

HEALTHCARE-ASSOCIATED INFECTIONS IN NEONATOLOGY IN MOROCCO AND WORLDWIDE: A SYSTEMATIC REVIEW

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Abstract

Introduction: Healthcare-associated infections are a major public health concern, particularly in neonatology, where they contribute to significant morbidity and mortality. This review aims to describe the pathogens involved in healthcare-associated infections in neonatology and to assess their resistance to drugs. **Methods:** the current study gathered data from reputable sources, employing a systematic review approach, including PubMed, Scopus and Google Scholar databases. We customized our search to include studies published from 2015 to 2024. **Results:** of the 871 studies retrieved from the database. Twenty-seven studies were included. The overall prevalence of HAIs in neonatology ranged from 3.54% to 29%. Three infectious sites were predominant: bacteremia (21% to 91%), pneumonia (5.17% to 81.3%), and urinary tract infections (1.4% to 28.8%). The most frequently isolated pathogens were coagulase-negative Staphylococcus (27.86%), followed by Klebsiella spp (24.70%), Acinetobacter spp (13.75%), Pseudomonas spp (8.93%) and Staphylococcus aureus (6.27%). Multidrug-resistance bacteria were mainly represented by methicillin-resistance Staphylococcus aureus with rates ranging from 0% to 100%, extended spectrum beta-lactamase-producing Enterobacteriaceae, with rates ranging from 0% for Klebsiella isolates to 91.02%, and vancomycin-resistant Enterococcus, with rates ranged from 90% to 100%. **Conclusion:** understanding the bacterial ecology and resistance profiles of neonatal healthcare-associated infections are crucial to reducing their incidence and guiding empirical antibiotic therapy. This systematic review recommends the rigorous application of hygiene measures throughout neonatal care and the reduction of the number and duration of invasive procedures to limit neonatal mortality caused by these infections.

Keywords: Antibiotic resistance, associated infections, Infant, Neonatology, Newborn, Morocco

Introduction

To this day, healthcare-associated infections (HAIs) remain a significant burden for hospitals and the healthcare system as a whole. They are defined as infections that are neither present nor incubating when the patient is admitted, and which are contracted during or after the patient's care [1,2]. They are known throughout the world, affecting both developed and resource-poor countries. Their prevalence in Europe was estimated at 5.1% in 2012 [3,4]. While, their annual incidence was around 25 to 28.6% in Japan in 2008, 34% in Brazil, and 28% in Egypt in 2012 [5-7]. They constitute a real public health problem due to their frequency, severity, and socio-economic cost. They are frequent in neonatology, particularly in premature babies, due to the immaturity of their immune systems [3,8]. Several factors increase the likelihood of infection, such as premature birth, low birth weight, mother-to-

child transmission, perinatal infections and inappropriate use of antibiotics [9-11].

The risk of newborns contracting a HAI has always existed, and increases proportionally with the development of care, although this care is more effective, it is often more invasive, as it can be accompanied by contamination by pathogens of various origins.

The surveillance of HAIs in neonatology is primarily based on the identification of the main germs involved in these types of infections and the assessment of their resistance to antibiotics, in order to initiate targeted antibiotic therapy and thereby limit therapeutic failures.

The current systematic falls within the scope of this surveillance, the main aim of which was to describe the bacteriological profile of HAIs in neonatology and to assess the rate of antibiotic resistance of pathogens involved in this type of infection worldwide and particularly in Morocco. This knowledge is essential for promoting better

policies and implementing strategies to reduce neonatal mortality.

Material and Methods

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol.

Research strategy

A systematic search of the literature was carried out, following the analyses of different studies dealing with the subject without language restriction. We utilized databases such as PubMed, Scopus and Google Scholar. We carefully selected the following keywords: “healthcare-associated infections”, “nosocomial infections”, “cross infection”, “healthcare-related infections”, “neonatology”, “newborn”, “neonate”, “neonatal intensive care unit”, “micro-organisms”, “germs”, “antimicrobial resistance”, “antimicrobial profile”, “antimicrobial pattern”, “bacterial profile”, “Morocco”. Logical operators like AND and OR were used to combined the keywords. Grey literature data (theses and dissertations) were also included in our study. We customized our search to include studies published from 2015 to 2024.

Inclusion and exclusion criteria

Included were studies published between 2015 and 2024, carried out on newborns who developed healthcare-associated infections and which describe the germs involved and their antibiotic resistance profiles.

