YLD components), the number of BSI cases, and the number of deaths, all with their CIs based on the entered parameters. The simulations were performed with 20,000 iterations to ensure robust estimates. For enhanced accuracy, two different sets of life tables were used. One set was derived from the mortality data for 2020 estimated by the Economic Commission for Latin America and the Caribbean [21], which accounts for variations in life expectancies based on biological sex (Table S1 and Table S2 in the online supplementary material). The other set used the Global Burden of Diseases 2010 (GBD 2010) life tables, which provide an average life expectancy without consideration of biological sex differences (Table S3 in the online supplementary material). The incidence rate used for the simulations was set (1000 cases per 1000 persons) because all individuals in the study sample were infected. A 2% discount rate was also applied, consistent with previous studies using Monte Carlo estimations [17].

Results

During the study period, 6805 BSI cases were identified among 6456 patients who underwent blood culture. Of all patients, only 1542 yielded positive blood cultures for any pathogen. Among these infection cases, 1373 were attributed to bacteria, with 774 cases due to GNB. Among the patients with GNB-BSIs, 553 (71.4%) were admitted to the hospital, while 221 (28.6%) were treated only in the emergency room. After applying exclusion criteria (excluding cases lacking hospital discharge dates [n = 1] and those under 18 years old [n = 33]), the final sample comprised 519 GNB-BSI cases. Gram-negative bacilli identified included *Klebsiella pneumoniae* complex (n = 173), *Escherichia coli* (172), *Enterobacter cloacae* complex (n = 33), *Pseudomonas aeruginosa* (n = 32), *Serratia marcescens* (n = 22), *Acinetobacter baumannii* (n = 14), *Citrobacter freudii* (n = 3), and others (Figure 1).

Of the 519 cases included in the study, 61.1% were males, with a mean age of 59.92 ± 17.97 years. In addition, 457 (88.2%) individuals presented with at least one comorbidity, with a mean Charlson score of 4.00 ± 2.25.

Regarding the infections, the mean Pitt score was 3.49 ± 4.37, with most cases identified as health care–associated infections (n = 462, 89.0%). Of these cases, 293 (56.5%) were categorized as secondary BSIs, with urinary tract infection being the primary source, accounting for 129 cases (44.0%). Overall, 170 (32.7%) cases were caused by CR-GNB. Notably, 142 (27.4%) patients experienced septic shock, and the outcome was fatal for 162 individuals (Table S4 in the online supplementary material).

Significant associations were observed between carbapenem CR-GNB and various variables, highlighting the most relevant factors. First,

