

## Major Article

# Surveillance of multidrug-resistant bacteria in pediatric and neonatal intensive care units in Rio de Janeiro State, Brazil

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### Abstract

**Introduction:** Multi-drug-resistant bacteria surveillance (MDR) systems are used to identify the epidemiology of MDR bacteria in neonates and children. This study aimed to describe the patterns by which MDR bacteria colonize and infect neonatal (NICU) and pediatric intensive care unit (PICU) patients in the state of Rio de Janeiro State, Brazil. **Methods:** A cross-sectional survey was performed using electronic data on NICU and PICU patients reported to the Rio de Janeiro State MDR bacteria surveillance system. All healthcare institutions that reported at least one case during the study period were included. **Results:** Between 2014 and 2017, 10,210 MDR bacteria cases, including 9261 colonizations and 949 infections, were reported. Among the colonizations, 5379 occurred in NICUs and 3882 in PICUs, while 405 infections occurred in NICUs and 544 in PICUs. ESBL producing *Klebsiella* sp and *E. coli* were the most reported colonization-causing agents in NICUs (1983/5379, 36.9%) and PICUs (1494/3882; 38.5%). The main causing bacteria reported in catheter-associated bloodstream infection (CLABSI), ventilator associated pneumonia, and catheter-associated urinary tract infection in NICUs were *Klebsiella* sp and *E. coli* (56/156, 35.9%), carbapenem-resistant Gram-negative bacteria (CRGNB) (22/65, 33.9%), and CRGNB (11/36, 30.6%) respectively, while in PICUs, they were MRSA (53/169, 31.4%), CRGNB (50/87, 57.4%), *Klebsiella* sp and *E. coli* (18/52, 34.6%), respectively. **Conclusions:** MDR Gram-negative bacteria (ESBL producers and carbapenem-resistant bacteria) were the most reported agents among MDR bacteria reported to Rio de Janeiro surveillance system. Except for CLABSI in children, they caused all device-associated infections in NICUs and PICUs.

**Keywords:** Surveillance. Neonates. Children. Healthcare-associated infection. Multidrug-resistant bacteria.

### INTRODUCTION

The recent increase in multidrug-resistant bacteria (MDR) in healthcare settings is recognized as a global public health problem. Antimicrobial resistance, which has become a natural phenomenon over time, could be accelerated by the misuse of antibiotics in animals and humans, leading to limited treatment options, causing life-threatening infections and increasing hospital costs<sup>1</sup>. In order to implement a multimodal approach, which guarantees the best treatment possible and prevents

MDR bacterial infections, in 2015, the World Health Assembly adopted the global action plan on antimicrobial resistance<sup>2</sup>.

MDR bacteria are present in children and neonate hospitals, especially in intensive care units. A recent systematic review by Le Doare et al, which has been reporting MDR since 2001, described regional databases of Gram-negative bacteremia in children in low- and low-middle-income countries. In the review, 71,326 children from 30 studies were included, and Gram-negative bacteria were isolated from 4,710 (66.8%) out of 7,056 blood cultures. The review revealed that in neonates in Asian countries, the resistance of *Klebsiella pneumoniae* to cephalosporins and ampicillin was 84% and 94%, respectively, and in African countries, it was 50% and 100%, respectively. The authors observed that multidrug resistance, including resistance to ampicillin, chloramphenicol, and cotrimoxazole,

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was 30% (interquartile range [IQR], 0-59.6) in Asia and 75% (IQR, 30-85.4) in Africa<sup>3</sup>. Another study performed at a single neonatal intensive care unit (NICU) in Taiwan revealed that MDR Gram-negative bacilli (GNB) accounted for 18.6% of all neonatal GNB bacteremia, and drug resistance was more frequently reported in neonates with previous broad-spectrum antibiotic therapy<sup>4</sup>.

MDR, which causes healthcare-associated infections (HAI), is also a problem in Brazilian health units. Folgori et al, described HAI epidemiology in neonatal/pediatric intensive care units (NICU/PICU), as well as the impact of MDR in three pediatric hospitals being 1 from Italy and 2 from Brazil. The cumulative incidence of HAI in the different hospitals was 3.6/100 ICU admissions, and the crude 30-day fatality rate was 5.7/1,000 admissions. Of the 206 HAI episodes reported in Brazilian ICUs, 122 (60.1%) were due to MDR bacteria<sup>5</sup>.