Excluded were studies with insufficient or missing data, as well as those focused on maternal-fetal infections.

Data collection process

A data extraction table was used to identify data relevant to the study such as author’s name, year of publication, study type, period of study, sample size, prevalence, infectious sites, implicated germs and their antibiotic resistance profiles.

Results

The flowchart shown in Fig.1 details the studies selection strategy. The systematic search identified 871 studies, of which 63 were duplicates. In the end, 27 studies were considered eligible meeting our inclusion criteria (Fig.1).

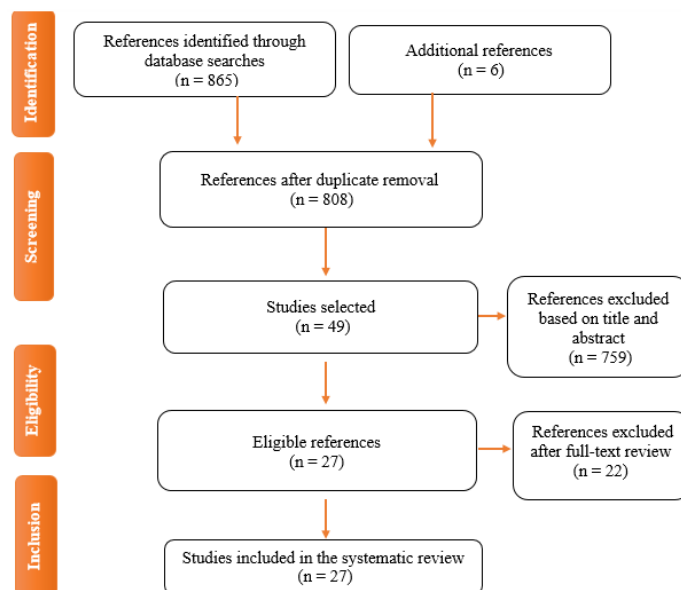


Fig.1. Flowchart showing the search and study selection strategy

Characteristics of the studies included in the review

The 27 included studies were conducted took place in 16 countries: 5 studies in Morocco, one in each of Algeria, Benin, Bulgaria, Colombia, Vietnam, Congo, Belgium, Gabon, Egypt, India, and

Madagascar; Two studies in each of Iran and Mexico; Four studies in Turkey and three in Italy. The sample size of the included studies ranges from 60 to 6068 patients. Most of the research was done in 2019 and in 2020, followed by 2015, 2023, 2016, 2022, 2021 and 2017 (Table I).

Table I: Characteristics of included studies (n=27)

Author	publication	Country	Type of study	Study period	Sample size
Rahmouni H. [12]	2022	Morocco	prospective /descriptive	13 February 2021 - 02 July 2021	331
Abdellaoui C.[13]	2022	Morocco	prospective /descriptive/ observational	27 December 2020 - 27 Mars 2021	440
Bighoumdan K. [14]	2020	Morocco	retrospective /descriptive	1 st January 2016 - 31 December 2018	200
Helyaich A. et al [15]	2019	Morocco	Retrospective	June 2015 -December 2016	920
Benabbas DR, Kara S. [16]	2019	Algeria	Retrospective descriptive	1 st January -31 December 2018	229
d'Almeida M et al. [17]	2017	Benin	Retrospective analytical	1 st November 2015-31 January 2016	717
Ceyhun C, et al. [18]	2015	Turkey	prospective	1 st July 2012 -30 June 2013	377
Kajiyazdi M, et al.[19]	2020	Iran	historical cohort	mars 2017 -September 2018	60
Rangelova V, et al [20]	2020	Bulgaria	prospective cohort	1 st January 2017 -31 June 2018	507
Javier Torres-Muñoz et al.[21]	2023	Colombia	observational cross-sectional	August 2016 - December 2018	226
Peters L, et al. [22]	2019	Vietnam	prospective cohort	march 2016 -October 2017	327
Choobdar F, et al [23]	2020	Iran	descriptive cross-sectional prospective	December 2015 - December 2016	654
Kissi Kamgaing E, et al.[24]	2019	Gabon	retrospective descriptive	December 2012 - December 2016	521
Kilic A, et al. [25]	2019	Turkey	prospective cohort	1 st July 2011 -30 June 2012	352
Ertugrul S, et al. [26]	2016	Turkey	retrospective	January 2011 - December 2014	126
Bukasa JC, et al. [27]	2021	Congo	descriptive longitudinal	1 st November 2016-1 st February 2017 & 2 nd February 2017-2 nd May 2017	6068
Bedir Demirdağ T, et al.[28]	2021	Turkey	multicenter point- prevalence		849
Crivaro V, et al. [29]	2015	Italy	retrospective	2006-2010	1699
El-Feky EA, et al. [30]	2016	Egypt	descriptive	march 2012 -September 2013	1053
Kartikeswar G a. P.et al. [31]	2023	India	prospective cohort	1 st may 2017 -31 July 2019	1442
Chabah M, el al. [32]	2016	Morocco	retrospective	1 st January 2012 -31 December 2013	1287
Scamardo MS,et al.[33]	2020	Italy	retrospective	2013-2017	1265
Ceparano M, et al.[34]	2023	Italy	retrospective cohort	1 st march 2018 -28 February 2022	564
Garcia H, et al [35]	2015	Mexico	Case-control		380
Verstraete EH, et al. [36]	2016	Belgium	historical cohort	2002 -2011	5134
Garcia H, et al [37]	2023	Mexico	Case-control	May 2016-November 2017	213
Ramanampamonjy MTM, et al.[38]	2022	Madagascar	Case-control	1 st January 2019 – 31 march 2021	1071