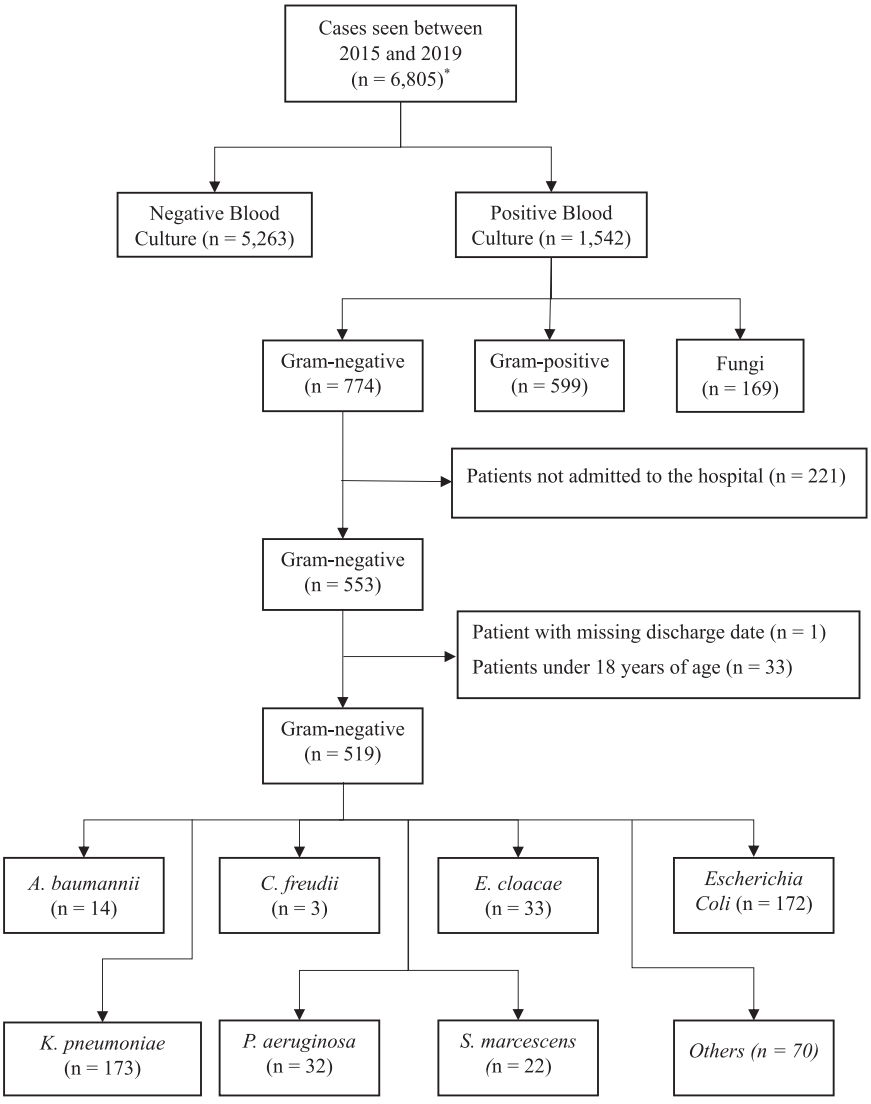

Figure 1. Flowchart of selection of cases to define study samples. BSI, bloodstream infection. *If the individual tested negative on all BSI cultures, it counted as one; if only one of the BSI cultures was positive, it counted as one; if the individual had more than one blood culture positive for the same bacterium, it counted as one; if the individual had more than one blood culture positive, with a different type of bacterium, it counts the number of different bacteria and the number of times he/she was infected.

a higher Pitt score was positively associated with CR-GNB compared with lower Pitt scores (OR = 2.13, 95% CI: 1.40-3.24). Similarly, positive associations were found between BSI caused by CR-GNB and infection with *K. pneumoniae* (OR = 5.18, 95% CI: 3.24-8.41) or *A. baumannii* (OR = 6.80, 95% CI: 2.21-23.32), both compared with *E. coli* infections. Lastly, a positive association between death and CR-GNB was observed compared with survival (OR = 2.20, 95% CI: 1.49-3.24) (Table 1).

Figure 2 shows the annual number of DALYs based on the type of bacterial infection (CR-GNB vs non–CR-GNB). The overall DALYs were calculated without distinguishing between these two infection types. Given the relatively short duration of bacterial infections, nearly all estimates resulted in zero YLD; the graphs directly represent the DALY values. Each calculation was made using the two life tables mentioned in the Method section. Because the life expectancy according to the GBD 2010 is slightly higher than that calculated for Brazilians, the results of the DALYs calculated with the GBD 2010 were slightly higher. The data reveal that the year with the highest total DALYs for Brazilian life tables and GBD 2010 was 2018 (752 DALYs, 95% uncertainty interval [UI]: 520-1021 and 782 DALYs, 95% UI: 540-1062, respectively). However, 2019 recorded the lowest DALYs because data were only included for the first 4 months of the year. For precise values of the estimates, refer to supplementary material (Table S5).

The simulation outcomes were normalized according to the calculator to a population of 1000 (because we are talking about people in the hospital, the unit indicates how many DALYs per 1000 patient days) to compare the DALYs each year for bacterial infections. In 2015, a minimal difference between the two infection types was observed. However, for subsequent years, cases of CR-GNB infection were associated with a higher DALY count. The peak DALYs occurred for CR-GNB in 2017 and resulted in a loss of 7050 DALYs (95% CI: 3200-12,150) 1000 patient days with Brazilian life tables and 7350 (95% CI: 3350-12,700) 1000 patient days with GBD 2010. The second-highest DALY count for CR-GNB was in 2016, with a slightly lower value but nearly equivalent (Figure 3). For precise estimate values, see the supplementary material (Table S6).

To determine whether these values were not due to chance, the analysis of DALYs was also performed by dividing the cases by medical unit (ICU vs non-ICU). The DALYs per year were very similar, except in 2018. In 2018, the year with the highest number of deaths, the analysis of DALYs for CR-GNB and non–CR-GNB had already identified this year as having the most DALYs. When further dividing into ICU vs non-ICU groups, it was evident that most deaths occurred among patients in the ICU (729 DALYs, 95% CI: 461-1052) (Figure 4). For 2019, there was also a small difference in DALYs between groups. When the values were normalized per 1,000 patient days, the pattern remained consistent: similar DALYs between groups from 2015 to 2017 and significantly more DALYs in the ICU group for 2018 and 2019 (Figure 5). Overall, the values aligned with those observed for the CR-GNB vs non–CR-GNB groups. For precise estimates, see the supplementary material (Tables S7 & S8).

Table 1
Epidemiologic, demographic, and clinical characteristics of patients with bloodstream infections caused by gram-negative bacteria in a tertiary referral hospital in Salvador, Brazil (n = 519).