Nosocomial infection and multidrug-resistant bacteria surveillance systems could be useful in the understanding of MDR epidemiology in children and neonates within a geographical region, as well as from a global perspective. It could also help in the recognition of prevalent pathogens based on the site of infection, in the optimization of resources, and in the stimulation of rational antibiotic use, while contributing to multimodal strategies aimed at reducing MDR rates<sup>6</sup>. Well-structured nosocomial infection surveillance systems, which are governmental and non-governmental initiatives, are described around the world<sup>7-11</sup>.

The aim of this study was to describe colonization and infection-causing MDR bacteria patterns in neonatal (NICU) and pediatric intensive care unit (PICU) patients, reported to the Rio de Janeiro State surveillance system.

## METHODS

A cross-sectional survey was performed between 2014 and 2017 using electronic data from healthcare institutions with neonatal and/or pediatric beds, collected by the Rio de Janeiro State MDR bacteria surveillance system.

### Surveillance system

The Rio de Janeiro State MDR surveillance system, which excludes multi-resistant fungi, is a web-based surveillance system created in 2013. Since then, it has become mandatory for hospitals located in the state to report any identified case of multidrug-resistant (MDR) bacteria. Data input in this electronic system required information on the identified MDR type (Gram-positive/Gram-negative), a description of its association with colonization or infection, and the site of infection (if present).

### Inclusion/exclusion criteria

All healthcare institutions that notified at least one case during the study period were included.

### Definition of Multi-drug-resistant bacteria

The following MDR agents were reported: ESBL producing *Klebsiella* and *E.coli*, 3<sup>rd</sup> or 4<sup>th</sup> generation cephalosporins-resistant *Enterobacteriaceae* (*Enterobacter/Proteus/Morganella*

and *Citrobacter*), carbapenem- or polymyxin-resistant *Acinetobacter/Pseudomonas aeruginosa*, carbapenem- or polymyxin-resistant *Enterobacteriaceae* (*E.coli, Klebsiella spp, Enterobacter spp, Citrobacter spp, Serratia spp, Providencia spp, Proteus spp, Morganella spp, and Citrobacter*), vancomycin-resistant *Enterococcus*, methicillin-resistant *S. aureus*, vancomycin-intermediate *S. aureus* (MIC 4-8 µg/ml), and vancomycin-resistant coagulase-negative *Staphylococcus* (MIC > 4).

### Definition of Healthcare-associated infections

All infections were identified in accordance with the Brazilian National Health Surveillance Agency criteria (ANVISA) for neonates (0-28 days old) and children (>28 days-18 years old)<sup>12,13</sup>. Only infections presented and identified more than 48 h after admission to healthcare institution were considered HAI, otherwise, they were classified as colonization.

### Variables of interest

The following variables were analyzed: age, total colonizations and infections reported per year, MDR bacterial class identified in colonizations and infections, and MDR bacterial class based on site of infection.

### Data analysis

Patients were categorized as neonates or children, following their ages. In addition, MDR bacteria were categorized as Gram-positive or Gram-negative, and their colonization and infection frequencies were presented as percentages. Further, the frequencies of specific pathogens within the Gram-positive and Gram-negative groups were presented as percentages. Descriptive analysis was conducted using the Excel spreadsheet® version 2016. (Microsoft Corp., Redmond, WA, USA).

