Systematic review on screening for Antimicrobial-Resistant Gram-negative bacteria in hospitalised patients and risk of progression from colonisation to infection

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Abstract (200)

Background Transmission of antimicrobial-resistant Gram-negative bacteria (AMR-GNB) among hospitalised patients can lead to new cases of carriage, infection and outbreaks, hence the need for early carriers identification. We aim to explore two key elements that may guide control policies for colonisation/infection in hospital settings: screening practices on admission to hospital wards and risk of developing infection from colonisation.

Methods We searched on PubMed, Scopus and Cochrane databases for studies published from 2010 up to 2019 reporting on adult patients hospitalised in high-income countries.

Results The search retrieved 9496 articles. After screening, 92 studies were included. Combining target patient groups and setting type, we identified six screening approaches. The most reported approach was all admitted patients to high-risk (HR) wards (48.0%). The overall prevalence of AMR-GNB was 15.1% (95%CI 9.5-21.6) with significant differences across regions and over time. Risk of progression to infection among colonised patients was 15.8% (95%CI 11.1-21.0) and varied according to setting (p value=0.0004) and pathogens' group (p value<0.0001), with higher values reported for *Klebsiella* species (24.1%; 95%CI 11.5-38.9).

Conclusions According to our data, screening for AMR-GNB was heterogeneous and usually following targeted approaches. Risk of progression to infection in AMR-GNB colonised patients in hospital settings was substantial.

Introduction

Several antimicrobial-resistant Gram-negative bacteria (AMR-GNB) share a common feature of nosocomial transmission, as well as the risk of colonisation and subsequent clinical infection in the hospitalised patient.

These infections are increasingly being reported from patients both in healthcare settings and in the community[1,2,3]. Infections with these microorganisms are particularly difficult to treat, because limited or even no treatment options remain effective against them, due to high levels of antimicrobial resistance[4]. Furthermore, they are associated with high patient morbidity, attributable mortality and hospital costs[5]. For instance, it has been described how patients clinically infected or colonised by CRE/CPE, *Pseudomonas aeruginosa* or *Acinetobacter* spp., can act as reservoirs or source of transmission to other patients, resulting in carriage, infection or outbreaks[6].

At present there are incomplete information regarding the prevalence of AMR-GNB carriage within the community and features of at risk populations, mainly because most of the published data are obtained from non-systematic reporting of faecal carriage from active patient screening in various epidemiological settings, e.g. on admission, during outbreaks or

during stays in healthcare settings, after discharge from an acute care facility or a long term care facility (LTCF), among healthy people in the community and pre- and post- foreign travel[6]. Despite the lack of accurate data, infection control and management in the hospital setting is essential. Early identification of carriage at hospital admission or of infection at the insurgence of clinical symptoms may allow for appropriate and timely treatment of patients, implementation of adequate control measures (e.g. patient isolation, contact precautions) and ultimately to reduce the risk of onward transmission within the health care facility.
The objective of this systematic review was to explore two key elements that may guide early identification and management of antimicrobial-resistant Gram-negative bacteria colonisation and infection in the hospital setting in high-income countries, namely screening practices on admission to hospital/hospital wards and risk of progression from colonisation to infection.

Methods

Two systematic reviews have been conducted: (1) Systematic Review 1 (SR1) to describe patient groups undergoing screening on admission, describe screening procedures and estimate prevalence of AMR-GNB colonisation; (2) Systematic Review 2 (SR2) to estimate acquisition rate and risk of progression to infection in AMR-GNB colonised patients.
The study was conducted following PRISMA-P guidelines[7], and the protocol registered in PROSPERO (no. CRD42019144536).

Search strategy

We searched for studies published from 2010 to April 30th2019, reporting on screening practices to identify adult patients colonised by AMR-GNB on admission to hospital/hospital wards or risk of developing infection in AMR-GNB colonised patients during hospitalisation. The search strategies (*"Search strategy"*; Supplementary Material) was built on previously published review[8].We searched PubMed, Cochrane and PsycInfo databases for records reporting on: antibiotic-resistant Gram-negative bacteria colonisation, hospital settings, screening and risk of progression. Database searches were supplemented and complemented by a citation search in Scopus using articles resulting from the screening process. We also checked reference lists of relevant systematic reviews for eligible studies.

Eligibility criteria

For the purpose of this review, we included any nosocomial transmissible AMR-GNB capable of causing clinical disease in the hospitalised patient, such as Enterobacterales, *Pseudomonas aeruginosa* and Acinetobacter spp. among others (full list of included

pathogens available in the annex "Study protocol, table 3"). This rather broad definition reflects the heterogeneity of the available literature and our intention to investigate AMR-GNB sharing common features of nosocomial transmission.

We defined as colonised patient a hospitalised individual who is rectal/anal carrier of AMR-GNB (as defined before) and as infected patient a hospitalised individual who has a clinical infection resulting from AMR-GNB colonisation.

Regarding SR1, studies were included if they reported at least a description of patient groups undergoing screening, screening procedures and prevalence of carriage at admission. To be included in SR2, studies had to provide risk for developing infection during hospital stay among at least one of the following patient groups: patients colonised at hospital admission, individuals who acquired colonisation during hospitalisation and patients who were discovered to be colonised at an undefined time during hospitalisation. Studies reporting on acquisition rate during hospitalisation were included only if they fulfilled the minimum inclusion criteria of SR1 or SR2.