Variable	Carbapenem			
	Susceptible n (%)	Resistant n (%)	Odds ratio (95% confidence interval)	*P*-value
Age (years)				
18-44	76 (69.1)	34 (30.9)	Ref.	-
45-59	78 (60.0)	52 (40.0)	1.49 (0.88-2.59)	0.144
≥ 60	195 (69.9)	84 (30.1)	0.96 (0.60-1.57)	0.877
Gender				
Female	146 (72.3)	56 (27.7)	Ref.	
Male	203 (64.0)	114 (36.0)	1.46 (1.00-2.16)	0.051
Presence of any comorbidity				
No	44 (72.1)	17 (27.9)	Ref.	-
Yes	305 (66.7)	152 (33.3)	1.29 (0.73-2.39)	0.400
Charlson index[b]				
<3	92 (62.6)	55 (37.4)	Ref.	-
≥ 3	213 (68.7)	97 (31.3)	0.76 (0.51-1.15)	0.195
Pitt bacteremia score[c]				
< 4	225 (70.3)	95 (29.7)	Ref.	-
≥ 4	69 (52.7)	62 (47.3)	2.13 (1.40-3.24)	<0.001
Type of bloodstream infection				
Primary	156 (69.0)	70 (31.0)	Ref.	-
Secondary	193 (65.9)	100 (34.1)	1.15 (0.80-1.68)	0.448
Source of the secondary infection[d]				
Other	44 (80.0)	11 (20.0)	Ref.	-
Intraabdominal	34 (72.3)	13 (27.7)	1.53 (0.61-3.89)	0.365
Respiratory system	33 (53.2)	29 (46.8)	3.52 (1.57-8.31)	0.003
Urinary system	82 (63.6)	47 (36.4)	2.29 (1.11-5.05)	0.031
Bacterium				
E. coli	136 (79.1)	36 (20.9)	Ref.	-
K. pneumoniae	73 (42.2)	100 (57.8)	5.18 (3.24-8.41)	<0.001
A. baumannii	5 (35.7)	9 (64.3)	6.80 (2.21-23.32)	0.001
C. freudii	2 (66.7)	1 (33.3)	1.89 (0.09-20.26)	0.608
E. cloacae	24 (72.7)	9 (27.3)	1.42 (0.58-3.23)	0.422
P. aeruginosa	26 (81.3)	6 (18.8)	0.87 (0.31-2.16)	0.780
S. marcescens	21 (95.5)	1 (0.5)	0.18 (0.01-0.91)	0.099
Other	62 (88.6)	8 (11.4)	0.49 (0.20-1.06)	0.087
Sepsis status[e]				
None	144 (69.9)	62 (30.1)	Ref.	-
Sepsis	120 (70.6)	50 (29.4)	0.97 (0.62-1.51)	0.885
Septic shock	84 (59.2)	58 (40.8)	1.60 (1.02-2.51)	0.039
Type of infection				
Community-acquired infection	48 (84.2)	9 (15.8)	Ref.	-
Health care–associated infection	301 (65.2)	161 (34.8)	2.85 (1.43-6.35)	0.005
Death				
No	260 (72.8)	97 (27.2)	Ref.	-
Yes	89 (54.9)	73 (45.1)	2.20 (1.49-3.24)	< 0.001

Ref., reference.
Missing values:
[a] n = 1
[b] n = 62
[c] n = 68
[d] n = 226
[e] n = 1.

In the case of group separation by CAI vs HCAI, it was observed that for all years, there was a greater number of DALYs in the HCAI group (which was expected because 89.0% of the cases were HCAI). As in the CR-GNB DALYs' analysis, 2018 emerged as the year with the most DALYs, specifically, 691 DALYs (95% CI: 485-929) for the HCAI group. When standardized per 1000 patient days, the trend showed that in some years, the DALYs for both groups became almost equal (2016 and 2018), whereas in in other years (2015, 2017, and 2019), it was higher in the CAI group. This variation is clarified by the fact that the CAI group had very few individuals, leading to overestimated results, as reflected in the large CIs. For precise estimate values, see the supplementary material (Tables S9 & S10).

The annual number of deaths per 1000 patient days was calculated using the insights gathered from DALYs per 1000 patient days. Assuming a consistent pattern over the years, for every 1000 patient days of non–CR-GNB infections, more than 200 deaths are projected (potentially surpassing 300 deaths). Contrariwise, for CR-GNB cases, the anticipated death toll is approximately 400 deaths per 1,000 patient days (potentially exceeding 700 deaths per 1000 patient days). The values were the same as those of the Brazilian life tables and GBD 2010 (Table 2).

Discussion

To the best of our knowledge, this study represents one of the initial attempts to quantitatively assess the disease burden of BSI caused by GNB in Brazil using DALYs. These findings provide a basis for future comparisons and inform the development of prevention and control interventions measures.