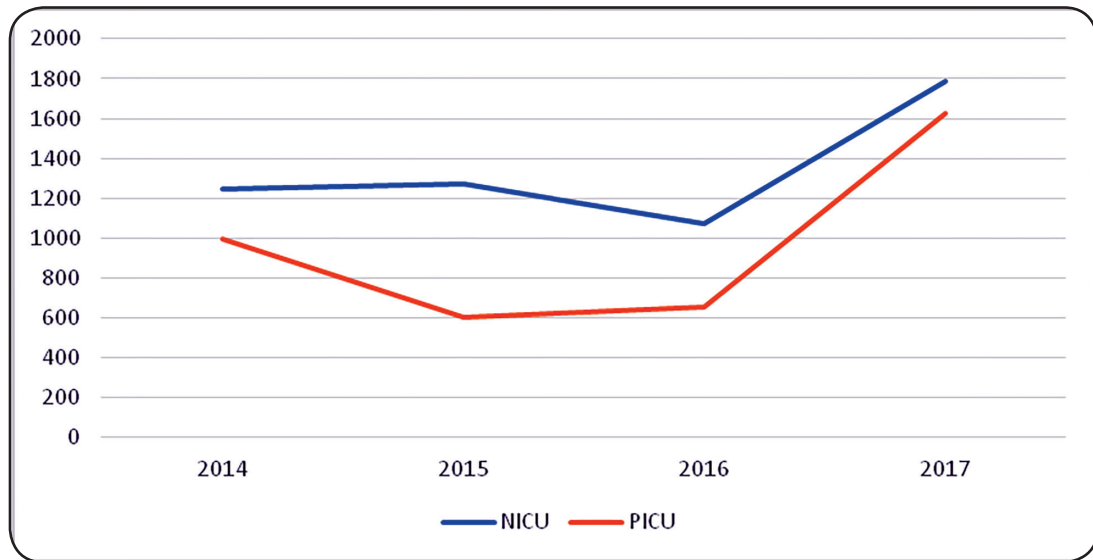
## RESULTS

Between 2014 and 2017, 139 healthcare institutions (78 NICUs and 61 PICUs), reported 10,210 MDR bacteria cases, which included 9,261 colonizations (5,379, NICUs; 3,882, PICUs) and 949 infections (405, NICUs and 544, PICUs), as shown in **Figure 1**.

The mean of colonization-causing MDR bacteria was 1,344.75/yr (1,075-1,788 range) in NICUs and 970.5/yr (656-1625 range) in PICUs. Compared with the different annual mean notifications, the number of colonizations in NICUs and PICUs in 2017 increased by 33% and 67.4%, respectively.

**Table 1** shows the absolute numbers and frequencies of the main NICU and PICU colonization-causing MDR bacteria reported. ESBL producing *Klebsiella sp* and *E.coli*, and MRSA, were the most reported colonization-causing MDR agents in neonates and children; however, regarding relative frequency, CRGNB represented an important group in PICUs.

The mean of infection causing MDR bacteria was 101.25/yr (65-125) in NICUs and 136/yr (101-185) in PICUs, and when they were compared with the different annual means, the results revealed that the number of reported infections in NICUs and PICUs in 2017 increased by 23.5% and 36%,



**FIGURE 1:** Multi-drug-resistant (MDR) bacteria colonizations in NICU and PICU patients, reported to the Rio de Janeiro State surveillance system (2014-2017).

**TABLE 1:** Absolute number and frequency (%) of the main multidrug-resistant (MDR) bacteria colonizing NICU and PICU patients, reported to the Rio de Janeiro state surveillance system (2014-2017).

Bacteria	NICUs N = 5,379 (%)	PICUs N = 3,882 (%)
ESBL-producing <i>Klebsiella sp/E.coli</i>	1983 (36.9)	1494 (38.5)
MRSA#	1,197 (22.2)	1,075 (27.7)
<i>Enterobacteriaceae</i> * resistant to 3 <sup>rd</sup> or 4 <sup>th</sup> generation cephalosporins	559 (10.4)	136 (3.5)
CRGNB**	533 (9.9)	396 (10.2)

#Methicillin-resistant *S. Aureus*, \*(Enterobacter/Proteus/Morganella, Citrobacter), \*\*CRGNB (Carbapenem-resistant Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter spp.*, and *Enterobacteriaceae*).

respectively, as shown in **Figure 2**. ESBL producing *Klebsiella sp* and *E.coli* were the most reported CLABSI- and surgical site infection (SSI)-causing MDR bacteria in NICUs, carbapenem-resistant Gram-negative (CRGNB) bacteria were the most reported catheter-associated urinary tract infection (CAUTI)- and ventilator-associated pneumonia (VAP)-causing MDR bacteria, and MRSA was the most reported neonatal sepsis-causing MDR bacteria (**Table 2**).