Studies reporting on prevalence of carriage, without discerning between colonisation at admission and acquisition of carriage during hospitalisation were included only if fulfilling eligibility criteria for SR2. Reports of randomised controlled trials, non-randomised comparative studies, observational studies and cross-sectional studies (only for SR1) were included in the analysis. Reports of narrative review, point-prevalence studies, case reports and other non-pertinent publication types were excluded. Only reports carried out in high-income countries (based on the World Bank definition of high-income countries)[9] were included. Reports of studies with hospitalised patients with less than 18 years of age or non-hospitalised patients or individuals admitted to long term care facilities were excluded. Language restrictions were applied (only reports written in English, Spanish, Italian or French were accepted). See *"Supplementary Tables 1 and 2"*.

Study selection

The results of searches have been downloaded and loaded in a bibliographic management software (EndNote X7.2.1). The articles selection phase consisted, in the first phase, of screening titles and abstracts according to the eligibility criteria by two reviewers, followed by assessment of selected articles in full-text by four reviewers. The reasons for exclusion were documented per article and summarised in the *"Supplementary Table 4 - Articles excluded in full text"*.

Data extraction and Quality assessment

Four investigators independently extracted data using a standard data collection form including study characteristics, setting, study population, screening approach and outcomes (details provided in *"Supplementary Table 3- Data extraction elements"*).
The unit for data extraction was study, defined as a screening approach for a defined population group, in a defined country, over a discrete period of time. According to this definition, a single article may present different studies.
Records included in the review were assessed for their quality based on study design with three different tools[10-11] (details provided in "Study protocol" and "*Quality Assessment Evaluation Tools"* Supplementary Material).

Data synthesis

Description of screening approaches

SR1 included studies were grouped according to: the reason for screening (outbreak, routine care or research purpose); setting (High risk wards vs Low-intermediate risk wards vs hospital-wide); patients group (All admitted vs High-risk patients).
We defined as "High risk wards" all studies reporting on screening conducted in ICU or multiple wards including ICU, in haematology, transplant, rehabilitation and burn units. When screening was performed in selected ward/s not defined as high risk (e.g. general medicine or surgery department), we classified the study setting as "Low-intermediate risk".
We defined as "Hospital-wide" all studies reporting on screening conducted at time of arrival to hospital, regardless of ward of admission.
We considered to be "high-risk patients" all individuals admitted to hospital with a history of previous hospitalisation, patients with defined clinical conditions (e.g. oncological patients), patients with travel history (including hospitalisation abroad) and individuals with a combination of above mentioned risks.
Due to non-comparability of screening activities in outbreak and non-outbreak situations, studies investigating outbreak scenarios were excluded from qualitative and quantitative synthesis of SR1 and were included only in SR2.

Prevalence of AMR-GNB in admitted patients

Prevalence of AMR-GNB on hospital admission has been evaluated according to the following groups: all pathogens included in our study (referred as GNB); *Klebsiella* spp. (KB); *Escherichia coli* (EC); other Enterobacterales (OE) – excluding *Klebsiella* spp. and *Escherichia coli; Pseudomonas aeruginosa* (PA); *Acinetobacter baumannii* (AB).
In addition, reported prevalence for each pathogen group was stratified according to screening approaches (patients/setting), geographical regions (EU/EEA including UK, Switzerland and Israel; Australia; USA and Asia) and study period (< 2010, 2010-2014, ≥ 2015).

Acquisition rate and risk of progression to infection

Risk for acquisition of colonisation during hospital stay in patients not colonised at admission and risk for progression to infection during hospitalisation were assessed according to setting; pathogen groups (excluding GNB) and further stratified for setting. When studies reporting on risk for acquisition/infection were limited, we grouped them into a unique category for the analysis if appropriate (i.e. hospital-wide settings, in low-intermediate risk wards - "HW/LIRW"). In addition, risk for progression to infection was assessed by time of acquisition (already colonised at admission; colonised during hospitalisation; no available information on time of detection).
As secondary outcomes we evaluated risk of death in patients already colonised by AMR-GNB at admission and among infected patients.

Statistical analysis

Prevalence for each study was summarized by calculating the proportion of subjects colonised by AMR-pathogens, infected or non-colonised at each stage of hospital stay. Study-specific proportions were pooled considering all studies included in both SRs and subgroup analyses were performed stratifying by setting, patients, pathogen (individually and grouped), geographic region, timeframe and combination of patient and ward. Pooled proportion were calculated using the Freeman-Tukey double arcsine transformation. Random effects model was used for all analyses and synthetized with forest plots. "metaprop" routine within the META R package (4.12) was used for the analyses[12]. Statistical heterogeneity between studies and groups was assessed applying Cochrane's Q-test. I^2

statistic was reported as quantification of study's heterogeneity. A p-value <0.10 was considered as indicative of statistical heterogeneity.

Results

Search results

During the literature search (Figure 1) 9,496 articles were retrieved: 6,717 from databases searching and 2,779 as additional records identified through other sources (e.g. Scopus and systematic reviews). Screening based on title/abstract resulted in the exclusion of 8,991 articles. The remaining 505 articles were screened in full text and 85 articles were included in the systematic review, counting as 92 studies[13-97].