Notably, over half (53.8%) of the sample comprised individuals aged 60 years or older, indicating that a significant proportion of reported

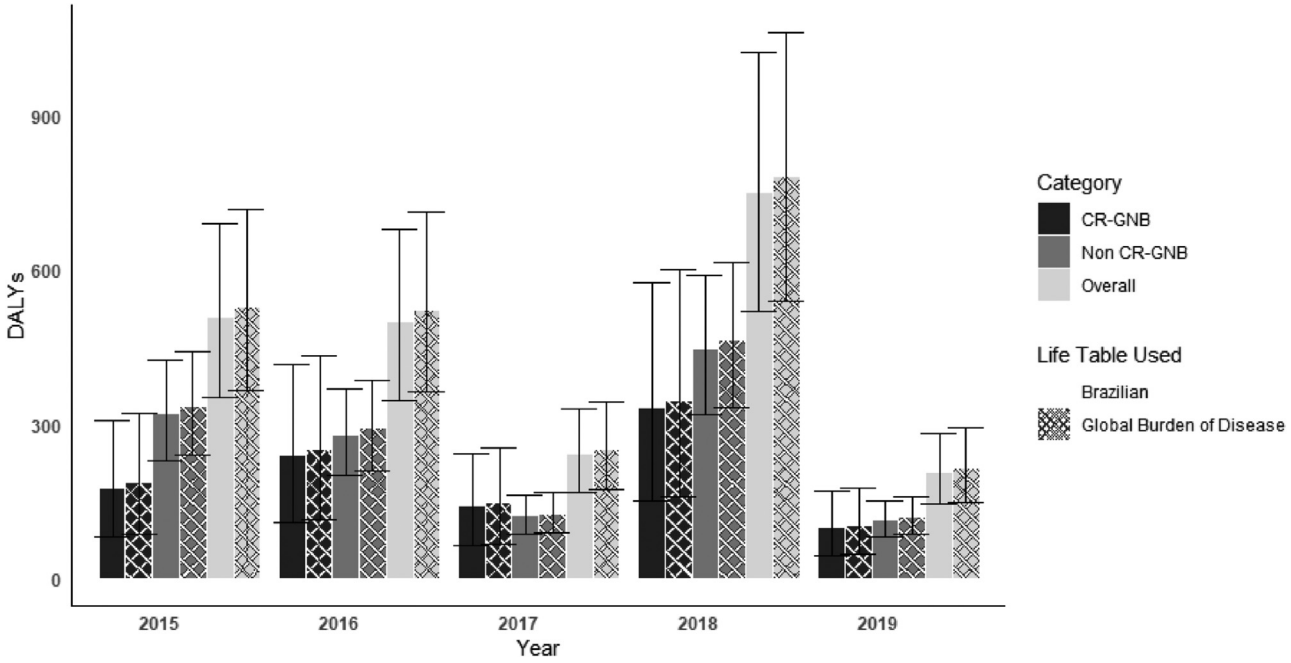

Figure 2. Breakdown of DALYs of GNB bloodstream infections in each infection group and life tables used by year. CR-GNB, carbapenem-resistant gram-negative bacteria; DALYs, disability-adjusted life-years.