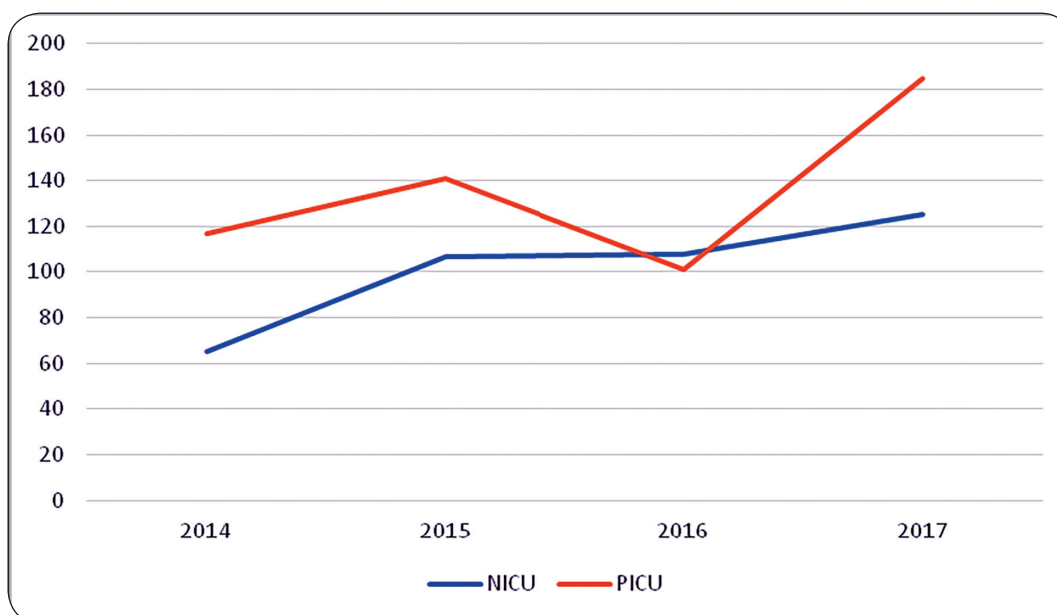
MRSA was the most reported CLABSI- and SSI-causing MDR bacteria, while ESBL producing *Klebsiella sp* and *E.coli* were the most reported CAUTI-causing MDR bacteria, and CRGNB were the most reported VAP-causing ones (**Table 3**).

**DISCUSSION**

Monitoring the regional distribution of HAI-causing MDR bacteria is one of the most important cornerstones of infection

control. It makes the recognition of prevalent agents and the establishment of governmental actions possible; thus, reducing their impact. Surveillance systems help in HAI tracking and prevention measure evaluation, provide data needed to identify critical issues, and contribute to HAI reduction<sup>14</sup>. Knowledge on colonized MDR bacteria patients contributes to the establishment of better infection control practices that prevent their spread in neonatal and pediatric intensive care units, and the definition of appropriate antimicrobial schemes in case of infection<sup>15,16</sup>.

Rio de Janeiro is the third most populous Brazilian state, with approximately 16.7 million inhabitants. Since 2013, efforts have been made to increase the reporting of colonization- and infection-associated MDR bacteria in adult and pediatric hospitals. In this study, an increase in the absolute number of



**FIGURE 2:** Infections by multi-drug-resistant (MDR) bacteria in NICU and PICU patients, reported to the Rio de Janeiro State surveillance system (2014-2017).

**TABLE 2:** Multi-drug-resistant (MDR) bacteria in neonates admitted to NICUs, according to infection site, reported to the Rio de Janeiro State surveillance system (2014-2017)

		CLABSI (%)	VAP (%)	CAUTI (%)	SSI (%)	Neonatal sepsis (%)
Gram-positive	MRSA <sup>#</sup>	25 (16)	13 (20)	-	3 (37.5)	14 (43.8)
	VISA <sup>##</sup>	3 (1.9)	-	-	-	-
	VRE <sup>###</sup>	1 (0.6)	-	1 (2.8)	-	-
Gram-negative	ESBL-producing <i>Klebsiella sp/E.coli</i>	56 (35.9)	2 (3.1)	8 (22.2)	5 (62.5)	11 (34.4)
	<i>Enterobacteriaceae</i> * resistant to 3 <sup>rd</sup> or 4 <sup>th</sup> generation cephalosporins	13 (8.3)	20 (30.8)	8 (22.2)	-	2 (6.3)
	CRGNB <sup>**</sup>	25 (16)	22 (33.9)	11 (30.6)	-	5 (15.6)
Others	33 (21.1)	8 (12.3)	8 (22.2)	-	-	
Total		156 (100)	65 (100)	36 (100)	8 (100)	32 (100)

**CLABSI:** Catheter-associated bloodstream infection; **VAP:** Ventilator-associated pneumonia; **CAUTI:** Catheter-associated urinary tract infection; **MRSA:** Methicillin-resistant *S. aureus*, **CRGNB:** Carbapenem-resistant Gram-negative bacteria. <sup>#</sup>Methicillin-resistant *S. aureus*, <sup>##</sup>Vancomycin-intermediate *S. aureus*, <sup>###</sup>Vancomycin-resistant Enterococcus, \*Enterobacter/Proteus/Morganella, Citrobacter, \*\*CRGNB (Carbapenem-resistant Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter spp.*, and *Enterobacteriaceae*).