Eighty-six studies were included in SR1[13-91]. Six studies [30,92-95,97] were excluded from SR1 but included in SR2 and 49 studies fulfilled eligibility criteria for both SR1 and SR2[13,14,16,19-24,26-29,31-34,36,39,40,43,45-47,49,50,52,53,55-59,64,65,67,68,71-73,77,82,84,86,89-91].

Description of studies

Most studies were conducted in Europe (n= 73, 79.3%)[13,15,16,18,20,22-29,31-33,35-55,57,58,62-65,67-69,71-73,75,77-90,92-94,97], mainly in France (n=21)[24,32,33,37,41,43,45,47,48,53-55,63,64,77,79,85,93,97] and Italy (n=10)[18,22,28,35,62,67,68,72,94]. Five studies were conducted in Asia (n=5, 5.4%)[17,34,60,70], mainly in Korea (n= 3)[34,70]. The remaining studies were conducted in USA (n=12; 13.0%)[14,19,30,59,61,66,74,76,91,95,96] and in Australia (n=2)[21,56]. Seventy-six studies were carried out in University or tertiary hospitals (82.6%)[13,15-20,22-30,32-36,39,41-43,45-48,50,52,53,56-74,76-81,83,85-88,90-97], 8 studies in general hospitals (8.7%)[21,31,44,54,55,75,84,89] and the others in multiple hospital types[14,37,38,40,49,51,82]. Fifteen studies (16.3%) were carried out before 2010[17,24,29,37,39,47,52,57,63,65,73,74,77,88,90], 47 studies (51.1%) between 2010 and 2014[14,15,18-20,23,26,27,30-34,38,40-42,44,45,54,56,58-61,63,64,66,67,69-71,75,79,82,84,86,87,89,92-95,97] and 29 (31.5%) from 2015 onwards[13,16,22,25,28,30,35,36,43,46,48-51,53,55,62,68,72,76,78,80,81,83,85,91,96]. For one study[21] time period was not available.

Based on type of study, we retrieved 55 (59.8%) prospective observational[13,16-18,21-27,29,32,34-38,41,43-47,51,53-56,59-61,65,69-72,74,75,78,79,82,84-86,88-94,96] and 22 (23.9%) retrospective observational studies[19,30,31,33,40,42,62-64,68,76,80,81,83,87,95,97], 12 (13.0%) case-control and cohort studies[14,20,28,48-50,52,57,66,73,77,94] and 3 (3.3%) RCT/quasi-experimental studies[15,39,58]. Eighty studies (87.0%) were assessed as high-quality studies[13-20,22-24,26,27,29-35,38,40,41,43-52,54,55,59-96], 8 (8.7%) as low quality[21,25,36,37,42,53,56,97] and 4 (4.3%) as very low-quality studies[28,39,57,58].