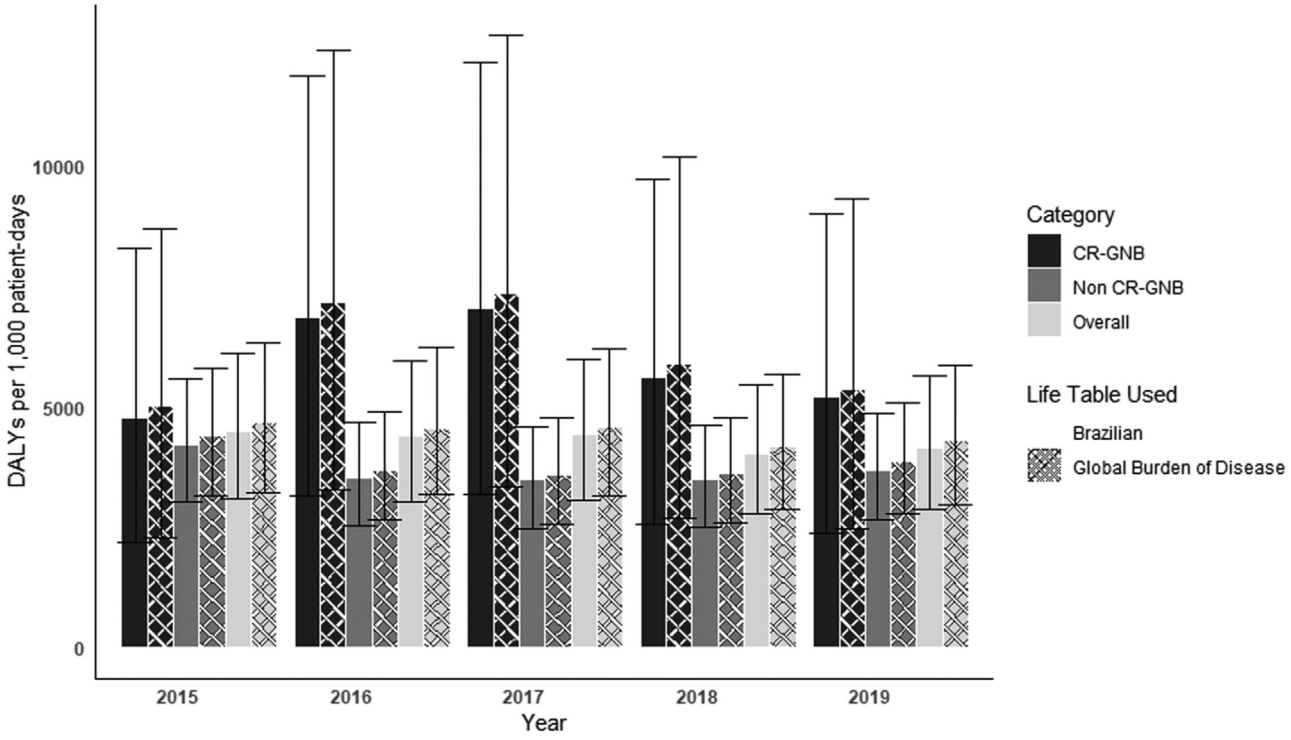

Figure 3. Breakdown of DALYs of GNB bloodstream infections in each infection group and life tables used by year per 1000 patient days. CR-GNB, carbapenem-resistant gram-negative bacteria; DALYs, disability-adjusted life-years.

cases involved high-risk individuals. This observation is further supported by the fact that among the 162 reported deaths, 114 occurred in individuals aged 60 years or older (data not shown).

Furthermore, *K. pneumoniae* (along with *E. coli*) emerged as the most frequent bacterial pathogen in BSI. The prominence of *K. pneumoniae* is of particular concern, aligning with existing literature that underscores the rising incidence of antibiotic-resistant cases, particularly, those associated with *K. pneumoniae* [18,22]. This trend was reflected in our study, where of the 173 cases of CR-GNB, 100 were attributed to *K. pneumoniae* (data not shown). In addition, *K. pneumoniae* exhibited the highest OR with great statistical significance for CR-GNB compared with *E. coli* isolates in this study. It is also highlighted that although there was no significant difference in the CR-GNB odds in the BSI groups, a large increase in CR-GNB odds was observed for those with BSI secondary to respiratory tract infection compared with those with BSI secondary to other body systems. This leads to the identification of respiratory infections (especially *K. pneumoniae* infections) as being at a higher risk for causing health complications.