**TABLE 3:** Infection-causing multi-drug-resistant (MDR) bacteria in children admitted to PICUs, according to the site, reported to the Rio de Janeiro state surveillance system (2014-2017)

		CLABSI (%)	VAP (%)	CAUTI (%)	SSI (%)
Gram- positive	MRSA <sup>#</sup>	53 (31.4)	6 (6.9)	1 (1.9)	13 (56.5)
	VISA <sup>##</sup>	4 (2.4)	1 (1.1)	-	-
	VRE <sup>###</sup>	3 (1.8)	-	-	-
Gram-negative	ESBL-producing <i>Klebsiella sp</i> and <i>E.coli</i>	23 (13.6)	12 (13.8)	18 (34.6)	2 (8.7)
	<i>Enterobacteriaceae</i> * resistant to 3 <sup>rd</sup> or 4 <sup>th</sup> generation cephalosporins	5 (3.0)	3 (3.4)	2 (3.8)	1 (4.3)
	CRGNB**	51 (30.2)	50 (57.5)	17 (32.7)	5 (21.7)
Others	30 (17.8)	15 (17.2)	14 (26.9)	2 (8.7)	
Total		169 (100)	87 (100)	52 (100)	23 (100)

**CLABSI:** Catheter-associated bloodstream infection; **VAP:** Ventilator-associated pneumonia; **CAUTI:** Catheter-associated urinary tract infection; **MRSA:** Methicillin-resistant *S. aureus*; **CRGNB:** Carbapenem-resistant Gram-negative bacteria. <sup>#</sup>Methicillin-resistant *S. aureus*, <sup>##</sup>Vancomycin-intermediate *S. aureus*, <sup>###</sup>Vancomycin-resistant *Enterococcus*, <sup>\*</sup>*Enterobacter/Proteus/Morganella, Citrobacter* <sup>\*\*</sup>CRGNB ( Carbapenem-resistant Gram-negative bacteria- Includes *Pseudomonas aeruginosa, Acinetobacter spp,* and *Enterobacteriaceae*).

colonizations and infections in NICUs and PICUs was observed when the annual values were compared with the mean value of the study period.

This survey revealed that ESBL producing *Klebsiella sp* and *E.coli* were the most reported colonization causing agents in both NICUs and PICUs, followed by MRSA. Critical agents such as carbapenem-resistant Gram-negative bacteria (CRGNB) were reported in 9.9% of neonates and 10.2% of children. Compared with this study, different rates of MDR bacteria colonization are reported in other studies. For example, Mammina *et al.* described a rate of 55.2% in neonates colonized by multidrug-resistant Gram-negative bacilli (MDRGN) during a one-year follow-up in a NICU in Italy<sup>17</sup>. However, Rybczmiska *et al.*, in their study on the prevalence of ESBL bacteria colonization in a NICU in Sweden reported a rate of 1.77%<sup>18</sup>. Tifha *et al.*, reported a 4.9% rate of MDR acquisition during hospitalization in a PICU in Tunisia, and 7.84% at discharge, with ESBL-producing *E. coli* and *K. pneumoniae* being most frequently detected at discharge (52.7%)<sup>15</sup>.

In this study, the frequency of reported device-associated infection-causing MDR bacteria was described, and different patterns were identified among the most reported agents in neonates and children, based on the site of infection. For instance, ESBL-producing *Klebsiella* and *E.coli* were the most reported MDR bacteria, causing 35.9% of CLABSI in NICUs, while MRSA was the most reported agent, causing 31% of CLABSI in PICUs. Data from São Paulo State

(Brazil) HAI surveillance system (2017) presented a global bloodstream infection-antibiotic resistance of 37.1% in NICUs, and 34% of CLABSI-causing *Klebsiella pneumoniae* isolates were 3<sup>rd</sup> generation cephalosporin-resistant, 50% of *S. aureus* were oxacillin-resistant and 75% of coagulase-negative staphylococci were oxacillin-resistant<sup>19</sup>. The Brazilian surveillance system, which compiled data from the entire country in 2016, reported 54% of oxacillin-resistant *S. aureus* in CLABSI from PICUs, 44.4% of carbapenems-resistant *Acinetobacter spp*, and 29.1% 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins-resistant *Klebsiella pneumoniae*. When CLABSI data from NICUs were analyzed, it was observed that 53.6% of *S. aureus* were oxacillin-resistant, 37.8% of *Klebsiella pneumoniae* were 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporin-resistant, and 30.4% of *E.coli* were 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporin-resistant<sup>11</sup>.