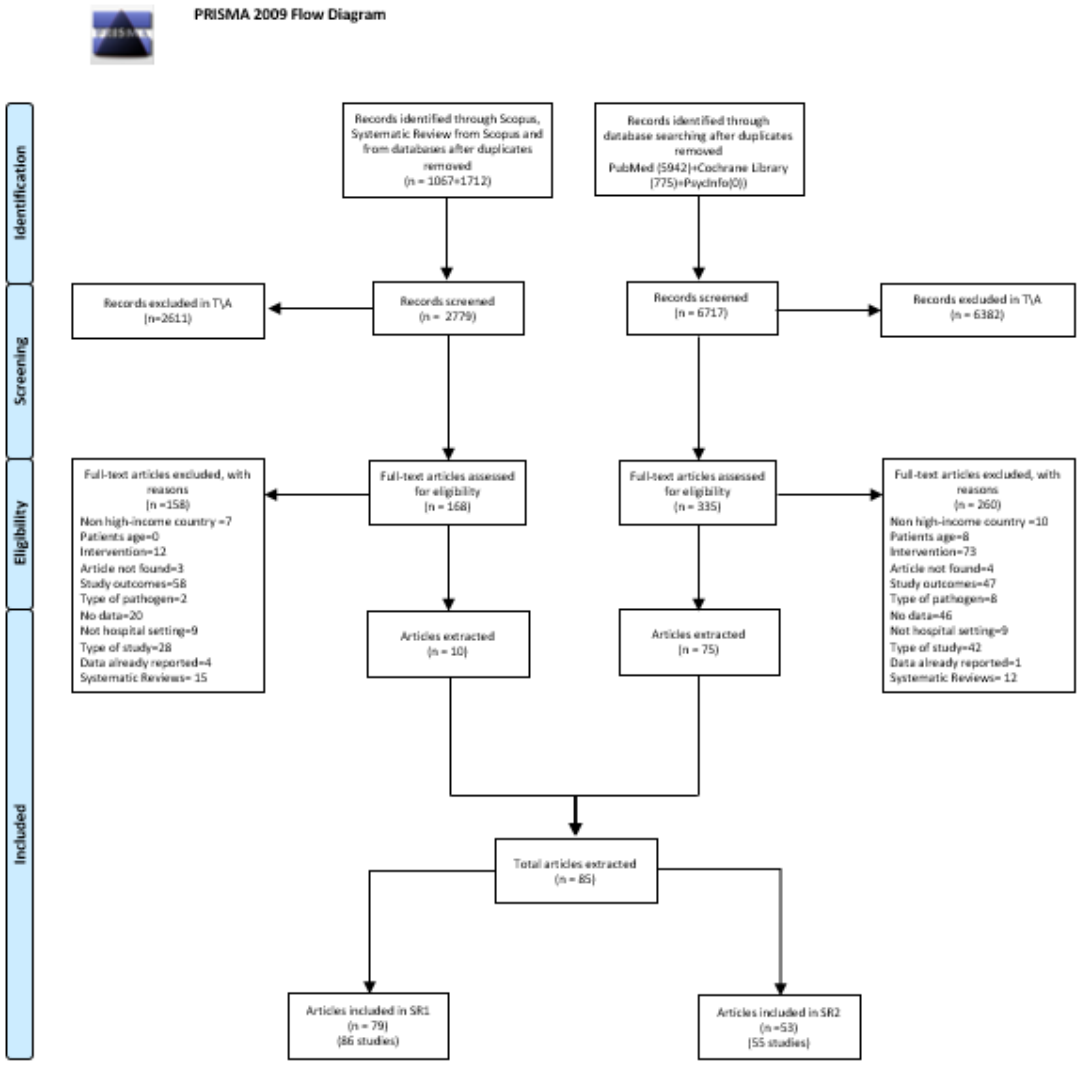

Figure 1. PRISMA flowchart of included articles for systematic review 1 and 2.

Description of screening approaches

Out of 86 studies included in SR1[13-91], 75 were included in qualitative analysis[13,14,16-25,27,28,30,32-36,38-41,43-72,74-83,85,86,90,91] as two reported on repeated screening procedures (excluding two studies[34,63]) and nine reported on screening activities in outbreak situations[15,29,31,37,42,84,87-89]. Among included studies, 24 concerned routine care screenings[41,43,45,47,48,50,53-55,59,62,64,66,72,76,80-83,85,90] and 51 screening procedures adopted to respond to a specific research question[34-36,38-40,44,46,49,51,52,56-58,60,61,63,65,67-71,74,75,77-79,86,91]. Screening was performed at hospital admission in 35 studies[13,14,17,21,24,25,27,30,41,44,48,50,51,54,60-63,66,69,70,74-76,78-83,90] and at admission and repeatedly in 40 studies[16,18-20,22,23,26,28,32-36,38-40,43,45-47,49,52,53,55-59,64,65,67,68,71,72,77,85,86,91].

Screening of all admitted patients was conducted either at the time of arrival to hospital (n=6; 8%)[19,44,63,74,78,82] or at admission to a specific ward (n=45; 60%)[13,14,16,17,20,21,23-26,28,32-

[34,36,38-40,43,45-47,51-53,55,57-60,62,64,67,69-72,75-77,80,81,86,90]. High-risk patients-based screening (n=24 studies, 32%) targeted patients with defined clinical conditions (mostly oncologic patients) (9, 37%)[22,35,41,50,56,65,68,83,91], returning travellers (7, 29%)[27,33,48,54,61,79,81], previously hospitalised patients (4, 17%)[30,62,66,82] and individuals with multiple risks (4, 17%)[18,30,49,85]. Studies performing screening in hospital-wide (HW) setting were 15[18,19,44,48,49,61,63,66,73,74,78,79,81,82,85], while studies performing screening in selected ward/s not defined as high risk were 11[13,17,21,23,24,46,51,62,68,86]. Screening in high risk setting (n=48 studies, 64.0%)[14,16,20,22,25,26,28,30,32-36,38-41,43,45,47,50,52-60,64,65,67,69-72,75-77,80,81,83,90,91] was performed largely in ICU or ICU and other wards (n=35; 72.9%)[14,16,20,26,30,32-34,38-41,43,45,47,50,52-56,59,60,64,69-71,73,75-77,80,81]; the remaining studies were conducted in haematology (n=6)[22,35,65,83,90,91], transplant units (n=5)[25,28,36,58,67] and rehabilitation wards (n=2)[57,72]. One study[27] has not been categorized neither as high-risk nor low-intermediate risk ward.

Combining target patient groups and setting type, we identified six screening approaches: all admitted patients (AA) to hospital (6 studies, 8.0%)[19,44,63,74,78,82], AA patients to high risk ward/s (36, 48.0%)[14,16,20,25,26,28,32-34,36,38-40,43,45,47,52,53,55,57-60,64,67,69-73,75-77,80,81,90], AA patients to low/intermediate risk wards (LIRW) (9, 12.0%)[13,17,21,23,24,46,51,62,86], high-risk (HR) patients admitted to hospital (9, 12.0%)[18,48,49,61,66,79,81,82,85], HR patients admitted to high risk ward/s (12, 16.0%)[22,30,33,35,41,50,54,56,65,83,91], HR patients admitted to low/intermediate risk wards (LIRW) (2; 2.7%)[62,68].