Prevalence of Healthcare-Associated Infections (HAIs) in neonatology

The prevalence was investigated in 17 studies, four of which were carried out in Morocco, 11 in developing countries (Benin, Turkey, Iran, India, Madagascar and Algeria), and only one in a

developed country (Belgium). The overall prevalence of HAIs in neonatology ranged from 3.54% in Madagascar to 29% in Morocco. It varied from 15.7% to 29% in Morocco, from 3.54% to 25.7% in developing countries and reached 6.7% in developed countries (Belgium) (Table II).

Table II: Prevalence of Healthcare-Associated Infections (HAIs) in the included Studies

Etude	pays	Prevalence (%)
Rahmouni H. [12]	Morocco	15,7
Bighouman K.[14]	Morocco	29
Helyaich A, et al. [15]	Morocco	17 ,39
Benabbas DR, Kara S.[16]	Algeria	22,3
d'Almeida M, et al. [17]	Benin	6,3
Ceyhun C, et al.[18]	Turkey	9
Kajiyazdi M, et al.[19]	Iran	6,12
Rangelova V, et al.[20]	Bulgaria	9,46
Choobdar F, et al.[23]	Iran	13,5
Kissi Kamgaing E, et al.[24]	Gabon	25,7
Kilic A, et al.[25]	Turkey	10,5
Bedir Demirdağ T, et al.[28]	Turkey	7,6
Kartikeswar G a. P,et al. [31]	India	9,08
Chabah M,et al. [32]	Morocco	22,37
Verstraete EH, et al.[36]	Belgium	6,7
Garcia H, et al.[37]	Mexico	33,3
Ramanampamonjy MTM, et al. [38]	Madagascar	3,54

Infectious sites of HAIs in neonatology

In this review, we focused on six infectious sites: bacteremia, urinary tract infections, meningitis, surgical site infections, and enterocolitis. Three

infectious sites were predominant: bacteremia in 15 studies (21% to 91%), pneumonia in 16 studies (5.17% to 81.3%) and urinary tract infections in 12 studies (1.4% to 28.8%) (Table III).

Table III: Infectious sites of HAIs in neonatology

Study	Bacteremia	Pneumonia	Meningitis	Urinary tract infection	Surgical site infection	Enterocolitis
Abdellaoui C. [13]	48,98	26,53	2,04	16,33		
Bighoumdan K. [14]	88	5,17		5,17		
Benabbas DR, Kara S. [16]	21			9		
d'Almeida M, et al. [17]			6,7			17,8
Ceyhun C, et al.[18]	50	10,3	20,6	14,7		
Kajiyazdi M, et al.[19]	30	21,7	5	6,6		10
Rangelova V, et al [20]	23,64	67,27				
JavierTorres-Mu~noz et al . [21]	73	27				
Petr L, et al. [22]		81,3				
Choobdar F, et al.[23]	80,7	9		2,3	8	
Kilic A, et al.[25]	70	18,3		6,7	1,7	
CrivaroV et al. [29]		25,5	1,3	28,8		
El-Feky EA, et al. [30]	91	9				
Scamardo MS,et al. [33]	69,6	20		8,8		1,6
Ceparano M, et al.[34]	69,44	30,55				
Garcia H, et al. [35]	28	17	0,8	1,6	6,5	
Garcia H, et al.[37]	36,6	16,2		1,4	9,9	
Chabah M, et al. [32]	70,6	8,8		11,7		

Bacterial Profile of HAIs in Neonatology

2631 bacterial strains were isolated. The result of studies showed that the germs responsible for HAIs were predominantly gram-negative bacteria in 60.81% of cases, while gram-positive bacteria were responsible for 39.18% of cases.