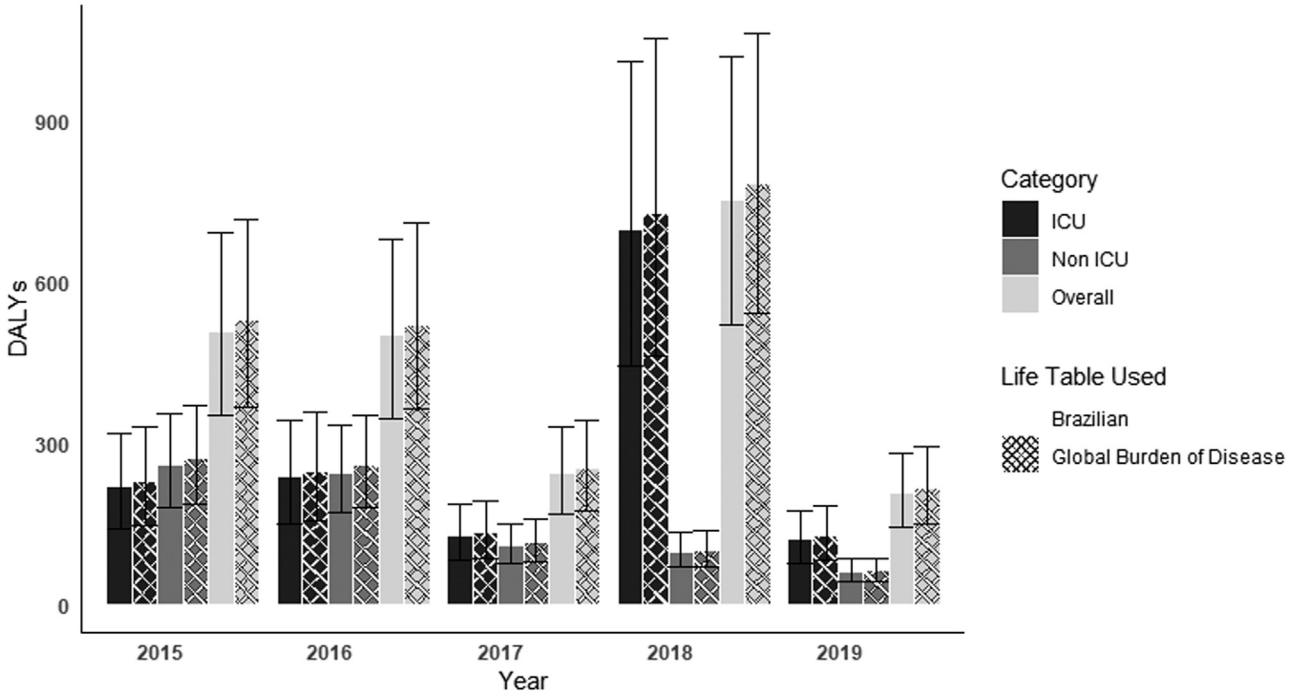

Figure 4. Breakdown of (DALYs) of gram-negative bacteria bloodstream infections dividing the cases by medical unit (ICU vs non-ICU) and life tables used by year. DALYs, disability-adjusted life-years; ICU, intensive care unit.

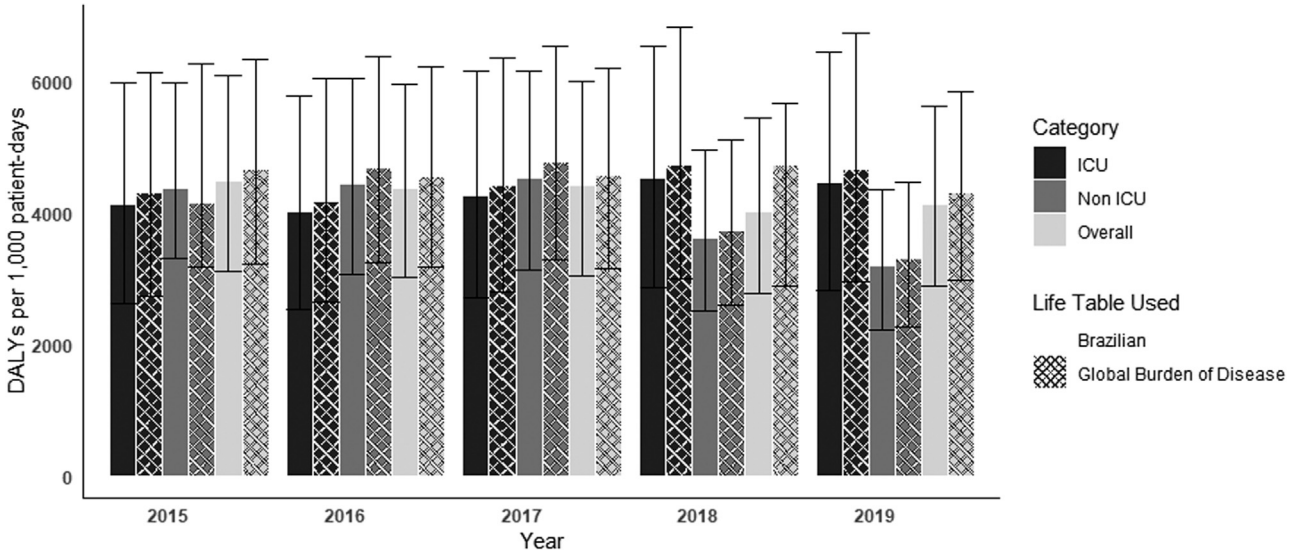

Figure 5. Breakdown of DALYs of gram-negative bacteria bloodstream infections dividing the cases by medical unit (ICU vs non-ICU). and life tables used by year per 1000 patient days. DALYs, disability-adjusted life-years; ICU, intensive care unit.

In most years, cases of non–CR-GNB infections exhibited a higher number of DALYs. This underscores the significant lethality associated with any BSI, although it is proportionally lower than that observed in cases of CR-GNB. Consequently, both susceptibility profiles contribute substantially to the overall burden of DALYs. A similar pattern is observed when comparing ICU vs non-ICU cases because both groups contributed a considerable amount of DALYs. However, in the case of the CAI vs HCAI groups, the overestimation of DALYs due to the small number of individuals in the CAI group compared with the HCAI group prevents any definitive conclusions from being drawn.

Our findings indicate that all age groups contributed to the total DALYs, reflecting fatalities across various age ranges. Nevertheless, it is noteworthy that the number of cases and deaths increases with the advancing age for both infection types. This observation suggests a potential correlation between the aging demographic in Brazil and an increasing burden of these infections [21].

The findings regarding death estimates are deeply concerning. For non–CR-GNB, the projection suggests that over 25.0% of every 1000 patient days may result in mortality, potentially surpassing 33.0%. In the case of CR-GNB cases, the outlook is even more severe, with an estimated mortality rate of approximately 40.0% per 1000 patient days, potentially exceeding 70.0%. Given that Brazil's population exceeds 200 million and that, as of 2018, the aging population constitutes over 14.0% and is increasing, this poses a significant public health emergency [22–24].