Of all the reported MDR bacteria, carbapenem-resistant Gram-negative bacteria were the most reported VAP-causing agents in both NICUs and PICUs. In children and neonates, CRGNB represented more than half and a third of the reported VAP-causing MDR bacteria, respectively. These agents, which are considered critical by the World Health Organization (WHO), and for which there is an urgent need to development new antibiotics, usually have high levels of antimicrobial resistance (AMR), and are associated with high mortality<sup>20</sup>. When other healthcare institutions or surveillance systems were compared, the data available were limited, as described in a recent systematic review which investigated the main

VAP-causing pathogens in Brazilian NICUs. The review reported that VAP incidence density ranged between 3.2 and 9.2 per 1,000 ventilator-days, and none of the papers reviewed in this study reported which pathogens were associated with VAP<sup>21</sup>. Lake *et al.*, described pathogen distribution and antimicrobial resistance patterns for HAIs, including VAP reported to the National Healthcare Safety Network (NHSN) by pediatric locations from 2011–2014. Their study revealed that in NICUs, 13.4% and 9.1% of VAP-causing *Pseudomonas aeruginosa* and *Acinetobacter spp.*, respectively, were carbapenem-resistant, while in PICUs, 16.3% and 12.5% of VAP-causing *Pseudomonas aeruginosa* and *Klebsiella pneumoniae/oxytoca*, respectively, were carbapenem-resistant<sup>9</sup>.

Interestingly, CRGNB were also the most reported and second most reported CAUTI causing agents among MDR bacteria in NICUs and PICUs, respectively. Like VAP, limited data is available in Brazilian surveillance systems on which CAUTI-causing agents are prevalent, and on the value of their resistance rates. Duenas *et al.* studied device-associated infections, including CAUTI, in a NICU and PICU in El Salvador during a 2-year follow-up period. Their study revealed that the main pathogens associated with CAUTI in children were *Candida sp* (36.3%), *Pseudomonas sp* (18.2%), and *Klebsiella sp* (18.2%), although no information about resistance was available<sup>22</sup>. United States' data on bacterial resistance in HAI children and neonates showed a lower percentage of CAUTI-causing carbapenem-resistant bacteria in PICUs. For example, HAI-related bacteria resistance to carbapenems was 7.2%, 2.8%, 1.1%, and 0.7% for *Pseudomonas aeruginosa*, *Enterobacter sp*, *Klebsiella pneumoniae/oxytoca*, and *E.coli*, respectively, in PICUs, and the report described only data from PICUs and pediatric wards<sup>9</sup>.

In order to reinforce the role of surveillance, Rio de Janeiro State has compiled data on colonization-causing MDR bacteria and device-associated infection in NICUs and PICUs since 2014. The present study showed a high rate of MDR Gram-negative, specifically carbapenem-resistant bacteria, among all the MDR bacteria reported in NICUs and PICUs. MDR microorganism surveillance is one of the global action plans of WHO on antimicrobial resistance strategic objectives, published in 2015<sup>1</sup>, after which, Brazil instituted a national prevention and control plan against antimicrobial resistance in 2018, including the development of scientific evidence in this area, and the expansion and development of a national MDR microorganisms-monitoring network<sup>23</sup>.

Compilation of data on MDR bacteria from different healthcare institutions with different rate of MDR presentation and the creation of regional benchmarking could be interpreted as limitations of this study. Secondly, retrospective data from an electronic web-based file was used; however, some healthcare units were unable to report MDR bacteria cases due to the lack of access to the system. Lastly, some healthcare institutions may have not entered data, due to MDR agent reporting incompetence.

In conclusion, MDR Gram-negative bacteria, including ESBL producing and carbapenem-resistant bacteria, were the most reported agents among all MDR bacteria cases that were reported to the Rio de Janeiro State surveillance system between

2014 and 2017, causing all device-associated infections in NICUs and PICUs, with the exception of CLABSI in PICUs. Efforts to increase MDR bacteria reporting to the surveillance system are necessary. This will contribute to the development of strategies to reduce the impact of HAI on neonates and children in the state of Rio de Janeiro.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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