Prevalence of AMR-GNB in admitted patients

Out of 86 studies[13-91], only 77[13,14,16-25,27,28,30,32-36,38-41,43-72,74-83,85,86,90,91] reported quantitative data on prevalence of AMR-GNB carriage (Table 1). The overall prevalence rate of any GNB was 15.1%, followed by 9.6% for *E. coli*, 7.6% for *P. aeruginosa* and 4.1% for *Klebsiella* spp. AMR-GNB prevalence varied across geographical regions (Table 1), with higher prevalence (12.4%) reported in USA for *Klebsiella* spp[14], and in USA (15.0%) and Asia (16.0%) for *E. coli*. Due to the high number of studies conducted in Europe, we decided to separate included studies conducted in northern European countries (England, Belgium, Denmark, France, Germany, Netherlands, Switzerland) from southern European countries or countries considered highly endemic (Italy, Greece, Israel, Poland, Spain). In Europe, prevalence of *Klebsiella* spp. presented a considerable north-south gradient, with southern countries presenting a higher prevalence (5.7%) compared to northern European countries (1.7%). In addition, prevalence of carriage varied over time, with all pathogens groups except EC and AB presenting a higher prevalence during the 2010-2014 period. For instance, reported KB-

prevalence varied from 4.2% (before 2010) to 6.5% during 2010-2014, reaching its minimum (2.4%) for studies performed from 2015 onwards.

Table 1. Prevalence of AMR-GNB carriage at hospital admission, by pathogen groups, geographical region and timeframe. * England, Belgium, Denmark, France, Germany, Netherlands, Switzerland ** Italy, Greece, Israel, Poland, Spain

TABLE. 1

Prevalence of AMR-GNB by screening approach

Reported prevalence for each pathogens group was studied according to screening approaches. Due to limited studies reporting on screening in hospital-wide settings or in low-intermediate risk wards, we grouped these two setting types into a unique category, referred as "HW/LIRW". Except for prevalence of *Klebsiella* spp and *P. aeruginosa*, no statistical difference was observed according to screening approaches (Table 8, Supplementary material).

Here we describe detailed analysis for KB-prevalence, which varied according to screening approaches (Table 2). Studies performed in high-risk wards (n=21)[14,22,25,26,32,34,35,40,41,50,52,53,55,56,67,69,70,75,80,81,83] presented a prevalence significantly higher than those (n=13)[13,17,18,21,46,48,62,68,78,79,81,85,86] conducted in the entire hospital or in low-intermediate risk wards (5.8% vs 2.0%).

Taking into account screening approaches based on patients' groups and setting, KB carriage rate varied from 2.7% in HR patients in high-risk wards to 2.4% in HR patients in HW/LIRW, reaching its maximum (7.2%) in AA patients in high risk wards and its minimum (1.8%) in AA patients in hospital-wide/low-intermediate risk units.

The risk of KB-carriage related to the admission ward was significantly different (p=0.0005) between studies performing screening for AA patients in high-risk wards (7.2%) and for AA patients in hospital-wide/low-intermediate risk setting (1.8%). No statistical difference was observed in reference to patients type only: HW/LIRW-HR vs HW/LIRW-AA.

Table 2. Prevalence of KB-carriage at hospital admission by screening approaches and evaluation of risk of colonisation attributable to patient or ward type.

TABLE. 2

Acquisition of AMR-GNB colonisation during hospitalisation

Fifty-five studies were included in SR2[13,14,16,19-24,26-29,31-34,36,39,40,43,45-47,49,50,52,53,55-59,64,65,67,68,71-73,77,82,84,86,89-97]. Most studies (n=41; 77.3%) were performed in high-risk wards[16,20,22,26,28,29,31-34,36,39,40,43,45,47,50,52,53,55-59,64,65,67,71-73,77,84,89-93,95,97].

Rate of colonisation acquisition during hospitalisation was reported in 40 studies[16,19,20,23,26,28,29,31-34,39,40,43,45-47,49,52,53,55-59,64,65,67,68,71-73,77,86,89-91].

The proportion of patients who acquired AMR-GNB carriage during hospitalisation was 10.5% (n=40; 95% CI:8.2-13.1), irrespective of length of stay. The acquisition rate varied significantly according to pathogens group as reported in table 3, ranging from a minimum of 5.1% (n=21[19,23,28,32,34,39,43,45,46,49,53,55,59,64,71,72,82,86,90,91]; 95%CI:3.7-6.7) for Enterobacterales to a maximum of 26.5% (n=6[26,40,52,67,68,89]; 95%CI:13.7-41.6) for *Klebsiella* spp. In addition, a statistically significant difference (p=0.0002) was observed between studies conducted in HR wards (n=33[16,20,26,28,29,31-34,39,40,43,45,47,52,53,55-59,64,65,67,71-73,77,89-91];12.5%; 95% CI:9.6; 15.6) compared to HW-LIRW (n=7[19,23,46,49,68,82,86];3.9%; 95% CI:1.5; 7.2). A significant difference for type of setting was observed also evaluating risk of acquisition *Klebsiella* spp and Enterobacterales specific: Enterobacterales (HR n=15[28,32,34,39,43,45,53,55,59,64,71,72,90,91]; 6.1%; 95% CI:4.3;8.1 vs LIRW n=6[19,23,46,49,82,86]; 3.0%; 95% CI:1.2;5.6) and *Klebsiella* spp. (HR n=5[26,40,52,67,89]; 30.2%; 95% CI:17.9;44.2 vs LIRW n=1[68]; 11.1%; 95% CI:8.6;13.9).