The DALY results from our study significantly exceed those of comparable studies conducted in different countries. For instance, a study in Japan covering the years 2015 to 2018 found a median DALY value

Table 2
Estimated deaths due to bloodstream infections by year 1000 patient days.

Year	Estimated number of deaths		
	Non–CR-GNB	CR-GNB	Overall
2015	263 (184-355)	405 (189-703)	310 (212-416)
2016	266 (190-354)	400 (171-686)	307 (211-421)
2017	257 (200-343)	400 (200-700)	309 (218-418)
2018	266 (188-352)	407 (186-695)	305 (214-417)
2019	258 (194-355)	421 (158-684)	300 (220-420)

CR-GNB, carbapenem-resistant gram-negative bacteria.

per 1000 population (using their Japanese life table) by the prefecture to be 1.46 (95% UI: 1.08-1.72) [17]. In a European study using GBD 2010 for 2015, the DALYs value was 1.22 (95% UI: 1.08-1.38) per 1000 population [16].

The notable difference in these values arises from the methodology used. Other studies considered all identified BSI cases within their specified time frames and calculated the incidence of multidrug-resistant or carbapenem-resistant bacteria cases (which are less common) to conduct simulations. In contrast, our study directly projected the number of DALYs per 1000 patient days based on their characteristics. It is crucial to highlight that our study, conducted in a single hospital, may overestimate results owing to the limited sample size. Nonetheless, given the higher prevalence of bacterial infections in Brazil, despite these limitations, our findings could offer valuable insights for other Brazilian states and neighboring countries in South America.

Limitations

The study had several limitations. First, the parameters used for calculating the disability burden associated with the disease were drawn from existing studies. Moreover, the assigned weight for this calculation only accounted for physical impairment and severe infections, excluding any comorbidities the individuals experienced (Table S11). Second, the estimates only reflect BSI's behavior within a single hospital setting (the values should differ according to the geographic area). Finally, these results only consider the information collected during hospital admission and do not encompass any sequelae from the infection.

Conclusion

In summary, while acknowledging the need for cautious interpretation due to the nature of simulations, this study provides an initial insight into the burden of GNB-BSI in Brazil. The results serve as a valuable baseline and emphasize the importance of bacterial infections as a public health concern. Nevertheless, further efforts are necessary to enhance our understanding and address this issue more comprehensively.

Declarations of competing interest

The authors have no competing interests to declare.

Funding

This research was conducted with financial support from Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB) /PP-SUS 0014/2018. Instituto Nacional de Pesquisa em Resistência Antimicrobiana (INPRA), CNPq 465718/2014-0, FAPERGS 17/2551-0000514-7.

Ethics committee approval

Ethics clearance was obtained from the research ethics committee of the Nursing School of the Federal University of Bahia (655.681) and the medical board and ethics committee of the hospitals (30904614.2.3006.5606 and 79250817.4.0000.0048).

Acknowledgments

The authors thank the Mount Sinai International Exchange Program for Minority Students, funded by the National Institute of Minority Health and Health Disparities (T37 MD001452).

Author contributions

KC, MS, and JR conceived the study and drafted the first manuscript. KC constructed the model and ran the simulations. AV, AC, MSB, and MGB aggregated and managed the raw data. KC, MS, AV, AC, MSB, MGB, MR, ISM, and JR critically reviewed the manuscript. All authors approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2024.100401.