In order of frequency, the main germs isolated were: *coagulase-negative Staphylococcus* (27.86%) followed by *Klebsiella spp* (24.70%), *Acinetobacter spp* (13.75%), *Pseudomonas spp* (8.93%), and

Staphylococcus aureus (6.27%). Other pathogens were isolated less frequently (Table IV).

For gram-positive bacteria, the most frequently isolated pathogens were coagulase-negative *Staphylococcus* (71.02%), followed by *Staphylococcus aureus* (15.98%), *Enterococcus* (10.36%) and *Streptococcus* (1.55%). While, for gram-negative bacteria, the main isolated pathogen was *Klebsiella* (40.62%), followed by *Acinetobacter* (22.62%), *Pseudomonas* (14.68%), and *Escherichia* (8.56%) (Table IV).

Table IV: the pathogens responsible for HAI in neonatology

pathogens		n (%)		
Gram-positive	Staphylococcus	733	898	
	<i>Coagulase-negative staphylococci</i>	165		
	<i>Staphylococcus aureus</i>	107		
	<i>Enterococcus</i>	16		
	<i>Streptococcus</i>	3		
	<i>Aerococcus viridans</i>	1		
	<i>Kocuria</i>	3		
	<i>Corynebacterium spp</i>	3		
Gram-negative	Enterobacteriaceae	<i>Escherichia coli</i>	137	983 (37,36%)
		<i>Klebsiella spp</i>	650	
		<i>Enterobacter spp</i>	123	
		<i>Serratia marascens</i>	44	
		<i>Proteus mirabilis</i>	1	
		<i>Kluyira Ascorbata</i>	3	
		<i>Salmonella heidelberg</i>	17	
	Haemophilus	<i>Citrobacter spp</i>	8	3 (0,11%)
		<i>Haemophilus paraphrophilis</i>	1	
	Non fermentative Gram-négative	<i>Haemophilus influenza</i>	2	614 (23,33%)
		<i>Acinetobacter spp</i>	362	
		<i>Pseudomonas spp</i>	235	
		<i>Burkholderia cepacia</i>	4	
<i>Achromobacter spp</i>		5		
<i>Chryseobacterium spp</i>		3		
	<i>Elizabethkingia spp</i>	5		

In Morocco, the MAIN isolated pathogens were *coagulase-negative Staphylococcus* (35, 16%), followed by *Klebsiella* (26.22%), *Acinetobacter* (14.28%), *Enterobacter* (5.49%), and *Escherichia* (4.57%). Other pathogens were isolated less frequently. In the other countries of the world, the most frequently isolated germ was *coagulase-*

negative Staphylococcus (25.45%), followed by *Klebsiella* (25.11%), *Pseudomonas spp* (14.32%), *Acinetobacter spp* (13.97%) and *Escherichia spp* (5.42%). Other germs were isolated less frequently (Fig.2).

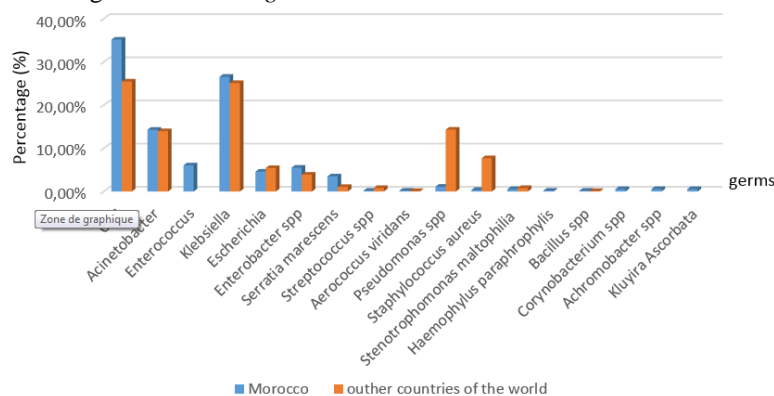


Fig.2. The proportion of bacterial species

Antibiotic resistance of germs responsible of HAIs in neonatology

Of the 27 studies included in our study, only 10 reported antimicrobial resistance of pathogens.