Table 3. Distribution of patients who acquired AMR-GNB colonisation by pathogen groups and setting.

	Risk of acquisition	
	n studies	prevalence %; 95%CI
Tot	40	0.1055 [0.0821; 0.1314]
Pathogens (except		
Tot		
E	21	0.0511 [0.0371; 0.0671]
PA	4	0.1816 [0.1463; 0.2197]
KB	6	0.2646 [0.1372; 0.4157]
AB	2	0.0773 [0.0007; 0.2512]
EC	2	0.1544 [0.1157; 0.1976]
p-value	***< 0.0001***	
Wards		
Tot		
Low risk	7	0.0390 [0.0154; 0.0723]
High risk	33	0.1247 [0.0959; 0.1565]
p-value	***0.0002***	

Risk of progression among colonised patients

The overall risk of progression to infection among previously colonised patients was 15.8% (n=35; 95%CI:11.1-21.0)[13,14,16,19,21,22,24,27,28,31,36,43,46,50,52,57,64,67,68,72,82,84,89-97] (Figure 2, Table 4), varying significantly according to pathogen type (p <0.001) and setting (p=0.004). The majority of studies included in SR2 reported on Enterobacterales and specifically on *Klebsiella* spp., that showed respectively a risk of progression to infection of 9.8% (n=16[13,14,19,24,28,43,46,50,64,72,82,90,91,91,92,93]; 95%CI:5.2; 15.6) and 24.1% (n=10 [21,30,52,67,68,84,89,94,97]; 95%CI:11.5; 38.9). The highest risks were observed for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, 57.0% (n=2[16]; 95%CI:28.3; 83.0) and 41.8% (n=2[31,95]; 95%CI:1.8-90.5); while the lowest for *Escherichia coli*, 7.2% (n=2[57]; 95%CI:2.9;13.0). When stratifying by type of setting, we observed a risk of 22.0% for patients hospitalised in high-risk wards (n=25[14,16,22,28,31,36,43,50,52,57,64,67,72,84,89,90-93,95,97]; 95%CI:15.2-29.6) and 5.6% in HW-LIRW (n=9[13,19,21,24,30,46,68,82,94]; 95%CI: 1.2-12.2) (p=0.0004).

Risk of progression for patients colonised at hospital admission was 13.9% (n=15; 95%CI:5.4-24.9), 23% for patients who acquired carriage during hospitalisation (n=7; 95%CI:5.9-45.2) and 16.9% for patients with unknown time of colonisation (n=13; 95%CI:11.2-23.4) (Table 4), although no statistical difference was observed, not even when stratifying by type of pathogen or setting (Table 4).

Overall proportion of deaths among infected patients was 34.7% (n=8; 95%CI:22.7-47.6)[43,50,67,68,84,90,93,96].

Figure 3. Distribution of risk of progression to infection according to pathogens group

HR: high-risk wards; HW-LIRW: Hospital-wide/ low-intermediate risk wards

Table 4. Risk of progression to infection by time of colonisation stratified by ward and pathogen group.

	Risk of progression to infection						
	Total colonised		Col at admission		Acquired		
	n studies	prevalence %; 95%CI	n studies	prevalence %; 95%CI	n studies	prevalence %; 95%CI	*p-value*
Tot	34	0.1580 [0.1112; 0.2101]	15	0.1392 [0.0543; 0.2486]	7	0.2305 [0.0587; 0.4516]	0,2850
Pathogens (except for GNB)							
Tot	32	0.1544 [0.1065; 0.2080]	12	0.1237 [0.0368; 0.2424]	7	0.2305 [0.0587; 0.4516]	0,2282
E	16	0.0985 [0.0519; 0.1562]	7	0.0760 [0.0053; 0.1992]	1	0.0000 [0.0000; 0.2044]	0,5029
PA	2	0.5699 [0.2928; 0.8298]	1	0.6154 [0.3327; 0.8653]	1	0.3333 [0.0000; 0.9411]	0,4252
KB	10	0.2408 [0.1154; 0.3885]	3	0.2174 [0.0667; 0.4091]	4	0.4004 [0.2913; 0.5138]	0,0953
AB	2	0.4183 [0.0182; 0.9055]					
EC	2	0.0720 [0.0289; 0.1299]	1	0.0769 [0.0171; 0.1680]	1	0.0678 [0.0150; 0.1488]	0,8472
p-value		***< 0.0001***		***0.0004***		***< 0.0001***	
Wards							
Tot	34	0.1632 [0.1154; 0.2164]	14*	0.1526 [0.0615; 0.2692]			
Low risk	9	0.0563 [0.0120; 0.1217]	5	0.0000 [0.0000; 0.0124]			
High risk	25	0.2204 [0.1521; 0.2959]	9	0.2531 [0.1521; 0.3679]	7	0.2305 [0.0587; 0.4516]	
p-value		***0,0004***		***< 0.0001***			

Discussion

Our work was prompted by the need for comprehensive systematic reviews on the subject of screening approaches and clinical evolution of AMR-GNB colonisation in hospitalised patients. To our knowledge, in previous literature, no systematic review evaluated the risk of developing infection during hospitalisation amongst adult patients colonised by any AMR-GNB. We identified only one systematic review studying risk of subsequent infection in patients colonised by CRE at hospital admission[98]. We described the different screening approaches for colonisation and the resulting prevalence estimates, then we investigated the acquisition rate and the risk of developing an infection during hospitalisation due to AMR-GNB faecal carriage.