References

[1] Viscoli C. Bloodstream Infections: the peak of the iceberg. *Virulence* 2016;**7**:248–51. doi:10.1080/21505594.2016.1152440.
[2] Lutwick L, Radel K, Bearman G. Central line associated bloodstream infections, Guide to infection control in the healthcare setting. In: Memish ZA, editor, https://isid.org/guide/hospital/central-line-associated-bloodstream-infections/; 2021 [accessed 15 August 2023].
[3] Center for Disease Control and Prevention (CDC). Bloodstream infection event (central line-associated bloodstream infection and non-central line associated bloodstream infection), National Healthcare Safety Network (NHSN) patient safety component manual, https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf; 2023 [accessed 15 August 2023].
[4] Mehl A, Åsvold BO, Lydersen S, Paulsen J, Solligård E, Damås JK, et al. Burden of bloodstream infection in an area of Mid-Norway 2002–2013: a prospective population-based observational study. *BMC Infect Dis* 2017;**17**:205. doi:10.1186/s12879-017-2291-2.
[5] Kern WV, Rieg S. Burden of bacterial bloodstream infection-a brief update on epidemiology and significance of multidrug-resistant pathogens. *Clin Microbiol Infect* 2020;**26**:151–7. doi:10.1016/j.cmi.2019.10.031.
[6] Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 2013;**19**:501–9. doi:10.1111/1469-0691.12195.
[7] Fortaleza CMCB, Padoveze MC, Kiffer CRV, Barth AL, Carneiro ICDRS, Giamberardino HIG, et al. Multi-state survey of healthcare-associated infections in acute care hospitals in Brazil. *J Hosp Infect* 2017;**96**:139–44. doi:10.1016/j.jhin.2017.03.024.
[8] Huerta-Gutiérrez R, Braga L, Camacho-Ortiz A, Díaz-Ponce H, García-Mollinedo L, Guzmán-Blanco M, et al. One-day point prevalence of healthcare-associated infections and antimicrobial use in four countries in Latin America. *Int J Infect Dis* 2019;**86**:157–66. doi:10.1016/j.ijid.2019.06.016.
[9] Jackson T, Nghiem HS, Rowell D, Jorm C, Wakefield J. Marginal costs of hospital-acquired conditions: information for priority-setting for patient safety programmes and research. *J Health Serv Res Policy* 2011;**16**:141–6. doi:10.1258/jhsrp.2010.010050.
[10] Steinkuller F. Entering infection prevention with a master of public health. *Am J Infect Control* 2019;**47**:599. doi:10.1016/j.ajic.2019.02.023.
[11] Haddadin Y, Annamaraju P, Regunath H. Central line–associated blood stream infections. *National Library Fo Medicine* 2022. https://www.ncbi.nlm.nih.gov/books/NBK430891/ [accessed 22 April 2024].
[12] World Health Organization (WHO). Report signals increasing resistance to antibiotics in bacterial infections in humans and need for better data, https://www.who.int/news/item/09-12-2022-report-signals-increasing-resistance-to-antibiotics-in-bacterial-infections-in-humans-and-need-for-better-data; 2022 [accessed 15 August 2023].
[13] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;**18**:268–81. doi:10.1111/j.1469-0691.2011.03570.x.
[14] Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis* 2018;**67**:1803–14. doi:10.1093/cid/ciy378.
[15] Jiménez Pearson MA, Galas M, Corso A, Hormazábal JC, Duarte Valderrama C, Salgado Marcano N, et al. Consenso latinoamericano para definir, categorizar y notificar patógenos multirresistentes, con resistencia extendida o panresistentes. *Rev Panam Salud Publ* 2019;**43**:e65. doi:10.26633/RPSP.2019.65.

[16] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;**19**:56–66. doi:10.1016/S1473-3099(18)30605-4.

[17] Tsuzuki S, Matsunaga N, Yahara K, Shibayama K, Sugai M, Ohmagari N. Disease burden of bloodstream infections caused by antimicrobial-resistant bacteria: a population-level study, Japan, 2015–2018. *Int J Infect Dis* 2021;**108**:119–24. doi:10.1016/j.ijid.2021.05.018.

[18] World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed [Internet], https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed; 2017 [accessed 18 August 2023].

[19] Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of clinimetric properties. *Psychother Psychosom* 2022;**91**:8–35. doi:10.1159/000521288.

[20] Henderson H, Luterbach CL, Cober E, Richter SS, Salata RA, Kalayjian RC, et al. The Pitt bacteremia score predicts mortality in nonbacteremic infections. *Clin Infect Dis* 2020;**70**:1826–33. doi:10.1093/cid/ciz528.

[21] Economic Commission for Latin America and the Caribbean (ECLAC), Demographic Observatory. Santiago. In: LC/PUB 2017/20-P;2017:66–7, https://repositorio.cepal.org/server/api/core/bitstreams/1a03099a-8f3b-4be5-9206-38f6141573cf/content; 2017 [accessed 27 September 2023].

[22] Conceição-Neto OC, da Costa BS, Pontes LDS, Silveira MC, Justo-da-Silva LH, de Oliveira Santos IC, et al. Polymyxin resistance in clinical isolates of K. pneumoniae in Brazil: update on molecular mechanisms, clonal dissemination and relationship with KPC-producing strains. *Front Cell Infect Microbiol* 2022;**12**:898125. doi:10.3389/fcimb.2022.898125.

[23] da Silva NCZ, da Rocha JA, do Valle FM, Silva ASDN, Ehrlich S, Martins IS. The impact of ageing on the incidence and mortality rate of bloodstream infection: a hospital-based case-cohort study in a tertiary public hospital of Brazil. *Trop Med Int Health* 2021;**26**:1276–84. doi:10.1111/tmi.13650.

[24] La Vanguardia. La población brasileña envejece y los mayores de 60 años llegan al 14,6 %, https://www.lavanguardia.com/vida/20180426/443024510040/la-poblacion-brasilena-envejece-y-los-mayores-de-60-anos-llegan-al-146-.html; 2018 [accessed 23 October 2023].