Resistance profile of germs to antibiotics in Morocco

Staphylococcus

- The resistance rate of coagulase-negative *Staphylococcus* was 97% for levofloxacin, erythromycin, ceftazidime, and gentamicin, while the resistance rate to penicillin was 100% [12].
- In one study, the only isolated *Staphylococcus aureus* strain was susceptible to methicillin and aminoglycosides [13].

Enterococcus

- The vancomycin resistance rate was reported in two studies and ranged from 90% to 100% [12,13].
- In one study, the resistance rate to tetracycline was 100% [12].

Acinetobacter spp

- In three studies, all *Acinetobacter* isolates were susceptible to colistin [12,13,15].
- The resistance rate to gentamicin was reported in two studies and ranged from 51% to 100% [13], [14].

Klebsiella spp

- The resistance rate to gentamicin and to ciprofloxacin was reported in two studies, ranged from 13% to 100% and 20% to 100%, respectively [13,14].
- The rate resistance to amoxicillin/clavulanic acid was reported in three studies, ranged from 95% to 100% [12-14].
- The resistance rate to ceftazidim was reported in two studies, ranged from 30% to 100% [13,14].

Escherichia spp

- In two studies, the resistance rate to amoxicillin and to amoxicillin/clavulanic acid was 100% [12,13].
- In one study the rate resistance to ceftazidim was estimated at 87.5% [13].

Enterobacter spp

- In two studies the rate resistance to imipenem was 0% [12,13].
- In one study the resistance rate to ceftazidime and to ceftriaxon was 100% [13].

Resistance profile of bacteria to antibiotics in developing countries

Of the included studies conducted outside Morocco, only five reported antibiotic resistance profile. These studies were carried out in countries classified as developing, namely, Algeria, India, Turkey, and Vietnam.

Staphylococcus

- The resistance rate of *coagulase-negative Staphylococcus* in Benin was estimated at 100% for gentamicin and ampicillin, and 0% for fosfomycin and imipenem [17].
- The resistance of *coagulase-negative Staphylococcus* to methicillin was estimated at 75% in a study conducted in Turkey [25].

Enterobacteriaceae

- The resistance of *Klebsiella* to gentamicin was reported in two studies, ranging from 8.1% in Algeria to 100% in Benin, while for *Escherichia* and *Enterobacter*, this resistance affected 100% and 70% of isolates in Benin, respectively [16,17].
- The resistance rate to colistin was reported in two studies, ranging from 13.3% in India to 16.9% in Vietnam for *Klebsiella* isolates, while for *Enterobacter* and *Escherichia* isolates, the resistance rate was 0% in India [22,31].

Non-fermenting Gram-negative bacteria

- The resistance of *Acinetobacter* to colistin was reported in two studies, ranged from 0% in India to 10.5% in Vietnam, while for *Pseudomonas* isolates, the resistance rate was 17.3% in Vietnam [22,31].
- The resistance rate of *Acinetobacter* to cephalosporins, ranged from 97.2% in Vietnam to 100% in India. While, this rate ranged from 89.4% in Vietnam to 100% in India for *Pseudomonas* isolates [22,31].

Multi-drug resistant bacteria

- In Morocco, multi-drug resistant bacteria (MDR) have been studied in three studies. The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in one study and was estimated at 0% [12]. The production of extended-spectrum beta-lactamases (ESBL) by *Enterobacteriaceae* was tested in three studies, ranged from 58% to 91.02% [12,13,32]. The rate of vancomycin-resistant *Enterococcus* was reported in two studies and ranged from 90% to 100% [12,13].
- Among studies conducted in other countries, the production of ESBL by *Enterobacteriaceae* was reported in four studies. In three of these, ESBL

rates in *Klebsiella pneumoniae* ranged from 0% to 100% [18, 25, 28], while for *Escherichia coli*, they ranged from 25% to 75% [18, 25]. In *Enterobacter spp.*, ESBL production reached 17% [25]. In the fourth study, 26 of 31 Enterobacteriaceae isolates (83.9%), mainly *Klebsiella pneumoniae* and *Salmonella heidelberg*, were identified as ESBL producers [16].

- The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in three studies ranged from 50% to 100% [24,28,38].