Our analysis included studies performed to assess prevalence of colonisation at baseline or following an outbreak episode. The decision to perform screening for carriage in hospital settings was conducted following two patterns: either according to the risk factors associated with the patient or to the risks associated with the ward where the patient is admitted. Even considering that screening strategies are strongly related to the incidence and prevalence of the screened multi-drug resistant pathogens in the study hospital, investigation on patients AMR-GNB colonisation status did not constitute routine standard of care in all health systems for which evidence was available. However, as reported in the WHO guidelines, surveillance screening should be based on the assessment of the patient's risk and the potential risk that these patients represent for others in their environment[99]. Therefore, both types of screening are valid and adaptable according to the context in which they are applied[100,101].

We observed a noticeable heterogeneity in timing and frequency of screening, ranging from *ad hoc* screening, at admission only, to regular screening timetable (e.g. every 48 hours, weekly, etc.). The reported screening patterns were likely related to the diverse objectives, settings and population characteristics of the included studies. While providing a comprehensive overview of the existing approaches, our study highlights the need for future assessment of their appropriateness and effectiveness.

Prevalence of any Gram-negative bacteria carriage at hospital admission was consistent across studies, allowing to estimate their burden in high income countries. Geographical differences were observed at least for the most represented pathogens. We noted a significantly lower prevalence of *Klebsiella* spp and *Escherichia coli* in Europe as compared to the US and Asia.

Based on pathogens groups, we observed that overall prevalence of AMR-GNB carriage varied over time, with higher prevalence reported for almost all considered pathogens during 2010-2014 and a significant decrease from 2015 onwards. These findings may be partially explained by the Carbapenemase-producing *Enterobacterales* spread in the early years of the decade leading to a heightened attention to this issue[102], increased research activities and adoption of new control policies, including screening[103].

Based on available evidence, we could not identify any significant difference in the prevalence of AMR-GNB carriage when patient-based approach screening was implemented as compared to the ward-based approach. However, the heterogeneity of the studies in terms of target population and definition of screening approaches, does not allow to draw conclusions on the sensitivity of either approach.

It is interesting to observe that the prevalence of *Klebsiella* spp. carriage for patients admitted to HR wards was three times higher than that reported for low-risk settings. However, we did not observe a comparatively higher prevalence when considering only the patient type (HR vs AA patients, in LIRW). Based on these results, we may argue that the risk of colonisation attributable to ward type was higher and largely unrelated to the patient individual's risk[64,104,105]. This could be explained by the higher risk that wards with high treatment intensity intrinsically have: the antibiotic therapies adopted, the vulnerable condition of patients who have frequent hospitalisation, the greater invasive manoeuvres performed, as well as endemic environmental contamination. The guidelines in fact argue that proper cleaning of the environment and proper staff hygiene can actually reduce the risk of transmission in these types of wards[99,101]. The fact that these findings were only applicable to *Klebsiella* spp, could be at least partially explained by the higher number of studies focusing on this pathogen than others.

Acquisition of GNB colonisation during hospital stay is an important concern for patient safety[14,106]. Indeed, our analysis showed that the risk of acquiring AMR-GNB colonisation during hospital stay is considerable (10.5%), although varying significantly for pathogen type and setting, with its highest value (26.0%) reached for *Klebsiella* spp and in high-risk settings (12.5%).

In our review, the overall risk of progression to infection during hospitalisation among AMR-GNB colonised patients was high (15.8%), in line with what reported by Tischendorf et al. among CRE-colonised patients[98]. It must be noted that this risk is strictly related to pathogen type and setting. The increased risk of acquisition and infection in high-risk wards compared to low-intermediate risk settings could be attributed to the risk factors associated with this type of wards (e.g. frequent hospitalisation, need of invasive medical procedures, parenteral nutrition)[107] as the same factors leading to colonisation in vulnerable patients may constitute a determinant for progression[23,108]. No relationship between timing of colonisation acquisition and the risk of progression to clinical infection was observed.

Our study presents some limitations. Our results could be partially influenced by the body of evidence available in the literature, possibly skewed towards studies reporting on screening strategies implemented in high endemic contexts. Despite the efforts to define *a priori* stringent inclusion and exclusion criteria, the included studies were quite heterogeneous in terms of geographic area, purpose, study design, setting and populations. Even though we focussed our work on antibiotic-resistance features of the pathogens, it was not possible to

estimate prevalence, risk of acquisition or progression stratified by type of resistance mechanisms, largely due to incompleteness of data reported in the primary studies.
In addition, data on screening for carriage during hospitalisation were not available for all patients tested negative at admission, leading to a possible underestimation of carriage acquisition rate. We tried to minimise inaccuracy in our calculation by including in the analysis only studies clearly mentioning that patients were monitored for carriage acquisition during their hospitalisation. Finally, due to limited data, we were only able to estimate the overall mortality among infected patients, and we could not investigate any potential association between mortality, time of acquisition of the colonisation and progression to infection.
In conclusion, screening for AMR-GNB in high-income countries mostly followed targeted approaches, although highly heterogeneous, with a considerable overall prevalence of AMR-GNB carriage at hospital admission. Although we recognise the need for screening approaches to be sensitive and tailored to local context features, our results highlight the importance of designing them according to available evidence of their effectiveness.
The available data showed high risk of clinical infection associated with colonisation by AMR-GNB fostering the importance of adequate control measures, including active search of carriage, to ensure patients' safety.