Discussion

The current systematic review included 27 studies. The highest prevalence of HAIs in neonatology was recorded in Morocco in the series conducted by Bighoumdan K. and was 29% [14]. The study was performed in the pediatric intensive care unit of the Centre Hospitalier Universitaire Mohammed VI in Marrakech and included neonates admitted for perioperative management of surgical conditions. This specific case-mix is particularly relevant, as surgical neonates are inherently exposed to multiple invasive procedures; central vascular access, mechanical ventilation, and prolonged hospitalization, all of which are well established risk factors for HAIs.

The high rate observed in this Moroccan series likely reflects both the intrinsic vulnerability of surgical neonates and challenges in infection prevention in high-acuity pediatric units. These findings underscore the importance of targeted infection control strategies, including strict hygiene measures, careful management of invasive devices, and staff training, to reduce HAIs in this high-risk population. In comparison with international reports, the prevalence reported by Bighoumdan et al. remains at the upper range, highlighting the need for continuous local surveillance and context-specific interventions. This result was comparable to that recorded in the study by Hmamouchi B. and al. [39] (21.9%) and higher than that reported in the series by Moulainine and al. [40] (7.2%), differences that may be explained by heterogeneity in patient populations, intensity of care, and infection prevention practices. These findings highlight the need for standardized multicenter surveillance and reinforced infection prevention strategies, particularly in high-acuity neonatal settings.

The lowest prevalence was recorded in Madagascar with rate of 3.54%. [38] Other studies reported different results, such as the study by Zinnig W, and al. and the study by Sarvikivi E, and al. whose prevalence was 5.1% and 6.4%, respectively [4,41]. The predominant infectious sites were bacteremia (21% to 91%), followed by pneumonia (5.17% to 81.3%) and urinary tract infections (1.4% to 28.8%). This result is similar to that of the study by Zoukal

S. and al, in which the predominant infectious sites were bacteremia (2.5 to 100%) and pneumonia (6.3 to 40%) [42].

The most common germs were *coagulase-negative Staphylococcus* (27.86%), followed by *Klebsiella* (24.70%), *Acinetobacter* (13.75%), *Pseudomonas spp* (8.93%) and *Staphylococcus aureus* (6.27%). Other germs were isolated less frequently. This bacterial profile, mainly characterized by nosocomial germs, reflects the implementation of advanced tertiary-level neonatal care, marked by the frequent use of invasive devices.

Our finding, is comparable to that of the study by Zinnig W, and al. [4] and the study by Felipe Teixeira and al [43]. Were the most isolated germs was *coagulase-negative Staphylococcus*, with rates of 31% and 33.5%, respectively. However, other studies, reported different results, such as the systematic review by Zoukal S, and al. [42] in which the most frequently isolated germ was *Klebsiella pneumonia* (22.7% to 41%).

Concerning multi-drug resistant bacteria, the rate of *methicillin-resistant Staphylococcus* ranged from 0% to 100%. Other reviews reported different rates such as the study by Zoukal S. and al [42] and the study by Felipe Teixeira and al [43], where the MRSA rates ranged from 4.5% to 11.1% and from 1.2% to 28.3%, respectively. The production of ESBL by *Enterobacteriaceae* ranged from 0% for *Klebsiella* isolates to 91.02%. This result is comparable to that reported by Zoukal S and al, were the ESBL rate was 96.9% [42].

In the review conducted by Felipe Teixeira and al [43], the percentage of *Enterobacteriaceae* resistant to third-generation ranged from 23.3% to 36.6%.

The rate of vancomycin-resistant *Enterococcus* ranged from 90% to 100%, while Felipe Teixeira and al [43] reported in their results that only study reported one single sample of vancomycin resistant *Enterococcus sp.*

Limitations

Several limitations should be considered when interpreting the findings of this review; the studies included varied in methodology, including differences in sample size and infection definitions, which may affect the comparability of results. In addition, the geographic variability in infection prevalence and pathogen profiles limits the generalizability of the results across different settings.

Conclusion

HAIs are a serious public health problem. In neonatology, they are responsible for a significant morbidity and mortality. In Morocco, studies on the epidemiological and bacterial profiles of neonatal healthcare-associated infections are limited.

Updated studies to determine germs involved in this type of infections and their assesse to drugs are necessary to better address the realities of HAIs in neonatal care stings. This systematic review recommends the rigorous application of hygiene measures throughout neonatal care and the reduction of the number and duration of invasive procedures to limit neonatal mortality caused by these infections. As a future perspective, given the extent of resistance, it is advisable to consider the development of bioactive compounds with antimicrobial properties.

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