Authors' contribution

Lara Tavoschi and Pierluigi Lopalco conceived the study. Guglielmo Arzilli, Giuditta Scardina, Virginia Casigliani, Lara Tavoschi, Andrea Porretta developed study protocol. Guglielmo Arzilli, Giuditta Scardina, Virginia Casigliani, Marco Moi performed the search, study selection and data extraction. Guglielmo Arzilli, Giuditta Scardina, Virginia Casigliani, Davide Petri, Ersilia Lucenteforte, Lara Tavoschi, Andrea Porretta performed data analysis and results interpretation. Guglielmo Arzilli, Giuditta Scardina, Lara Tavoschi, Andrea Porretta drafted the manuscript. Pierluigi Lopalco, Jordi Rello, Angelo Baggiani, Gaetano Privitera provided expert insights and contributed to protocol development, data interpretation and manuscript drafting. All authors reviewed and approved the final manuscript.

Declaration of interest

Giuditta Scardina, Davide Petri, Andrea Porretta, Ersilia Lucenteforte, Marco Moi, Angelo Baggiani, Gaetano Pierpaolo Privitera and Lara Tavoschi have no conflict of interest to declare. Guglielmo Arzilli and Virginia Casigliani were funded by GlaxoSmithKline with a

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TABLE. 1

	GNB		KB		
	n studies	prevalence %; 95%CI	n studies	prevalence % 95%CI	
Overall prevalence	12	15.1 (9.5-21.6)	35	4.1 (3.1-5.3)	
Geographical regions					
Northern Europe*	7[27,33,47,48,79,83]	14.1 (6.3-24.2)	15[13,32,41,46,48,50,53,55,78,79,81,83,85,86]	1.7 (1.0-2.6)	23
Southern Europe**	4[22,35,36,58]	16.9 (6.3-31.2)	14[18,22,25,26,35,40,52,62,67-69,75,80]	5.7 (3.7-8.3]	
Multicenter EU	..	..	..	..	
Asia	..	..	3[17,34,70]	7.1 (1.8-15.3)	
USA	..	..	1[14]	12.4 (9.1-16.2)	
Australia	1[56]	16.5(9.0-25.5)	2[21,56]	8.4 (3.9-14.4)	
p-value	*0,8989*		***< 0.0001***		
Period of time					
< 2010	1[46]	2.1 (1.0-3.5)	2[17,52]	4.2 (0.8-10.1)	
2010 - 2014	6[26,32,55,57,78]	24.1 (9.4-42.8)	14[14,18,26,32,34,40,41,56,67,69,70,75,79,86]	6.5 (4.1-9.3)	15[14,27,32,34
≥ 2015	5[21,34,35,47,82]	9.1 (5.0-14.3)	18[13,22,25,35,46,48,50,53,55,62,68,78,80,81,83,85]	2.4 (1.6-3.3)	16[13,22,35,43
p-value	***< 0.0001***		***0,0024***		

TABLE. 2

		KB-carriage at hospital admission	
	References	n studies	prevalence
Type of patient			%; 95%CI
All admitted (AA)	13,14,17,21,25,26,32,34,40,46,53,55,62,67,69,70,75,78,80,81,86,88	22	5.1 (3.5-6.9)
High risk (HR)	18,22,35,41,48,50,56,62,68,79,81,83,85	13	2.5 (1.6-3.5)
p-value		***0,0083***	
Type of ward			
Hospital-wide/Low-intermediate risk	13,17,18,21,46,48,62,68,78,79,81,85,86	14	2.0 (1.4-2.8)
High-risk	13,21,24,25,30,31,33,34,39,40,49,52,54,55,66,68,69,74,79,82,87	21	5.8 (3.5-8.6)
p-value		***0,0009***	
Ward/patients			
Hospital-wide/Low-intermediate - HR	18,48,62,68,79,81,85	7	2.4 (1.2-4.0)
Hospital-wide/Low-intermediate - AA	13,17,21,46,62,78,86	7	1.8 (1.1-2.6)
High-risk - HR	22,35,41,50,56,83	6	2.7 (1.1-4.8)

High-risk -AA	14,25,26,32,34,40,52,53,55,67,69,70,75,80,81	15	7.2 (3.9-11.5)
p-value		***0,0055***	
Risk attributable to type of ward			
Hospital-wide/Low-intermediate - AA	12,16,20,45,61,77,85	7	1.8 (1.1-2.6)
High-risk -AA	13,24,25,31,33,39,51,52,54,66,68,69,74,79,80	15	7.2 (3.9-11.5)
p-value		***0,0005***	
Risk attributable to type of patient			
Hospital-wide/Low-intermediate - HR	18,48,62,68,79,81,85	7	2.4 (1.2-4.0)
Hospital-wide/Low-intermediate - AA	12,16,20,45,61,77,85	7	1.8 (1.1-2.6)
p-value		*0,3222*	